Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion

Six-Month Results of the Phase 3 COPERNICUS Study

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Objective: To assess the efficacy and safety of intravitreal vascular endothelial growth factor (VEGF) Trap-Eye in eyes with macular edema secondary to central retinal vein occlusion (CRVO).

Design: Multicenter, randomized, prospective, controlled trial.

Participants: One hundred eighty-nine eyes with macular edema secondary to CRVO.

Methods: Eyes were randomized 3:2 to receive VEGF Trap-Eye 2 mg or sham injection monthly for 6 months.

Main Outcome Measures: The proportion of eyes with a ≥15-letter gain or more in best-corrected visual acuity (BCVA) at week 24 (primary efficacy end point), mean changes in BCVA and central retinal thickness (CRT), and proportion of eyes progressing to neovascularization of the anterior segment, optic disc, or elsewhere in the retina.

Results: At week 24, 56.1% of VEGF Trap-Eye treated eyes gained 15 letters or more from baseline versus 12.3% of sham-treated eyes ($P<0.001$). The VEGF Trap-Eye treated eyes gained a mean of 17.3 letters versus sham-treated eyes, which lost 4.0 letters ($P<0.001$). Central retinal thickness decreased by 457.2 μm in eyes treated with VEGF Trap-Eye versus 144.8 μm in sham-treated eyes ($P<0.001$), and progression to any neovascularization occurred in 0 and 5 (6.8%) of eyes treated with VEGF Trap-Eye and sham-treated eyes, respectively ($P = 0.006$). Conjunctival hemorrhage, reduced visual acuity, and eye pain were the most common adverse events (AEs). Serious ocular AEs were reported by 3.5% of VEGF Trap-Eye patients and 13.5% of sham patients. Incidences of nonocular serious AEs generally were well balanced between both groups.

Conclusions: At 24 weeks, monthly intravitreal injection of VEGF Trap-Eye 2 mg in eyes with macular edema resulting from CRVO improved visual acuity and CRT, eliminated progression resulting from neovascularization, and was associated with a low rate of ocular AEs related to treatment.

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Retinal vein occlusions remain the second most common cause of retinal vascular disease.[1,2] Although it is estimated that approximately 70% of vein occlusions are branch vein occlusions,[3] central retinal vein occlusions (CRVOs) were found in the Beaver Dam Eye Study to have a 15-year cumulative incidence of 0.5%.[4] The second eye becomes involved in an additional 7% to 11.9% of patients.[5] Although CRVO accounts for a minority of retinal vein occlusions, it is associated with more severe vision loss and a higher risk of neovascular glaucoma.[6,7]

For 2 decades, the recommended treatment of CRVO was based on the multicenter Central Vein Occlusion Study,[8] which showed no improvement in visual acuity with focal grid laser treatment for macular edema, nor an advantage to prophylactic panretinal photocoagulation for ischemia, and recommended laser treatment only if iris neovascularization or rubeotic glaucoma developed.[8–10] During most of the period since the trial, many treatments, both medical and surgical, were tried, but none in a rigorous, randomized, clinical trial setting. This has changed in the last 3 years, with the publication of 3 randomized clinical trials showing the benefit of pharmacologic agents for macular edema resulting from CRVO.[11–13]

Vascular endothelial growth factor (VEGF) is increased in the ocular fluids of patients with CRVO[14] and also is involved significantly in the pathogenesis of macular edema. The study Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety demonstrated a statistical

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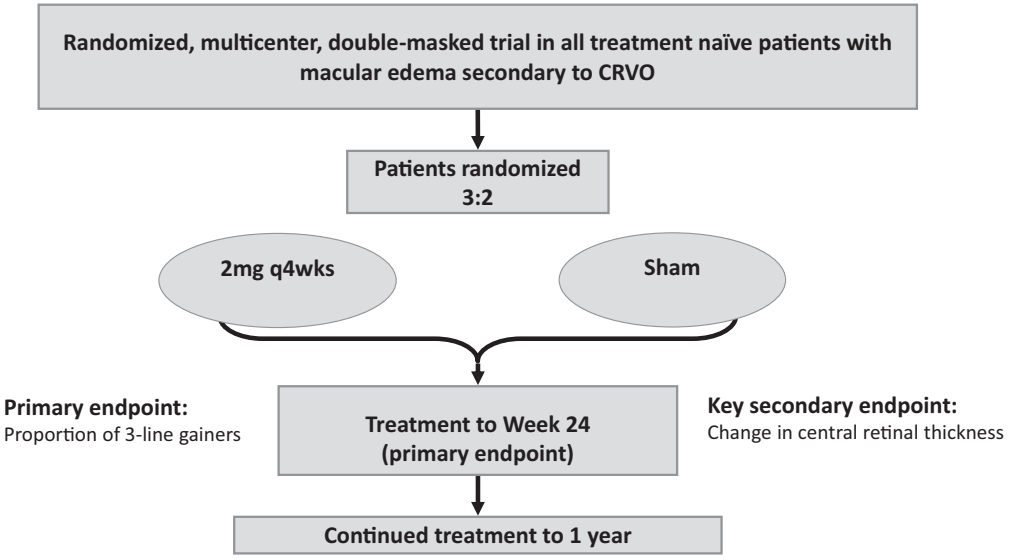

