

One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema

Diana V. Do, MD,¹ Quan Dong Nguyen, MD, MSc,¹ David Boyer, MD,² Ursula Schmidt-Erfurth, MD,³ David M. Brown, MD,⁴ Robert Vitti, MD,⁵ Alyson J. Berliner, MD,⁵ Bo Gao, PhD,⁵ Oliver Zeitze, MD,^{6,7} Rene Ruckert, MD,⁶ Thomas Schmelzer, PhD,⁶ Rupert Sandbrink, MD, PhD,^{6,8} Jeff S. Heier, MD,⁹ for the DA VINCI Study Group*

Purpose: To compare different doses and dosing regimens of Vascular Endothelial Growth Factor (VEGF) Trap-Eye with laser photocoagulation in eyes with diabetic macular edema (DME).

Design: Randomized, double-masked, multicenter, phase 2 clinical trial.

Participants: Diabetic patients (n = 221) with center-involved DME.

Methods: Participants were assigned randomly to 1 of 5 treatment regimens: VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4); 2 mg every 4 weeks (2q4); 2 mg every 8 weeks after 3 initial monthly doses (2q8); or 2 mg dosing as needed after 3 initial monthly doses (2PRN), or macular laser photocoagulation.

Main Outcome Measures: The change in best-corrected visual acuity (BCVA) at 24 weeks (the primary end point) and at 52 weeks, proportion of eyes that gained 15 letters or more in Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA, and mean changes in central retinal thickness (CRT) from baseline.

Results: As previously reported, mean improvements in BCVA in the VEGF Trap-Eye groups at week 24 were 8.6, 11.4, 8.5, and 10.3 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus 2.5 letters for the laser group ($P \leq 0.0085$ versus laser). Mean improvements in BCVA in the VEGF Trap-Eye groups at week 52 were 11.0, 13.1, 9.7, and 12.0 letters for 0.5q4, 2q4, 2q8, and 2PRN regimens, respectively, versus -1.3 letters for the laser group ($P \leq 0.0001$ versus laser). Proportions of eyes with gains in BCVA of 15 or more ETDRS letters at week 52 in the VEGF Trap-Eye groups were 40.9%, 45.5%, 23.8%, and 42.2% versus 11.4% for laser ($P = 0.0031$, $P = 0.0007$, $P = 0.1608$, and $P = 0.0016$, respectively, versus laser). Mean reductions in CRT in the VEGF Trap-Eye groups at week 52 were -165.4 μm , -227.4 μm , -187.8 μm , and -180.3 μm versus -58.4 μm for laser ($P < 0.0001$ versus laser). Vascular Endothelial Growth Factor Trap-Eye generally was well tolerated. The most frequent ocular adverse events with VEGF Trap-Eye were conjunctival hemorrhage, eye pain, ocular hyperemia, and increased intraocular pressure, whereas common systemic adverse events included hypertension, nausea, and congestive heart failure.

Conclusions: Significant gains in BCVA from baseline achieved at week 24 were maintained or improved at week 52 in all VEGF Trap-Eye groups. Vascular Endothelial Growth Factor Trap-Eye warrants further investigation for the treatment of DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2012;119:1658-1665 © 2012 by the American Academy of Ophthalmology.



Diabetic macular edema (DME) is the most common cause of vision loss for patients with diabetes mellitus.¹ The Wisconsin Epidemiologic Study found that the prevalence of macular edema was associated with an increasing duration of diabetes.^{2,3} Worldwide, the prevalence of adult diabetes is anticipated to rise from 4.0% in 1995 to 5.4% by 2025.⁴ Given this rising prevalence, it is expected that diabetic retinopathy and DME will continue to be common and will be important causes of vision impairment.

The complex pathophysiology of DME has been under investigation in recent years. In individuals with diabetic retinopathy, fluid can accumulate within the retina as a result of a breakdown in the blood-retinal barrier. Hyperglycemia associated with diabetes stimulates an inflamma-

tory response, which causes detrimental effects on the retinal vasculature.⁵ Vascular occlusion and ischemia results, and can lead to local hypoxia.⁶ Vascular endothelial growth factor (VEGF) and a host of other growth factors are up-regulated during hypoxic conditions, and an inflammatory cascade of events can ensue.

Vascular endothelial growth factor is thought to be a key factor in the pathogenesis of DME^{5,7} and is a vasoactive cytokine that both induces vascular permeability and stimulates angiogenesis. It is approximately 50 000-fold more potent in inducing permeability than histamine⁸⁻¹⁰ and affects endothelial tight junction proteins. Vascular endothelial growth factor is known to cause a breakdown of the blood-retinal barrier, followed by extracellular fluid accumulation and retinal edema.¹¹

Vascular endothelial growth factor concentrations are elevated in both the vitreous fluid and aqueous humor of patients with active proliferative diabetic retinopathy.^{12,13} One study reported that VEGF concentrations in aqueous humor were elevated nearly 5-fold in DME eyes compared with that of age-matched controls.¹⁴ Another study showed that the VEGF concentrations in the aqueous humor of eyes with DME were 3-fold higher than in the plasma.¹² Moreover, these elevated VEGF levels were correlated significantly with the severity of DME.¹² Elevated VEGF concentrations are associated with extensive macular leakage in diabetic eyes, and numerous studies have shown that VEGF inhibitors are effective for reducing retinal thickness and improving visual acuity.^{15–22}

