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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 $\geq$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 2015;■:1–8 © 2015 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) ($\geq$15 Early Treatment of Diabetic Retinopathy Study [ETDRS] letters), up to 25% of eyes lose additional VA after therapy initiation, and approximately 50% of eyes do not achieve a final VA level ($\geq$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

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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 neovasculature may play a role in reduction of fibrous evolution of the neovascular complex associated with wet age-related macular degeneration.[11,12]

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-naïve 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).