Figure 1. Diagram showing study design. Eligible eyes were randomized 3:2 to receive a monthly injection of vascular endothelial growth factor Trap-Eye 2 mg or a sham injection for 24 weeks. Between weeks 24 and 52, masking was maintained and all eyes were dosed on an as-needed basis according to predetermined criteria. The primary end point was proportion of eyes with a gain of 15 letters or more in best-corrected visual acuity from baseline, and secondary end points were assessed at week 24. CRVO = central retinal vein occlusion; q4wks = every 4 weeks.

and clinical benefit of treating patients monthly with ranibizumab (Lucentis; Genentech/Roche, South San Francisco, CA), a 50-kD Fab fragment that binds all isoforms of VEGF-A.[11] Two randomized clinical trials also demonstrated a benefit with the use of intravitreal steroids: triamcinolone acetonide (Trivaris; Allergan, Irvine, CA)[13] and the dexamethasone intraocular implant (Ozurdex; Allergan),[12] showing improved visual acuity and decreased macular thickening compared with control treatment at various time points.

Vascular endothelial growth factor Trap-Eye (aflibercept injection; Regeneron Pharmaceuticals, Tarrytown, NY) is a 115-kD decoy receptor fusion protein comprising the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2 fused to the Fc domain of human immunoglobulin G1.[15] Its binding affinity for VEGF is substantially greater than that of either bevacizumab or ranibizumab,[16] leading to a mathematical model predicting that it could have a substantially longer duration of action in the eye[17] and allowing for less frequent dosing, as supported by early clinical trials.[18] These phase 2 studies in wet age-related macular degeneration (AMD) patients have shown that the 2-mg dose administered monthly generally is well tolerated, and higher doses did not seem to improve the visual acuity results further.[18,19] Phase 3 results of VEGF Trap-Eye efficacy and safety in wet AMD recently have been reported (Nguyen QD, Heier J, Brown D, et al. Randomized, double-masked, active controlled phase 3 trial of the efficacy and safety of intravitreal VEGF Trap-Eye in wet AMD: 1-year results of the VIEW-1 study. Invest Ophthalmol Vis Sci 2011;52:E-Abstract 3073; Schmidt-Erfurth U, Chong V, Kirchhof B, et al. Primary results of an international phase III study using intravitreal VEGF Trap-Eye compared to ranibizumab in patients with AMD (VIEW-2). Invest Ophthalmol Vis Sci 2011;52:E-Abstract 1650). The study reported herein describes the results of a randomized, prospective clinical trial of monthly injections of intravitreal VEGF Trap-Eye for the treatment of macular edema resulting from CRVO.

Patients and Methods

Study Design

The primary objective of the study was to compare the efficacy of intravitreal VEGF Trap-Eye with the standard of care (observation [sham injection]) in improving best-corrected visual acuity (BCVA) in eyes with macular edema secondary to CRVO. Key secondary objectives were to assess safety and tolerability and the effects on central retinal thickness (CRT) of intravitreal VEGF Trap-Eye compared with the standard of care.

The COPERNICUS (Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion [CRVO]) is an ongoing 2-year, phase 3, prospective, randomized, double-masked study conducted at 70 sites in the United States, Canada, India, Israel, Argentina, and Colombia. This study began after all criteria for enrollment were met and patients were followed up for a total of 2 years (Fig 1). At baseline, patients were assigned randomly in a 3:2 ratio to receive VEGF Trap-Eye 2 mg or sham injections every 4 weeks for 24 weeks, for a total of 6 monthly doses of VEGF Trap-Eye or sham injection. Between weeks 24 and 52, patients in both groups were evaluated monthly and were reinjected with VEGF Trap-Eye if they met protocol-specified retreatment criteria or received a sham injection if retreatment was not indicated. After the first year of masked dosing, patients continued in a 1-year extension phase with as needed (*pro re nata*) dosing. Data for this 24-week report were obtained between July 2009 and October 2010.

Randomization was stratified using a centralized interactive voice randomization system, by geographic region (North America vs. the rest of the world), and by using a baseline BCVA score (>20/200 [35 to 73 letters] and ≤20/200 [34 to 24 letters]). One

eye per patient was randomized. The VEGF Trap-Eye 2 mg was injected in a volume of 50 μl. Sham injections were performed by pressing an empty, needleless syringe barrel to the conjunctival surface to simulate an injection. All patients were eligible to receive panretinal photocoagulation at any time during the study at the discretion of the investigator. if they progressed to anterior segment neovascularization, neovascularization of the disc, or neovascularization elsewhere.

The study protocol was approved by the ethics committee at each institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. The study was compliant with the rules and regulations under the Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent to participate in the study. The COPERNICUS study is registered with ClinicalTrials.gov (NCT00943072).