Vascular Endothelial Growth Factor Trap-Eye is a 115-kDa recombinant fusion protein comprising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1.²³ Vascular Endothelial Growth Factor Trap-Eye is a panisoform VEGF-A inhibitor whose binding affinity to VEGF is substantially greater than that of either bevacizumab or ranibizumab,²³ leading to a mathematical model predicting it could have substantially longer duration of action in the eye.²⁴ In addition, VEGF Trap-Eye binds placental growth factors 1 and 2, which have been shown to contribute to excessive vascular permeability and retinal neovascularization.²⁵

The phase 2 clinical trial DME And VEGF Trap-Eye: INvestigation of Clinical Impact (DA VINCI) was designed to compare intravitreal VEGF Trap-Eye with macular laser photocoagulation. Results at week 24 (primary end point data) from the current study have been published previously,²⁶ and all VEGF Trap-Eye arms showed significant gains in visual acuity compared with laser treatment ($P \leq 0.0085$) at week 24. Patients in this study continued with their assigned dosing regimen and continued follow-up to determine if these visual acuity gains were maintained through week 52. The 1-year results are reported here.

Patients and Methods

The DA VINCI study was a randomized, double-masked, active-controlled multicenter phase 2 clinical trial. Thirty-nine sites in the United States, Canada, and Austria participated in the trial, and patients were enrolled between December 2008 and June 2009. The primary objective was to assess the efficacy of various doses and dose intervals of intravitreal VEGF Trap-Eye (aflibercept injection) on BCVA. The primary end point was the change in BCVA from baseline to week 24. Secondary objectives were to assess the effects of intravitreal VEGF Trap-Eye on retinal thickness assessed by optical coherence tomography (OCT) and to assess safety and tolerability of intravitreal VEGF Trap-Eye in eyes with DME. Secondary outcomes were the change in BCVA from baseline at week 52, the proportion of eyes that gained at least 15 ETDRS letters in BCVA compared with baseline at weeks 24 and 52, the change in central retinal thickness (CRT; central subfield on OCT) from baseline to weeks 24 and 52, and the number of focal laser treatments given.

The study protocol was approved by the institutional review board or ethics committee at every institution and was conducted according to the recommendations of Good Clinical Practice and

the tenets of 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 DA VINCI study is registered with ClinicalTrials.gov (NCT00789477).

Participants

The study enrolled adult patients 18 years of age or older with type 1 or 2 diabetes mellitus with clinically significant DME with center involvement of the fovea, defined as a central subfield measurement of 250 μm or more on time-domain OCT (Stratus OCT; Carl Zeiss Meditec, Jena, Germany). In addition, patients had an ETDRS BCVA letter score at 4 m of 73 to 24 (20/40 to 20/320) in the study eye.^{27,28} Patients were excluded if any of the following were present in the study eye: history of vitreoretinal surgery, panretinal or macular laser photocoagulation within 3 months of screening, previous use of intraocular or periorbital corticosteroids within 3 months of screening, or other ocular disorders that could contribute to vision loss and could confound the study results. In addition, previous treatment with antiangiogenic drugs for either eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) was not allowed within 3 months of screening. Patients with uncontrolled diabetes mellitus or hypertension (systolic blood pressure >180 mmHg or >160 mmHg on 2 consecutive measurements or diastolic blood pressure >100 mmHg on optimal medical regimen) also were excluded from the study.

Treatments

Eyes were assigned randomly using a 1:1:1:1:1 ratio to one of the following treatment regimens (Fig 1): (1) 0.5 mg VEGF Trap-Eye every 4 weeks (0.5q4); (2) 2 mg VEGF Trap-Eye every 4 weeks (2q4); (3) 2 mg VEGF Trap-Eye every 8 weeks after 3 initial monthly doses (2q8); (4) 2 mg VEGF Trap-Eye, with dosing as needed after 3 initial monthly doses (2PRN); (5) laser photocoagulation using a modified ETDRS protocol²⁷ at baseline and then as needed (but no more frequently than every 16 weeks). Eyes in the laser group also received a sham injection every 4 weeks.

Vascular Endothelial Growth Factor Trap-Eye, provided by Regeneron Pharmaceuticals, Inc (Tarrytown, New York), was administered by intravitreal injection with a 30-gauge needle using standard ophthalmic techniques. Vascular Endothelial Growth Factor Trap-Eye was formulated as a sterile liquid to a final concentration of either 10 mg/ml or 40 mg/ml VEGF Trap-Eye. The injection volume was 50 μl (0.05 ml), which provided the delivery of 0.5 mg or 2 mg of VEGF-Trap-Eye. Sham injections were performed following the identical treatment protocol used for the active injections, but only gentle application of the hub of the syringe (without the needle) to the sclera was used to mimic an injection.

Laser photocoagulation was performed using the modified ETDRS protocol (baseline treatment at week 1).^{3,28} After topical anesthesia and placement of a contact lens, grid therapy was applied to the thickened areas of the retina with diffuse leakage, focal therapy, or both being applied to leaking microaneurysms within the areas of retinal thickening. Sham laser treatments consisted of placing a contact lens on the study eye and positioning the patient in front of the laser machine for the approximate duration of a laser treatment, while the laser remained in the off position.

