The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing

Jeffrey S. Heier, MD,[1] David Boyer, MD,[2] Quan Dong Nguyen, MD, MSc,[3] Dennis Marcus, MD,[4] Daniel B. Roth, MD,[5] George Yancopoulos, MD, PhD,[6] Neil Stahl, PhD,[6] Avner Ingerman, MD, MSc,[6] Robert Vitti, MD, MBA,[6] Alyson J. Berliner, MD, PhD,[6] Ke Yang, PhD,[6] David M. Brown, MD,[7] for the CLEAR-IT 2 Investigators

Objective: To evaluate anatomic outcomes and vision, injection frequency, and safety during the as-needed (PRN) treatment phase of a study evaluating a 12-week fixed dosing period followed by PRN dosing to week 52 with vascular endothelial growth factor (VEGF) Trap-Eye for neovascular (wet) age-related macular degeneration (AMD).

Design: Multicenter, randomized, double-masked trial.

Participants: We included 159 patients with subfoveal choroidal neovascularization (CNV) secondary to wet AMD.

Methods: Patients were randomly assigned to 1 of 5 intravitreal VEGF Trap-Eye treatment groups: 0.5 mg or 2 mg every 4 weeks or 0.5, 2, or 4 mg every 12 weeks during the fixed-dosing period (weeks 1–12). From weeks 16 to 52, patients were evaluated monthly and were retreated PRN with their assigned dose (0.5, 2, or 4 mg).

Main Outcome Measures: Change in central retinal/lesion thickness (CR/LT), change in total lesion and CNV size, mean change in best-corrected visual acuity (BCVA), proportion of patients with 15-letter loss or gain, time to first PRN injection, reinjection frequency, and safety at week 52.

Results: The decrease in CR/LT at week 12 versus baseline remained significant at weeks 12 to 52 (−130 μm from baseline at week 52) and CNV size regressed from baseline by 2.21 mm^2 at 48 weeks. After achieving a significant improvement in BCVA during the 12-week, fixed-dosing phase for all groups combined, PRN dosing for 40 weeks maintained improvements in BCVA to 52 weeks (5.3-letter gain; $P<0.0001$). The most robust improvements and consistent maintenance of visual acuity generally occurred in patients initially dosed with 2 mg every 4 weeks for 12 weeks, demonstrating a gain of 9 letters at 52 weeks. Overall, a mean of 2 injections was administered after the 12-week fixed-dosing phase, and the mean time to first reinjection was 129 days; 19% of patients received no injections and 45% received 1 or 2 injections. Treatment with VEGF Trap-Eye was generally safe and well tolerated, with few ocular or systemic adverse events.

Conclusions: PRN dosing with VEGF Trap-Eye at weeks 16-52 maintained the significant anatomic and vision improvements established during the 12-week fixed-dosing phase with a low frequency of reinjections. Repeated dosing with VEGF Trap-Eye was well tolerated over 52 weeks of treatment.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2011;118:1098–1106 *© 2011 by the American Academy of Ophthalmology.*

Vascular endothelial growth factor (VEGF) is a critical regulator of normal ocular vasculogenesis and angiogenesis during development.[1–3] Vascular endothelial growth factor also plays a central role in the abnormal growth of new blood vessels in the retina, as well as in vascular leakage that causes retinal edema and thickening, both of which characterize diseases such as neovascular (wet) age-related macular degeneration (AMD) and diabetic retinopathy that lead to loss of retinal function.[3–6] Of the various members of the VEGF gene family, VEGF-A and placental growth factor (PlGF) are the factors implicated in pathologic angiogenesis and the pathogenesis of AMD (Invest Ophthalmol Vis Sci 50 [Suppl]: 2943,2009).[7–9]

An improved understanding of the pivotal role of VEGF in pathologic angiogenesis has resulted in the development and use of intravitreal anti-VEGF therapies in wet AMD and other eye diseases that have an angiogenesis-based etiology.[10–12] Pegaptanib, an oligoribonucleotide aptamer,

 © 2011 by the American Academy of Ophthalmology
Published by Elsevier Inc.

ISSN 0161-6420/11/$–see front matter
doi:10.1016/j.ophtha.2011.03.020

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 1 of 10

and ranibizumab, a humanized monoclonal antibody fragment, are anti-VEGF therapies currently available for intravitreal treatment of neovascular AMD. In pivotal trials, pegaptanib mainly slowed loss of visual acuity, whereas ranibizumab improved visual function in a substantial proportion of patients.[13–16] Bevacizumab is an off-label intravitreal anti-VEGF therapy that has also been shown in less rigorous studies to improve visual function.[17–20]

The beneficial results with ranibizumab were obtained with a fixed-dosing regimen requiring an injection of ranibizumab 0.5 or 0.3 mg every month for 2 years in the pivotal phase 3 studies, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR).[13,15] Several studies were undertaken to examine different dosing regimens for ranibizumab. In a large, randomized study in which patients were initially treated with a 3-month loading regimen of ranibizumab and then dosed at regular quarterly intervals, the initial gains after the loading regimen were not maintained at a year.[21] A 40-patient uncontrolled, open-label, single-site, Prospective Optical Coherence Tomography Imaging of Patients Treated with intra-Ocular ranibizumab (PrONTO) trial evaluated an as-needed (PRN) dosing regimen (based on monthly evaluation of changes in retinal thickness and edema using optical coherence tomography [OCT]) after 3 consecutive monthly injections. Visual acuity outcomes at 12 and 24 months were comparable with those observed in the pivotal phase 3 studies and were attained with fewer intravitreal injections.[22,23] However, in a larger randomized study, the gains in visual acuity after an initial 3-month loading regimen of ranibizumab were not maintained with subsequent protocol-defined retreatment.[24]