Eligibility

The study enrolled adult patients with center-involved macular edema secondary to CRVO diagnosed within 9 months of study initiation. Eyes had mean central subfield retinal thickness of 250 μm or more on ocular coherence tomography (OCT) from Zeiss Stratus OCT (version 4.0 or later; Carl Zeiss Meditec, Jena, Germany) and Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye.

Key exclusion criteria were history of vitreoretinal surgery in the study eye, including radial optic neurotomy or sheathotomy; current bilateral retinal vein occlusion; previous panretinal or macular laser photocoagulation; other causes for decreased visual acuity; ocular conditions with poorer prognosis in the fellow eye; history or presence of AMD, diabetic macular edema, or diabetic retinopathy; any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months; iris neovascularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane that significantly affected central vision; ocular inflammation; uveitis; any intraocular surgery in the preceding 3 months; aphakia; uncontrolled glaucoma, hypertension, or diabetes; spherical equivalent of a refractive error of more than −8 diopters; myopia; infectious blepharitis, keratitis, scleritis, or conjunctivitis; cerebral vascular accident or myocardial infarction in the preceding 6 months; and other conditions that may interfere with interpretation of the results or increase the risk of complications. A relative afferent pupillary defect was not an exclusion, nor was nonperfusion.

Patients were not allowed to use other systemic or local medications for treating CRVO in the study eye over the first 52 weeks of the study. Cataract surgery was not allowed during the 3 months before randomization. A noninvestigational therapy could be used to treat CRVO in the fellow eye.

End Points and Assessments

The primary efficacy end point was the proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24. Secondary efficacy end points were change from baseline to week 24 in the following variables (order reflects the test sequence; see below): BCVA, CRT, proportion of eyes progressing to ocular neovascularization, and National Eye Institute 25-item Visual Function Questionnaire total score.

During the first 6 months, assessments were performed at regularly scheduled clinic visits on day 1, at week 4, and every 4 weeks thereafter to week 24. A full ocular examination was conducted at each visit, including visual acuity testing by examiners masked to patient treatment arm, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement (preinjection and 30 minutes after injection), and OCT. Fundus photography and fluorescein angiography were performed at baseline, week 12, and week 24. The National Eye Institute 25-item Visual Function Questionnaire was administered at baseline and week 24. Adverse events (AEs) and concomitant medications were recorded, and vital signs were obtained at each visit; laboratory assessments, including measurement of anti-VEGF Trap-Eye antibodies, were performed at baseline and weeks 12 and 24.

Best-corrected visual acuity was assessed by certified examiners using the ETDRS protocol at 4 m. Examiners were masked to treatment assignment. Retinal characteristics were determined by OCT scans read at a masked independent central reading center (Duke Reading Center, Durham, NC). The CRT 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). The anatomic features of the retinal vasculature were evaluated by fundus photography and fluorescein angiography. Angiographic images were obtained by certified photographers and were transmitted to an independent reading center (Digital Angiographic Reading Center, New York, NY) for review by masked graders. Vision-related quality of life was assessed with the National Eye Institute 25-item Visual Function Questionnaire in an interviewer-administered format

Table 1. Patient Disposition

	Control (Sham)	Vascular Endothelial Growth Factor Trap-Eye 2 mg	Total
No. randomized	74	115	189
Treated, n (%)	74 (100%)*	114 (99.1%)†	188 (99.5%)
Completed week 24, n (%)	60 (81.1%)	110 (95.7%)	170 (89.9%)
Discontinued before week 24, n (%)	14 (18.9%)	5 (4.3%)	19 (10.1%)
Withdrawal of consent‡	1 (1.4%)	3 (2.6%)	4 (2.1%)
Protocol deviation	1 (1.4%)	0	1 (0.5%)
Adverse event§	3 (4.1%)	0	3 (1.6%)
Death	2 (2.7%)	0	2 (1.1%)
Lost to follow-up	2 (2.7%)	1 (0.9%)	3 (1.6%)
Treatment failure	4 (5.4%)	0	4 (2.1%)
Other‖	1 (1.4%)	1 (0.9%)	2 (1.1%)

*One patient was excluded from the full analysis set because of having no past baseline assessment.

†One patient was randomized but not treated after a retinal tear was identified at visit 2.

‡One patient in the sham group discontinued with no reason given and with no adverse events (AEs) reported. Three patients in the vascular endothelial growth factor Trap-Eye group discontinued for the following reasons: 1 patient had an AE associated with small-cell lung cancer; 1 patient declined return for follow-up, no ocular AEs were reported; and 1 patient had no information available.

§Reasons for discontinuations as a result of AE were: 1 patient with elevated intraocular pressure, rubeosis, and vitreous hemorrhage; 1 patient with neovascular glaucoma; and 1 patient with rubeous and vitreous hemorrhage.

‖One patient in the sham group discontinued because of an ocular AE with a 29-letter Early Treatment Diabetic Retinopathy Study decrease in best-corrected visual acuity and possible rubeosis. The subinvestigator determined it was in the best interest of the patient. One patient in the vascular endothelial growth factor Trap-Eye group discontinued after a retinal tear was identified before the first injection.

