A Phase 1 Study of Intravitreous E10030 in Combination with Ranibizumab in Neovascular Age-Related Macular Degeneration

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Purpose: To assess the safety and tolerability of E10030 (Fovista; Ophthotech, New York, NY), a platelet-derived growth factor (PDGF) antagonist, when administered in combination with an anti-vascular endothelial growth factor (VEGF) agent, ranibizumab (Lucentis; Genentech, South San Francisco, CA) 0.5 mg, by intravitreal injection in participants with neovascular age-related macular degeneration (NVAMD).

Design: Prospective phase 1 clinical trial.

Participants: A total of 23 participants diagnosed with NVAMD and aged 50 years or older were enrolled.

Methods: Part 1 included 15 participants. Three participants received a single intravitreal E10030 (0.03 mg) injection and were subsequently given intravitreal ranibizumab (0.5 mg) injections at weeks 2, 6, and 10. Twelve participants (3 per group) received E10030 (0.03, 0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) at day 0, month 1, and month 2 in an ascending manner. In Part 2 (8 participants), E10030 (0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) was injected at day 0, month 1, and month 2.

Main Outcome Measures: Safety at week 12 was the primary outcome and included assessment of vital signs, laboratory tests, and serial eye examinations. Other safety metrics included assessment through week 24 of Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA) and biomarker changes evaluated by optical coherence tomography (OCT) and fluorescein angiography (FA).

Results: All doses of intravitreal E10030 administered in combination with ranibizumab were well tolerated. No dose-limiting toxicities or relevant safety events were noted at any dose level during the study. Investigators did not report adverse events related to E10030 or ranibizumab. Mean VA change was a gain of 14 letters, and 59% of participants gained ≥15 letters from baseline at week 12. On FA at week 12, there was an 85.5% mean reduction from baseline in choroidal neovascularization (CNV) size. On OCT at the week 12 visit, there was a mean decrease in center point thickness and central subfield thickness of 38.9% and 33.7%, respectively.

Conclusions: Intravitreal E10030 administered at doses up to 3 mg in combination with ranibizumab was well tolerated without evidence of systemic or ocular toxicity in participants with NVAMD. The changes in both mean VA and imaging biomarkers suggest a favorable short-term safety profile for the combination therapy of E10030 and ranibizumab. Ophthalmology 2016;123:78-85 © 2016 by the American Academy of Ophthalmology.

Supplemental material is available at www.aaojournal.org.

Neovascular age-related macular degeneration (NVAMD) is the leading cause of visual loss in individuals aged more than 55 years in the western world.1 The current standard of care for NVAMD is the intravitreal delivery of agents targeting vascular endothelial growth factor (VEGF), one of the proteins involved in the molecular orchestration of the pathologic neovascular cascade.2

Anti-VEGF agents have greatly improved visual outcomes in patients with NVAMD.3-5 However, a significant unmet need exists with anti-VEGF monotherapy regardless of the dose or administration regimen. Most eyes treated with anti-VEGF monotherapy do not gain significant visual acuity (VA) (≥15 Early Treatment of Diabetic Retinopathy Study [ETDRS] letters), up to 25% of eyes lose additional VA after therapy initiation, and approximately 50% of eyes do not achieve a final VA level (≥20/40) that is better than or equal to that required to drive in most American states.3

Furthermore, postregistration analyses of claims data show that on average, participants lose additional VA 3 to 4 years after initiation of therapy in a “real-world” setting.6,7 The efficacy of anti-VEGF monotherapy in NVAMD is primarily mediated by a marked reduction in hyperpermeability associated with pathologic neovascular complexes.8,9 However, VEGF antagonism does not seem to
significantly alter or induce regression of those neovascular complexes.10

