Protocol Title: A Phase I/II Trial for Intravitreous Treatment of Severe Ocular von Hippel-Lindau Disease Using a Combination of the PDGF Antagonist E10030 and the VEGF Antagonist Ranibizumab

Abbreviated Title: ER-VHL

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Total Requested Accrual:

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0 Healthy Volunteers

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PROTOCOL ABBREVIATION LIST

≥	Greater Than or Equal To
µL	Microliter
AE	Adverse Event
AMD	Age-related macular degeneration
ATE	Arterial thromboembolic event
BCVA	Best-corrected visual acuity
CBC	Complete blood count
CC	Clinical Center
CD	Clinical Director
CRADA	Cooperative Research and Development Agreement
DME	Diabetic macular edema
DoH	Declaration of Helsinki
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
EVA	Electronic visual acuity
FA	Fluorescein angiography
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
HIF	Hypoxia inducible factor
HRPP	Human Research Protection Program
IOP	Intraocular pressure
IRB	Institutional Review Board
mL	Milliliter
Mm	Millimeter
NCI	National Cancer Institute
NEI	National Eye Institute
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurologic Disorders and Stroke
NVAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
OHSRP	Office of Human Subject Research Protection
PDGF	Platelet-derived growth factor
PDGFR-β	PDGF Receptor-β
PDT	Photodynamic therapy
PI	Principal Investigator
pVHL	VHL protein
RCH	Retinal capillary hemangioma(s)
SAE	Serious Adverse Event
SOP	Standard operating procedure
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau

PRÉCIS

Objective: Von Hippel-Lindau (VHL) disease is an autosomal dominant heritable disorder in which multiple benign and malignant neoplasms and cysts of specific histopathologies develop in the kidney, adrenal gland, pancreas, brain, spinal cord, eye, inner ear, epididymis and broad ligament. The disease affects about 7,000 individuals in the United States. Retinal capillary hemangiomas (RCH) are the most common and often the earliest manifestation of VHL disease and may lead to significant vision loss. In some such eyes, inexorable progression of RCH leads to blindness and phthisis bulbi despite aggressive treatment. Levels of vascular endothelial growth factor (VEGF), a potent mediator of angiogenesis and vascular permeability, have been shown to be elevated in multiple cell types deficient in the VHL protein (pVHL). Platelet-derived growth factor (PDGF), which has an important role in stabilization of immature new vessels during angiogenesis, is upregulated in pVHL-defective cell lines and expressed in other pVHL-defective tumors. Anti-VEGF therapy alone had no beneficial effect on ocular VHL disease in two previous phase 1 studies. The objective of this study is to investigate the safety and possible efficacy of combination investigational treatment with serial intravitreal injections of E10030, a PDGF-B antagonist, and ranibizumab, a VEGF-A antagonist, in participants with severe ocular VHL disease.

Study Population: Three participants with severe ocular VHL disease will receive the combination investigational treatment in one eye and will be followed for 104 weeks.

Design: In this phase I/II, single-center, prospective, open label, non-randomized, uncontrolled, single group trial, one eye of eligible participants will be treated with investigational products, E10030, a PDGF-B antagonist, and ranibizumab, a VEGF-A antagonist. Participants will receive combination investigational treatment consisting of intravitreal injections of E10030 (1.5 mg in 0.05 mL) and ranibizumab (0.5 mg in 0.05 mL) every four weeks from baseline through Week 16 (totaling five treatments) and then every eight weeks through Week 48 (totaling nine treatments from baseline). All participants will be followed for 104 weeks.

Outcome Measures: The primary outcome for the study will be safety of the combination investigational treatment, assessed by tabulation of adverse events (AE) reported through Week 52. Secondary outcomes will include tabulation of AEs at Week 104, and the following

measures in the study eye at Week 52 and 104: the proportion of participants experiencing reduction in size of at least one RCH in the absence of other ablative treatment (assessed by fundus photography and fluorescein angiography [FA]); the proportion of participants experiencing moderate vision loss (defined as a loss of ≥ 15 letters from baseline on Electronic Visual Acuity [EVA] testing); mean change in visual acuity; change in size of RCH (measured by fundus photography and FA); change in exudation (measured by fundus photography, optical coherence tomography [OCT] and FA); change in epiretinal proliferation, fibrosis or retinal traction (assessed by OCT and fundus photography); proportion of participants undergoing ablative treatment of RCH or ocular surgery; proportion of participants with successful ablative treatment of RCH; and the proportion of participants with appearance of one or more new RCH.