Retreatment Criteria

After the 3 initial monthly doses, eyes assigned to the 2PRN arm received an injection of study drug if any one of the following criteria were present: a more than 50- μm increase in CRT com-

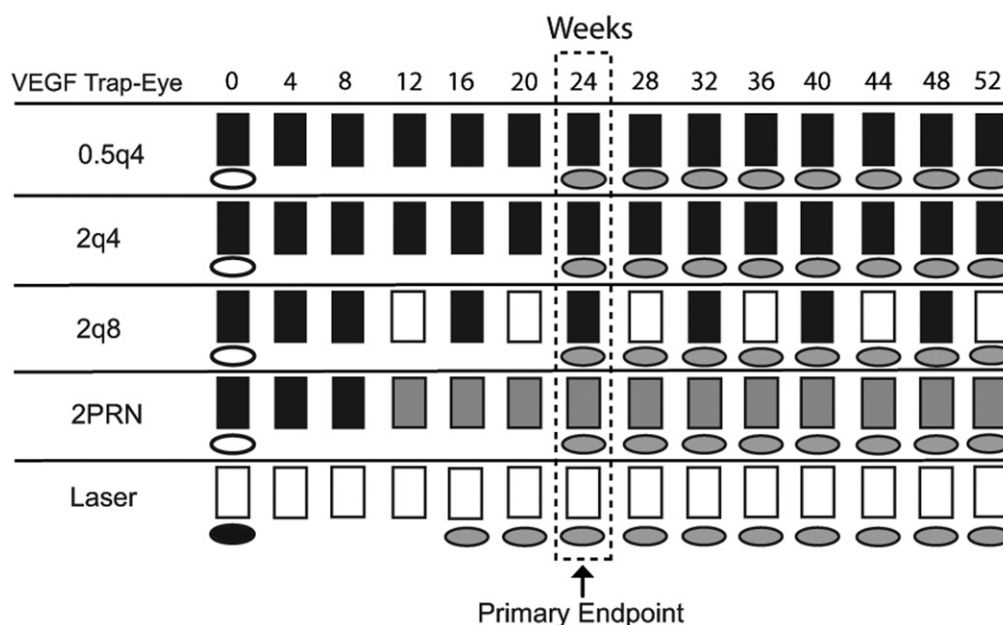


Figure 1. Diagram showing study design with interventions and schedule of visits throughout the course of the 12-month study. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; box = injection; grey = as needed; oval = laser; outline = sham; solid = active; VEGF = vascular endothelial growth factor.

pared with the lowest previous measurement; new or persistent cystic retinal changes, subretinal fluid, or persistent diffuse edema of 250 μm or more on OCT; a loss of 5 or more letters of BCVA from the best previous measurement in conjunction with any increase in CRT; and an increase in BCVA between the current and most recent visit of 5 letters or more. Eyes assigned to the 2PRN arm received sham injections if none of the retreatment criteria above were met.

Eyes in the laser photocoagulation arm of the study received their initial laser at week 1 (Fig 1). Starting at week 16, eyes were assessed for retreatment according to the following ETDRS criteria and were retreated if any one of the criteria were met: an increase in retinal thickness at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula, if associated with thickening of adjacent retina; zone(s) of retinal thickening 1 disc area or larger (any part of which was within 1 disc diameter of the center of the macula).

Starting at week 24 (month 6), these same three criteria were used to assess eyes in the VEGF Trap-Eye arms for laser rescue. Eyes in the VEGF Trap-Eye arms that met the criteria for laser rescue received laser 1 week after the scheduled visit, which they qualified for laser rescue. Subsequent laser rescue treatments could be performed at 16-week intervals.

Masking

Treatments (study drug injection, sham injection, laser or sham laser photocoagulation) were performed by an unmasked physician. A separate masked physician was assigned to assess adverse events (AEs) and retreatment and rescue criteria and to supervise the masked assessment of efficacy. Every effort was made to ensure that all other study site personnel remained masked to treatment assignment to facilitate an unbiased assessment of efficacy and safety.

Measurements

Visual acuity was measured using the ETDRS protocol.²⁸ Retinal and lesion characteristics of the study eye were evaluated using time-domain OCT (Zeiss Stratus OCT equipped with software version 3.0 or greater; Carl Zeiss Meditec, Jena, Germany). The study eye was evaluated by dilated funduscopy examination, fundus photography, and fluorescein angiography. The severity of each patient's diabetic retinopathy was assessed using the Diabetic Retinopathy Severity Score.²⁹ Intraocular pressure of the study eye was measured using Goldmann applanation tonometry (Haag-Streit AG, K niz, Switzerland) or the Tono-Pen (Reichert Technologies, DePew, New York) before dosing and again approximately 5 to 10 minutes after dosing. Safety assessments included ophthalmic examinations, clinical AEs, laboratory measures, and serum samples for potential development of anti-VEGF Trap-Eye antibodies.

Concomitant Medications

Patients were not allowed to receive any treatment for their DME in the study eye other than the assigned study treatment with VEGF Trap-Eye or laser until week 52 or until the early termination visit assessments were completed.