Accordingly, pharmacologic strategies that both modify choroidal neovascular membranes (choroidal neovascularization [CNV]) by inducing neovascular regression and reduce permeability may result in improved visual outcomes in eyes with NVAMD. Furthermore, pericytes have been shown to be a major source of myofibroblasts, which are predominantly involved in deposition of pathologic matrix leading to tissue fibrosis. Pericytes are increasingly implicated in the deposition of pathologic matrix in a number of diseases of organ fibrosis, including those of the liver, lung, and kidney. In addition, advanced NVAMD often includes the formation of subretinal fibrosis.3 Therefore, pericyte loss from the choroidal neovascularization may play a role in reduction of fibrous evolution of the neovascular complex associated with wet age-related macular degeneration.1,12

Multiple mechanisms have been described to explain the resistance of pathologic neovascularization to anti-VEGF monotherapy. Pericyte coverage of endothelial cells on their external surface is one such mode of resistance.13 Pericytes are derived from the same progenitor cells as vascular smooth muscle. They are contractile cells that intimately cover the underlying endothelial cells via a shared common basement membrane.14 This anatomic relationship permits pericytes to locally provide endothelial cells with VEGF and other growth and survival factors via paracrine and juxtacrine signals.15 Therefore, it has been proposed that pericytes may protect the endothelial cells in the face of anti-VEGF agents and play an important role in anti-VEGF resistance.16 Preclinical ophthalmic and oncologic models of angiogenesis confirm this pericyte-mediated anti-VEGF resistance.17,18 Other proposed mechanisms of anti-VEGF resistance may include persistent inflammation and upregulation of mediators other than VEGF that are involved in the molecular cascade that drives angiogenesis.19

Platelet-derived growth factor (PDGF)-BB is a homodimer consisting of a dimeric molecule of disulfide-bonded B-polypeptide chains. Platelet-derived growth factor-BB binds to a dimerized protein tyrosine kinase receptor on pericytes. This ligand-receptor complex is critical for pericyte survival, recruitment, and maturation.20 Inhibition of PDGF-BB results in pericyte loss in genetic deletion studies and in vivo models of pathologic angiogenesis.21 Because pericytes protect endothelial cells from VEGF inhibition, pericyte loss within a neovascular complex may render the underlying endothelial cells susceptible to the effects of VEGF blockade.18,22 E10030 is a 32-mer-pegylated aptamer that binds and inhibits PDGF-BB. In preclinical models, E10030 potently strips and induces pericyte loss.23

This report describes the phase 1 trial of an intravitreally delivered anti-PDGF aptamer, E10030 (Fovista; Ophthotech, New York, NY) combined with an anti-VEGF protein. This phase 1 trial was initiated in treatment-naive participants with NVAMD to assess the safety of intravitreal administration of E10030 in a dose-escalation scheme when administered in combination with ranibizumab (Lucentis, Genentech, South San Francisco, CA). The study is based on the premise that inducing neovascular pericyte loss will enhance the effects of anti-VEGF agents on unprotected endothelial cells and therefore will induce neovascular tissue regression and modify the underlying disease.

Methods

Study Design

This prospective study is registered at ClinTrials.gov, Identifier NCT00569140; was conducted at 11 study sites in compliance with the Declaration of Helsinki, US Code 21 of Federal Regulations, and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996); and was reviewed and approved by the appropriate Ethics Committees or institutional review boards at each study center. Informed consent was obtained from all study participants. Twenty-three participants who had a diagnosis of NVAMD and were aged ≥50 years were enrolled between July 2009 and April of 2010. When aptamers such as E10030 are manufactured for therapeutic use, increasing drug concentrations cause increased viscosity. Doses of E10030 >3.0 mg were deemed to be too viscous for intravitreal administration. Thus, 3.0 mg was the highest E10030 dose tested. Part 1 of the study used an ascending dose design that included 15 participants. Three participants received a single intravitreal administration of E10030 (0.03 mg), and then ranibizumab (0.5 mg) was administered subsequently at weeks 2, 6, and 10. This was a dose-escalating safety study, and once the safety of 1 dose (in combination with ranibizumab) was demonstrated, the next higher dose was given. Accordingly, 12 participants, 3 in each dose group, received E10030 (0.03, 0.3, 1.5, or 3.0 mg) in an ascending manner in combination with ranibizumab (0.5 mg) at day 0, month 1, and month 2. Part 2 of the study used a parallel dose design and included 8 participants who were given E10030 (0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) at day 0, month 1, and month 2. The primary end point was at 12 weeks, and follow-up continued through week 24. There was no control group, and the study was not double-masked in this phase 1 protocol. The protocol design is shown in Figure 1.