1.0 INTRODUCTION/SCIENTIFIC RATIONALE

1.1 VHL Disease

VHL disease is an autosomal dominant heritable disorder in which multiple benign and malignant neoplasms and cysts of specific histopathologies develop in the kidney, adrenal gland, pancreas, brain, spinal cord, eye, inner ear, epididymis and broad ligament. VHL disease arises from germ line mutations in the VHL tumor suppressor gene at chromosome 3p25-26. Incidence is approximately one in 40,000 to one in 54,000 live births, with prevalence of approximately 7,000 affected individuals in the United States.[1]

The two proteins encoded by the VHL gene, designated together as pVHL, play a key role in the cellular response to varying levels of oxygen. Under normoxic conditions, pVHL serves as the substrate-binding subunit of an ubiquitin ligase complex that targets the alpha subunit of the transcription factor hypoxia inducible factor (HIF) for proteasomal degradation through polyubiquitylation.[2,3,4] HIF is a master transcription regulator for over a hundred genes, important for adaptation and survival of cells in the setting of hypoxia. In VHL disease, germline mutation in one allele of the VHL gene, followed by somatic loss of the remaining allele in a vulnerable cell, results in unchecked activity of HIF under normoxic conditions and consequent transcription of a wide variety of growth factors and cytokines stimulating anaerobic metabolism, cell proliferation, angiogenesis and cell survival. pVHL possesses other functions independent of the HIF signaling pathway; for example, it exerts effects on the primary cilium of the cell and on the extracellular matrix.[5] Both HIF-dependent and HIF-independent effects may contribute to the tumor suppressor activity of pVHL in various cell types.

1.2 Ocular VHL Disease

Retinal capillary hemangiomas (RCH) are the most common and often the earliest manifestation of VHL and may lead to significant vision loss.[1] Arising within the neurosensory retina and composed of endothelial cells, pericytes and foamy stromal cells, RCH are benign lesions classified by their location in the retina (juxtapapillary or peripheral) and by their morphology (endophytic, exophytic or sessile).[6] Though RCH can remain stable for years or even rarely spontaneously regress, the majority enlarge. Small RCH appear as a subtle red or grayish lesion of the neurosensory retina; early juxtapapillary lesions are more variable in appearance.

With growth, many RCH develop one or more dilated and tortuous feeding arterioles and draining venules, though juxtapapillary RCH often do not. RCH demonstrate a variable amount of vascular leakage and exudation, manifesting as intraretinal edema, lipid deposition, exudative retinal detachment or hemorrhage. Though early leakage is usually confined to the retina in proximity to the RCH, the macula can become affected with resulting decrease in vision. Epiretinal fibrous proliferation stimulated by the RCH can develop. Fibrovascular proliferation, similar in some respects to the retinal neovascularization that occurs in ischemic retinopathies, can appear in the presence or absence of RCH. Vision loss can result from intraretinal and subretinal exudation and lipid deposition, epiretinal fibrous or fibrovascular proliferation resulting in macular pucker or tractional retinal detachment, or intraocular hemorrhage.

