Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration

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Objective: To evaluate the biologic effects and safety of vascular endothelial growth factor (VEGF) Trap-Eye during a 12-week fixed-dosing period in patients with neovascular (wet) age-related macular degeneration (AMD).

Design: Multicenter, prospective, randomized, double-masked clinical trial with initial 12-week fixed dosing period. Data were analyzed to week 16.

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

Methods: Patients were randomized 1:1:1:1:1 to VEGF Trap-Eye during the fixed-dosing phase (day 1 to week 12): 0.5 or 2 mg every 4 weeks (0.5 mg q4wk, 2 mg q4wk) on day 1 and at weeks 4, 8, and 12; or 0.5, 2, or 4 mg every 12 weeks (0.5 mg q12wk, 2 mg q12wk, or 4 mg q12wk) on day 1 and at week 12.

Main Outcome Measures: The primary endpoint was change from baseline in central retinal/lesion thickness (CR/LT) at week 12; secondary outcomes included change in best-corrected visual acuity (BCVA), proportion of patients with a gain of $\geq$15 letters, proportion of patients with a loss of $>$15 letters, and safety.

Results: At week 12, treatment with VEGF Trap-Eye resulted in a significant mean decrease in CR/LT of 119 μm from baseline in all groups combined ($P<0.0001$). The reduction in CR/LT with the 2 mg q4wk and 0.5mg q4wk regimens was significantly greater than each of the quarterly dosing regimens. The BCVA increased significantly by a mean of 5.7 letters at 12 weeks in the combined group ($P<0.0001$), with the greatest mean gain of $>$8 letters in the monthly dosing groups. At 8 weeks, BCVA improvements were similar with 2 mg q4wk and 2 mg q12wk dosing. After the last required dose at week 12, CR/LT and visual acuity were maintained or further improved at week 16 in all treatment groups. Ocular adverse events were mild and consistent with safety profiles reported for other intraocular anti-VEGF treatments.

Conclusions: Repeated monthly intravitreal dosing of VEGF Trap-Eye over 12 weeks demonstrated significant reductions in retinal thickness and improvements in visual acuity, and was well-tolerated in patients with neovascular AMD.

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Age-related macular degeneration (AMD) is a leading cause of vision loss among older adults in Western countries.[1,2] The vast majority of patients with AMD have the dry form of the disease, but severe vision loss occurs most frequently in patients who develop choroidal neovascularization (CNV).[3] Neovascular AMD is characterized by the growth of anomalous vessels originating from the choroidal vascular network, which causes hemorrhage and leakage in the subretinal and intraretinal spaces resulting in metamorphopsia and decreased vision.

The pathophysiology of ocular neovascularization is complex, but vascular endothelial growth factor (VEGF)-A is an important stimulus for both the growth of new blood vessels and increased vascular leakage resulting in retinal edema as seen in animal models and human AMD.[4–7] The mammalian VEGF family also includes VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF), but the members predominantly involved in ocular neovascularization are VEGF-A and PlGF.[8,9] Of at least the 4 major isoforms of human VEGF-A, $VEGF_{165}$ is the most abundantly expressed, although the other isoforms are also biologically active.[8,10] The biological activities of VEGF-A are mediated through 2 receptor tyrosine kinases, VEGF receptor (VEGFR)1 and VEGFR2. Found predominantly on the surface of vascular endothelial cells, VEGFR2 plays a key role in mediating endothelial cell survival, migration, and proliferation, both during normal development as well as in a variety of pathophysiologic conditions. Initially discovered as a vascular permeability factor, VEGF–A also decreases barrier functions of the endothelium, resulting in increased extravasation of water and macromolecules.[10,11] Vascular

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endothelial growth factor-A is a potent promoter of vascular permeability (approximately 50 000 times more potent than histamine), and the onset of this effect is very rapid.

Vascular endothelial growth factor increases permeability of the pathologic choroidal vessels, leading to extravasation of fluid into and under the retina. The resulting increase in central retinal thickness is responsible in part for the decrease in central visual acuity. Although not always correlative with visual acuity, the change in central retinal thickness, as measured by optical coherence tomography, has become one of the established means of monitoring the disease and its response to treatment.

The related angiogenic factor, PlGF, binds to VEGFR1 and collaborates with VEGF-A in promoting angiogenesis and vascular permeability, particularly in pathologic conditions.[9,12,13] The mechanism of action of PlGF has not yet been fully elucidated,[11,14] but it has been shown that PlGF ligation of VEGFR1 promotes leukocyte chemotaxis,[13] and that PlGF may play a role in recruiting inflammatory cells into the diseased retina, leading to release of VEGFs and other inflammatory mediators, perpetuating the cycle of angiogenesis and inflammation.[15]

Most current anti-VEGF treatments target VEGF-A. Of the currently approved anti-VEGF agents for ocular disease, pegaptanib is specific for $VEGF_{165}$,[16] and ranibizumab targets multiple VEGF-A isoforms and their degradation products.[17] Bevacizumab, a full-length humanized monoclonal anti-VEGF antibody that is used off-label to treat AMD, is derived from the same mouse antibody as ranibizumab and is also directed against all isoforms of VEGF-A.[18,19]