Study Population

To be included in the trial, participants had to be aged ≥50 years, had to have been newly diagnosed with subfoveal CNV secondary to NVAMD, and had to have some classic CNV component documented on fluorescein angiography (FA). The total area of the lesion (including blood, neovascularization, and scar/atrophy) was required to be ≤5 disc areas, of which at least 50% was required to be active CNV. The other main inclusion criteria were as follows: (1) ETDRS best-corrected VA in the study eye between 20/63 and 20/200 inclusive; (2) presence of clear ocular media and adequate pupillary dilation to permit sufficient resolution of the stereoscopic fundus photographic images; and (3) intraocular pressure (IOP) ≤21 mmHg. A more detailed list of inclusion and exclusion criteria is listed in the Appendix (available at www.aaojournal.org).

One participant was enrolled erroneously because he had a diagnosis of diabetes, a protocol exclusion. The patient received a single dose of E10030 and ranibizumab at day 0 but no further treatment; this patient withdrew from the study and was excluded from the per-protocol dataset (n = 22).
Drug Administration Procedure

Intravitreal injections were given according to standard-of-care techniques used in modern retinal practice. Briefly, a sterile lid speculum was placed, and local anesthesia was administered. The conjunctiva and ocular adnexa were prepared with 5% povidone iodine. A 27-gauge needle was used for all injections, which were given 3.5 mm from the limbus. In patients in whom both intravitreal ranibizumab and E10030 were given, the injections were given consecutively (50 μl each), and ranibizumab was administered first. In these eyes, the IOP was measured 30 minutes after the first injection was given. The IOP had to be ≤21 mmHg or within 5 mmHg of the baseline IOP on the day of injection, before the E10030 injection could be administered. The IOP was monitored after the second injection until it was less than 30 mmHg.

Safety Assessments

Drug tolerability and safety metrics were monitored closely during the trial. A thorough clinical evaluation was performed at each visit and included slit-lamp examination of the anterior segment and lens, and biomicroscopic and ophthalmoscopic examination of the posterior segment; data from each of these examinations were recorded. In addition, IOP, adverse ocular and systemic events, and laboratory test result data were collected. Laboratory tests performed in the clinical trial included the following: hematology: hemoglobin, platelet count, white blood cell, and differential; renal function: serum creatinine and blood urea nitrogen; hepatic function: serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase, serum glutamic oxaloacetic transaminase/aspartate transaminase, and serum glutamic pyruvic transaminase/alanine aminotransferase; electrolytes: sodium, potassium, chloride, bicarbonate, calcium, and phosphate; and complete urinalysis. Safety biomarker data also were collected. These biomarkers included changes in visual function, as measured by VA, quantitative retinal thickness changes as determined by optical coherence tomography (OCT), and CNV lesion size assessed by FA. A Stratus OCT system (Zeiss Meditec, Dublin, CA) was used to obtain OCT scans. The OCT images were obtained with the fast macular thickness map protocol at investigator study sites. Investigators recorded quantitative imaging data including the center point value and central subfield value onto standardized case report forms. Those case report form data were confirmed and then analyzed internally. Stereo FA was obtained on field 2 of a modified 3-field imaging protocol at early (as soon as dye was first seen in the eye), mid (1–3 minutes), and late (5 minutes) phases. Two independent retinal specialists used Adobe Photoshop CS4 Extended software (Adobe Systems, Inc, San Jose, CA) to precisely outline the area(s) of CNV on FAs at standardized magnification. The software contains measurement and analytic tools that were used to quantify (in pixel area) the corresponding CNV size at baseline and week 12. The CNV size was determined during the FA mid-phase when the neovascular membrane is well defined, but before the development of significant leakage (Fig 2). The primary end point was at 12 weeks, and follow-up continued through week 24.