The goal of treatment for RCH is ablation of the lesion, resulting in cessation of exudation, hemorrhage and epiretinal proliferation.[6] Choice of ablative treatment depends on the location and size of the lesions. Small (< 1.5 mm in diameter) peripheral RCH are readily treated with thermal laser photocoagulation. Larger (1.5 – 3.0 mm in diameter) peripheral RCH can be treated with laser photocoagulation, but often respond more readily to trans-scleral cryotherapy. Cryotherapy causes more inflammation and post-treatment exudation than laser photocoagulation, and this can lead to retinal detachment and epiretinal scarring in some cases. Still larger lesions (> 3.0 mm) are more difficult to treat, especially if associated with significant exudation, hemorrhage or fibrosis. Episcleral brachytherapy and external beam radiotherapy have been employed with limited success. Photodynamic therapy (PDT) has also been used for refractory tumors, both juxtapapillary and peripheral, with mixed results. In some reported cases, PDT may help stabilize tumor size and exudation.[7,8,9] Vitreoretinal surgery is used as an adjunct to ablative therapy in order to address vision-threatening epiretinal proliferation, tractional or rhegmatogenous retinal detachment, or vitreous hemorrhage.[1] RCH arising in proximity to the optic nerve head and/or macula represent a particularly problematic subset of lesions because of the risk of iatrogenic vision loss from present ablative modalities.[10] RCH refractory to one or more sessions of laser photocoagulation and/or cryotherapy are also problematic, particularly when large in size or in the setting of substantial regions of retinal vascular incompetence with or without exudative and/or tractional retinal detachment. Even small and medium-sized RCH can be hazardous to treat with laser and cryotherapy in the setting of multiple tumors; evolving hyaloid or epiretinal condensation and traction; or chorioretinal scarring from previous ablative attempts.

1.3 Vascular Endothelial Growth Factor (VEGF) in VHL Disease

The highly vascular nature of tumors in VHL disease suggest that VEGF, a HIF-inducible factor and potent mediator of angiogenesis and vascular permeability, might be important in the evolution of both the benign and malignant lesions found in this disease. Renal carcinoma cell lines defective for pVHL manifest increased production of VEGF mRNA and protein, and show a corresponding decrease when pVHL function is restored.[11] VEGF protein levels are elevated in pathologic specimens from renal carcinomas exhibiting mutations of the VHL gene.[12] Neutralizing antibodies to VEGF reduce rates of progression among patients with advanced clear cell renal carcinoma, in which sporadic tumors harbor frequent inactivation of pVHL.[13,14] VEGF messenger RNA is upregulated in the hepatic cavernous hemangiomas seen in mice heterozygous for VHL mutation.[15] pVHL-defective cell lines derived from central nervous system hemangioblastomas and RCH have not been developed. However, analysis of pathologic specimens has revealed increased VEGF production.[16,17,18] Vacuolated stromal cells in VHL-associated RCH exhibit high levels of VEGF messenger RNA and protein. Finally, VEGF upregulation has been shown to lead to tumor hypervascularity in C6 glioma xenografts engineered to overexpress VEGF.[19]

Administration of VEGF antagonists has been evaluated in ocular VHL not amenable or refractory to standard ablative treatment. Dahr et al. evaluated use of intravitreal injections of pegaptanib sodium (3 mg) in five patients with VHL manifesting juxtapapillary or large peripheral RCH.[20] Pegaptanib sodium, a pegylated aptamer antagonizing the $VEGF_{165}$ isoform, was administered every six weeks for at least six injections, and two of five patients completed the course of treatment and one year of follow-up. These two patients experienced a decrease in RCH-associated exudation, but no change in size of the tumors. The other three patients demonstrated progression of ocular disease and did not complete the course of treatment.

Wong et al. (NCT00089765) studied use of intravitreal ranibizumab in five patients with RCH not amenable or responsive to standard treatments.[21] Ranibizumab (0.5 mg), a humanized monoclonal antibody fragment binding all VEGF-A isoforms, was given every four weeks for six months, with additional treatment considered through 12 months. Participants received a mean of 10 injections over an average of 47 weeks. Visual acuity decreased by nine (± 20) letters and there was no consistent improvement in RCH exudation or tumor size. No SAEs were reported. The only related AE consisted of transient eyelid edema and erythema immediately following an injection.

