Dual Antagonism of PDGF and VEGF in Neovascular Age-Related Macular Degeneration: A Phase IIb, Multicenter, Randomized Controlled Trial

Dual Antagonism of Platelet Derived Growth Factor (Fovista®) and Vascular Endothelial Growth Factor (ranibizumab) in neovascular Age-Related Macular Degeneration (nAMD): Results of a Phase 2b (449 patients), global, multicenter, randomized controlled trial

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Running head: Fovista® Combination Therapy for Neovascular AMD

Précis

Dual antagonism of platelet derived growth factor and vascular endothelial growth factor with Fovista® and ranibizumab, respectively, in neovascular age-related macular degeneration demonstrated a favorable safety and efficacy profile across multiple clinically relevant visual endpoints that correlated with a trend in biomarker response.

Abstract

Purpose: To assess the safety and efficacy of Fovista® (Ophthotech, NY), a Platelet Derived Growth Factor (PDGF) antagonist, when administered in combination with anti-Vascular Endothelial Growth Factor (anti-VEGF) agent ranibizumab (Roche, Basel) compared to ranibizumab monotherapy in subjects with neovascular Age-related Macular Degeneration (nAMD).

Design: Phase 2b, global, multicenter, randomized, prospective, double-masked, controlled superiority trial.

Participants: 449 subjects with treatment-naïve subfoveal nAMD.

Methods: Subjects were randomized in a 1:1:1 ratio to one of the following three intravitreal treatment groups: Fovista® 0.3 mg in combination with ranibizumab 0.5 mg, Fovista® 1.5 mg in combination with ranibizumab 0.5mg, 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 pre-specified primary endpoint was the mean change in visual acuity (ETDRS letters) from baseline to 24 weeks.

Results: No significant safety issues were observed in any treatment group. The Fovista® (1.5mg) combination therapy regimen met the pre-specified primary endpoint of superiority in mean visual acuity (VA) gain compared to anti-VEGF monotherapy (10.6 ETDRS letters at week 24, compared to 6.5 ETDRS letters, p=0.019). A dose-response relationship was evident at each measured timepoint commencing at 4 weeks. VA outcomes favored the Fovista® (1.5 mg) combination therapy group irrespective of baseline VA, lesion size or central subfield thickness on OCT. All clinically relevant treatment endpoints of visual benefit (≥15 ETDRS letters gain, final VA 20/40 or better 20/25 or better) and visual loss (≥1 ETDRS line loss, ≥2 ETDRS line loss, final VA 20/125 or worse or 20/200 or worse) favored the Fovista® (1.5 mg) combination group.

Conclusions: In this phase 2b clinical trial, a 62% relative benefit from baseline was noted in the Fovista® (1.5 mg) combination therapy group compared to the anti-VEGF monotherapy group. A large sample sized dataset demonstrated a favorable safety and efficacy profile of Fovista® combination therapy for nAMD across multiple clinically relevant endpoints. This highly powered study provides strong rationale for a confirmatory phase 3 clinical trial.

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.[1-4] However, the past decade has highlighted numerous limitations of anti-VEGF strategies. Despite "continuous" (monthly) dosing over one year, 18-22% of patients lose visual acuity (VA), approximately 50% do not achieve 20/40 or better VA necessary for an unrestricted drivers license in regions of the United States, and approximately 62-75% do not achieve significant VA gain of 3 or more ETDRS lines.[5-7] "Discontinuous" (less-than-monthly or bimonthly) dosing results in worse relative visual outcomes.[1, 3] Furthermore, the ceiling of anti-VEGF monotherapy has been reached; despite increasing anti-VEGF dosage or varying its regimen, no additional benefit is evident.[2, 4] Unfortunately, post-registration "real world" analyses reveal even worse VA outcomes compared to randomized clinical trials (RCTs).[8-16] During the first four years of treatment or sooner, VA declines beyond baseline levels in a majority of patients.[9, 10, 14, 15, 17-20] This experience over the past decade clearly highlights the limitations of anti-VEGF agents and the unmet need for more effective therapy.

Many studies implicate pericytes to be responsible for the limitations related to anti-VEGF therapy.[21-24] They share a common basement membrane with endothelial cells, intimately coating them. Pericytes provide endothelial cells with VEGF and other growth and cell survival factors by paracrine and/or juxtacrine signaling mechanisms.[25] Consequently, the neovascular endothelial cells are protected in the setting of anti-VEGF therapy.

Pericyte recruitment, maturation, and survival is mediated by Platelet Derived Growth Factor (PDGF). Fovista® is a 32-mer-pegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB homo and hetero-dimers, 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.[24, 26-29] In a preclinical model, Fovista® has been shown to potently strip neovascular

pericytes from the underlying endothelial cells.[30] Pericyte stripping from a neovascular complex may therefore leave the underlying endothelial cells in an unprotected and vulnerable state, thereby increasing their sensitivity to the effects of VEGF blockade.[21, 24, 27, 30, 31]

Dual targeting of PDGF and VEGF in nAMD has been assessed in a Phase 1 clinical trial of Fovista® administered in combination with ranibizumab; this therapy exhibited a favorable safety profile, improved VA, and biomarker changes supporting the enhanced efficacy.[32] This report presents the results of a subsequent phase 2b randomized prospective clinical trial in treatment-naïve eyes with nAMD, comparing Fovista® in combination with anti-VEGF therapy to anti-VEGF monotherapy. To the best of our knowledge, this clinical trial represents the largest phase 2b pharmacologic superiority study conducted to date for a retinal disorder.