Results

Baseline Study Population Characteristics

The mean participant age was 75 years (range, 56–88 years), 13 were women, and 14 right eyes and 9 left eyes were enrolled. The
mean best-corrected VA was 49.2 letters (range, 24–73.5) on the Early Treatment Diabetic Retinopathy (ETDRS) chart. The average OCT central subfield thickness by OCT was 386.5 μm (range, 249.5–599 μm).

Safety

E10030 was well tolerated. There was no dose-limiting toxicity at any dose level, and no safety concerns were identified. There were no ocular serious adverse events. As would be expected in a trial of intravitreally delivered medications, many participants developed ocular adverse events related to the injection itself, such as ocular irritation and subconjunctival hemorrhage (Table 1). However, no ocular adverse events were attributed to E10030 or ranibizumab.

The combination of E10030 and ranibizumab did not result in complications of the anterior segment, such as corneal toxicity, lens toxicity, or ocular inflammation. Furthermore, posterior segment complications, including inflammation and abnormalities of the normal vasculature, were not observed.

There was a small mean IOP increase after each injection was given; the IOP returned to pre-dose levels by the following visit. At weeks 12 and 24, mean IOP was again similar to baseline levels. There was no indication of a cumulative increase in IOP after multiple injections.

There were no systemic serious adverse events with 1 exception: an 87-year-old woman developed atrial fibrillation. This participant in the multiple-dose arm received E10030 0.3 mg and received the first intravitreal injections of ranibizumab and

Table 1. Ocular Adverse Events (Occurring in >1 Patient)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dose Group</th>
<th>0.03 mg (n = 6)</th>
<th>0.3 mg (n = 8)</th>
<th>1.5 mg (n = 5)</th>
<th>3.0 mg (n = 4)</th>
<th>All (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 event</td>
<td>6 (100%)</td>
<td>5 (63%)</td>
<td>3 (60%)</td>
<td>4 (100%)</td>
<td>18 (78%)</td>
<td></td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>4 (67%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (50%)</td>
<td>6 (26%)</td>
<td></td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>2 (33%)</td>
<td>3 (38%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5 (22%)</td>
<td></td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0 (0%)</td>
<td>2 (25%)</td>
<td>1 (20%)</td>
<td>1 (25%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>Myodesopsia</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>1 (25%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>2 (33%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td>Anterior chamber cell</td>
<td>1 (17%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>0 (0%)</td>
<td>1 (13%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Macular degeneration*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>1 (25%)</td>
<td>2 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

*Macular degeneration refers to the development of neovascular age-related macular degeneration in the fellow eye.
E10030 on June 23, 2008. Subsequent injections were given per protocol on July 21 and August 14, 2008, without incident. On September 17, 2008, atrial fibrillation developed and was judged to be mild in severity and not related to study drug or injection procedure. The atrial fibrillation was noted on a routine study electrocardiogram, and the patient was asymptomatic.

There were no significant changes in measured laboratory values for the study population at the tested drug doses. As a result of this overall safety profile and because it was not possible to evaluate doses higher than 3.0 mg, as described in the “Methods” section, a maximum tolerated dose was not identified.