Table 2. Baseline Demographic and Clinical Characteristics

Characteristic	Control (Sham; n = 73)	Vascular Endothelial Growth Factor Trap-Eye 2 mg (n = 114)	Total (n = 187)
Mean age (SD), yrs	67.5 (14.3)	65.5 (13.6)	66.3 (13.9)
Gender (%M:%F)	52:48	61:39	57:43
Race, n (%)			
White	59 (80.8%)	88 (77.2%)	147 (78.6%)
Black	5 (6.8%)	5 (4.4%)	10 (5.3%)
Asian	2 (2.7%)	7 (6.1%)	9 (4.8%)
American Indian/Alaska native	0	2 (1.8%)	2 (1.1%)
Native Hawaiian/Pacific Islander	1 (1.4%)	0	1 (0.5%)
Not reported/multiracial	6 (8.2%)	12 (10.5%)	18 (9.6%)
BCVA >20/200, n(%)	55 (75.3%)	86 (75.4%)	141 (75.4%)
BCVA ≤20/200, n(%)	18 (24.7%)	28 (24.6%)	46 (24.6%)
Mean central retinal thickness (SD), μm	672.4 (245.3)	661.7 (237.4)	665.8 (239.8)
Mean visual acuity (ETDRS)	48.9 (14.4)	50.7 (13.9)	50.0 (14.1)
Retinal perfusion status, n (%)			
Perfused*	50 (68.5%)	77 (67.5%)	127 (67.9%)
Nonperfused	12 (16.4%)	17 (14.9%)	29 (15.5%)
Indeterminate	11 (15.1%)	20 (17.5%)	31 (16.6%)
Mean intraocular pressure (mmHg)	15.0 (2.81)	15.1 (3.26)	15.1 (3.08)
Mean time since CRVO diagnosis (mos)	1.88 (2.19)	2.73 (3.09)	2.40 (2.80)
CRVO diagnosis time (mos), n (%)			
≤2	52 (71.2%)	64 (56.1%)	116 (62.0%)
>2	21 (28.8%)	49 (43.0%)	70 (37.4%)
Mean NEI VFQ-25 scores (SD)			
Total	77.78 (16.25)	77.67 (15.96)	77.71 (16.03)
Near activities	70.72 (20.22)	69.96 (21.94)	70.25 (21.23)
Distance activities	78.08 (21.25)	75.99 (21.26)	76.80 (21.22)
Vision dependency	82.76 (27.41)	83.26 (25.51)	83.07 (26.20)

BCVA = best-corrected visual acuity; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; F = female; M = male; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; SD = standard deviation.
*Less than 10 disc areas of nonperfusion.

and was administered by masked site personnel before intravitreal injection.

Starting at week 24, eyes were assessed for retreatment and received an injection of VEGF Trap-Eye if any of the following retreatment criteria were met: a more than 50-μm increase in CRT on OCT, new or persistent cystic retinal changes of subretinal fluid on OCT or persistent diffuse edema of 250 μm or more in the central subfield on OCT, a decrease of visual acuity between the current and most recent visit of 5 letters or more. If none of the retreatment criteria were met, eyes received a sham injection.

Safety assessments included ocular AEs in the study and fellow eye, nonocular AEs, ocular and nonocular serious AE (SAEs), AEs of interest, laboratory assessments, vital signs, and measurement of antidrug antibody in serum.

Statistical Analyses

The sample size calculation was based on the assumptions that the difference in the proportion of eyes gaining at least 15 letters of vision at week 24 would be 25% (15% in the sham group[9] and 40% in the VEGF group[20]), and the dropout rate would be 9%. With these assumptions, a total sample size of 165 eyes (99 in the VEGF group and 66 in the sham group) was required to detect this difference in the primary analysis with 90% power at a 5% significance level using a 2-sided Fisher exact test.

Primary efficacy analyses were conducted in the full-analysis set, which included all randomized patients who received any study medication and had a baseline efficacy assessment and at least 1 efficacy assessment after baseline. In the primary analysis of the primary end point, patients who discontinued prematurely (before week 24) and had fewer than 5 injections of VEGF Trap-Eye or sham were evaluated as nonresponders; otherwise, missing values were imputed using last observation carried forward analyses. Pure last observation carried forward analyses were performed as a sensitivity analysis. Proportions of 15-letter gainers were compared with a 2-sided Cochran-Mantel-Haenszel test, stratified for region and baseline BCVA. Secondary end point analyses were performed sequentially according to the order in which the variables were defined to preserve an α of 0.05. The hypothesis was tested only if all the previous null hypotheses in the sequence could be rejected. The sequence of analysis was as follows: (1) change from baseline in BCVA score at week 24; (2) change from baseline in CRT at week 24; (3) proportion of subjects progressing to anterior segment neovascularization, neovascularization of the optic disc, or neovascularization of the retina elsewhere at week 24; and (4) change from baseline in the National Eye Institute 25-item Visual Function Questionnaire total score at week 24. Proportions were analyzed with the Cochran-Mantel-Haenszel test, and continuous variables were analyzed with an analysis of covariance main effects model with treatment group, region, and baseline BCVA as fixed factors and the