Methods:

Study Design:

This global phase 2b clinical trial (www.clinicaltrials.gov, identifier NCT01089517) employed a parallel group, randomized, double-masked, prospective superiority design to establish the safety and efficacy of intravitreal Fovista® administered in combination with an anti-VEGF agent, in subjects with nAMD. The study was conducted at 76 study sites in 9 countries (in North and South America, Europe, and Israel) between April 2010 and January 2012. The appropriate Ethics Committees (ECs) or Institutional Review Boards (IRBs) at each study center approved the protocol. Informed consent was administered to all subjects.

Study Population, Eligibility Criteria:

Eligibility criteria included age ≥ 50 years, study eye with treatment-naïve subfoveal CNV with some classic component on fluorescein angiography (FA), and total area of the neovascular lesion (including blood, neovascularization, and scar/atrophy) ≤ 5 disc areas

(DA), of which at least 50% was active. Other inclusion criteria included best-corrected ETDRS VA in the study eye between 20/63 and 20/200 Snellen equivalent, and presence of subretinal, intraretinal, and/or sub RPE fluid by OCT.

Key exclusion criteria included prior treatment for nAMD in the study eye, prior intravitreal drug exposure regardless of indication (including steroid), subretinal hemorrhage >50% of the total lesion size, and RPE tears. Diabetic patients 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 detailed list of inclusion and exclusion criteria is presented in the appendices.

Randomization, Sample Size, Treatment Groups and Masking

Patients were centrally randomized in a 1:1:1 ratio into one of the following treatment groups: Fovista® 0.3mg in combination with ranibizumab 0.5mg, Fovista® 1.5mg in combination with ranibizumab 0.5mg, and sham in combination with ranibizumab 0.5mg. 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. Subjects 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 as to treatments. One investigator performed the study drug or sham injection. A separate masked investigator supervised masked assessment of efficacy and assessed adverse events.

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. The intraocular pressure (IOP) was measured 30 minutes after the first injection (ranibizumab, 0.5 mg/eye, 50 µl) to detect delayed normalization of the IOP in any subgroup of patients. The IOP was monitored after the second injection until it was less than 30 mm Hg.

Schedule of Visits and Assessments:

Efficacy and safety assessments were performed at study visits on day zero and weeks 4, 8, 12, 16, 20 and 24; there was a ±3 day visit window centered on the week 4 timepoint and a ±7 day visit window centered on the subsequent timepoints. Certified masked examiners performed protocol refraction and ETDRS VA testing at each study visit to assess best-corrected VA at 4 meters. At each study visit, subjects underwent assessment of vital signs, IOP testing, and examination of the anterior and posterior segment. In addition, OCT was performed at screening and weeks 4, 8, 12, and 24. FA was performed at screening and weeks 4, 12, and 24. Image acquisition and assessment parameters for OCT, fundus photos, and FA are included in the appendices. Laboratory tests included: hematology, renal function, hepatic function, electrolytes, and urinalysis; a complete list of laboratory tests is included in the appendices.

Endpoints and Statistical Analysis:

The pre-specified primary efficacy endpoint was the mean change in VA at week 24, when compared to baseline for subjects treated with the combinations of Fovista® and ranibizumab 0.5mg versus those receiving ranibizumab 0.5mg monotherapy. Patients were centrally allocated to one of three treatment groups. Secondary VA endpoints included the mean change in VA at week 12 and the proportion of subjects gaining ≥15 ETDRS letters from baseline at weeks 12 and 24. Secondary anatomic endpoints included the mean change in CNV area as determined by FA. Additional supportive VA endpoints included the proportion of subjects who gained or lost significant VA based on a change in the number of ETDRS lines read.

The Duke Reading Center (Duke RC) independently analyzed and graded FA and OCT images in a masked fashion. OCT anatomic parameters identified prior to the study onset for analysis with respect to their presence or absence at baseline and at 24 weeks, included RPE atrophy, intra and subretinal fluid relative to the foveal location, as well as Subretinal Hyper-Reflective Material (SHRM, referring to tissue external to

photoreceptors and internal to RPE and/or Bruch's membrane, thought to represent CNV components that may include fibrin, blood vessels, blood, and fibrosis).*

Safety endpoints included adverse events (AE), vital signs, laboratory variables, and ophthalmic variables including VA, IOP, ophthalmic exam findings, FA and OCT findings.

According to the statistical analysis plan (SAP), the Hochberg procedure was used to address multiplicity. In addition, Intention-to-treat (ITT) Last Observation Carried Forward (LOCF) methodology was pre-specified to account for missing values and descriptive statistics were employed for secondary and supportive analysis. The safety analysis was conducted on all patients who had at least one administration of trial drug.