Safety Biomarkers

Visual Acuity. There were no adverse VA safety signals identified in the study group. There was a general trend toward a mean increase in VA (number of ETDRS letters) at all time points, when compared with baseline, for both the overall population and all treatment groups. At week 12, there was a mean increase in VA of 14 letters (standard deviation, 11.3) from baseline. The majority of participants gained VA at all time points during the study period. At week 12 (1 month after the final injection for most participants), 59% of participants gained ≥15 ETDRS letters (Figs 3 and 4).

Optical Coherence Tomography. Adverse safety signals were not identified by OCT. Mean center point and central subfield thickness decreased at all time points for all treatment groups. The absolute thickness changes from baseline are summarized in Figures 5 and 6. At the week 12 visit, 1 month after the last scheduled drug administration, there was a mean decrease in center point thickness and central subfield thickness of 38.9% and 33.7%, respectively (Fig 5, Table 2).

Fluorescein Angiography. One of the 22 participants in the per-protocol dataset was allergic to fluorescein and had only a baseline FA performed. Therefore, 21 participants provided data for the FA analyses. All participants analyzed demonstrated regression in CNV area from baseline to week 12 (Figs 6 and 7). Mean reduction in CNV area was 85.5%. Five participants had complete (100%) CNV regression. Fifteen of the 21 participants (71%) had >90% CNV area regression (Table 2).

Discussion

In the present investigation, escalating intravitreal doses of an anti-PDGF pegylated aptamer E10030 (0.03, 0.3, 1.5, and 3.0 mg) were administered in combination with ranibizumab, an anti-VEGF antibody fragment. This is the first clinical trial to target PDGF and VEGF via intravitreal combination therapy in treatment-naïve subjects with NVAMD. The experimental regimen was well tolerated. No local or systemic adverse safety signals were observed after administration of the individual investigational drug or the combination of active agents.

According to the study design, E10030 was first given in isolation, followed by ranibizumab at later time points. The initial dose of E10030 was given in isolation rather than in combination with ranibizumab to ensure that an adverse reaction to Fovista monotherapy did not occur; this study was the first human ocular exposure to the drug, and this conservative approach was taken to ensure patient safety. Once it was relatively clear that E10030 monotherapy was well tolerated, the clinical paradigm of same-day combination was subsequently used. This latter approach reflects our belief that same-day or sequential combination therapy may be the regimen used in future studies or the clinical setting.
Adverse events specific to the intravitreal delivery of aptamers are not known, to the best of our knowledge. As expected, no such adverse events were evident in this trial. In particular, local ocular adverse events, including intraocular inflammation, media opacification, retinal or choroidal vasculopathy, or other evidence of retinal tissue toxicity, were not seen. Transient changes known to be associated with the intravitreal injection procedure itself were expected and observed (e.g., ocular irritation and subconjunctival hemorrhage). Furthermore, no ocular E10030/ranibizumab drug–drug interaction side effects were identified, and systemic adverse events due to the experimental regimen were not seen. Increased drug viscosity at higher concentrations limited additional dose escalation. Therefore, 3.0 mg was the highest dose tested, and the maximum tolerated dose was not identified.

Theoretically, PDGF inhibition could result in stripping of pericytes associated with the normal host vasculature. Therefore, a resulting phenotype analogous to that seen in diabetic retinopathy is plausible. However, on meticulous fundus photograph and angiographic image evaluation at the 3- and 6-month follow-up time points, no morphologic alterations, such as microaneurysms suggestive of an incipient diabetic retinopathy-like picture, were observed. Lack of such vascular alterations is consistent with the preclinical studies of ocular and tumor angiogenesis in which normal host pericytes are resistant to PDGF antagonism. The mechanisms related to this form of normal host vasculature resistance are unknown. Pericytes share a common basement membrane with the underlying endothelial cells and have strong intercellular junctional complexes. Therefore, an underlying mechanical resistance to pericyte “stripping” may explain these findings. Alternatively, proliferating pericytes may express PDGF receptors, which are loosely associated with the neovascular endothelial cells, whereas quiescent pericytes with strong junctional processes to the underlying endothelial cells on the host vasculature may not express PDGF receptors. Such differential receptor expression may result in stripping of neovascular pericytes while sparing the pericytes on normal host vessels. However, a longer duration of follow-up with chronic therapy is required to adequately assess the potential pericyte loss in normal host vasculature consequent to PDGF inhibition.