Vascular endothelial growth factor Trap-Eye (VEGF Trap-Eye) is a potent, specific VEGF antagonist that binds and inactivates circulating VEGF and VEGF in the extravascular space. It was developed specifically as an ultrapurified, isoosmotic solution for ophthalmic use.[25] Consisting of extracellular portions of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G, VEGF Trap-Eye binds both VEGF-A or PlGF and forms an inert 1:1 complex with the growth factor dimers.[24,25] Thus, VEGF Trap-Eye has broader anti-VEGF activity compared with pegaptanib, which binds only the VEGF-A_{165} isoform,[26] and ranibizumab, which neutralizes all active isoforms of VEGF-A, but not PlGF.[27] Because VEGF Trap-Eye contains only human sequences, its potential for immunogenicity is low. A key differentiating feature of VEGF Trap-Eye is its picomolar affinity for VEGF ligands, which is substantially higher than that of the natural receptors or anti-VEGF monoclonal antibodies.[25,28,29] The clinical relevance of the higher binding affinity of VEGF Trap-Eye remains unknown, but it is thought that it might lead to more persistent VEGF blockade and a theoretically longer dosing interval between injections to maintain visual acuity relative to currently available anti-VEGF treatments.[30]

The clinical efficacy of VEGF-Trap Eye was initially demonstrated in the CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial (CLEAR-IT 1), a 6-week phase 1 sequential cohort, single-ascending-dose (0.05 to 4 mg) study of intravitreal VEGF Trap-Eye in patients with neovascular AMD.[31] The efficacy and safety of repeated dosing with VEGF Trap-Eye were subsequently examined in the phase 2 CLEAR-IT 2 study, which consisted of an initial 12-week fixed dosing period with 1 of 5 monthly or quarterly regimens of VEGF Trap-Eye, followed by PRN dosing from weeks 16 to 52. Detailed results to 16 weeks for the fixed-dosing phase, including the primary endpoint at week 12, are presented in the accompanying article (Brown et al., in this issue, pp 1089-97). At 12 weeks, treatment with VEGF Trap-Eye resulted in a significant reduction in central retinal/lesion thickness (CR/LT) of -119 μm and a significant improvement in mean BCVA of 5.7 letters for all groups combined, and gains of >8 letters in the monthly dosing groups. The finding that improvements in visual acuity and retinal thickness were greater in the monthly dosing groups than in the quarterly dosing groups at week 12, support the need for an initial intensive monthly loading dose phase. Patients were treated with a PRN dosing regimen through week 52 to explore whether the high affinity of VEGF Trap-Eye for VEGF-A and PlGF could translate into the maintenance of initial visual acuity gains through 1 year with less frequent intravitreal injections. Results of the continued dosing phase of the CLEAR-IT 2 study are reported herein.

Materials and Methods

Study Design

The primary objectives of the study were to assess the effect of intravitreal VEGF Trap-Eye on CR/LT and to assess the ocular and systemic safety and tolerability of repeated doses of VEGF Trap-Eye in patients with choroidal neovascularization (CNV) associated with wet AMD. A key secondary objective was to assess the effect of VEGF Trap-Eye on BCVA.

This study was a double-masked, prospective, randomized, dose- and interval-ranging study in which 5 groups of approximately 30 patients each were assigned to a fixed-dose of intravitreal VEGF Trap-Eye in the study eye during the first 12 weeks of dosing, followed by PRN dosing from weeks 16 to 52 (Fig 1, available online at http://aaojournals.org). The VEGF Trap-Eye regimens were 0.5 mg or 2 mg at 4-week intervals (0.5q4 or 2q4 on day 1 and at weeks 4, 8, and 12 for a total of 4 treatments) or 0.5, 2, or 4 mg every 12 weeks (0.5q12, 2q12, or 4q12 on day 1 and week 12 for a total of 2 treatments). During the PRN dosing phase beginning at week 16, patients received the same dose of VEGF Trap-Eye (0.5, 2, or 4 mg) as received during the fixed-dosing phase (Fig 2).

The study protocol was approved by the ethics committee at every 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 CLEAR-IT 2 study is registered with ClinicalTrials.gov (NCT00320788).

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 2 of 10

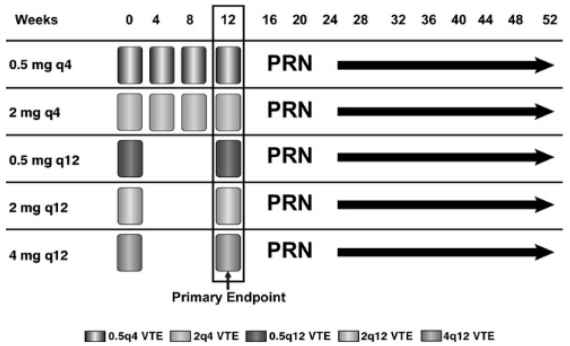

Figure 2. Study schedule. During the 12-week fixed dosing phase, patients in the monthly dosing groups received 0.5 or 2 mg of VEGF Trap-Eye every 4 weeks on day 0 and at weeks 4, 8, and 12 for a total of 4 doses; those in the quarterly dosing groups received 0.5, 2, or 4 mg of VEGF Trap-Eye every 12 weeks on day 0 and at week 12 for a total of 2 doses. Beginning at week 16 and continuing to week 52, patients were assessed every 4 weeks and, if needed, were retreated with the same dose of VEGF Trap-Eye as in the fixed dosing phase. The primary study endpoint was assessed at week 12. q = every; PRN = as-needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Patient Population

The study enrolled patients >50 years old who had a diagnosis of subfoveal CNV secondary to wet AMD and central retinal thickness ≥300 μm, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA of 73 to 34 letters, loss of ≥5 ETDRS letters in BCVA over the preceding 6 months for previously treated patients with minimally classic or occult lesions, linear diameter of lesion ≤5400 μm by fluorescein angiography (FA), subretinal hemorrhage sparing the fovea and comprising ≤50% of total lesion, area of scar ≤25% of total lesion, and sufficient clarity of ocular media to allow retinal photography.

