AMERICAN ACADEMY™
OF OPHTHALMOLOGY

# Dual Antagonism of PDGF and VEGF in Neovascular Age-Related Macular Degeneration

## *A Phase IIb, Multicenter, Randomized Controlled Trial*

*Glenn J. Jaffe, MD,[1] Thomas A. Ciulla, MD, MBA,[2] Antonio P. Ciardella, MD,[3] Francois Devin, MD,[4] Pravin U. Dugel, MD,[5] Chiara M. Eandi, MD,[6] Harvey Masonson, MD,[2] Jordi Monés, MD, PhD,[7] Joel A. Pearlman, MD, PhD,[8] Maddalena Quaranta-El Maftouhi, MD,[9] Federico Ricci, MD,[10] Keith Westby, MBA,[2] Samir C. Patel, MD[2]*

***Purpose:*** To assess the safety and efficacy of E10030 (Fovista; Ophthotech, New York, NY), a platelet-derived growth factor (PDGF) antagonist, administered in combination with the anti−vascular endothelial growth factor (VEGF) agent ranibizumab (Lucentis; Roche, Basel, Switzerland) compared with ranibizumab monotherapy in patients with neovascular age-related macular degeneration (nAMD).

***Design:*** Phase IIb global, multicenter, randomized, prospective, double-masked, controlled superiority trial.

***Participants:*** Four hundred forty-nine patients with treatment-naïve nAMD.

***Methods:*** Participants were randomized in a 1:1:1 ratio to 1 of the following 3 intravitreal treatment groups: E10030 0.3 mg in combination with ranibizumab 0.5 mg, E10030 1.5 mg in combination with ranibizumab 0.5 mg, and sham in combination with ranibizumab 0.5 mg (anti-VEGF monotherapy). Drugs were administered monthly in each of the groups for a total duration of 24 weeks.

***Main Outcome Measures:*** The prespecified primary end point was the mean change in visual acuity (VA; Early Treatment Diabetic Retinopathy [ETDRS] letters) from baseline to 24 weeks.

***Results:*** No significant safety issues were observed in any treatment group. The E10030 (1.5 mg) combination therapy regimen met the prespecified primary end point of superiority in mean VA gain compared with anti-VEGF monotherapy (10.6 compared with 6.5 ETDRS letters at week 24; $P = 0.019$). A dose-response relationship was evident at each measured time point commencing at 4 weeks. Visual acuity outcomes favored the E10030 1.5 mg combination therapy group regardless of baseline VA, lesion size, or central subfield thickness on optical coherence tomography. All clinically relevant treatment end points of visual benefit (≥15 ETDRS letter gain, final VA ≥20/40 or ≥20/25) and visual loss (≥1 ETDRS line loss, ≥2 ETDRS line loss, final VA ≤20/125 or ≤20/200) favored the E10030 1.5 mg combination group.

***Conclusions:*** In this phase IIb clinical trial, a 62% relative benefit from baseline was noted in the E10030 1.5 mg combination therapy group compared with the anti-VEGF monotherapy group. A favorable safety and efficacy profile of E10030 combination therapy for nAMD was evident across multiple clinically relevant end points. This highly powered study provides strong rationale for a confirmatory phase III clinical trial. *Ophthalmology 2016;■:1−11 © 2016 by the American Academy of Ophthalmology*

*Supplemental material is available at www.aaojournal.org.*

Currently, all commonly used anti−vascular endothelial growth factor (VEGF) agents for the treatment of neovascular age-related macular degeneration (nAMD) show similar safety and efficacy profiles.[1−5] However, research over the past decade has highlighted numerous limitations of anti-VEGF strategies. Despite continuous (i.e., monthly) dosing over 1 year, 18% to 22% of patients lose visual acuity (VA), approximately 50% do not achieve 20/40 or better VA necessary for an unrestricted driver's license in regions of the United States, and approximately 62% to 75% do not achieve a significant gain of 3 lines or more of Early Treatment Diabetic Retinopathy (ETDRS) VA.[5−7] Discontinuous (i.e., less than monthly or bimonthly) dosing results in worse visual outcomes compared with continuous doing.[1,3] Furthermore, the ceiling of anti-VEGF monotherapy has been reached with currently available agents; despite increased anti-VEGF dosage or various regimens, no additional benefit is evident.[2,4,5] Unfortunately, post-drug approval real-world analyses reveal even worse VA outcomes compared with randomized clinical trials.[8−17] During the first 4 years of treatment or sooner, VA declines beyond baseline levels in most patients.[10−12,16]



http://dx.doi.org/10.1016/j.ophtha.2016.10.010
ISSN 0161-6420/16

This experience over the past decade highlights the limitations of anti-VEGF agents and the unmet need for more effective therapies.

Many studies indicate that pericytes play an important role in the limitations of anti-VEGF therapy, in both the short and long term.[18–24] Pericytes share a common basement membrane with endothelial cells, intimately coating them.[25] Pericytes provide endothelial cells with VEGF and other growth and cell survival factors by paracrine and/or juxtacrine signaling mechanisms.[26] Consequently, the neovascular endothelial cells are protected in the setting of anti-VEGF therapy.