Vascular endothelial growth factor Trap-Eye (VEGF Trap-Eye) is a fully human, soluble recombinant decoy VEGFR that is biologically engineered to contain key binding domains of VEGFR1 and VEGFR2 fused to the constant Fc region of IgG1.[20] Unlike currently available anti-VEGF agents, VEGF Trap-Eye inhibits PlGF in addition to all isoforms of VEGF-A.[20] Because the binding affinity of VEGF Trap-Eye for VEGF-A isoforms (K_D, 0.5–1 pmol/L) and PlGF (K_D, 39–392 pmol/L) is higher than that of native receptors (K_D of 10–30 pmol/L for VEGFR1 and 100-300 pmol/L for VEGFR2), it effectively blocks VEGF binding and activation of these receptors, even when VEGF Trap-Eye is present at low concentrations. The binding affinity of anti-VEGF monoclonal antibodies by contrast is many fold lower (K_D, 0.1–10 nmol/L).[21,22] Tight binding of VEGF Trap-Eye to all VEGF-A isoforms and PlGF could theoretically offer a differential impact on visual acuity. As shown in modeling studies, high-affinity blockade of VEGF-A and PlGF activity with VEGF Trap-Eye may increase the duration of effect, thus allowing an extended dosing interval.[23] VEGF Trap-Eye also forms a stable, inert 1:1 complex with VEGF dimers, unlike the rapidly cleared multimeric immune complexes formed with an antibody.[24]

Preclinical studies support a therapeutic role for VEGF Trap-Eye in multiple vascular eye diseases, including wet AMD. Blockade of VEGF with VEGF Trap-Eye inhibited CNV, suppressed VEGF-induced breakdown of the blood-retinal barrier, and promoted regression of newly formed and established blood vessels (Invest Ophthalmol Vis Sci 5307 [Suppl]:46,2005; Invest Ophthalmol Vis Sci 1411 [Suppl]:46,2005; and Invest Ophthalmol Vis Sci 5300 [Suppl]:46,2005).[25] Primate studies showed VEGF Trap-Eye rapidly reversed vascular leakage in retinal injury models and had a favorable ocular safety profile (Invest Ophthalmol Vis Sci 1751 [Suppl]:47,2006).

The clinical activity of VEGF Trap-Eye was initially demonstrated in a 6-week, sequential, single ascending-dose, phase 1 study (*CL*inical *E*valuation of *A*nti-angiogenesis in the *R*etina *I*ntravitreal *T*rial [CLEAR-IT 1]) in patients with neovascular AMD (Invest Ophthalmol Vis Sci 1751 [Suppl]:47,2006). After receiving single intravitreal injections of VEGF Trap-Eye (0.05–4 mg), patients showed a dose-dependent improvement in visual acuity, which correlated with anatomic improvement. At 6 weeks, an overall mean decrease in foveal thickness of 104.5 μm and mean increase in visual acuity of 4.4 letters was reported for all groups combined. In the 2 highest dose groups (2 and 4 mg) combined, best-corrected visual acuity (BCVA) increased by a mean of 13.5 letters, and by 6 weeks, vision had stabilized or improved in 95% of patients. Anatomic benefits and visual gains were maintained out to 12 weeks in 3 of 6 patients who received single administrations of higher doses. Based on these encouraging results from CLEAR-IT 1, a dose- and interval-ranging phase 2 study (*CL*inical *E*valuation of *A*nti-angiogenesis in the *R*etina *I*ntravitreal *T*rial [CLEAR-IT 2]) was designed to investigate the safety and biologic effects of VEGF Trap-Eye after repeated dosing. The study consisted of a fixed-dosing phase during which patients received 1 of 5 regimens of VEGF Trap-Eye for 12 weeks, followed by as-needed (PRN) dosing from weeks 16 through 52. The details of the PRN dosing phase are presented in the accompanying article.[26] The primary endpoint and results from the fixed-dosing period are presented herein.

Materials and Methods

Study Design

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

The CLEAR-IT 2 was a prospective, double-masked, randomized study conducted at 33 sites in the United States. Patients were enrolled between May 2006 and April 2007. Five groups of approximately 30 patients each were randomized in a balanced ratio to receive an intravitreal injection of VEGF Trap-Eye 0.5 or 2 mg every 4 weeks, (0.5 mg q4wk or 2 mg q4wk) 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 (0.5 mg q12wk, 2 mg q12wk, or 4 mg q12wk) on day 1 and week 12 for a total of 2 treatments (Fig 1). The PRN dosing phase began at week 16 and continued through week 52.[26] The primary endpoint (change in CR/LT) and BCVA were assessed at week 12 (after 1 or 3 doses in the quarterly and monthly dosing groups, respectively) and the results of the fixed dosing phase were assessed at week 16 (after 2 or 4 doses in the quarterly and monthly dose groups, respectively). Although the primary endpoint of the study was at week 12, results at week 16 were evaluated to assess the impact of the final fixed dose from each dose group on anatomic outcomes and BCVA.