Key exclusion criteria were history of vitreous hemorrhage in preceding 4 weeks; aphakia or pseudophakia with absence of a posterior capsule (unless as a result of a yttrium aluminum garnet capsulotomy); significant subfoveal atrophy or scarring; presence of other causes of CNV in either eye; previous treatments for AMD in the study eye within 12 weeks for photodynamic therapy, 8 weeks for pegaptanib sodium, or 24 weeks for intravitreal or juxtascleral steroids; no other treatments for AMD (thermal laser, surgery, or intraocular/systemic anti-VEGF therapy) were allowed; any retinal vascular disease other than CNV in either eye; active ocular inflammation or infection; history of trabeculectomy or pars plana vitrectomy; history of myocardial infarction, stroke, transient ischemic attack, symptomatic peripheral vascular disease, or treatment for congestive heart failure within the last 6 months; and other conditions or laboratory abnormalities that might interfere with patient participation in the study.

Retreatment Criteria

During the fixed-dosing phase, 1 eye was designated as the study eye and all evaluations were conducted on that eye as described previously (Brown et al, in this issue, pp 1089-97). Beginning at week 16, patients were evaluated every 4 weeks to determine the need for continued dosing. After week 16, the study eye was reinjected with VEGF Trap-Eye if any of the following changes were observed by the evaluating practitioner: An increase in CR/LT ≥100 μm as measured by OCT; a loss of ≥5 ETDRS letters in conjunction with recurrent fluid as indicated by OCT; persistent fluid as indicated by OCT; new-onset classic neovascularization; new or persistent leak on FA; or new macular hemorrhage.

Endpoints and Assessments

Assessments were performed at scheduled clinic visits on days 1 and 7, at week 4, and every 4 weeks thereafter to week 52. At each visit, patients underwent a full ophthalmologic examination, including visual acuity testing, indirect ophthalmoscopy and slit lamp examination, intraocular pressure (IOP) measurement, and OCT. Fundus photography and FA were performed at baseline and at weeks 4, 12, 24, 36, and 48.

The primary efficacy endpoint was reduction of CR/LT from baseline to 12 weeks, at the end of the fixed-dosing phase. The variables assessed during the PRN dosing phase included change from baseline in CR/LT and mean change from baseline in CNV size determined by FA at 48 weeks, the last mandatory FA in the study; BCVA at 52 weeks; proportions of patients with avoidance of moderate vision loss (loss of <15 letters); stabilization or improvement in visual acuity (gain of ≥0 letters); and significant vision gain (gain of ≥15 letters) at 52 weeks; time to first reinjection after week 12; and mean number of injections over the PRN period.

The CR/LT was determined from Stratus OCT (Version 4.0 or higher; CarlZeiss, Jena, Germany) scans read at a masked independent central reading center (Digital OCT Reading Center, Cleveland, OH). The CR/LT was defined as the distance between the inner limiting membrane and posterior border of retinal pigment epithelial/choriocapillaris complex including any subretinal fluid and thickness of any observable choroidal neovascular membrane or scar tissue in central 1 mm of posterior pole scan.

Changes in the size of the total lesion and the CNV component were evaluated with FA. The CNV size was defined as the area of visible CNV (classic or occult) with angiographic evidence of late leakage or pooling of dye. Angiographic images were transmitted to the masked reading center for review (Digital Angiography Reading Center, New York, NY). At least 1 designated photographer was certified by the Reading Center before enrollment of the first patient at each site.

Certified examiners assessed BCVA by using the ETDRS protocol at 4 m. Examiners were masked to treatment assignment, and performed no other study assessments.

Safety assessments included IOP (measured preinjection and approximately 30 minutes postinjection), ophthalmologic examinations for ocular toxicity, adverse events (AEs), serious AEs (SAEs), clinical laboratory tests, and vital signs.

Statistical Analysis

Efficacy assessments were made on the full analysis set, which included all patients who received study treatment and had a baseline and ≥1 postbaseline assessment. Safety assessments were performed on all patients who received study treatment.

The primary analysis was a paired comparison *t* test of the change in CR/LT from baseline to week 12 for all groups combined. If this was significant, an analysis of covariance was done on the 5 individual groups. A similar analysis was done for all continuous measures at all time points. Missing values were imputed using the last-observation-carried-forward method for continuous measures. The durability of the effect was assessed by evaluating all of the endpoints out to week 52. All of the analyses shown below were done using the same methods at week 12 and week 52 (week 48 for FA parameters).

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 3 of 10

Table 2. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated Patients (n = 157)
Age, y (mean [range])	78.3 (53–94)
Gender (%M:%F)	38:62
Disease duration, months (mean [range])	3.9 (0–67)
Previous treatment	20 (12.7%)
Lesion size (mean ± SD) in disc area	3.11 ± 2.12
Lesion type (n [%])	
Predominantly classic	60 (38.2)
Minimally classic	37 (23.6)
Occult lesions	60 (38.2)
Disease status (mean [range])	
Central retinal/lesion thickness (μm)	456 (186–1316)
Foveal thickness (μm)	327 (116–1081)
Best-corrected visual acuity (ETDRS letters)	56 (27–83)

ETDRS = Early Treatment of Diabetic Retinopathy Study; F = Female; M = Male; SD = standard deviation.

Results

Patient Disposition

Of 159 patients who were randomized, 157 were treated and 134 (85.4%) completed 52 weeks in the study (Table 1 available online at http://aaojournal.org). For the 23 patients (14.6%) who were withdrawn before completion of 52 weeks, 6 (3.8%) withdrawals were at the request of the patient.