Statistical Analyses

The full analysis set, which was used for the efficacy analysis, included all randomized patients who received any study medication and had at least 1 assessment after baseline. The safety analysis set, used for all safety and tolerability assessments, included all participants who received any study medication. The last observation carried forward approach was used to account for missing data. A sample size of 200 patients (40 per group) provided 84% power to detect an 8-letter difference between each of the 4 VEGF Trap-Eye arms and the laser arm (assuming a standard

Table 3. Treatment and Exposure Summary for Vascular Endothelial Growth Factor Trap-Eye and Laser Treatments over the Course of the First 48 Weeks

Study Arm	Mean No. of Vascular Endothelial Growth Factor Trap-Eye Injections (SD)	Mean No. of Laser Treatments (SD)
0.5q4 (n = 44)	11.7 (2.49)	0.8 (0.83)
2q4 (n = 44)	10.8 (2.87)	0.5 (0.66)
2q8 (n = 42)	7.2 (1.74)	0.8 (0.86)
2PRN (n = 45)	7.4 (3.19)	0.7 (0.77)
Laser (n = 44)	N/A	2.5 (0.87)

0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; N/A = not applicable; SD = standard deviation.

deviation of 10 letters per group, with a 2-sided *t* test at an α level of 5%/4 = 0.0125). Change from baseline in BCVA and OCT were analyzed using analysis of covariance, models with the baseline value as covariate and the treatment as fixed factor. Hochberg's procedure was used for the primary analysis to control for the multiple comparisons. No adjustments for multiplicity were made for the secondary variables. The proportions of patients in the VEGF Trap-Eye arms gaining 10 letters or more (15 letters or more) were compared with the laser arm using the Fisher exact test. Other secondary end points, as well as demographic, baseline, and safety data, were evaluated using summary statistics.

Results

Patient Disposition and Demographics

A total of 221 eyes were randomized, 219 were treated, and 176 completed the 52-week study (Table 1, available at <http://aaojournal.org>). Forty-three patients discontinued the study after receiving at least 1 treatment for the following reasons: lost to follow-up (n = 11), withdrew consent (n = 11), death (n = 6), treatment failures (n = 2), AE (n = 7), protocol deviation (n = 2), other (n = 4). Discontinuations were distributed evenly among all the treatment groups. Demographic information and baseline characteristics are provided in Table 2 (available at <http://aaojournal.org>). The groups generally were similar, although the VEGF Trap-Eye 2q8 group had a higher prevalence of proliferative diabetic retinopathy (regressed at baseline) compared with the other treatment groups. In addition, a history of cardiac disease was more common in the VEGF Trap-Eye groups compared with the laser group.

Treatment and Exposure Summary

Over the 52 weeks of the study, the mean number of VEGF Trap-Eye injections administered was similar to the number of required injections for the group (Table 3). The VEGF Trap-Eye groups received an average of less than 1 laser treatment between month 6 and month 12 (up to 2 laser treatments were allowed from week 24 to week 48). For the laser treatment group, the mean number of laser treatments was 2.5 (up to 4 laser treatments were allowed from baseline to week 48).

Efficacy

Treatment with VEGF Trap-Eye produced statistically significant improvements in BCVA in all treatment groups compared with

laser at both week 24 (the primary outcome) and week 52 (week 52, $P < 0.001$; Fig 2).²⁷ The ranges of improvement were +8.5 to +11.4 letters at week 24 and +9.7 to +13.1 letters at week 52. No significant differences were observed among the VEGF Trap-Eye treatment groups. Waterfall plots displaying BCVA changes for individual eyes indicate that few patients in the VEGF Trap-Eye groups experienced any loss of vision (Fig 3). At week 52, the proportion of eyes that gained 15 letters or more was statistically greater ($P \leq 0.001$) than that in the laser treatment group in all VEGF Trap-Eye groups except 2q8 (Fig 4). The percentages of eyes that gained 10 letters or more were 57%, 71%, 45%, 62%, and 30%, for the 0.5q4, 2q4, 2q8, 2PRN, and the laser groups, respectively.

Eyes treated with each VEGF Trap-Eye dosing regimen experienced statistically significant reductions in CRT compared with eyes undergoing laser treatment (week 52, $P < 0.0001$; Fig 5). For eyes on the VEGF Trap-Eye treatment regimens, CRT continued to decrease through week 52.

For each study eye, baseline diabetic retinopathy severity was recorded using the Diabetic Retinopathy Severity Score (Table 2, available at <http://aaojournal.org>). At week 52, 40%, 31%, 64%, and 32% of the 0.5q4, 2q4, 2q8, and 2PRN VEGF Trap-Eye groups, respectively, had an improvement in their Diabetic Retinopathy Severity Score compared with 12% in the laser group. In addition, eyes treated with VEGF Trap-Eye were less likely to have worsening of their Diabetic Retinopathy Severity Score compared with laser-treated eyes (0%, 13%, 0%, and 14% in the 0.5q4, 2q4, 2q8, and 2PRN VEGF Trap-Eye groups and 24% in the laser group).

Safety

Vascular Endothelial Growth Factor Trap-Eye was well tolerated, and the most common ocular AEs that occurred were typical of those associated with intravitreal injections (Table 4, available at <http://aaojournal.org>). The most frequent were conjunctival hemorrhage, eye pain, increased intraocular pressure, ocular hyperemia, cataract, and vitreous floaters. Approximately 11% of patients treated with VEGF Trap-Eye experienced an AE of increased intraocular pressure immediately after the intravitreal injection; however, only 2 of these patients had an increase of more than 10 mmHg. Two patients who were randomized to

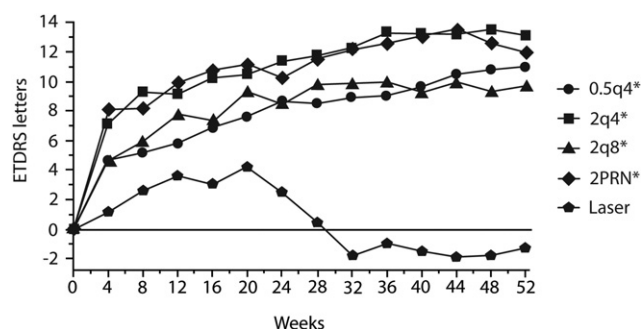


Figure 2. Graph showing mean changes in best-corrected visual acuity letter score by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5 q4] and 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). Difference between each treatment versus laser at week 52 was assessed using an analysis of covariance. * $P < 0.0001$. ETDRS = Early Treatment Diabetic Retinopathy Study.