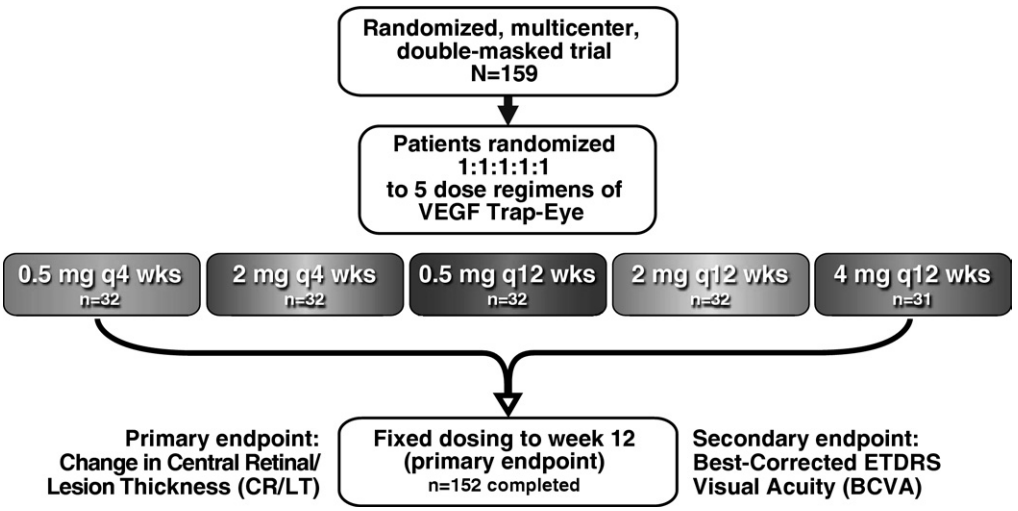

Figure 1. Study design. During the fixed-dosing phase of the CLEAR-IT 2 study, patients were randomized in equal ratios to receive 1 of 5 different regimens of VEGF Trap-Eye for 12 weeks: 0.5 or 2 mg every 4 weeks, or 0.5, 2, or 4 mg every 12 weeks. The primary endpoint, change from baseline in CR/LT, and a key secondary endpoint, BCVA, was measured at 12 weeks. BCVA = best-corrected visual acuity; CLEAR-IT = CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial; CR/LT = central retinal/lesion thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor.

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 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).

Study Population

Patients eligible for the study were ≥50 years old, had a diagnosis of subfoveal CNV secondary to wet AMD, and met the following inclusion criteria: CR/LT ≥300 μm, Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA letter score of 73 to 34 letters (20/40–20/200), 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, subretinal hemorrhage (if present) 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.

Exclusion criteria were 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; active ocular inflammation; corneal transplant; previous uveitis in either eye; or history of macular hole of grade 3 or higher. Patients who had previously received any of the following treatments in the study eye were excluded: Subfoveal thermal laser therapy, any operative intervention for AMD, extrafoveal laser coagulation treatment or photodynamic therapy in preceding 12 weeks, pegaptanib sodium in preceding 8 weeks, systemic or intravitreal treatment with VEGF Trap-Eye, ranibizumab, or bevacizumab at any time, juxtascleral steroids, anecortave acetate, or intravitreal triamcinolone acetonide or other steroids in preceding 24 weeks. Additional reasons for exclusion were other causes of CNV in either eye; active ocular infection; congenital lid anomalies that might interfere with intravitreal administration; any retinal disease other than CNV in either eye; previous trabeculectomy or pars plana vitrectomy; cup-to-disc ratio ≥0.8, intraocular pressure >25 or receipt of >2 agents for treatment of glaucoma; allergy to povidone iodine, fluorescein, or recombinant proteins; absolute neutrophil count <1000 cells/mm^3; human immunodeficiency virus positivity, active systemic infection requiring antibiotics; proteinuria >1$^+$ or urine protein:creatinine ratio ≥1 on 2 repeated determinations within 1 week; New York Heart Association class III or IV; symptomatic cardiovascular or peripheral vascular disease, malignancy other than basal cell carcinoma in preceding 2 years; and any other conditions or laboratory abnormalities that could interfere with disease assessment or patient participation in the study. The use of standard agents or other anti-VEGF agents was not permitted before week 16.

Endpoints and Assessments

The 12-week assessment measured anatomic and visual changes after administration of 3 doses of VEGF Trap-Eye in the monthly dose group and 1 dose in the quarterly dosing group. All assessments at week 12 were performed before the planned injection. Results at week 16 were evaluated to assess the impact of the final fixed dose at week 12 from each dose group on these parameters.

One eye was designated as the study eye, with all evaluations performed on that eye. Criteria, in descending order, for selection of the study eye in cases of bilateral exudative AMD were worse visual acuity, clearer ocular media, and nondominant eye. If these factors were similar in both eyes, the right eye was chosen as the study eye.