Baseline Characteristics

The study population was representative of the AMD population in the United States. Patients ranged in age from 53 to 94 years (mean, 78.3) and the majority were women (62%; Table 2). The mean time from diagnosis was 3.9 months (range, 0–67), and 12.7% of patients had received previous treatment. The distribution of CNV lesions was 38.2% predominantly classic, 23.6% minimally classic, and 38.2% occult with no classic. The treatment groups were well-balanced overall for baseline disease severity, but mean CR/LT and mean foveal thickness were somewhat higher in the 4 mg q12wk group (Table 3).

Change in Central Retinal/Lesion Thickness

The primary efficacy endpoint of the study was mean change in CR/LT at week 12. In all treatment groups combined, the significant decrease from baseline in CR/LT observed at week 12 (−119 μm) was maintained to week 52 (−130 μm; $P<0.0001$) after 40 weeks of PRN dosing with VEGF Trap-Eye (Fig 3A). The decrease in CR/LT was also maintained in all individual dosing groups after PRN dosing and was significant compared with baseline values. The greatest decreases in CR/LT at week 52 versus baseline occurred in the 4 mg q12wk group (−161 μm; $P = 0.0002$) and the 2 mg q4wk group (−143 μm; $P<0.0001$; Fig 3B).

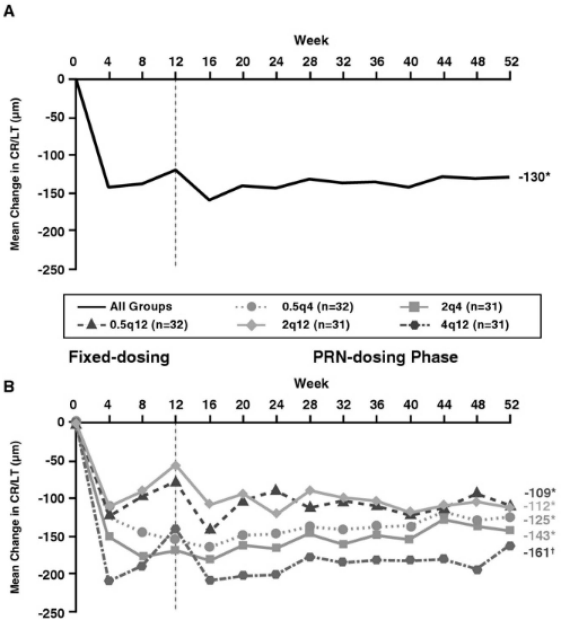

Figure 3. Mean change in central retinal/lesion (CR/LT) thickness in (**A**) all treatment groups combined and (**B**) individual treatment groups. The CR/LT was measured with optical coherence tomography. Change in CR/LT from baseline at 12 weeks was the primary study endpoint. In the combined treatment group, a significant (*$P<0.0001$) decrease in CR/LT at week 12 was maintained to week 52 (−130 μm). The decrease in CR/LT in individual treatment groups was maintained between weeks 12 and 52 with PRN dosing was significant (*$P<0.0001$; †$P = 0.0002$) compared with baseline values. The last-observation-carried-forward method was used to impute missing data. CR/LT = central retina/lesion thickness; PRN = as-needed; 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Change in Angiographic Measures

Fluorescein angiography (FA) was performed at baseline and at weeks 4, 12, 24, 36, and 48. In all groups combined and in each treatment group, there were no significant changes in total lesion

Table 3. Baseline Disease Status by Treatment Group

Mean (Range)	0.5q4 (n = 32)	2q4 (n = 31)	0.5q12 (n = 32)	2q12 (n = 31)	4q12 (n = 31)	All Groups (n = 157)
CR/LT (μm)	434 (282–710)	453 (232–960)	442 (186–762)	447 (265–948)	507 (240–1316)	456 (186–1316)
Foveal thickness (μm)	329 (212–509)	307 (171–524)	319 (116–559)	334 (186–762)	360 (177–1081)	327* (116–1081)
BCVA (ETDRS letters)	54 (27–76)	58 (32–83)	56 (30–72)	57 (32–72)	53 (28–80)	56 (27–83)

BCVA = best-corrected visual acuity; CR/LT = central retinal/lesion thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; q = every.
*In all groups (n = 157), 25 patients at week 52 showed foveal thickness measurements of <150 μm.

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 4 of 10

size from baseline to week 12 and week 48 (data not shown). The decrease in total lesion size for the 2 mg q4wk group at week 12 (−0.75 mm^2; −0.30 disc area [DA]) and week 48 (−1.75 mm^2; −0.69 DA; $P<0.04$) achieved significance.

The area of CNV (defined as classic and/or occult CNV demonstrating angiographic evidence of late leakage or pooling of dye) was also measured. In all treatment groups combined, PRN treatment with VEGF Trap-Eye resulted in a consistent decrease in the CNV size versus baseline at weeks 12 and 48, with a decrease of −2.21 mm^2 (−0.87 DA) at week 48 ($P<0.001$; Fig 4A, available online at http://aaojournal.org). All treatment groups other than the 0.5 mg q12wk group experienced a decrease in active CNV size at 48 weeks (−1.42 to −3.41 mm^2; −0.56 to −1.34 DA), with the greatest reduction in the 2 mg q4wk group (−3.41 mm^2, −1.34 DA; $P<0.001$; Fig 4B).