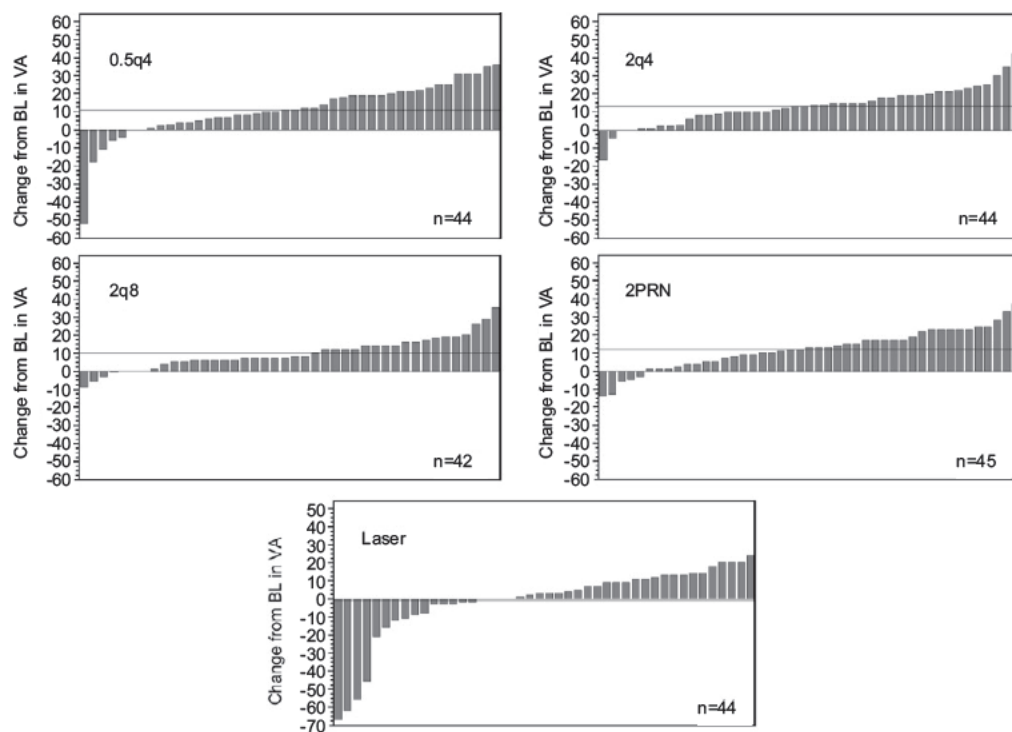


Figure 3. Graphs showing individual changes in best-corrected visual acuity (BCVA) letter score by treatment groups (laser and Vascular Endothelial Growth Factor Trap-Eye). Each bar corresponds to an individual patient. Dotted line represents median BCVA. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg for 3 initial monthly doses then every 8 weeks; 2PRN = 2 mg for 3 initial monthly doses then as needed; BL = baseline; PRN = as needed; VA = visual acuity.

VEGF Trap-Eye experienced injection-related endophthalmitis, and uveitis developed in 1 patient. Serious nonocular AEs were infrequent in all treatment groups (Table 5). The most common systemic AEs were hypertension, nausea, and congestive heart failure. Because of its limited sample size, this phase 2 study was not powered adequately to assess the significance of differences in AEs among the treatment arms.

Seven deaths occurred during the study. One patient in the laser group died of cardiac arrest. One patient in the 0.5q4 group died of multiorgan failure. Three patients in the 2q4 group died: one of cerebral infarction, another from non-small-cell lung cancer, and the third from sudden death. Two patients in the 2q8 group died: one of renal failure and the other of acute coronary syndrome. None of the events that led to death in these patients was judged by

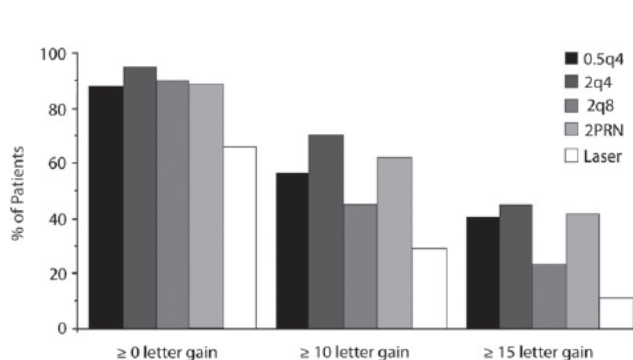


Figure 4. Bar graph showing percentage of patients with changes in best-corrected visual acuity at 12 months by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5q4], 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). $P = 0.0031$, 0.5q4; $P = 0.0007$, 2q4; $P = 0.1608$, 2q8; $P = 0.0016$, 2PRN; all are compared with laser (analysis of covariance).