The primary efficacy endpoint was change in CR/LT from baseline at 12 weeks, as assessed by Stratus (software version 4.0 or higher) optical coherence tomography scans (Carl Zeiss Meditec, Inc., Dublin, CA) read at a masked independent central reading center (Digital Optical Coherence Tomography Reading Center [DOCTR], Cleveland, OH). The CR/LT was defined as the distance between the inner limiting membrane and the inner border of the retinal pigment epithelium/choriocapillaris complex, including any subretinal fluid and thickness of any observable choroidal neovascular membrane or scar tissue in the central 1 mm of the posterior pole scan. A posterior pole scan was obtained, consisting of a high-resolution 7-mm scan from a single scan line from the meridian of the optic disc margin, declined at a 5-degree angle

Table 1. Patient Disposition

No. of Patients	0.5 q4	2 q4	0.5 q12	2 q12	4 q12	All patients
Screened						301
Randomized	32	32	32	32	31	159
Treated	32	31	32	31	31	157
Completed week 12	31	31	31	29	30	152 (96.8%)
Withdrawn by week 12	1		1	2	1	5 (3.2%)

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.

through the presumed foveal center. The placement of the scan line was based on anatomic landmarks as visualized by a trained, certified operator to offer better registration.

Key secondary endpoints included the change in BCVA as measured by ETDRS letter score at 12 weeks and the 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 12 weeks. Certified examiners assessed BCVA using the ETDRS protocol (at 4 m). Examiners were masked to treatment assignment and performed no other study assessments. Safety was monitored with reporting of adverse events (AEs) and serious AEs, clinical laboratory tests, vital signs, and ophthalmic examination.

Statistical Analyses

Efficacy analyses were performed on the full analysis set, which included all enrolled patients who underwent baseline and ≥1 postbaseline assessment. The last observation carried-forward method was used to impute missing data. The safety analysis set included 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 BCVA measurements. Results are presented for all 5 treatment groups combined as well as for the individual groups.

Results

Disposition

Patient disposition is shown in Table 1. Among the 159 patients who were randomized, 157 received treatment. Two patients, 1 each in the 2-mg monthly and 2-mg quarterly groups, were withdrawn before receiving treatment. Of the 157 patients who received treatment, 152 (96.8%) completed the 12-week visit, and 5 patients were withdrawn. Reasons for withdrawal were death (n = 1, 4q12 group), AE (n = 1, 2q12 group), inability to attend visits (n = 1, 2q12 group), investigator decision (n = 1, 0.5q12 group), and subject request (n = 1, 0.5q4 group).

Baseline Characteristics

The study population was representative of the exudative AMD population in the United States. The mean age of patients overall was 78.2 years (range, 53–94) and a majority were women (62%). The duration of disease ranged from 0 to 67 months, with a mean of 3.9 months, and 20 patients had received previous treatment (photodynamic therapy [n =5], focal laser photocoagulation [n = 4], intravitreal pegaptanib sodium [n = 3], intravitreal triamcinolone [n = 1], and combination [n = 7]). All CNV lesion types were represented in the following distribution: Predominantly classic (38.2%), minimally classic (23.6%), and occult-no-classic (38.2%; Table 2). Of note, the baseline CR/LT was thicker (507 μm) in the 4 mg q12wk arm (Table 3).

Primary Endpoint: Change in Central Retinal Lesion Thickness

At week 12, treatment with VEGF Trap-Eye resulted in a significant decrease in mean CR/LT of 119 μm from baseline in all treatment groups combined ($P<0.0001$; Fig 2A). A significant mean improvement from baseline was observed as early as week 1 (−103 μm for all treatment groups combined; $P = 0.04$). The significant reduction in CR/LT was observed in each treatment group at week 12, with monthly dosing with 0.5 or 2 mg providing a more profound and consistent effect (Fig 2B). At 12 weeks, the mean reductions in CR/LT with the 0.5 mg q4 wk (−153.5 μm; standard deviation [SD] = 113.3) and 2 mg q4wk (−169.2 μm; SD = 138.5) regimens were significantly greater than mean reductions with each of the quarterly dosing regimens (0.5 mg q4: $P = 0.0022$, $P<0.0001$, and $P = 0.0255$; 2 mg q4: $P = 0.0010$, $P<0.0001$, and $P = 0.0129$ versus 0.5 mg q12, 2 mg q12, and 4 mg q12, respectively).