Change in Visual Acuity

The significant improvement from baseline in BCVA that was noted at 12 weeks was maintained through the PRN dosing phase to week 52. The combining of all treatment groups showed a mean gain of 5.7 letters at week 12 and 5.3 letters at week 52 ($P<0.0001$ vs baseline; Fig 5A). The greatest improvement in BCVA occurred in the 2 mg q4wk treatment group, with a mean increase of 8.3 letters at week 12 and of 9.0 letters at week 52 ($P<0.0001$ vs baseline; Fig 5B). Visual acuity improvements compared with baseline were also maintained in all other treatment groups at week 52.

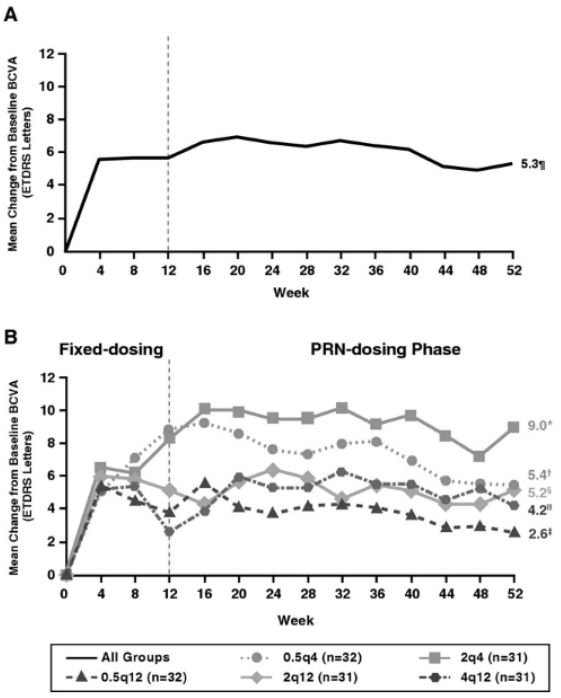

Figure 5. Mean change in best-corrected visual acuity (BCVA) in (**A**) all treatment groups combined and (**B**) individual treatment groups. The BCVA was assessed with the Early Treatment of Diabetic Retinopathy Study protocol at 4 m. Significant improvements from baseline in BCVA were noted in all treatment groups combined at week 12 (5.7 letters) and were maintained to week 52 (5.3 letters; ¶$P<0.0001$). The 2 mg q4wk group showed the greatest gain in BCVA at 12 weeks, which was maintained to 52 weeks (9.0 letters; *$P<0.0001$; †$P = 0.085$; ‡$P = 0.0412$; §$P = 0.0154$; and ‖$P = 0.344$ for individual groups versus baseline). The last-observation-carried-forward method was used to impute missing data. ETDRS = Early Treatment of Diabetic Retinopathy Study; PRN = as-needed.

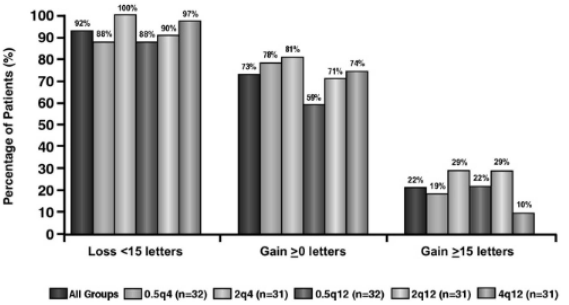

Figure 6. Visual acuity changes at week 52. The proportions of patients who avoided moderate vision loss (≥15 letters), had an improvement in visual acuity (gain of ≥0 letters), or had a significant vision gain (≥15 letters) in the treatment groups combined and individual dosing groups at week 52 are shown. In the treatment groups combined, only 8% of patients experienced moderate loss of vision, whereas 22% showed a significant gain in vision of ≥15 letters at week 52 after 40 weeks of as-needed (PRN) dosing. The last-observation-carried-forward method was used to impute missing data. 0.5q4 = 0.5 mg every 4 weeks; 2q4 = 2 mg every 4 weeks; 0.5q12 = 0.5 mg every 12 weeks; 2q12 = 2 mg every 12 weeks; 4q12 = 4 mg every 12 weeks.

Frequency of Patients with Visual Acuity Changes

In all treatment groups combined, moderate loss of vision (loss of ≥15 letters) was avoided in 98% of patients at week 12 and 92% at week 52 after treatment with VEGF Trap-Eye. In the individual treatment groups, 88% to 100% of patients avoided moderate loss of vision at week 52 (Fig 6). Overall, 12 patients experienced moderate vision loss at week 52, including 4 in the 0.5 mg q4wk group, 4 in the 0.5 mg q12wk group, 3 in the 2 mg q12wk group, and 1 in the 4 mg q12wk group. None of the patients in the 2 mg q4wk group experienced moderate vision loss.

Stabilization or improvement in visual acuity (gain of ≥0 letters) occurred in 74.5% of patients in all treatment groups combined at week 12 and in 73% of patients at week 52. In the individual treatment groups, the proportion of patients experiencing stable or improved visual acuity ranged between 59% and 81%, with the highest proportion in the 2 mg q4wk group. Overall, these proportions remained steady from week 12 to week 52.

The frequency of patients in all treatment groups combined with a significant gain in vision (≥15 letters) was 18.5% at week 12 and 22% at week 52. Groups treated with 2 mg, either monthly or quarterly, had the highest frequency of patients with significant visual gain (26% and 16%, respectively, at week 12, and 29% in each group at week 52).

The proportion of patients with ≤20/200 vision in all treatment groups combined was 11.5% at baseline and remained stable at 10.8% at week 52. The proportion of patients with ≥20/40 vision increased from baseline (15%) to week 52 (41%) for all groups combined, with the 0.5mg q4wk and 2mg q4wk groups increasing from 13% and 16% to 47% and 45%, respectively (Fig 7, available online at http://aaojournal.org).