Results:

Patient Disposition and baseline characteristics:

A total of 449 patients with treatment naïve nAMD were randomized into each of the treatment groups as follows: 1.5 mg Fovista® combination therapy (n=152), 0.3 mg Fovista® combination therapy (n=149), and anti-VEGF monotherapy (n=148). Of these 449 patients, 14 withdrew prior to completion. There were 4 withdrawals in the anti-VEGF monotherapy group (2.7%) and 5 withdrawals in each of the Fovista® combination therapy groups (3.3% overall). As summarized in figure 1, the most common reason for withdrawal was subject request (8 subjects), followed by adverse events (3 subjects), investigator decision (1 subject), sponsor decision (1 subject) and being lost to follow up (1 subject). Baseline demographic features were balanced between treatment groups. (Table 1) The majority of patients were female and Caucasian. The mean subject age

* Subretinal Hyper-Reflective Material (SHRM) defined by Glenn Jaffe, M.D.

was 78 years and the mean baseline VA was 50 ETDRS letters.

Primary Endpoint Analysis:

The 1.5 mg Fovista® combination therapy group met the pre-specified superiority primary endpoint of mean change in VA from baseline to 24 weeks, compared to anti-VEGF monotherapy (Figure 2). At 24 weeks, subjects receiving 1.5 mg Fovista® combination therapy had a statistically significant improvement in mean VA (10.6 ETDRS letters) compared to those subjects receiving anti-VEGF monotherapy (6.5 ETDRS letters) (p=0.019). Subjects receiving 0.3 mg Fovista® combination therapy gained a mean of 8.8 ETDRS letters at week 24, an improvement compared to those receiving anti-VEGF monotherapy (p=0.17).

Other Key Visual Acuity Endpoints:

At week 12, subjects receiving 1.5 mg Fovista® combination therapy had an increase in mean VA of 8.7 ETDRS while subjects treated with anti-VEGF monotherapy had a mean increase of 5.1 ETDRS letters (p=0.0164). A dose-response relationship was evident at each measured timepoint commencing at 4 weeks. Relative to the anti-VEGF monotherapy group, the visual acuity benefit favoring the 1.5 mg Fovista® combination therapy patients increased in magnitude over time (Figure 3). In addition, a larger percentage of subjects receiving 1.5 mg Fovista® combination therapy had ≥3 lines improvement at weeks 12 and 24 (32%, and 39% respectively) compared to those receiving anti-VEGF monotherapy (22% and 34% respectively). VA outcomes favored the 1.5 mg Fovista® combination therapy group irrespective of baseline VA, lesion size and central subfield thickness on OCT (Figure 4).

Multiple clinically relevant treatment endpoints of visual gain and loss favored the 1.5 mg Fovista® combination therapy group compared to anti-VEGF monotherapy group (Figure 5). At 24 weeks, the proportion of subjects treated with 1.5 mg Fovista® combination therapy were both more likely to experience marked amount of VA gain (> 4 and >5 ETDRS lines) and more likely to achieve improved final VA (≥20/40 and

≥20/25) compared to subjects receiving anti-VEGF monotherapy.

At 24 weeks, the proportion of subjects treated with 1.5 mg Fovista® combination therapy were both less likely to lose vision (≥1 and ≥2 ETDRS lines), and less likely to have a lower final VA score (20/125 or worse and 20/200 or worse), compared to subjects treated with anti-VEGF monotherapy.

Safety:

Fovista® ranibizumab combination therapy was well tolerated. There were no significant differences in injection procedure AEs, study drug AEs, AEs leading to study discontinuation, or serious adverse events among the treatment arms. Very few patients developed study drug AEs and the majority of AEs were mild or moderate in intensity.

The most frequently reported AEs were ophthalmic AEs in the study eye, related to the injection itself, such as surface irritation and subconjunctival hemorrhage. Transient elevation of IOP, consistent with a volume effect, was observed and returned to pre-injection IOP level in all arms at the next visit at the next visit and at the end of the study. There were no glaucoma related adverse events and there was no cumulative increase in IOP following multiple injections. On ophthalmic examination, there were no other notable ophthalmic AEs that were not related to the injection procedure.

Non-ophthalmic AEs were less frequently reported than ocular AEs. The most frequently occurring systemic AEs included hypertension, headache, nasopharyngitis and urinary tract infection, commonly occurring conditions in the general population. There were no clinically meaningful laboratory abnormality trends and no significant vital sign changes.

The incidence of serious adverse events (SAEs) in the combination and monotherapy groups were similar and are summarized in Figure 6. There was a low incidence of APTC (Antiplatelet Trialists' Collaboration) events and no imbalance among groups. There

were no events of endophthalmitis, retinal detachment, retinal tear or iatrogenic traumatic cataract after a total of 4431 intravitreal injections (1776 injections of Fovista® and 2655 injections of ranibizumab).

Key Anatomic Endpoints:

There was a decrease in mean area of CNV for all treatment groups at week 24 compared to baseline. The mean reductions in CNV area between the study arms when evaluated as a full cohort in each treatment group was -0.7 DA for anti-VEGF monotherapy, -0.7 DA for 0.3 mg Fovista® combination therapy, -0.6 DA for 1.5 mg Fovista® combination therapy.