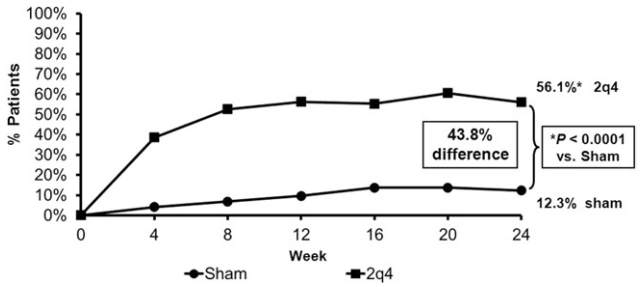

Figure 2. Graph showing the percentage of eyes with best-corrected visual acuity (BCVA) improvement of 15 letters or more from baseline to week 24 after treatment with vascular endothelial growth factor (VEGF) Trap-Eye 2 mg or sham treatment. At week 24, BCVA improvement of 15 letters or more was achieved in a significantly higher proportion of eyes treated with VEGF Trap-Eye than in the sham-treated group (*P<0.001). The last observation carried forward method was used to impute missing data. For week 24, patients who discontinued before 24 weeks and had fewer than 5 injections were considered nonresponders. 2q4 = VEGF Trap-Eye 2 mg every 4 weeks.

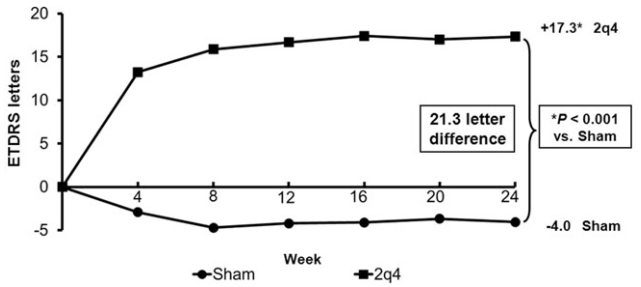

Figure 3. Graph showing the mean change from baseline in best-corrected visual acuity (BCVA) over 24 weeks after treatment with vascular endothelial growth factor (VEGF) Trap-Eye 2 mg or sham treatment. A significant improvement from baseline in BCVA was observed in the VEGF Trap-Eye group compared with the sham-treated group (*P<0.001). The last-observation-carried-forward method was used to impute missing data. 2q4 = VEGF Trap-Eye 2 mg every 4 weeks; ETDRS = Early Treatment Diabetic Retinopathy Study.

respective baseline variable as a covariate (using last observation carried forward). Additional analyses were performed to assess the sensitivity of the results to the statistical methods used, including per protocol and observed cases analyses. Safety analyses included all randomized patients who received any study treatment. Adverse events were summarized using the *Medical Dictionary for Regulatory Activities* preferred term within primary organ class.

Results

Patient Disposition

The study randomized 115 eyes to VEGF Trap-Eye and 74 eyes to sham injection (Table 1). A total of 110 patients (95.7%) in the VEGF Trap-Eye group and 60 patients (81.1%) in the sham treatment group completed 24 weeks in the study. The primary reason for premature discontinuation from the study before week 24 in the VEGF Trap-Eye group was withdrawal of consent (n = 3; 2.6%) and in the sham group it was treatment failure (n = 4; 5.4%).

Table 3. Proportion of Patients with Vision Gain or Loss at Week 24*

	Control (Sham; n = 73)	Vascular Endothelial Growth Factor Trap-Eye (n = 114)
Letter gain, no. letters (%)		
≥15	9 (12.3%)	66 (57.9%)
≥10	16 (21.9%)	87 (76.3%)
≥5	29 (39.7%)	97 (85.1%)
≥0	38 (52.1%)	107 (93.9%)
Letter loss, no. letters (%)		
≥5	29 (39.7%)	5 (4.4%)
≥10	22 (30.1%)	2 (1.8%)
≥15	20 (27.4%)	2 (1.8%)

*Full analysis set, last observation carried forward.

Baseline Characteristics

At baseline, patient demographic and disease characteristics were comparable for the treatment groups (Table 2). The average age of patients was 66.3 years, the mean BCVA at baseline was 50.0 ETDRS letters (Snellen equivalent, 20/100), and mean CRT was 665.8 μm; 67.9% of eyes were graded as perfused and 15.5% were graded as nonperfused, with the remainder being indeterminate (resulting from poor visualization of the retinal vasculature). The mean National Eye Institute 25-item Visual Function Questionnaire score was 77.71. Most patients (62.0%) had been diagnosed with CRVO within fewer than 2 months.

Visual Outcomes

In the primary analysis, 56.1% of eyes treated with VEGF Trap-Eye 2 mg gained 15 letters or more from baseline, compared with 12.3% of sham-treated eyes, with a difference of 43.8% (difference adjusted for region and baseline BCVA was 44.8%; 95% confidence interval [CI], 33.0%–56.6%; P<0.001). Improvement in visual acuity with VEGF Trap-Eye was evident as early as 4 weeks after the first injection (Fig 2). Most eyes (93.9%) in the VEGF Trap-Eye group gained 0 letters or more compared with 52.1% of eyes in the sham group. More patients in the sham group than in the VEGF Trap-Eye group lost 15 letters or more (27.4% vs. 1.8%, respectively; Table 3).