Pericytes function to stabilize vessels and help to induce a state of neovascular quiescence. Inhibition of pericyte function theoretically could result in unwanted leakage by altering the neovascular barrier properties or inducing endothelial cell activation. This phenomenon was not seen in this study by imaging studies (OCT and FA). However, the potent antipermeability property of the co-administered anti-VEGF agent may have modified or masked any enhanced permeability alteration. Furthermore, this study was of relatively short duration, and longer-term confirmatory studies with E10030 are required to confirm the favorable safety profile seen thus far.

Functional visual outcome data were obtained as part of the safety assessment (i.e., adverse effects on VA). This phase 1 study used a dose-escalation scheme resulting in a small and imbalanced sample in each dose group (Table 1). The small sample size resulted in a lack of statistical power to permit subgroup analysis, particularly in the presence of a marked variability in baseline factors that affect visual outcomes and absence of a uniform regimen in the lower dose groups in this heterogeneous disease. Therefore, the visual outcome data and biomarkers were analyzed in a pooled fashion. No safety signals related to the loss of mean VA were identified in these pooled data.

Imaging biomarkers assessed by FA and OCT also did not show any drug-related adverse effects. Center point and central subfield thickness on OCT decreased by 38.9% and 33.7%, respectively, at week 12. Combining ranibizumab with E10030 did not reduce this beneficial effect of anti-VEGF therapy.

Qualitative and quantitative analysis of FA data demonstrated regression in CNV area from baseline to week 12.
with an overall mean decrease of 85.5%. The combination of CNV regression and mean VA increase of 14 letters from baseline, and the finding that 59% of participants gained ≥15 letters at week 12 may indicate potential bioactivity with the dual antagonism of PDGF and VEGF in NVAMD. However, great caution should be exercised in the interpretation of functional VA data given the small sample size, absence of a control group, relatively short-term follow-up, and high variability of VA measurement in eyes with NVAMD. However, choroidal neovascular membrane regression observed in this study stands in contrast to most prospective studies of anti-VEGF monotherapy, in which CNV size is not significantly reduced over time.10,25 This concordance with preclinical studies demonstrating similar neovascular regression may signal the modification of 1 mode of anti-VEGF resistance, namely, pericyte-mediated endothelial cell protection.

Given the potential for pericyte-mediated anti-VEGF resistance in NVAMD, this phase 1 study was designed to address the safety of combined VEGF and PDGF inhibition in NVAMD. Therefore, it was logical to combine an anti-PDGF agent such as E10030 with an anti-VEGF agent. The anti-PDGF agent has the potential to actively strip pericytes and inhibit their function, rendering the CNV more susceptible to anti-VEGF therapy.18 E10030 injection in doses up to 3 mg was well tolerated without evidence of systemic or ocular toxicity in participants with NVAMD. The absence of safety signals, the VA benefit, and the potential to modify the disease, thereby causing CNV regression in the acute phase and reduced fibrosis in the chronic phase, support the approach of combining E10030 and ranibizumab and call for a prospective study with a larger sample size and longer follow-up. Additional investigation will help build evidence for the concept of dual VEGF and PDGF antagonism to improve visual outcomes and address unmet need in NVAMD.

**References**


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CVN = choroidal neovascularization; ETDRS = Early Treatment of Diabetic Retinopathy Study; FA = ﬂuorescein angiography; IOP = intraocular pressure; NVAMD = neovascular age-related macular degeneration; OCT = optical coherence tomography; PDGF = platelet-derived growth factor; VA = visual acuity; VEGF = vascular endothelial growth factor.

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