Pericyte recruitment, maturation, and survival are mediated by platelet-derived growth factor (PDGF).[27] E10030 (Fovista; Ophthotech, New York, NY) is a 32-mer pegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB homodimers and heterodimers, respectively, thereby disrupting the interaction with their cognate tyrosine kinase receptors (PDGF-BB with PDGFR-αα, PDGFR-ββ, and PDGFR-αβ; PDGF-AB with PDGFR-αα and PDGFR-αβ). These receptors are commonly expressed on cells of mesenchymal origin, such as pericytes.[18,24,27–29] In a preclinical model, E10030 potently stripped neovascular pericytes from the underlying endothelial cells.[30] Pericyte stripping from a neovascular complex may leave the underlying endothelial cells in an unprotected and vulnerable state, thereby increasing their sensitivity to the effects of VEGF blockade.[18,19,21,24,28,31]

Dual targeting of PDGF and VEGF in nAMD has been assessed in a phase I clinical trial of E10030 administered in combination with ranibizumab (Lucentis); this therapy had a favorable safety profile, produced improved VA when compared with baseline, and caused biomarker changes supporting the enhanced efficacy.[32] In this article, we describe the results of a subsequent phase IIb randomized, prospective clinical trial of treatment-naïve nAMD eyes, comparing E10030 in combination with anti-VEGF therapy versus anti-VEGF monotherapy. To the best of our knowledge, this clinical trial represents the largest phase IIb pharmacologic superiority study conducted to date for a retinal disorder.

## Methods

### Study Design

This global phase IIb clinical trial (www.clinicaltrials.gov identifier, NCT01089517) used a parallel-group, randomized, double-masked, prospective superiority design to establish the safety and efficacy of intravitreal E10030 administered in combination with an anti-VEGF agent in patients with nAMD. The study was conducted at 69 study sites in 9 countries (in North and South America, Europe, and Israel) between April 2010 and January 2012. A list of study sites and investigators can be found in Appendix 1 (available at www.aaojournal.org). The appropriate ethics committees or institutional review boards at each study center approved the protocol. Informed consent was obtained from all participants. All data were collected in a Health Insurance Portability and Accountability Act–compliant manner.

### Study Population Eligibility Criteria

Eligibility criteria included age 50 years or older, study eye with treatment-naïve subfoveal choroidal neovascularization (CNV), a classic component on fluorescein angiography (FA), and total neovascular lesion area (including blood, neovascularization, and scar or atrophy) of 5 disc areas (DAs) or less, of which at least 50% was active. Other inclusion criteria included best-corrected ETDRS VA between 20/63 and 20/200 Snellen equivalent in the study eye and the presence of subretinal fluid, intraretinal fluid, subretinal pigment epithelium (RPE) fluid, or a combination thereof on optical coherence tomography (OCT). The VA inclusion cutoff at 20/63 Snellen equivalent (instead of 20/40 Snellen equivalent) was selected to minimize the potential influence of a ceiling effect that could confound the mathematical inference(s) in a superiority trial design.

Key ocular exclusion criteria included prior treatment for nAMD in the study eye, prior intravitreal drug exposure regardless of indication (including corticosteroids), subretinal hemorrhage more than 50% of the total lesion size, and RPE tears. Patients with diabetes were excluded. Eligibility was confirmed by masked assessment of FA and OCT images by a centralized and independent image reading center (Duke Reading Center). A comprehensive list of inclusion and exclusion criteria can be found in Appendix 2 (available at www.aaojournal.org).

### Sample Size, Treatment Groups, and Masking

Patients were randomized centrally in a 1:1:1 ratio to one of the following treatment groups: 0.3 mg E10030 in combination with 0.5 mg ranibizumab, 1.5 mg E10030 in combination with 0.5 mg ranibizumab, and sham in combination with 0.5 mg ranibizumab. The study planned for the enrollment of at least 148 patients (to account for patient dropout) in each of these groups, for a total of approximately 444 patients. Participants were treated monthly with intravitreal injection, according to their assigned dose group, at day 0 and weeks 4, 8, 12, 16, and 20 (6 doses). Patients were masked to treatments. One investigator performed the study drug or sham injection. A separate masked investigator supervised masked assessment of efficacy and assessed adverse events (AEs).

### Drug Administration Procedure

Intravitreal injections were performed in accordance with standard-of-care techniques that included the use of 5% povidone iodine and a sterile lid speculum. Intraocular pressure (IOP) was measured 30 minutes after the first injection (ranibizumab, 0.5 mg/eye, 50 μl) to detect delayed normalization of IOP in any patient subgroup. The IOP was monitored after the second injection until it was less than 30 mmHg.

### Schedule of Visits and Assessments

Efficacy and safety were assessed at study visits on day 0 and weeks 4, 8, 12, 16, 20, and 24; there was a ±3-day visit window centered on the week 4 time point and a ±7-day visit window centered on the subsequent time points. Certified masked examiners performed protocol refraction and ETDRS VA testing at each study visit to assess best-corrected VA at 4 m. At each study visit, participants underwent assessment of vital signs, IOP testing, and examination of the anterior and posterior segments. In addition, OCT was performed at screening and weeks 4, 8, 12, and 24. Fluorescein angiography was performed at screening and weeks 4, 12, and 24. Image acquisition and assessment parameters for OCT, fundus photographs, and FA can be found in Appendix 3 (available at www.aaojournal.org). Laboratory tests included hematologic analysis, renal function analysis, hepatic function analysis, electrolyte concentrations, and urinalysis; a complete list of