Smaller than mean area (≤1.62 DA) and larger than mean area (>1.62 DA) CNV at baseline were retrospectively analyzed to allow for a more arithmetically optimized investigation of CNV regression. This supportive analysis showed a greater decrease in CNV area in the Fovista® combination therapy arms for both small CNV at baseline (-0.15 DA and -0.12 DA for the 0.3 mg and 1.5 mg Fovista® combination arms, respectively compared to -0.06 DA for anti-VEGF monotherapy arm) and for large CNV at baseline (-1.69 DA and -1.73 DA for the 0.3 and 1.5 mg Fovista® combination therapy arms, respectively, compared with -1.59 DA for the anti-VEGF monotherapy).

Additional ad hoc supportive analyses were performed to assess change in CNV area for eyes gaining > 3 lines (15 ETDRS letters) of VA at Week 24. This analysis showed a greater relative decrease in CNV area for eyes in the Fovista® combination therapy arms compared to the anti-VEGF monotherapy arm. (Figure 7A) The decrease in CNV area was particularly evident for eyes with large CNV at baseline: -1.48 and -2.33 DA for the 0.3 and 1.5 mg Fovista® combination therapy arms respectively, compared with -0.24 DA for the anti-VEGF monotherapy arm.

Changes in total macular volume, intraretinal fluid, subretinal fluid, or sub-RPE fluid

were determined to evaluate alterations in vascular permeability in each treatment group. There were no significant differences in these parameters amongst the treatment groups. (Figure 8)

A greater proportion of eyes treated with 1.5 mg Fovista® combination therapy had complete resolution of SHRM from baseline when compared to eyes treated with anti-VEGF monotherapy (SHRM absent in 32% versus 23% respectively). In subjects who experienced significant visual gain (at week 24), an even greater proportion of eyes treated with 1.5 mg Fovista® combination therapy had resolution of SHRM from baseline when compared to eyes treated with anti-VEGF monotherapy (SHRM absent in 54% vs. 38% respectively). (Figure 7B).

A retrospective masked analysis was also conducted with respect to the development and progression of subretinal fibrosis. The amount of subretinal fibrous was evaluated by the analysis of color fundus photos using a continuous grading scale from 0 to 4 (absent, barely visible, mild, moderate, or severe) in all subjects experiencing visual loss.† Fibrosis development or progression was defined as a two-step progression on this scale. In those eyes with vision loss at 24 weeks, the mean change in severity of subretinal fibrosis from baseline to 24 weeks was less in the 1.5 mg Fovista® combination therapy group compared to the anti-VEGF monotherapy group (0.97 vs. 2.0, P = 0.003). In this subgroup at 24 weeks, a greater percentage of patients receiving anti-VEGF monotherapy were noted to have the development and progression of subretinal fibrosis (51% and 54% respectively) compared to those receiving 1.5 mg Fovista® combination therapy (10% and 27% respectively).

RPE atrophy (RPE loss or disruption with overlying photoreceptor atrophy and signal penetration into the choroid) was also assessed by OCT in a masked fashion by the Duke RC. At 24 weeks, RPE atrophy was evident in 21% of eyes in the anti-VEGF monotherapy group (n=30/144), 17% in the 0.3 mg Fovista® combination therapy group

† Duke RC and Dr. Usha Chakravarthy

(n=24/143), and 16% in the 1.5 mg Fovista® combination therapy group (n=23/145), respectively (Figure 9).

Discussion:

To the best of our knowledge, this clinical trial represents the largest phase 2b pharmacotherapeutic superiority study ever conducted for a retinal disorder. It confirms the initial findings of the phase 1 clinical trial, which suggested a favorable safety profile, improved visual outcomes, and biomarker changes consistent with the mechanism of action of Fovista® combination therapy in nAMD.[32] This Phase 2b study demonstrated a statistically and clinically significant visual acuity benefit when Fovista® (1.5 mg) was added to a continuous anti-VEGF regimen ("Fovista® combination therapy") for nAMD over 6 months, reflected by the 62% additive improvement in mean visual acuity from baseline to 24 weeks. A dose-dependent benefit of Fovista® combination therapy over anti-VEGF monotherapy was evident early and was sustained to the last measured time point at 24 weeks. Moreover, there was a suggestion of increasing benefit of Fovista® combination therapy compared to anti-VEGF monotherapy over time with no drug-related safety imbalances between the groups. The relative treatment benefit in the Fovista® combination therapy arm was evident irrespective of baseline VA, lesion size and central subfield thickness on OCT and evident in multiple treatment endpoints measuring visual gain and reduction of vision loss.