Changes in Best-corrected Visual Acuity

At week 12, BCVA, as measured by ETDRS letters score, showed a significant mean increase from baseline of 5.7 letters in all

Table 2. Baseline Demographic and Clinical Characteristics

Characteristic	All Treated Patients (n = 157)
Age, years (mean [range])	78.2 (53-94)
Gender (%M:%F)	38:62
Disease duration, mos (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	456 μm (186–1316 μm)
Foveal thickness	327 μm (116–1081 μm)
Best corrected visual acuity (ETDRS letters)	56 (27–83)

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

Table 3. Baseline Disease Status by Treatment Group

	0.5q4 (n = 32)	2q4 (n = 31)	0.5q12 (n = 2)	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; 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. Values are presented as mean (range).

treatment groups combined ($P<0.0001$; Fig 3A). A significant gain in BCVA was noted as early as week 1 (mean gain of 3 letters). Each treatment group showed an improvement in visual acuity at week 12 (Fig 3B). Mean increases were similar among all treatment groups at week 8 ($P\geq0.25$ for all pairwise comparisons, analysis of covariance), after which in the monthly treatment groups of 0.5 mg q4wk and 2 mg q4wk, vision continued to improve, with a mean gain of 8.8 (SD = 9.2) and 8.3 (SD = 10.1) letters, respectively, at week 12. Of note, the mean improvement in visual acuity at 8 weeks was similar after administration of a single 2-mg dose (quarterly dose group) or 2 monthly 2-mg doses.

Frequency of Changes in Best-corrected Visual Acuity

After 12 weeks, 98% of patients in all treatment groups combined (range, 94%–100% in the individual dose groups) avoided vision

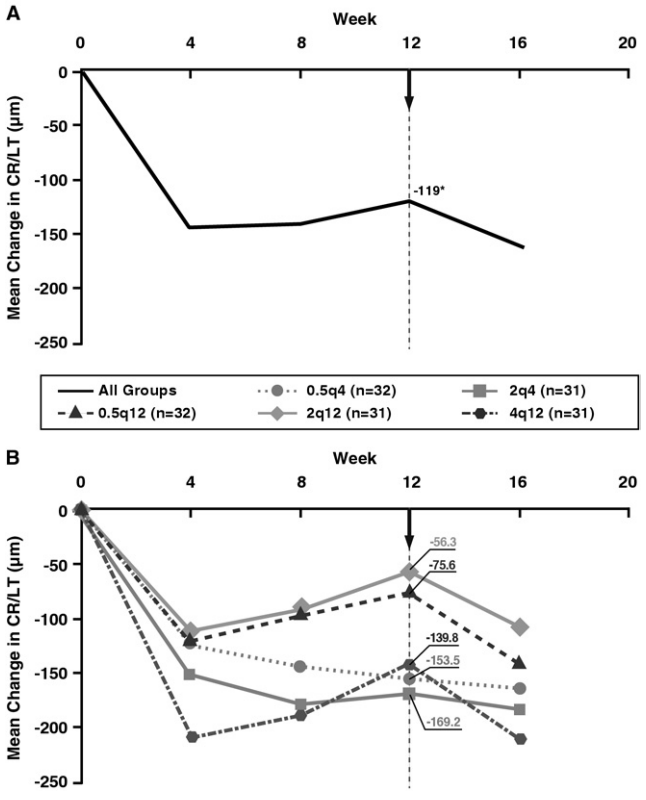

Figure 2. Mean change from baseline in central retinal/lesion thickness (CR/LT) for (**A**) all groups combined and (**B**) individual dosing groups. Change in CR/LT from baseline at 12 weeks was the primary study endpoint; in the combined treatment group, a significant decrease of 119 μm was observed at week 12. *$P<0.0001$ versus baseline. All treatment groups demonstrated a significant reduction in CR/LT from baseline at week 12, with the greatest reductions in the monthly dosing groups. The last-observation-carried-forward method was used to impute missing data. CR/LT = central retinal/lesion thickness; 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.