By week 24, eyes in the VEGF Trap-Eye arm had a mean gain of 17.3±12.8 letters compared with a mean loss of 4.0±18.0 letters in the sham group. The least squares mean difference in BCVA between the VEGF Trap-Eye and sham groups, adjusted for region and baseline BCVA, was 21.70 (95% CI, 17.36–26.04; P<0.001; Fig 3). The BCVA improved steadily in the VEGF Trap-Eye group beginning at week 4 and continuing through week 24 and decreased in the sham group.

Subgroup analyses of visual acuity in eyes by baseline BCVA, baseline perfusion status, and time since diagnosis also were performed. The mean change from baseline at week 24 in BCVA letter score was +21.9 versus 0 for VEGF Trap-Eye versus sham treatment for baseline BCVA of 20/200 or worse and +15.9 versus −5.4 for baseline BCVA better than 20/200. A gain of 15 letters or more was noted in 67.9% versus 16.7% for VEGF Trap-Eye versus sham treatment for baseline BCVA of 20/200 or worse (difference of 51.2%; 95% CI, 26.8%–75.6%) and in 52.3% and 10.9% for BCVA better than 20/200 (difference of 41.4%; 95% CI, 28.0%–54.8%).

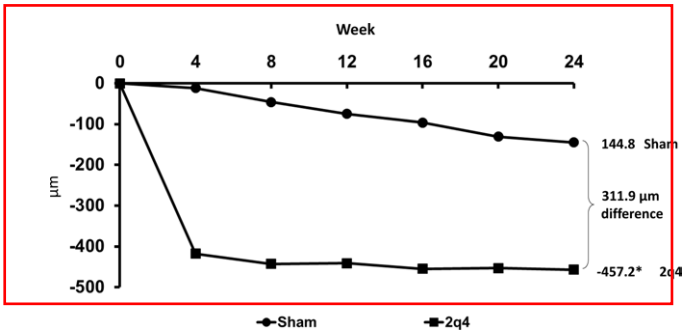

Figure 4. Graph showing the mean change from baseline in central retinal thickness (CRT) over 24 weeks after treatment with vascular endothelial growth factor (VEGF) Trap-Eye 2 mg or sham treatment. Central retinal thickness was measured with optical coherence tomography. A significant decrease from baseline in CRT was observed in the VEGF Trap-Eye group compared with the sham-treated group (*P<0.001). The last-observation-carried-forward method was used to impute missing data. 2q4 = VEGF Trap-Eye 2 mg every 4 weeks.

The baseline perfusion status did not affect response rates. Mean change from baseline at week 24 in BCVA letter score was +17.8 versus −2.3 for VEGF Trap-Eye versus sham treatment in nonperfused (≥10 disc areas of nonperfusion) eyes and +17.1 versus −4.8 in perfused (<10 disc areas of nonperfusion) eyes. Similarly, proportions of eyes gaining 15 letters or more were 51.4% versus 4.3% for VEGF Trap-Eye versus sham treatment in nonperfused eyes (difference of 47.0%; 95% CI, 28.9%–65.1%) and 58.4% versus 16.0% (difference of 42.4%; 95% CI, 27.5%–57.4%) in perfused eyes.

Improvements in visual acuity were quantitatively larger when the time from diagnosis was 2 months or less compared with more than 2 months. In the subgroup treated within 2 months of diagnosis, 68.8% treated with VEGF Trap-Eye gained 15 letters or more at week 24 versus 15.4% with sham treatment (difference of 53.4%; 95% CI, 38.36%–68.37%). Among subjects treated more than 2 months after diagnosis, a gain of 15 letters or more was obtained in 38.8% versus 4.8% for VEGF Trap-Eye versus sham treatment (difference of 34.0%; 95% CI, 17.61%–50.42%). Mean change from baseline at week 24 in BCVA letter score was +20.2 versus −5.5 for VEGF Trap-Eye versus sham treatment in subjects treated within 2 months and +13.4 versus −0.5 in subjects treated more than 2 months after diagnosis.

Anatomic Outcomes

The VEGF Trap-Eye group demonstrated a robust and rapid reduction in CRT beginning at the first measurement after baseline at week 4 and continuing through week 24 (Fig 4). At week 24, the mean change in CRT was −457.2 µm in the VEGF Trap-Eye group compared with −144.8 µm in the sham group. The least squares mean difference in CRT reduction between groups adjusted for region and baseline BCVA was −311.9 (95% CI, −389.4 to −234.4; P<0.001). Subjects with a perfused status at baseline had a greater mean decrease in CRT of −450.0 µm with VEGF Trap-Eye compared with −81.8 µm with sham treatment; in eyes that were nonperfused at baseline, mean decreases in CRT were −473.0 µm with VEGF Trap-Eye and 309.4 µm with sham treatment.