Multiple mechanisms involving dual antagonism of VEGF and PDGF signaling pathways may result in a variety of disease-modifying tissue responses (i.e. neovascular complex regression, reduction of fibrovascular and/or fibrous scar). First, in preclinical pathologic angiogenesis, when PDGF signaling is disrupted, pericytes are stripped from neovascular endothelial cells. The resulting endothelial lined neovascular tubes are highly vulnerable to the effects of anti-VEGF therapy, thereby inducing neovascular regression. [21, 24, 27, 30] Second, immunolabeling experiment studies of spatiotemporal cellular events in laser CNV models suggest that pericytes play a key role during the initial formation and growth of CNV.[33] Third, recent findings show that pericytes play an important role in

local inflammatory response by orchestrating the navigation of leukocytes within the interstitial space to sites of inflammation.[34] Pericytes coordinate this interstitial leukocyte trafficking through expression of cell surface adhesion molecule ICAM-1 (allowing pericytes to physically engage neutrophils and monocytes/macrophages) and releasing chemoattractant MIF (macrophage migration-inhibitory factor).[34] Fourth, PDGF itself is chemotactic for RPE cells and inflammatory cells and glial cells,[35-37] all of which are known components of surgically extracted fibrovascular and fibrous CNV.[38] Lastly, there is strong supporting evidence that pericytes are a major source of myofibroblasts, which are responsible for the deposition of pathologic matrix.[26, 39] In other organs systems, pericytes have been shown to drive renal and hepatic fibrosis.[26, 39] PDGF is also central to wound healing and fibrosis systemically, as manifested by the FDA approval of recombinant PDGF dermatologic gel for promoting wound healing in diabetic ulcers, as well as the recent FDA approval of Nintedanib for idiopathic pulmonary fibrosis, which is known to involve PDGF signaling. In the eye, Fovista® mediated PDGF inhibition has been shown to significantly reduce epiretinal fibrosis in an animal model of retinal scarring.[30] Taken together, we hypothesize that these multiple mechanisms may contribute to varying degrees with subsequent beneficial effects on tissue responses and visual outcome observed in this study with the administration of Fovista® combination therapy. The dual PDGF and VEGF inhibition may induce neovascular regression following stripping of pericytes. In addition, the effects of PDGF inhibition on non-neovascular components (myofibroblasts, inflammatory, RPE and glial cells)[40] may limit the amount of fibrovascular and fibrous tissue evolution in nAMD.

Clinically, the findings in this study were consistent with the aforementioned preclinical mechanisms. Neovascular complex regression after treatment with Fovista® combination therapy was evident by the resolution of SHRM, which also correlated with visual benefit. With respect to fluorescein angiography, a similar CNV regression effect was suggested by separate evaluation of small and large CNV at baseline. This division was undertaken to address the confounding effect resulting from the disproportional numerical influence on regression imparted by the larger baseline CNV area group.

Consistent with the mechanisms highlighted in preclinical studies above, Fovista® combination therapy was more effective than anti-VEGF monotherapy in limiting the development and progression of fibrosis. The implication related to this finding is relevant, as nAMD-associated fibrosis is a key cause of decreased VA in anti-VEGF treated eyes.[41, 42] In the present trial, approximately half of the eyes that did not gain visual acuity while receiving anti-VEGF monotherapy developed subretinal fibrosis. In the Comparison of Age-related Macular Degeneration Treatment Trials (CATT), approximately 25% of eyes developed fibrosis by two years despite treatment with anti-VEGF monotherapy.[41, 42] One CATT publication showed SHRM as a significant risk factor for scar formation.[41] The authors of that publication postulated that Fovista® mediated PDGF inhibition and associated SHRM resolution may be one explanation for the resulting visual benefit noted in this study, which requires confirmation in future clinical trials.[41]

In summary, Fovista® combination therapy yielded robust visual outcomes across multiple meaningful parameters consistent with the mechanism of action. The overall trend in biomarker responses were consistent with visual benefit associated with Fovista® combination therapy. To the best of our knowledge, in the current anti-VEGF monotherapy era, no biomarker has correlated with improvement in visual outcome, following the initial resolution of exudation in the induction phase. Large confirmatory phase 3 clinical trials in nAMD are underway, comparing 1.5 mg Fovista® combined with each of the three commonly utilized anti-VEGF agents (ranibizumab, aflibercept, and off-label bevacizumab) to the respective anti-VEGF agent administered as monotherapy.

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Figure Legends

Figure 1. Patient Disposition:

A total of 449 patients were randomized into the study. This included 148 patients in the ranibizumab monotherapy arm, 149 patients in the Fovista® 0.3 mg/ranibizumab combination arm and 152 in the Fovista® 1.5 mg/ranibizumab combination arm. There were 14 withdrawals, evenly balanced across the treatment arms.

Figure 2. Primary Efficacy Endpoint – Mean Change in Visual Acuity from Baseline at 24 Weeks:

The primary efficacy endpoint was the mean change in visual acuity from baseline at the Week 24 visit. There was a statistically significant difference between the Fovista®1.5 mg/ ranibizumab arm and the sham/ranibizumab arm (10.6 ETDRS letters at Week 24, compared to 6.5 letters, p=0.019), representing a 62% additional benefit from baseline.

Figure 3. Mean Change in Visual Acuity from Baseline Over Time:

There was a benefit of Fovista®/ ranibizumab treatment over sham/ranibizumab in terms of mean VA gain from Week 4 onwards for both dose levels. A dose response relationship was evident at each time point for the Fovista® 0.3 mg/ ranibizumab and Fovista®1.5 mg/ ranibizumab treatment arms. There was expanding benefit over time.

Figure 4. Baseline Variables and Visual Outcomes at 24 Weeks:

Visual outcomes favored the higher dose Fovista® combination therapy group irrespective of baseline VA, lesion size and central subfield thickness on OCT.