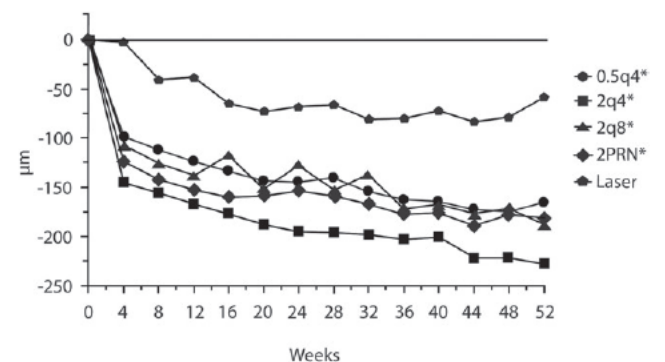


Figure 5. Graph showing mean change in central retinal thickness (in micrometers) by treatment groups (laser and Vascular Endothelial Growth Factor [VEGF] Trap-Eye) over the course of 12 months using last observation carried forward analysis: n = 44 (laser; VEGF Trap-Eye 0.5 mg every 4 weeks [0.5q4], 2 mg every 4 weeks [2q4]); n = 42 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then every 8 weeks [2q8]); n = 45 (VEGF Trap-Eye 2 mg for 3 initial monthly doses then as needed [2PRN]). * $P < 0.0001$, difference between each treatment versus laser analysis of covariance.

Table 5. Serious Systemic Adverse Events and Deaths by Treatment Group of 4% or More in Any Treatment Arm

	Macular Laser Photocoagulation	Vascular Endothelial Growth Factor Trap-Eye Treatment Groups				All Vascular Endothelial Growth Factor Trap-Eye
		0.5 mg Every 4 Weeks	2 mg Every 4 Weeks	2 mg for 3 Initial Monthly Doses Then Every 8 Weeks	2 mg for 3 Initial Monthly Doses Then as Needed	
No. (safety analysis set)	44	44	44	42	45	175
No. of subjects with at least 1 AE, n (%)	10 (22.7%)	14 (31.8%)	13 (29.5%)	12 (28.6%)	6 (13.3%)	45 (25.7%)
Cardiac failure, congestive	0	0	3 (6.8%)	1 (2.4%)	2 (4.4%)	6 (3.4%)
Cellulitis	0	3 (6.8%)	2 (4.5%)	0	1 (2.2%)	6 (3.4%)
Chest pain	0	0	2 (4.5%)	0	3 (6.7%)	5 (2.9%)
Cerebrovascular accident	1 (2.3%)	1 (2.3%)	2 (4.5%)	0	0	3 (1.7%)
Hypertension	0	0	2 (4.5%)	1 (2.4%)	0	3 (1.7%)
Anemia	0	1 (2.3%)	2 (4.5%)	0	0	3 (1.7%)
Dehydration	0	0	0	2 (4.8%)	0	2 (1.1%)
Hyperglycemia	0	0	2 (4.5%)	0	0	2 (1.1%)
Myocardial infarction and acute myocardial infarction	0	3 (6.8%)	0	0	0	3 (1.7%)
Deaths*	1 (2.3%)	1 (2.3%)	3 (6.8%)	2 (4.5%)	0	7 (4.0%)

AE = adverse event.

*One death occurred after a patient in the 2 mg every 4 weeks group discontinued because of an AE.

the investigators to be related to the study drug or to the study procedure.

Discussion

In this phase 2 clinical trial, all VEGF Trap-Eye doses and dosing regimens were found to be superior to macular laser photocoagulation for the treatment of DME over the course of 52 weeks and produced similar results in terms of preserving and improving visual acuity. Patients who received VEGF Trap-Eye benefited from significantly greater increases in mean visual acuity at 1 year (+9.7 to +13.1 letters of improvement) compared with laser treatment alone (−1.3 letters change; $P < 0.0001$). However, it should be noted that this study was not powered adequately to be able to discern differences with regard to efficacy among the VEGF Trap-Eye treatment groups. In addition, a study of longer duration may be able to detect further improvements in visual acuity for the laser treatment arm.

The administration of VEGF Trap-Eye over the course of this study generally was consistent with the number of treatments that had been planned, indicating good compliance with the protocol. There were a similar number of injections in the 2PRN (7.2) and 2q8 (7.4) groups. These numbers are consistent with the number of injections in the RESTORE (Efficacy and Safety of Ranibizumab [Intravitreal Injections] in Patients with Visual Impairment Due to Diabetic Macular Edema) trial for patients treated over 12 months with ranibizumab or ranibizumab plus laser (7.0 and 6.8 injections, respectively).²² Longer intervals between dosing may provide advantages compared with monthly dosing in terms of less frequent monitoring visits and a decreased number of injections. Benefits of an extended dosing interval may include not only improved safety with

fewer injection-related complications such as endophthalmitis, but also a decreased burden to the patient and their caregivers with fewer office visits. This benefit holds particularly true for the 2q8 treatment schedule, which could reduce the number of visits by half (after the loading phase), whereas monthly visits would be needed for determining the need for treatment in a PRN schedule.

The average number of laser treatments administered to eyes randomized to VEGF Trap-Eye was fewer than 1 (of a maximum of 2 possible lasers), with most patients not requiring laser photocoagulation, indicating that the visual acuity and anatomic benefits achieved were the result of VEGF Trap-Eye and not laser treatment. Eyes that were randomized to the laser group received an average of 2.5 laser treatments (of a maximum of 4 possible lasers), indicating that nearly the maximum amount of laser was applied during the 52-week study period. For comparison, during the first year of Protocol I from the Diabetic Retinopathy Clinical Research Network (DRCR) study, eyes that were randomized to macular laser photocoagulation received a median of 3 laser treatments, with 40% of eyes requiring 2, 1, or 0 additional treatments after the initial laser.³⁰

A larger proportion of eyes in all the VEGF Trap-Eye treatment groups experienced 15-letter or more gains in visual acuity at week 52 compared with eyes in the laser arm, and these differences were statistically significant for 0.5q4, 2q4, and PRN treatments. The 2q4 treatment group had the highest percentage of eyes with visual acuity improvements at every level (≥ 0 , ≥ 10 , and ≥ 15 letters gained). The 2q8 group seemed to have less improvement in BCVA than in the other 2-mg groups. However, this difference was observed during the first 3 months of the study, despite the identical 2-mg loading dose, and persisted through the end of the study; therefore, this difference in visual acuity gains likely is attributable to baseline differ-

ences among treatment groups, rather than to the dosing interval.