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 5 of 10

Table 4. Retreatment Outcomes with VEGF Trap-Eye

Treatment Regimen	Mean No. of Injections over PRN Phase (Weeks 12–52)	Mean No. of Days to First Injection over PRN Phase (Weeks 12–52)	Median No. of Days to First Injection over PRN Phase (Months 3–12)
0.5 mg q4	2.52	102	85
2 mg q4	1.55	160	150
0.5 mg q12	1.84	133	86
2 mg q12	2.48	113	86
4 mg q12	1.7	138	111
All groups	2.01	129	110

PRN = as-needed.

Reinjection Outcomes

Beginning at week 16, patients were evaluated monthly for the need for reinjection. Over the 40-week PRN dosing phase, the mean number of reinjections received for all groups combined was 2.01, ranging from 1.55 injections in the 2 mg q4wk group to 2.52 in the 0.5 mg q4wk group (Table 4). During the PRN dosing phase, 29 patients (19%) did not receive any injections of VEGF Trap-Eye, 45% received 1 to 2 injections, and only 5% of patients received ≥5 injections (Fig 8). The most common reason for retreatment was the presence of persistent fluid on OCT examination (63%); in 26% of patients who needed retreatment, a new or persistent leak was noted on FA, and 25% of patients had a loss of BCVA of ≥5 ETDRS letters with recurrent fluid on OCT (Table 5 available online at http://aaojournal.org).

The average time from the last mandatory injection at week 12 to the first PRN injection was 129 days for all treatment groups combined. The longest initial treatment-free interval was in the 2 mg q4wk group (160 days; Table 4). This calculation accounts for the 29 patients who were not reinjected by assigning them a reinjection time at 52 weeks and is therefore an underestimate of the true mean. Kaplan–Meier analysis of the time to first reinjection showed a median time to reinjection for all groups combined of 110 days. The longest median time to reinjection was 150 days in the 2 mg q4wk group (Fig 9, available online at http://aaojournal.org; Table 4).

Safety

The types and frequencies of ocular AEs occurring in the study eye were consistent with AEs previously reported with intravitreal anti-VEGF treatment and were generally related to the intravitreal injection procedure (Table 6). In all treatment groups combined, conjunctival hemorrhage (38.2%) was the most frequently reported AE in the study eye. Most ocular AEs in the study eye were mild (58%), with 4 events considered severe (conjunctival hemorrhage, reduced visual acuity, uveitis, and increased IOP). Seven patients (4.5%) had an increase in IOP in the study eye that was considered related to study treatment, but the increased IOP was not considered an SAE and did not lead to withdrawal of patients from the study. Most ocular events that occurred in the fellow eye were mild (41.4%) or moderate (12.7%); the most frequently reported AE in the fellow eye was vitreous detachment (8.9%).

The number of patients with systemic AEs was similar among treatment groups. The most commonly reported systemic AEs were urinary tract infection (10.2%), bronchitis (9.6%) and upper respiratory tract infection (9.6%). A total of 58 systemic SAEs were reported in 35 patients, but none of the events was deemed to be related to study treatment. Two deaths occurred during the study, one from pancreatic carcinoma and the other from preexisting pulmonary hypertension. Four ocular SAEs were reported: Culture-negative endophthalmitis/uveitis (0.5 mg q4wk group) and decreased visual acuity (0.5 mg q12wk group) in the study eye and increased IOP (4 mg q12wk group) and retinal detachment (0.5 mg q12wk group) in the fellow eye. Stroke was reported in 1 patient in the 0.5 mg q4wk group who had a history of stroke. No cases of vascular death were reported in this study.

Adverse events resulted in withdrawal of 7 patients from the

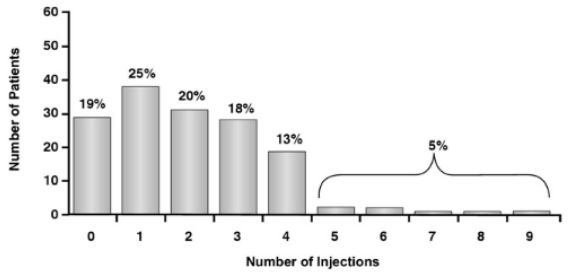

Figure 8. Number of injections after loading phase. Numbers of patients receiving 0 to 9 injections of VEGF Trap-Eye during the as-needed dosing period are shown. Overall, 19% of patients required no retreatment, 45% received 1 or 2 retreatments, and only 5% required 5 to 9 retreatments. VEGF = vascular endothelial growth factor.

Table 6. Ocular Adverse Events in the Study Eye (Frequency ≥5% in All Groups Combined*)

Adverse Event	Number (n)	Percent (%)
Conjunctival hemorrhage	60	38.2
Increased IOP (transient postinjection)	29	18.5
Refraction disorder	26	16.6
Retinal hemorrhage	22	14.0
Visual acuity reduced (patient reported)	21	13.4
Vitreous detachment	18	11.5
Eye pain	15	9.6
Vitreous floaters	14	8.9
Detachment of retinal pigment epithelium	12	7.6
Retinal edema	10	6.4
Visual disturbance	8	5.1
Blepharitis	8	5.1
Subretinal fibrosis	8	5.1

IOP = intraocular pressure.
*Patients receiving treatment with VEGF Trap-Eye (n = 157).

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 6 of 10

study: Three ocular (retinal edema and retinal hemorrhage in the study eye and increased IOP in the fellow eye) and 4 systemic (non-Hodgkin's lymphoma, hip fracture, colon cancer, and bronchitis). There were no differences in frequency of AEs or SAEs between the treatment groups.