Figure 5. Vision Gained and Lost at 24 Weeks:

A greater proportion of subjects treated with Fovista® 1.5 mg/ ranibizumab gained VA (>3, >4 and >5 ETDRS lines) at 24 weeks compared to those treated with ranibizumab (upper left). In addition, a greater proportion of subjects treated with Fovista® 1.5 mg/ ranibizumab experienced better visual outcomes (20/40 or better, 20/25 or better) at 24 weeks compared to those treated with ranibizumab (upper right). A lower proportion of subjects treated with Fovista® 1.5 mg/ ranibizumab lost VA (≥1 and ≥2 ETDRS lines) or experienced poor visual outcomes (20/125 or worse and 20/200 or worse) at 24 weeks compared to subjects treated with ranibizumab at week 24 (lower panels).

Figure 9. Summary of Serious Adverse Events:

Fovista®/ranibizumab combination therapy was well tolerated. The incidence of serious adverse events (SAEs) in the Fovista® 1.5 mg/ ranibizumab arm, Fovista® 0.3 mg/ranibizumab arm, and sham/ ranibizumab arm was similar. There was a low incidence of APTC (Antiplatelet Trialists' Collaboration) events with no imbalance between groups.

Figure 7A. Biomarker Changes Associated with >3 Line Gainers - Change in CNV Size in > 3 Line Gainers at 24 Weeks:

An ad hoc supportive analysis was performed to assess change in CNV size for patients with smaller than mean area (≤ 1.62 DA) or larger than mean area (>1.62 DA) CVN at baseline. In those patients gaining > 15 ETDRS letters of VA at Week 24, the decrease in area of CNV was -0.1 DA for the Fovista® 1.5 mg/ ranibizumab arm compared to -0.01 DA for the sham/ranibizumab arm in the small CNV (upper left panel); the decrease in area of CNV was -2.33 DA for the Fovista® 1.5 mg/ ranibizumab arm compared to -0.24 DA for the sham/ranibizumab arm in the large CNV (upper right panel). A representative Fovista® 1.5 mg/ ranibizumab case is shown in the bottom panels; at baseline, note the 1.5 DA classic subfoveal CNV with some blockage from mild subretinal hemorrhage nasally (lower left panel), which decreased in size at 24 weeks (lower right panel).

Figure 7B. Biomarker Changes - Absence of Subretinal Hyper-Reflective Material in > 3 Line Gainers at 24 Weeks:

A retrospective review of OCT images was performed in patients gaining > 15 ETDRS letters of VA at Week 24. In those patients gaining > 15 ETDRS letters of VA at Week 24, SHRM was absent in 54% of those patients in the Fovista® 1.5 mg/ ranibizumab arm compared to 38% in the sham/ ranibizumab arm (upper panels). A representative Fovista® 1.5 mg/ ranibizumab case is shown in the bottom panels; at baseline, note the prominent SHRM subfoveally (lower left panel), which had resolved at 24 weeks (lower right panel).

Figure 8. OCT Analysis of Permeability Alterations at 24 Weeks:

Analysis of permeability alterations included evaluation of total macular volume, or the absence of subretinal fluid, intraretinal cystic fluid, or subRPE fluid. No meaningful difference was noted between the groups.

Figure 9. Patients with RPE Atrophy at Week 24 as Viewed on OCT:

At 24 weeks, the presence of RPE atrophy was evident in 16% in the Fovista® 1.5 mg/ ranibizumab arm, 17% in the Fovista® 0.3 mg/ ranibizumab, and 21% in the sham/ranibizumab group.

Table 1: Baseline Demographics

		Arm A **Sham/**	**Arm B** **0.3 mg Fovista®/**	**Arm C** **1.5 mg Fovista®/**	**Total Fovista®** **(0.3 mg+1.5 mg)**
	Female	93 (62.8%)	90 (60.4%)	92 (60.5%)	182 (60.5%)
Ethnicity	Hispanic / Latino	10 (6.8%)	5 (3.4%)	9 (5.9%)	14 (4.7%)
	Not Hispanic / Latino	138 (93.2%)	144 (96.6%)	143 (94.1%)	287 (95.3%)
Race	White	144 (97.3%)	145 (97.3%)	149 (98.0%)	294 (97.7%)
	Other	4 (2.7%)	4 (2.7%)	3 (2.0%)	7 (2.3%)
Iris color	Light	56 (38.1%)	56 (37.6%)	46 (30.3%)	102 (33.9%)
	Medium	68 (46.3%)	70 (47.0%)	79 (52.0%)	149 (49.5%)
	Dark	23 (15.6%)	23 (15.4%)	27 (17.8%)	50 (16.6%)
Age*	Mean	78.0	77.6	77.8	77.7
(years)	Std Dev	7.98	8.19	8.36	8.27
	Median	79.4	78.3	78.8	78.4
	Range				
Current smoking	Not Active	135 (91.2%)	128 (85.9%)	134 (88.7%)	262 (87.3%)
status	Active	13 (8.8%)	21 (14.1%)	17 (11.3%)	38 (12.7%)
Study eye	OD	71 (48.0%)	70 (47.0%)	77 (50.7%)	147 (48.8%)
	OS	77 (52.0%)	79 (53.0%)	75 (49.3%)	154 (51.2%)
Total Lesion Size	Disk Areas	1.8	1.9	1.5	1.7

* Age at randomization. ITT population

Appendix 1

Inclusion Criteria

Ophthalmic Inclusion Criteria

The following inclusion criteria applied to the study eye:

1. Subfoveal choroidal neovascularization (CNV) due to AMD with some classic Component (i.e., predominantly classic or minimally classic) as documented by fluorescein angiogram.