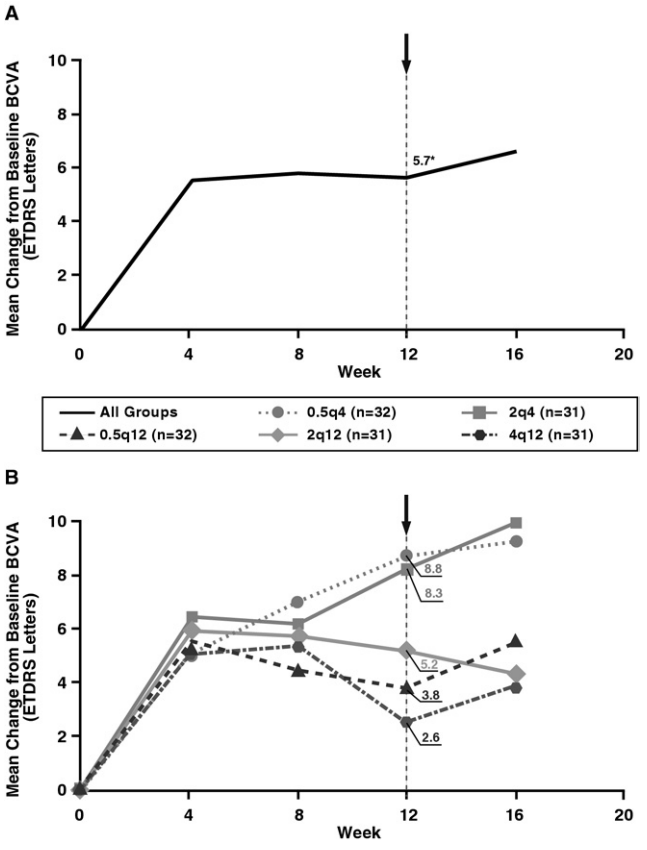

Figure 3. Mean change from baseline in best-corrected visual acuity (BCVA) for (**A**) all groups combined and (**B**) individual dosing groups. The combined treatment group showed a significant gain of 5.7 letters ($P<0.0001$ versus baseline). The BCVA was improved in all treatment groups at week 12, but the greatest improvements were observed in the monthly dosing groups. The last observation-carried-forward method was used to impute missing data. BCVA = best corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; 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.

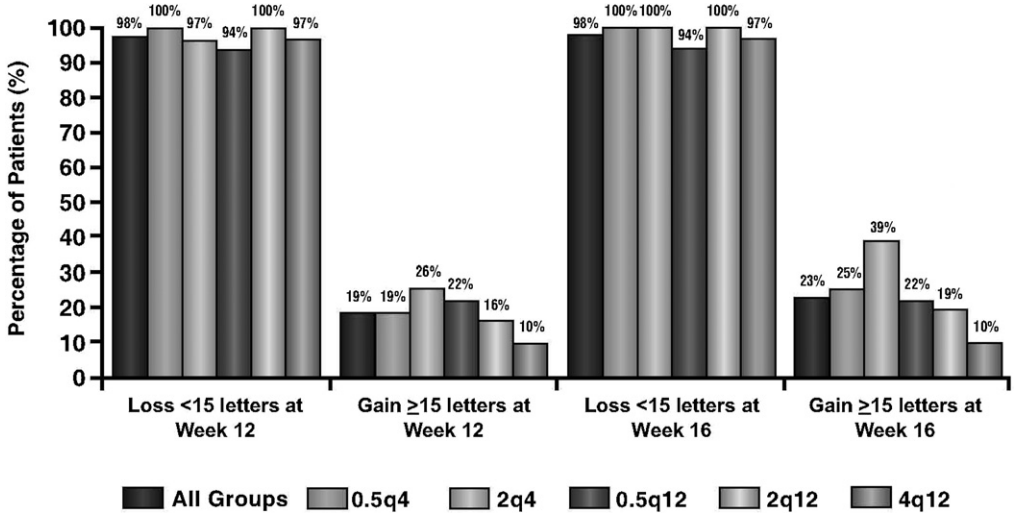

Figure 4. Visual acuity changes at weeks 12 and 16. The proportions of patients who avoided moderate vision loss (loss of ≥15 letters) or had significant vision gain (gain of ≥15 letters) in the combined treatment group and individual dosing groups are shown. At both 12 and 16 weeks, only 2% of patients in the combined treatment group experienced a loss of ≥15 letters, whereas 19% of patients showed a significant gain in vision at 12 weeks; in individual treatment groups, the proportions of patients showing a significant gain in vision remained steady or increased at week 16. 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. Decreases in visual acuity were due to retinal pigment epitheliopathy as reported by the investigators (n = 1), subretinal hemorrhage (n = 1), retinal hemorrhage (n = 1), and unexplained (n = 6).

loss of ≥15 letters (Fig 4). Overall, 4 patients (2.5%) experienced vision loss of ≥15 letters, including 2 patients in the 0.5 mg q12wk group, 1 patient in the 2 mg q4wk group, and 1 patient in the 4 mg q12wk group. In all treatment groups combined, the proportion of patients experiencing a clinically significant gain in vision (≥15 letters) was 19% at week 12. Again, the frequency of clinically significant vision gain was highest in the 2 mg q4wk group (26% at 12 weeks).

By week 12, monthly dosing reduced the proportion of patients with vision of ≤20/200, and all dose regimens of VEGF Trap-Eye (Fig 5) increased the proportion of patients with ≥20/40 vision. The proportion of patients with ≤20/200 vision was higher in the quarterly treatment groups than in the monthly treatment groups at week 12; none of the patients in the 2 mg q4wk group had ≤20/200 vision (data not shown). Conversely, a lower proportion of patients who received quarterly doses achieved ≥20/40 vision; the 2 mg q4wk dose group again had the highest proportion of patients (58%) with ≥20/40 vision.

Results at 16 Weeks (Fixed-Dose Phase)

Although the primary endpoint was assessed at week 12, the data collected at week 16 were indicative of the response to the last mandatory injection of the fixed-dosing phase at week 12. In the treatment groups combined, a further decrease in CR/LT was noted from a mean of −119 μm at week 12 to a mean of −160 μm at week 16 (Fig 2A). In the monthly treatment groups, CR/LT decreased continuously from baseline to week 16; in the quarterly treatment group, the reduction in CR/LT was attenuated by week 12 but was noted again at 16 weeks (after administration of the second dose at week 12).