Discussion

Among patients with neovascular AMD, PRN dosing with VEGF Trap-Eye maintained efficacy established during a 12-week monthly or quarterly fixed-dosing phase for an additional 40 weeks. For all groups combined, a clinically significant improvement in visual acuity achieved at 12 weeks (5.7-letter gain) was maintained to 52 weeks (5.3-letter gain), accompanied by a decrease in CR/LT (−119 μm at week 12 and −130 μm at week 52). Among patients in all treatment groups combined, 22% experienced a gain of ≥15 letters and only 8% of patients had a loss of ≥15 letters at the end of the study period. These improvements were achieved with an average of only 2 additional injections of VEGF Trap-Eye over the 40-week PRN phase; notably, 44% of patients required either no retreatment or only 1 reinjection, suggesting a long duration of effect in these patients. Repeated intravitreal dosing of VEGF Trap-Eye was generally safe and well tolerated. The overall safety profile was similar to that previously reported with other intravitreal anti-VEGF agents.

Anti-VEGF treatment offers the hope of improved vision and is now the standard of care for neovascular AMD; however, the need for frequent monitoring and treatment places a significant burden on both the patient and the clinician. In addition, the injection procedure itself has associated risks, which, although rare, may be increased with repeated injections. Hence, a less frequent dosing regimen that is maximally effective in preserving or improving visual acuity is a desirable goal of anti-VEGF treatment for AMD.

With VEGF Trap-Eye, the improvements in visual acuity achieved with a 12-week fixed dosing schedule were maintained to week 52 with an average of 2 injections over the 9-month period after fixed dosing. In the 2 mg q4wk group, ≥50% of patients remained injection free for 150 days after week 12. The best visual acuity outcomes to date with ranibizumab have been achieved with 3 consecutive monthly injections, followed by continuous monthly injections.[13,15,32] Less frequent dosing with ranibizumab using both fixed and PRN schedules has been investigated. In the 2-year Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Safety and Efficacy of Ranibizumab (PIER), study a regimen of 3 consecutive monthly injections followed by fixed quarterly injections provided vision gains at 3 months that were comparable with those in the pivotal clinical studies; however, these gains declined with quarterly dosing and returned to baseline levels at 12 months.[21] Results of a phase 3b study designed to evaluate the long-term effect of ranibizumab in patients with all subtypes of neovascular AMD (The Safety Assessment of Intravitreal Lucentis for AMD [SAILOR]) suggested that treating patients with ranibizumab on a PRN basis was less effective than monthly dosing, although retreatment criteria and follow-up schedules in this study were less well-defined and investigator determined.[33] In the open-label HORIZON extension study, patients received PRN dosing with ranibizumab after 2 years of monthly dosing, resulting in a decline in visual acuity gain at years 3 and 4 (Invest Ophthalmol Vis Sci 50 [Suppl]:3093, 2009).

The 52-week results of the CLEAR-IT 2 study suggest that the efficacy of VEGF Trap-Eye, established with an initial fixed-dosing regimen, is maintained with PRN dosing and that VEGF Trap-Eye has an extended duration of action. The average time from last mandatory injection to first PRN injection for all groups combined was >4 months and for the 2 mg q4wk group, >5 months. The high binding affinity of VEGF Trap-Eye, its presumed long intravitreal half-life, and activity against multiple VEGF family members, including PlGF, may contribute to more sustained and comprehensive VEGF suppression than may be achieved with currently used anti-VEGF agents. Based on its binding affinity and estimated intravitreal half-life in humans, a mathematical model has predicted that, after intravitreal injection, VEGF Trap-Eye would maintain biological activity for 10 to 12 weeks, whereas ranibizumab would maintain such activity for 30 days, supporting the concept of less frequent dosing with VEGF Trap-Eye.[30]

By the end of the fixed-dosing phase at week 12, VEGF Trap-Eye showed a significant improvement in visual acuity from baseline, and this efficacy was maintained to week 52. However, patients randomized to monthly injections during the fixed dosing phase had a trend toward improved visual acuity outcomes at 52 weeks compared with those randomized to quarterly injections. This difference was apparent at 12 weeks and was maintained throughout the 40-week PRN phase, despite the fact that all patients were treated as often as necessary during this phase. Therefore, initial sequential monthly loading doses seem to provide better control of neovascular leakage and lead to superior gains in visual acuity that can be subsequently maintained with less frequent dosing.

Ongoing phase 3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in wet Age-Related Macular Degeneration, VIEW-1 and VIEW-2) are evaluating VEGF Trap-Eye doses of 0.5 and 2 mg every 4 weeks and 2 mg every 8 weeks after 3 initial monthly doses, compared with ranibizumab 0.5 mg every 4 weeks. The rationale for the 2 mg q8wk dose was based on an observation from the fixed-dosing phase of CLEAR-IT 2: At 8 weeks, the improvement in BCVA after a single 2-mg dose was similar to that obtained with 2 mg dosed monthly to 8 weeks and that the effect in visual acuity gain for the single dose groups began to wane by week 12.

After the first year of treatment on the above schedule, patients in the VIEW-1 and -2 studies will be evaluated monthly and treated on a PRN basis. To prevent undertreatment, the PRN dosing schedule during the second year of the study does not allow any patient to remain untreated for >12 weeks. Although many patients in the CLEAR-IT 2 study did maintain initial visual acuity gains for >12 weeks, the design of the phase 3 program is meant to optimize visual improvements for all patients by using this capped

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 7 of 10

PRN dosing schedule. These studies should provide further information on the duration and extent of the clinical benefit of VEGF Trap-Eye.

In conclusion, PRN dosing of VEGF Trap-Eye after 12 weeks of monthly or quarterly fixed dosing maintained clinically and statistically significant improvements in vision and retinal thickness to week 52 in patients with neovascular AMD, with a low frequency of reinjection. VEGF Trap-Eye was generally well-tolerated, with a safety profile similar to that reported with other intravitreally administered anti-VEGF agents.

Acknowledgment. Technical writing and editorial assistance was provided by Meher Dustoor, PhD.