In this clinical trial, combination treatment of VEGF Trap-Eye with laser photocoagulation was not investigated formally. Although eyes randomized to VEGF Trap-Eye could receive macular laser photocoagulation starting at week 24, most study eyes achieved gains in visual acuity with VEGF Trap-Eye monotherapy and did not require the addition of laser. Similarly, other studies^{20,21} demonstrated that the combination of VEGF inhibitor with laser does not seem to provide any additional benefit in visual acuity gains or reductions in retinal thickness compared with VEGF inhibition alone.

Significantly greater mean reductions in retinal thickness were observed at week 52 for eyes undergoing the VEGF Trap-Eye regimens than for those treated with laser alone. Retinal thickness continued to decrease for eyes in the VEGF Trap-Eye arms after the week 24 primary end point.

Eyes randomized to VEGF Trap-Eye also were more likely to have an improvement in their diabetic retinopathy severity scale compared with laser-treated eyes. The biologic activity of VEGF Trap-Eye not only may treat DME, but also it can reduce the severity of diabetic retinopathy. This positive effect can be beneficial to patients who are at risk for severe vision loss associated with the development of proliferative diabetic retinopathy.

Vascular Endothelial Growth Factor Trap-Eye was well tolerated, and the incidence of ocular AEs was low. The rate of endophthalmitis was consistent with that observed for ranibizumab in the RESOLVE (Safety and Efficacy of Ranibizumab in Diabetic Macular Edema With Center Involvement) study (2%).³¹ Most of the systemic AEs observed were attributed to the underlying medical conditions and cardiovascular comorbidities of these diabetic patients. Studies have shown that individuals with diabetes seem to have an approximately 2- to 4-fold greater risk for both heart disease and stroke.^{32–34} Most of the deaths that occurred in this study were associated with pre-existing heart disease. The DA VINCI study was not powered sufficiently to assess the relationship between VEGF inhibition and systemic AEs or mortality. The results from this study suggest that intravitreal VEGF blockade with VEGF Trap-Eye may be a safe treatment that confers an acceptable benefit-to-risk ratio for eyes with DME over a 1-year period.

Because there is considerable individual variation in the progression of DME, patients could benefit from an individualized, as-needed treatment regimen.³¹ At the same time, such individualized regimens may require close follow-up and monthly monitoring, which can be burdensome to patients and their caregivers. This intensive monitoring schedule may be mitigated by a dosing interval extended to 2 months. The results of this study support additional phase 3 clinical studies with every 2-month dosing of VEGF Trap-Eye after an initial loading dose.

Two phase 3 clinical studies of VEGF Trap-Eye, both with a primary end point of the change from baseline of BCVA in ETDRS letter score, have been initiated. The VIVID (DME and VEGF Trap-Eye: Investigation of Clinical Impact) DME study will evaluate 2 different dosing regimens of VEGF Trap-Eye compared with laser over the course of 1 year. The VISTA (Study of Intravitreal Admin-

istration of VEGF Trap-Eye [Bayer86-5321] in Patients with Diabetic Macular Edema) study will assess the efficacy of 2 different dosing regimens of VEGF Trap-Eye compared with laser over a 2-year period.

In conclusion, eyes receiving VEGF Trap-Eye experienced statistically significant improvements in BCVA compared with laser treatment at 6 months (primary end point), and these results were maintained or improved through 12 months. The long duration of efficacy (at least 8 weeks) is consistent with the tight binding characteristics and enhanced pharmacokinetic profile of VEGF Trap-Eye. Vascular Endothelial Growth Factor Trap-Eye generally was well tolerated. The ocular AEs were typical of those associated with intravitreal injections. Vascular Endothelial Growth Factor Trap-Eye represents a promising therapeutic agent for the management of diabetic macular edema.

References

1. Singh A, Stewart JM. Pathophysiology of diabetic macular edema. *Int Ophthalmol Clin* 2009;49:1–11.
2. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV. Diabetic macular edema. *Ophthalmology* 1984;91:1464–74.
3. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 2. *Ophthalmology* 1987;94:761–74.
4. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414–31.
5. Khurana RN, Do DV, Nguyen QD. Anti-VEGF therapeutic approaches for diabetic macular edema. *Int Ophthalmol Clin* 2009;49:109–19.
6. Nguyen QD, Shah SM, Van Anden E, et al. Supplemental oxygen improves diabetic macular edema: a pilot study. *Invest Ophthalmol Vis Sci* 2004;45:617–24.
7. Grant MB, Afzal A, Spoerri P, et al. The role of growth factors in the pathogenesis of diabetic retinopathy. *Expert Opin Investig Drugs* 2004;13:1275–93.
8. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol* 1995;146:1029–39.
9. Dvorak HF, Orenstein NS, Carvalho AC, et al. Induction of a fibrin-gel investment: an early event in line 10 hepatocarcinoma growth mediated by tumor-secreted products. *J Immunol* 1979;122:166–74.
10. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9:669–76.
11. Gardner TW, Antonetti DA, Barber AJ, et al. Diabetic retinopathy: more than meets the eye. *Surv Ophthalmol* 2002; 47(suppl):S253–62.
12. Funatsu H, Yamashita H, Noma H, et al. Increased levels of vascular endothelial growth factor and interleukin-6 in the aqueous humor of diabetics with macular edema. *Am J Ophthalmol* 2002;133:70–7.
13. Funatsu H, Yamashita H, Nakanishi Y, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with proliferative diabetic retinopathy. *Br J Ophthalmol* 2002;86:311–5.
14. Funk M, Schmidinger G, Maar N, et al. Angiogenic and inflammatory markers in the intraocular fluid of eyes with