As shown in Table 4, progression to ocular neovascularization during the first 24 weeks was eliminated in the VEGF Trap-Eye group (0% vs. 6.8% in the sham treatment group; P = 0.006). The sham treatment group included 5 eyes in which anterior segment neovascularization developed.

At weeks 12 and 24, more eyes in the VEGF Trap-Eye group (71.9% and 78.9%, respectively) had a capillary perfusion status of perfused compared with the sham-treated eyes (52.1% and 46.6%, respectively). At week 12, the incidence of nonperfused status was similar between treatment groups (13.7% for the sham-treated group and 9.6% for the VEGF Trap-Eye group); however, at week 24, more eyes in the sham group had a nonperfused status (23.3%) compared with the VEGF Trap-Eye eyes (7.9%). By week 24, panretinal photocoagulation had been performed on 4 sham-treated eyes (5.5%) and none of the eyes treated with VEGF Trap-Eye.

Patient-Reported Outcomes

By week 24, patients treated with VEGF Trap-Eye showed a clinically relevant improvement of 7.2 points in National Eye Institute 25-item Visual Function Questionnaire total score compared with an improvement of 0.8 points in the sham group (Table 5, available at http://aaojournal.org). The adjusted least squares mean difference in National Eye Institute 25-item Visual Function Questionnaire total score between the VEGF Trap-Eye and sham groups was 6.26 (95% CI, 2.61–9.91; P = 0.001). Clinically relevant improvements in National Eye Institute 25-item Visual Function Questionnaire subscale scores (near activities, distance activities, and vision dependency) also were observed.

Safety

During the first 24 weeks, 92.1% and 89.2% of patients in the VEGF Trap-Eye and sham groups, respectively, received all 6 of the planned injections (patients in the sham group received sham injections). Patients in both groups received the same number of injections (mean of 5.8 in the VEGF Trap-Eye group and 5.3 in the sham group).

Most patients in each treatment group (83.3% VEGF Trap-Eye and 85.1% sham) experienced at least 1 AE during the study. Ocular AEs occurred in similar proportions of patients in each group (VEGF Trap-Eye, 68.4%; sham, 68.9%). Ocular AEs that occurred more frequently in the sham group were consistent with the complications of CRVO (visual acuity decreased, retinal hemorrhage, vitreous hemorrhage, and iris neovascularization). The most common ocular AEs with VEGF Trap-Eye treatment were

Table 4. Incidence of Neovascularization during First 24 Weeks

	Control (Sham; n = 73)	Vascular Endothelial Growth Factor Trap-Eye (n = 114)
Any neovascularization, n (%)	5 (6.8)*	0
Anterior segment neovascularization	5 (6.8)	0
Neovascularization of the optic disc	0	0
Neovascularization of the retina elsewhere	0	0
Panretinal photocoagulation performed, n (%)	4 (5.5)	0

*P = 0.006, vascular endothelial growth factor Trap-Eye vs. sham (2-sided Cochran-Mantel-Haenszel test adjusted by regions and baseline best-correct visual acuity).

Table 6. Ocular Serious Adverse Events at Week 24

	Control (Sham; n = 74)	Vascular Endothelial Growth Factor Trap-Eye 2 mg (n = 114)
Patients with at least 1 SAE, n (%)	10 (13.5%)	4 (3.5%)
Vitreous hemorrhage	4 (5.4%)	0
Neovascular glaucoma	2 (2.7%)	0
Iris neovascularization	2 (2.7%)	0
Retinal hemorrhage	2 (2.7%)	0
Visual acuity reduced	1 (1.4%)	1 (0.9%)
Retinal artery occlusion	0	1 (0.9%)
Retinal tear	1 (1.4%)	0
Retinal vein occlusion	1 (1.4%)	0
Endophthalmitis	0	1 (0.9%)
Corneal abrasion	0	1 (0.9%)

SAE = serious adverse event.

conjunctival hemorrhage, eye pain, and maculopathy. Most ocular AEs were mild; SAEs were reported by only 4 patients (3.5%) receiving VEGF Trap-Eye. As assessed by investigators who were masked to treatment, a drug-related ocular AE was reported in 4 patients treated with VEGF Trap-Eye (1 case each of endophthalmitis, maculopathy, ocular discomfort, and retinal artery occlusion) and 2 in the sham group (eye irritation and macular edema). Ocular AEs in the study eye considered to be related to the injection procedure occurred at a higher frequency in the eyes that actually received an intravitreal injection of VEGF Trap-Eye group (35 patients [30.7%]) compared with eyes that received sham injections only (14 patients [18.9%]). The most common injection-related AEs were conjunctival hemorrhage (13 [17.6%] in the sham group and 17 [14.9%] in the VEGF Trap-Eye 2 mg every 4 weeks group), and eye pain (2 [2.7%] in the sham group and 12 [10.5%] in the VEGF Trap-Eye group).