2. Best corrected visual acuity in the study eye between 20/63 and 20/200, inclusive. The VA had to be re-confirmed at Day 0 prior to randomization.

3. Total area of the lesion (including blood, neovascularization, and scar/atrophy) was ≤ 5 disc areas (DA), of which at least 50% had to be active CNV. Active CNV was defined as the neovascular component of the lesion as defined by the fluorescein angiogram.

4. Presence on OCT of subretinal, intraretinal or sub-RPE fluid and/or subretinal thickening consistent with active CNV.

5. Clear ocular media and adequate pupillary dilatation to allow collection of fundus photographs and fluorescein angiograms of a sufficient quality to be analyzed by the central reading center.

6. Intraocular pressure (IOP) of 21 mmHg or less.

General Inclusion Criteria

1. Subjects of either gender, ≥50 or more years.

2. Performance Status ≤2 according to Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale.

3. Women had to agree to use two forms of effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test had to be performed within 14 days prior to the first injection with a negative result. The two forms of effective contraception had to be implemented during the trial and for at least 60 days following the last dose of test medication.

4. Adequate hematological function: hemoglobin ≥10g/dL; platelet count ≥130 x 109/L; WBC ≥3.8 x 109/L. Subjects with results outside these ranges might be enrolled in consultation with Ophthotech.

5. Adequate renal function: serum creatinine ≤2.5 mg/dl (≤ 221μmol/L) and BUN within 2 x the upper limit of normal (ULN). Subjects with results outside these ranges might be enrolled in consultation with Ophthotech.

6. Adequate liver function: serum bilirubin ≤1.5 mg/dl (≤ 25.6 μmol/L), GGT, SGOT/ALT, SGPT/AST, and alkaline phosphatase within 2 x ULN. Subjects with results outside these ranges might be enrolled in consultation with Ophthotech.

7. Provide written informed consent.

8. Ability to comply with study and follow-up procedures and return for all trial visits.

Exclusion Criteria

Ophthalmic Exclusion Criteria

1. Any prior treatment for AMD in the study eye prior to the baseline visit, except oral supplements of vitamins and minerals.

2. Any prior intravitreal treatment in the study eye prior to the baseline visit, regardless of

indication (including intravitreal corticosteroids).

3. More than 25% of the total lesion size made up of scarring or atrophy. Subjects with subfoveal scar or subfoveal atrophy were excluded.

4. More than 50% of the total lesion size consisting of subretinal hemorrhage.

5. Presence of retinal angiomatous proliferation (RAP).

6. Presence of significant serous pigment epithelial detachments (PEDs) such as large PEDs that constitute greater than 50% of the total lesion.

7. Presence of pigment epithelial tears or rips.

8. Presence of intraocular inflammation (≥ trace cell or flare), significant epiretinal membrane or vitreomacular traction, macular hole or vitreous hemorrhage.

9. Aphakia or absence of the posterior capsule. Absence of an intact posterior capsule was allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation.

10. History of idiopathic or autoimmune-associated uveitis in either eye.

11. Significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, or fundus photography in the study eye. Subjects were not to be entered if there was likelihood that they would require cataract surgery in the study eye in the next 12 months.

12. Presence of other causes of choroidal neovascularization, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25mm or more), the ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.

13. Any intraocular surgery or thermal laser within three (3) months of trial entry. Any

prior thermal laser in the macular region, regardless of indication.

14. Any ocular or periocular infection in the past twelve (12) weeks.

15. History of any of the following conditions or procedures in the study eye: Rhegmatogenous retinal detachment, pars plana vitrectomy, filtering surgery (e.g. trabeculectomy), glaucoma drainage device, corneal transplant.

16. Previous therapeutic radiation in the region of the study eye.

General Exclusion Criteria

1. Any of the following underlying diseases including:

- Diabetes mellitus, also defined as an HbA1c level ≥ (greater than or equal to) 6.5%.
- History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or coronary artery revascularization within 6 months, or ventricular tachyarrythmias requiring ongoing treatment.
- Clinically significant impaired renal (serum creatinine >2.5 mg/dl or s/p renal
- transplant or receiving dialysis) or hepatic function.
- Stroke (within 12 months of trial entry).
- Any major surgical procedure within one month of trial entry.

2. Any treatment with an investigational agent in the 60 days prior to randomization for any condition.

3. Known serious allergies to the fluorescein dye used in angiography (mild allergy amenable to treatment was allowable), to the components of the ranibizumab

formulation, or to the components of the Fovista® formulation.