- diabetic macular edema and influence of therapy with bevacizumab. *Retina* 2010;30:1412–9.
15. Nguyen QD, Tatlipinar S, Shah SM, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthalmol* 2006;142:961–9.
 16. Chun DW, Heier JS, Topping TM, et al. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology* 2006;113:1706–12.
 17. Fraser-Bell S, Kaines A, Hykin PG. Update on treatments for diabetic macular edema. *Curr Opin Ophthalmol* 2008;19:185–9.
 18. Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 2005;112:1747–57.
 19. Ng EW, Adamis AP. Anti-VEGF aptamer (pegaptanib) therapy for ocular vascular diseases. *Ann N Y Acad Sci* 2006;1082:151–71.
 20. Diabetic Retinopathy Clinical Research Network. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology* 2007;114:1860–7.
 21. Nguyen QD, Shah SM, Khwaja AA, et al. READ-2 Study Group. Two-year outcomes of the Ranibizumab for Edema of the macula in Diabetes (READ-2) study. *Ophthalmology* 2010;117:2146–51.
 22. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. RESTORE Study Group. The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–25.
 23. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A* 2002;99:11393–8.
 24. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol* 2008;92:667–8.
 25. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest Ophthalmol Vis Sci* 2003;44:3186–93.
 26. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011;118:1819–26.
 27. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Arch Ophthalmol* 2007;125:469–80.
 28. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–806.
 29. Wilkinson CP, Ferris FL III, Klein RE, et al. Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1677–82.
 30. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1987;94:761–74.
 31. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064–77.
 32. Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33:2399–405.
 33. Gregg EW, Gu Q, Cheng YJ, et al. Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med* 2007;147:149–55.
 34. American Diabetes Association. Diabetes Statistics. Available at: <http://www.diabetes.org/diabetes-basics/diabetes-statistics/>. Accessed February 3, 2011.

Footnotes and Financial Disclosures

Originally received: August 10, 2011.

Final revision: February 6, 2012.

Accepted: February 7, 2012.

Available online: April 24, 2012.

Manuscript no. 2011-1202.

¹ Wilmer Eye Institute, Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

² Retina Vitreous Associates Medical Group, Los Angeles, California.

³ Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

⁴ Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

⁵ Regeneron Pharmaceuticals, Inc, Tarrytown, New York.

⁶ Bayer Healthcare, Berlin, Germany.

⁷ Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Augenheilkunde, Hamburg, Germany.

⁸ Department of Neurology, Heinrich-Heine-Universität, Düsseldorf, Germany.

⁹ Ophthalmic Consultants of Boston, Boston, Massachusetts.

Presented in part at: Asia Pacific Academy of Ophthalmology Congress, March 2011, Sydney, Australia; and Association for Research in Vision and Ophthalmology Annual Meeting, May 2011, Fort Lauderdale, Florida.

Financial Disclosure(s):

The author(s) have made the following disclosure(s): Diana V. Do, Financial support, Genentech, Regeneron Pharmaceuticals; Quan Dong Nguyen, Financial support, Genentech, Regeneron Pharmaceuticals; David Boyer, Consultant, Genentech, Regeneron Pharmaceuticals, IÇO, Allergan; Lecturer, Genentech, Regeneron Pharmaceuticals, Allergan; Ursula Schmidt-Erfurth, Consultant, Alcon Labs, Bayer Healthcare, Novartis; Lecturer, Alcon Labs, Bayer Healthcare, Novartis, Regeneron Pharmaceuticals, Pfizer; David Brown, Consultant, Genentech, Regeneron Pharmaceuticals, Allergan; Lecturer, Genentech, Regeneron Pharmaceuticals, Allergan; Robert Vitti, Employee, Equity owner, Regeneron Pharmaceuticals; Alyson Berliner, Employee, Equity owner, Regeneron Pharmaceuticals; Oliver Zeitz, Employee, Bayer Healthcare; Rene Ruckert, Employee, Bayer Healthcare; Thomas Schmelter, Employee, Bayer Healthcare; Rupert Sandbrink, Employee, Bayer Healthcare; Jeff S. Heier, Consultant, Genentech, Regeneron Pharmaceuticals, Fovea; Lecturer, Genentech, Regeneron Pharmaceuticals.

Sponsored by Regeneron Pharmaceuticals, Inc, Tarrytown, New York, and Bayer Healthcare, Berlin, Germany.

A list of principal investigators of the DME And VEGF Trap-Eye: INvestigation of Clinical Impact Study is available at <http://aaojournal.org>.

Correspondence:

Diana V. Do, MD, The Wilmer Eye Institute, 600 North Wolfe Street, Maumenee No. 745, Baltimore, MD 21287. E-mail: ddo@jhmi.edu.