Four patients receiving VEGF Trap-Eye (3.5%) and 10 patients receiving sham treatment (13.5%) reported at least 1 ocular SAE (Table 6). The most common SAEs were vitreous hemorrhage (n = 4), neovascular glaucoma (n = 2), iris neovascularization (n = 2), and retinal hemorrhage (n = 2), all of which occurred in sham-treated eyes. One patient in each group reported a reduction in visual acuity. One case each of endophthalmitis, retinal artery occlusion, and corneal abrasion was reported in the VEGF Trap-Eye group.

Nonocular AEs were mild or moderate, with hypertension (n = 10; 8.8%) and upper respiratory tract infection (n = 6; 5.3%) reported most commonly in the VEGF Trap-Eye group. The incidence of nonocular SAEs was similar between the VEGF Trap-Eye group (n = 6 patients; 5.3%) and sham group (n = 6; 8.1%). Neoplasms were the most commonly reported SAE and occurred in 4 patients in the sham group and 1 patient in the VEGF Trap-Eye group. Two patients in the sham group had fatal nonocular SAEs: 1 was a myocardial infarction and 1 was arrhythmia.

Five patients in the sham treatment group discontinued study drug because of ocular AEs (vitreous hemorrhage, glaucoma, iris neovascularization, retinal hemorrhage, retinal tear) compared with 1 patient after VEGF Trap-Eye treatment (retinal artery occlusion). Differences between treatments in laboratory values or vital signs were not clinically meaningful, and no drug association was noted.

Discussion

The phase 3 COPERNICUS study met the primary efficacy end point of the proportion of eyes with a gain of 15 ETDRS letters or more from baseline to week 24 with VEGF Trap-Eye treatment compared with sham treatment (56.1% vs. 12.3%) and all of the secondary efficacy end points, including BCVA and improvement in CRT. Visual acuity improvement was rapid and was maintained throughout the course of the 24-week study, with the VEGF Trap-Eye arm having a mean gain of 17.3 letters compared with a mean loss of 4 letters in the sham group, a 21-letter difference.

The improvement in visual acuity was accompanied by a rapid decrease in CRT documented at 1 month, the first measured time point, and continuing through week 24, with an improvement of more than 300 μm in the eyes treated with VEGF Trap-Eye compared with sham-treated eyes. Along with causing a large reduction of macular edema, VEGF Trap-Eye prevented development of ocular neovascularization through 24 weeks. No eye in the VEGF Trap-Eye group progressed to any neovascularization, compared with approximately 7% of eyes in the sham group. These results also indicate that VEGF Trap-Eye therapy was effective in eyes that were nonperfused or indeterminate at baseline (14.9% and 17.5%, respectively, in the VEGF Trap-Eye group).

There was a marked increase in the National Eye Institute 25-item Visual Function Questionnaire score, with a clinically relevant improvement of 7.2 points in the VEGF Trap-Eye group, compared with 0.8 points in the sham group. The treatment was well tolerated, with little evidence of negative ocular or systemic effects. The overall incidence of ocular AEs related to VEGF Trap-Eye was low and was within the expected range. Most of the ocular AEs were those normally related to the injection procedure. The safety outcomes were consistent with those reported in the phase 2 and 3 studies of VEGF Trap-Eye in wet AMD.[18,19]

In this study, VEGF Trap-Eye was compared with sham injection rather than with ranibizumab, or the dexamethasone (Ozurdex) implant, the other treatment currently approved by the Food and Drug Administration for this indication. The Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety trial also compared eyes dosed monthly with the anti-VEGF drug ranibizumab and sham-treated eyes. In that trial, 46.2% and 47.7% of patients in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, had gained a mean of 15 letters or more at 6 months compared with 16.9% of sham-treated patients, and the mean letter gains were 12.7 and 14.9 with ranibizumab 0.3 mg or 0.5 mg, respectively, compared with 0.8 letters with sham treatment.[11] The improvement in visual acuity with VEGF Trap-Eye is of similar magnitude to that obtained with ranibizumab in the Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety trial.

It is hypothesized that the broad range of activity and high binding affinity of VEGF Trap-Eye for VEGF-A may lead to durable and comprehensive VEGF blockade and may require less frequent dosing than shorter-acting anti-

VEGF agents.[17] After the mandatory 6 months of dosing, all patients in COPERNICUS were transitioned to as-needed (*pro re nata*) dosing with VEGF Trap-Eye (no more frequently than every month) based on prespecified retreatment criteria. This will enable assessment of both the durability of VEGF Trap-Eye and its continued benefit in maintenance treatment. At 1 year, it will be possible to determine the extent to which visual acuity can be recovered after VEGF Trap-Eye therapy in patients previously randomized to sham therapy.

In conclusion, monthly intravitreal VEGF Trap-Eye reduced macular edema, improved visual acuity, and augmented vision-related function at week 24 compared with sham treatment in eyes with macular edema secondary to CRVO. Ocular neovascularization was not observed in eyes receiving anti-VEGF therapy. The VEGF Trap-Eye treatment was well tolerated and was associated with a low incidence of ocular adverse events. With its generally favorable safety profile, VEGF Trap-Eye may offer an effective treatment option for eyes with central retinal vein occlusion.

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