In addition, the BCVA improved from week 12 to week 16 in the combined treatment group and in most individual treatment groups (Fig 3B). In the combined treatment group, the BCVA improved further, from a mean of 5.7 letters at week 12 to a mean of 6.6 letters at week 16. The 0.5-mg and 2-mg monthly dose groups showed a continuing and consistent improvement in BCVA to week 16. In the quarterly dose groups, the BCVA, which had declined by week 12, showed mixed results at week 16, with improved acuity in the 0.5- and 4-mg dose groups, but with worsened vision in the 2-mg dose group. The proportion of patients experiencing a gain of ≥15 letters continued to increase between weeks 12 and 16 for the overall group (from 19% to 23%) and in both monthly dose groups (from 19% to 25% in the 0.5 mg q4wk group and from 26% to 39% in the 2 mg q4wk group; Fig 4).

Figure 5. Snellen equivalent of ≥20/40 vision. All treatment groups showed an increase from baseline in the proportion of patients with ≥20/40 vision at week 12. The last-observation-carried-forward method was used to impute missing data. BL = baseline; 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.

Safety

The mean total dose administered to each group was consistent with the anticipated amount based on the dosing schedule. The highest total exposure was in the 2 mg q4wk group, which received a mean total of 5.74 mg through week 12. All patients in the quarterly dosing groups, and 90.6% and 90.3% in the 0.5 mg q4wk

Table 4. Adverse Events in the Study Eye (Frequency ≥5% in All Groups Combined*) at Week 16

Adverse Event	Number (n)	Percent (%)
Conjunctival hemorrhage	42	26.8
Increased IOP (transient postinjection)	22	14.0
Refraction disorder	16	10.2
Retinal hemorrhage	14	8.9
Eye pain	12	7.6
Vitreous detachment	11	7.0
Detachment of retinal pigment epithelium	9	5.7
Visual acuity reduced (patient-reported)	9	5.7

IOP = intraocular pressure.
*Patients receiving treatment with vascular endothelial growth factor Trap-Eye (n = 157).

and 2 mg q4wk dose groups, respectively, received the required doses.

Most AEs were related to the injection procedure and no ocular serious AEs, clinically significant ocular inflammation, or endophthalmitis was reported in any study eyes during the first 16 weeks of the study. The ocular AEs that occurred through week 16 were mild and were similar to those reported for other intravitreally administered anti-VEGF compounds. An ocular AE was reported in 70.7% of patients in the treatment groups combined (Table 4). In general, fewer patients in the 0.5 mg q12wk and 2 mg q12wk groups (62.5% and 74.2%, respectively) reported an ocular AE compared with the 0.5 mg q4wk, 2 mg q4wk, and 4 mg q12wk groups (68.8%, 67.8%, and 80.7%, respectively).

Systemic serious AEs were observed in 12 patients. One case of angina pectoris (2 mg q4wk group), 2 cases of congestive heart failure (0.5 mg q4wk and 2 mg q4wk groups), and 2 cases of coronary artery diseases (2 mg q4wk and 4 mg q12wk groups) were reported during the treatment period. One death occurred during this part of the study from preexisting pulmonary hypertension. There did not seem to be any relationship between the VEGF Trap-Eye dose and the occurrence of any particular AE.

Discussion

During the 12-week fixed-dosing period of this phase 2 study, intravitreally administered VEGF Trap-Eye demonstrated significant anatomic and visual improvements from baseline at week 12 after repeated monthly dosing. Treatment with VEGF Trap-Eye 0.5 mg and 2 mg dosed every 4 weeks resulted in the greatest improvements in both measures at the 12-week endpoint. The CR/LT decreased by a mean of −153.5 and −169.2 μm from baseline, and BCVA mean letter score improved by 8.8 and 8.3 letters with 0.5- and 2-mg monthly dosing, respectively. In this index study, 60% of patients had occult or minimally classic lesions and 40% had predominantly classic lesions. In the pivotal trials of ranibizumab, the improvement in BCVA at 12 weeks after fixed monthly dosing was 10.0 and 6.8 letters with 0.5 and 0.3 mg ranibizumab, respectively, in patients with predominantly classic lesions[27] and 5.9 and 5.1 letters with 0.5 mg and 0.3 mg ranibizumab, respectively, in patients with minimally classic or occult lesions.[28] Although our smaller study did not compare VEGF Trap-Eye directly with ranibizumab and cross-trial comparisons must be made with caution, the improvements in BCVA with VEGF Trap-Eye are of similar magnitude to those noted at 12 weeks after fixed dosing with ranibizumab in the larger pivotal trials.[27-29]

Both monthly dose groups continued to show anatomic and vision improvements after administration of the fourth mandatory dose at week 12. Both mean visual acuity and frequency of patients with a significant gain in vision increased from weeks 12 to 16. Whether continued monthly dosing (rather than PRN dosing) beyond 12 weeks would offer further vision gains will be determined from ongoing phase 3 studies. The PRN dosing phase of the current study demonstrates that visual gains were maintained through week 52.[26]

