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 VE[illegible] 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 [illegible] 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.

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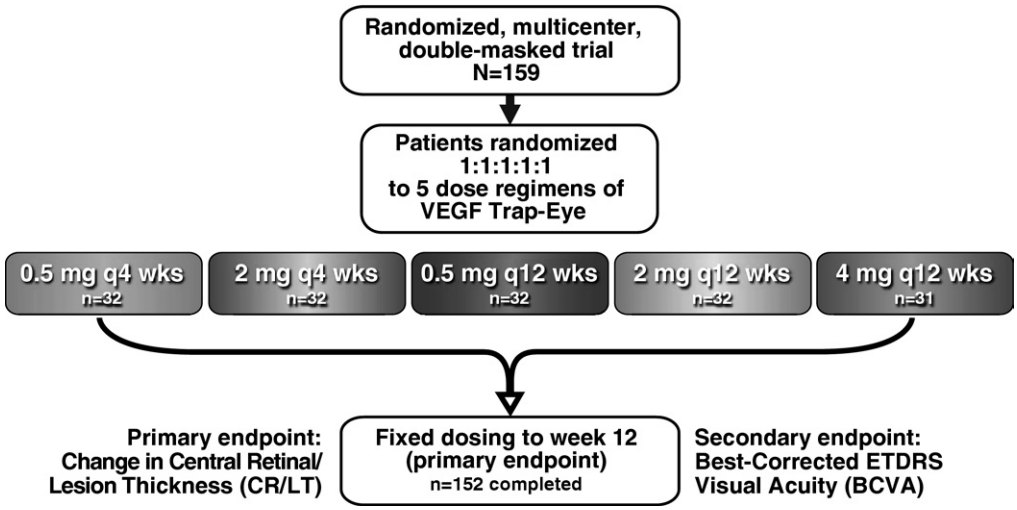

Figure 1. Study design. During the fixed-dosing phase of the CLEAR-IT 2 study, patients were randomized in equal ratios to receive 1 of 5 different regimens of VEGF Trap-Eye for 12 weeks: 0.5 or 2 mg every 4 weeks, or 0.5, 2, or 4 mg every 12 weeks. The primary endpoint, change from baseline in CR/LT, 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

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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.

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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

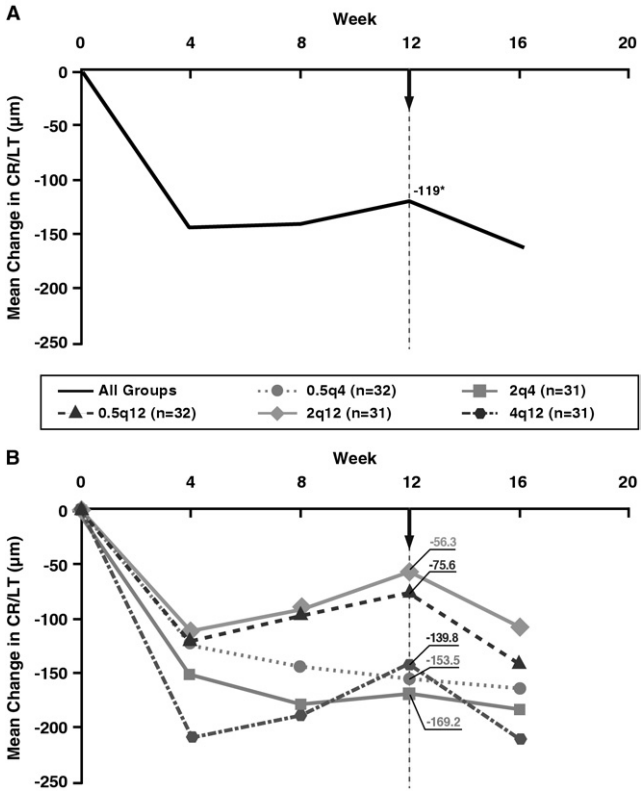

Figure 2. Mean change from baseline in central retinal/lesion thickness (CR/LT) for (**A**) all groups combined and (**B**) individual dosing groups. Change in CR/LT from baseline at 12 weeks was the primary study endpoint; in the combined treatment group, a significant decrease of 119 μm was observed 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.

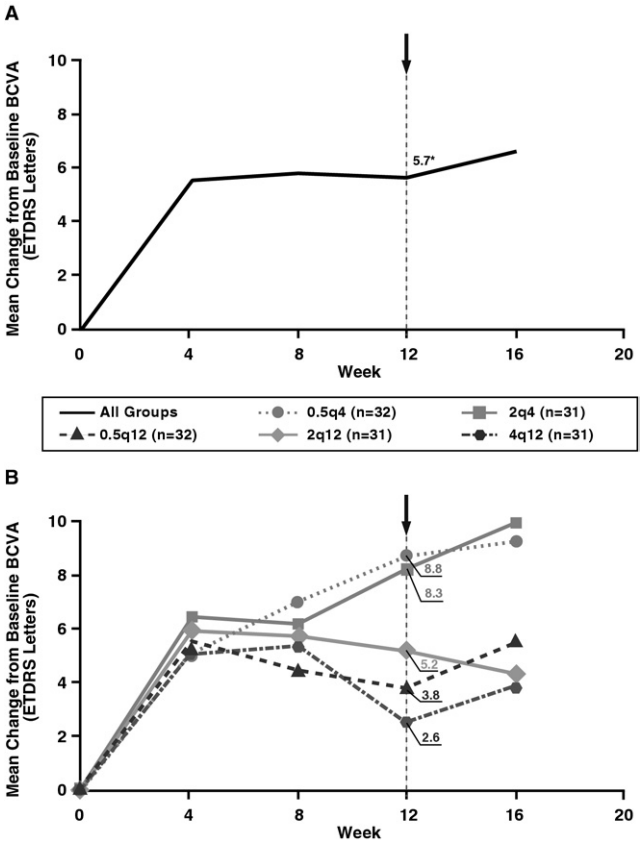

Figure 3. Mean change from baseline in best-corrected visual acuity (BCVA) for (**A**) all groups combined and (**B**) individual dosing groups. The combined treatment group showed a significant gain of 5.7 letters ($P<0.0001$ versus baseline). The BCVA was improved in all treatment groups at week 12, 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.

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