References

1. Maharaj AS, D'Amore PA. Roles for VEGF in the adult. Microvasc Res 2007;74:100–13.
2. Tammela T, Enholm B, Alitalo K, Paavonen K. The biology of vascular endothelial growth factors. Cardiovasc Res 2005; 65:550–63.
3. Penn J, Madan A, Caldwell R, et al. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008;27: 331–71.
4. Grisanti S, Tatar O. The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res 2008;27:372–90.
5. Krzystolik MG, Afshari MA, Adamis AP, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002;120:338–46.
6. Aiello L, Avery R, Arrigg P, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480–7.
7. Rakic J, 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.
8. Olsson A, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling-in control of vascular function. Nat Rev Mol Cell Biol 2006;7:359–71.
9. Boyer DS, Antoszyk AN, Awh CC, et al, MARINA Study Group. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:246–52.
10. Waisbourd M, Loewenstein A, Goldstein M, Leibovitch I. Targeting vascular endothelial growth factor: a promising strategy for treating age-related macular degeneration. Drugs Aging 2007;24:643–62.
11. van Wijngaarden P, Qureshi S. Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice. Clin Exp Optom 2008;91:427–37.
12. Ip M, Scott I, Brown G, et al. Anti–vascular endothelial growth factor pharmacotherapy for age-related macular degeneration: a report by the American Academy of Ophthalmology. Ophthalmology 2008;115:1837–46.
13. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
14. Wong TY, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology 2008;115:116–26.
15. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
16. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004;351:2805–16.
17. Gunther J, Altaweel M. Bevacizumab (Avastin) for the treatment of ocular disease. Surv Ophthalmol 2009;54:372–400.
18. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007; 143:679–80.
19. Park JE, Chen HH, Winer J, et al. Placenta growth factor: potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/KDR. J Biol Chem 1994;269:25646–54.
20. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006;113:363–72.
21. Regillo CD, Brown DM, Abraham P, et al, PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
22. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566–83.
23. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009;148:43–58.
24. Rudge J, Holash J, Hylton D, et al. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A 2007;104:18363–70.
25. 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.
26. Lee JH, Canny MD, De Erkenez A, et al. A therapeutic aptamer inhibits angiogenesis by specifically targeting the heparin binding domain of VEGF165. Proc Natl Acad Sci U S A 2005;102:18902–7.
27. Lowe J, Araujo J, Yang J, et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. Exp Eye Res 2007;85:425–30.
28. Konner J, Dupont J. Use of soluble recombinant decoy receptor vascular endothelial growth factor trap (VEGF Trap) to inhibit vascular endothelial growth factor activity. Clin Colorectal Cancer 2004;4(suppl):S81–5.
29. Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs 2009;18:1573–80.
30. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–8.
31. Nguyen QD, Shah SM, Browning DJ, et al. A phase I study of intravitreal vascular endothelial growth factor Trap-Eye in patients with neovascular age-related macular degeneration. Ophthalmology 2009;116:2141–8.
32. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2–13.
33. Boyer DS, Heier JS, Brown DM, et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009; 116:1731–9.

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 8 of 10

Footnotes and Financial Disclosures

Originally received: October 29, 2010.
Final revision: March 14, 2011.
Accepted: March 15, 2011. Manuscript no. 2010-1500.

[1] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[2] Retina Vitreous Association Medical Group, Beverly Hills, California.

[3] The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

[4] Southeast Retina Center, Augusta, Georgia.

[5] Retina-Vitreous Center, New Brunswick, New Jersey.

[6] Regeneron Pharmaceuticals, Inc., Tarrytown, New York.

[7] Retina Consultants of Houston, The Methodist Hospital, Houston, Texas.

Presented at: The Retina Society, October, 2009; American Academy of Ophthalmology Annual Meeting, October, 2009; International Symposium on Ocular Pharmacology and Therapeutics, December 2009; Association for Research in Vision and Ophthalmology Annual Meeting, April, 2010.

Financial Disclosure(s):
The authors have made the following disclosures:

Jeffrey S. Heier – Regeneron (C,S), Alcon (C), Genentech (C), Glaxosmithkline (C), Paloma (C), Neovista (C), Oraya (C).

David Boyer – Alcon (C,L), Genentech (C,L), Regeneron (C), Novartis (C), Pfizer (C), Eyetech (C), Allergan (C,L).

Quan Dong Nguyen – Genetech (S), Regeneron (S), Novartis (S), Pfizer (S), Lux Biosciences (S), Macu Sight (S), Bausch & Lomb (C).

Dennis Marcus – Genentech (C,S), Regeneron (S), Allergan (S), Neovista (S), Pfizer (S), Ophthotech (S), Alimaera (S).

Daniel B. Roth – Regeneron (C), Allergan (C), Notal Vision (C).

George Yancopoulos – Regeneron (E,O).

Neil Stahl – Regeneron Pharmaceuticals (E).

Avner Ingerman – Regeneron Pharmaceuticals (E).

Robert Vitti – Regeneron Pharmaceuticals (E).

Alyson J. Berliner – Regeneron Pharmaceuticals (E).

Ke Yang – Regeneron Pharmaceuticals (E, O).

David M. Brown – Thrombogenics(S), Molecular Partners (C,S), Schering Plough (S), Paloma (C,S), Alimaera (S), Ophthotech (S).

Supported by Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG. The sponsors participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and the preparation, review and approval of the manuscript.

Correspondence:
David M. Brown, MD, Retina Consultants of Houston, The Methodist Hospital, 6560 Fannin, Suite 750, Houston, TX 77030. E-mail: dmbmd@houstonretina.com.

Regeneron Ex. 2118
Alvotech v. Regeneron
PGR2025-00085
Page 9 of 10