In the phase 1 study, an extended duration of efficacy to 12 weeks was noted in 3 of 6 patients who received a single intravitreal injection of 2 or 4 mg of VEGF Trap-Eye (Invest Ophthalmol Vis Sci 1751 [Suppl]:47,2006). The phase 2 study of VEGF Trap-Eye in exudative AMD was designed to evaluate whether quarterly dosing could provide similar efficacy as could be achieved with monthly dosing. Although the fixed quarterly dosing regimens reduced retinal thickness and improved visual acuity at all time points, the effect in general was less robust than that achieved with monthly fixed dosing. The improvements in CR/LT and BCVA seen in the monthly dose groups (3 initial injections) were greater than those seen in the quarterly dose groups (1 initial injection). An initial intensive monthly loading dose period may be required to completely resolve edema and render the lesion fluid free and/or to maximize visual gain. Whether quarterly dosing could maintain efficacy after an initial, intensive anti-VEGF treatment period was not evaluated. Notably, a single 2-mg dose achieved an improvement in visual acuity that was similar to that achieved with 2 mg dosed monthly out to 8 weeks, raising the possibility that dosing with 2 mg every 8 weeks may be as effective as monthly dosing.

Based on these findings, 2 identical phase 3 pivotal studies of VEGF Trap-Eye, VIEW-1 and VIEW-2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration), were designed to test both of these hypotheses. The regimens evaluated in phase 3 were VEGF Trap-Eye at doses of 0.5 mg and 2 mg every 4 weeks and 2 mg every 8 weeks (after 3 monthly loading doses), compared with ranibizumab 0.5 mg every 4 weeks. Phase 3 data have been released (http://newsroom.regeneron.com/releasedetail.cfm?ReleaseID_532099 accessed December 21, 2010) and manuscripts are under preparation. These phase 3 results support the efficacy findings of the current study. The PRN phase of the CLEAR IT-2 study,[26] with PRN dosing from weeks 16 through 52 also provides further information on the durability of the anti-VEGF effect of VEGF Trap-Eye.

In conclusion, results from the fixed-dosing phase of the CLEAR-IT 2 study show that repeated intravitreal dosing with VEGF Trap-Eye administered monthly was associated with clinically and statistically significant improvements in CR/LT and BCVA at 12 weeks in patients with neovascular AMD. In all dosing groups, VEGF Trap-Eye was generally well-tolerated and there were no unexpected safety findings.

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References

1. Klaver CC, Wolfs RC, Vingerling JR, et al. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. Arch Ophthalmol 1998;116:653–8.
2. Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–72.
3. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984;102:1640–2.
4. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. Invest Ophthalmol Vis Sci 1996;37:1929–34.
5. Tolentino MJ, Miller JW, Gragoudas ES, et al. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. Arch Ophthalmol 1996;114:964–70.
6. Kliffen M, Sharma HS, Mooy CM, et al. Increased expression of angiogenic growth factors in age-related maculopathy. Br J Ophthalmol 1997;81:154–62.
7. 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.
8. Bhisitkul RB. Vascular endothelial growth factor biology: clinical implications for ocular treatments. Br J Ophthalmol 2006;90:1542–7.
9. 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.
10. Kaiser PK. Vascular endothelial growth factor Trap-Eye for diabetic macular oedema. Br J Ophthalmol 2009;93:135–6.
11. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling—in control of vascular function. Nat Rev Mol Cell Biol 2006;7:359–71.
12. Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med 2001;7:575–83.
13. Ziche M, Maglione D, Ribatti D, et al. Placenta growth factor-1 is chemotactic, mitogenic, and angiogenic. Lab Invest 1997;76:517–31.
14. Cao Y. Positive and negative modulation of angiogenesis by VEGFR1 ligands. Sci Signal [serial online] 2009;2:re1. Available at: http://stke.sciencemag.org/cgi/content/abstract/sigtrans;2/59/re1. Accessed February 11, 2011.
15. Murakami M, Zheng Y, Hirashima M, et al. VEGFR1 tyrosine kinase signaling promotes lymphangiogenesis as well as angiogenesis indirectly via macrophage recruitment. Arterioscler Thromb Vasc Biol 2008;28:658–64.
16. 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.
17. 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.
18. Kim KJ, Li B, Houck K, et al. The vascular endothelial growth factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies. Growth Factors 1992; 7:53–64.
19. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997;57:4593–9.
20. 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.
21. 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.
22. 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.
23. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–8.
24. Rudge JS, 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. Saishin Y, Saishin Y, Takahashi K, et al. VEGF-TRAP(R1R2) suppresses choroidal neovascularization and VEGF-induced breakdown of the blood-retinal barrier. J Cell Physiol 2003; 195:241–8.
26. Heier JS, Boyer D, Nguyen QD, et al. 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. Ophthalmology 2011;118:1098–106.
27. 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.
28. 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.
29. 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.

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