Appendix 2: Imaging Protocols

Optical Coherence Tomography Scan Protocols and Grading Methodology

Study sites were certified by the Duke Reading Center to obtain time domain or spectral domain optical coherence tomography (SD-OCT) scans according to a standardized study protocol. Images were obtained at each site from a Stratus (Carl Zeiss Meditech), Dublin CA), Spectralis (Heidelberg Engineering, Heidelberg Germany) or Cirrus (Carl Zeiss Meditec) system.

On each participant for whom images were obtained on the Stratus System, the following scan patterns were obtained on each eye: A fast macular thickness map comprising 6 radial scans spaced 30^0 from one another that covered a circle with diameter 6 mm area of the macula centered on the foveal centerpoint, and a macular thickness map comprising 6 radial scans spaced 30^0 from one another that covered a circle with diameter 6 mm area of the macula centered on the foveal centerpoint were used to image the neurosensory retinal layers and vitreoretinal interface.

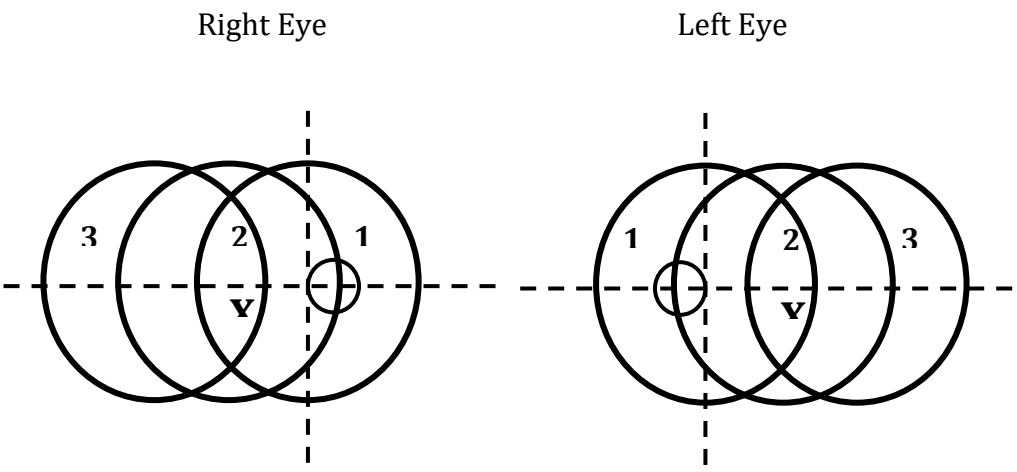
On each participant for whom images were obtained on the Spectralis System, the following scan patterns were obtained on each eye: A 49 line high speed pre-set scan covering a 20^0X20^0 area of the macula centered on the foveal centerpoint, in high speed mode with ART setting of 9 was used to image the neurosensory retinal layers and vitreoretinal interface; a 7 line high resolution preset scans pattern covering a 30^0 $X5^0$ area centered on the foveal centerpoint in high resolution mode was used to assess the central macula.

On each participant for whom images were obtained on the Cirrus System, the following scan patterns were obtained on each eye: A 512 X 128 macular cube covering a 6 mm X 6 mm square area of the macula centered on the foveal centerpoint, was used to image the neurosensory retinal layers and vitreoretinal interface; a 5 line raster (HD) preset raster scan pattern centered on the foveal centerpoint was used to assess the central macula.

All study OCT scans were submitted to the Duke Reading Center (Duke University, Durham, NC) for grading. Two certified readers in a masked and independent manner determined quantitative thickness parameters and made morphological assessments on coded scans for each subject. A data specialist entered all concordant values from the two readers into the trial database and flagged discrepant values. A third certified Senior Reader arbitrated the discrepant values. The senior reader reconciled all reader disagreements according to his best judgment and expertise, recording his decision as the final arbitrated value that the data specialist entered into the trial database. Each OCT categorical variable was graded as *present*, *absent*, or *unreadable* (due to poor quality or centration of the scan), according to either the agreed decision between masked readers or the arbitrated decision when the readers disagreed.

Fundus Photography and Fluorescein Angiography Acquisition Protocol and Grading methodology

Certification and study stereo color fundus photographs and Fluorescein angiograms were obtained according to a standard modified 3-field protocol at a 30-40^0 setting, as shown below:



Early, mid, and late field 2 fluorescein angiograms fluorescein angiograms were obtained on the study eye and fellow eye, and 3-field color fundus photographs were obtained on study and fellow eyes. In addition, stereo external photographs were obtained. Calibration images were obtained on a model eye to calibrate site digital cameras as part of the certification process.

All study color fundus photographs and fluorescein angiograms were submitted to the Duke Reading Center (Duke University, Durham, NC) for grading. Two certified readers in a masked and independent manner determined total lesion size, and size of individual lesion components. A third certified Senior Reader arbitrated discrepant values, as described above for OCT images.

Appendix 3

Laboratory Tests

- Hematology: hemoglobin, platelet count, WBC and differential
- Renal Function: serum creatinine and BUN
- Hepatic function: serum bilirubin, alkaline phosphatase, GGT, SGOT/AST AND
- SGPT/ALT
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium, and phosphate
- Serum pregnancy test (if of child-bearing potential)