No VEGF antagonist, administered intravitreally at doses sufficient to produce measurable biologic effects in other ocular diseases, has produced regression of VHL-associated RCH. Regression of pathologic neovascularization in other retinal diseases, such as neovascular age-related macular degeneration (NVAMD) and proliferative diabetic retinopathy, is often incomplete in the setting of VEGF antagonism. Experimental models suggest that an important factor limiting regression of neovascularization in response to VEGF antagonists and other anti-vascular treatments may be the maturity of new vessels.[22,23,24] Immature vessels often regress in the setting of VEGF blockade, while more mature vessels frequently do not. Limitations in the efficacy of VEGF antagonism in the treatment of cancer have led to consideration of pleiotropic inhibitors and combination therapies targeting multiple factors.[2,25,26] The search for agents capable of rendering pathologic vessels and tumors more susceptible to anti-VEGF therapy has led to consideration of PDGF blockade.

1.4 PDGF in Angiogenesis and in VHL Disease

An important pathway for stabilization of immature new vessels during angiogenesis involves release of PDGF-B by endothelial cells to attract PDGF receptor-β (PDGFR-β) positive mural cells.[27,28,29] PDGF-B – PDGFR-β signaling leads to mature capillaries invested with pericytes, which maintain an intimate supportive role with associated endothelial cells. Tissue-specific knock-out of PDGF-B and PDGFR-β shows reduction in pericyte populations, particularly in the central nervous system.[30,31] The retinal microvasculature shows a higher pericyte density than any other capillary bed, and an endothelium-specific PDGF-B mouse knock-out model has demonstrated capillary regression and retinal vascular proliferative lesions in retinas with pericyte counts less than 50 percent of normal. Neutralizing PDGFR-β antibodies disrupt normal capillary development in the mouse via effects on pericytes.[30,32]

pVHL has been shown to reduce expression of PDGF-B messenger RNA via a specificity protein 1 (Sp1)-mediated pathway, and PDGF expression is upregulated by HIF.[33,34] Co-expression of PDGFR-α and PDGFR-β has been demonstrated in the endothelial cells of central nervous system hemangioblastoma.[35] No analysis of RCH for expression of PDGF or its receptors has been reported, but the upregulation of PDGF in pVHL-defective cell lines, the expression of PDGF in other pVHL-defective tumors, and the hypervascular nature of RCH suggest that PDGF signaling may play an important role in pathogenesis of these ocular lesions.

1.5 Combined Inhibition of VEGF and PDGF

Study of angiogenesis in the context of development, wound healing and tumorigenesis has provided insight into the roles of VEGF and PDGF in controlling the growth and maturation of new blood vessels.[28] Pericytes recruited by PDGF have been demonstrated to promote survival of nearby endothelial cells by secretion of VEGF and other factors. In vitro studies have shown that pericytes release VEGF-A sensed by nearby endothelial cells.[36] Mural cells surrounding tumor vessels secrete VEGF-A.[37,38] Tumor vessels that lack pericytes are more dependent on VEGF-A for survival than vessels that have them.[22,24] Such observations have led to the hypothesis that pericyte-endothelial cell interactions may confer resistance of new vessels to VEGF blockade, and that combined antagonism of PDGF and VEGF pathways jointly targeting pericytes and endothelial cells may offer a strategy for circumventing such resistance. Investigation of this hypothesis in some models of tumorigenesis suggests the possible efficacy of this approach.[39,40]

The merits of combined blockade of VEGF and PDGF pathways have also been evaluated in pathologic ocular neovascularization. Jo et al. studied the effects of inhibiting PDGF-B, VEGF-A or both in murine models for corneal neovascularization and choroidal neovascularization.[41] PDGF-B antagonism, achieved with a monoclonal antibody (APB-5) against murine PDGFR-β, did not show appreciable effects on neovascularization in either model when used alone. VEGF-A inhibition, achieved using pegaptanib, resulted in a reduced area of new blood vessels in both models. But, combination treatment using both antagonists showed a significantly greater reduction in new blood vessel area in both models compared to VEGF inhibition alone.

1.6 VEGF-A Antagonist Ranibizumab and PDGF-B Antagonist E10030 for Treatment of NVAMD

Present treatment for NVAMD consists of intravitreal injections with the VEGF-A antagonists ranibizumab, bevacizumab and aflibercept. Ranibizumab was FDA-approved for treatment of NVAMD in 2006 on the basis of efficacy and safety demonstrated in randomized controlled clinical trials.[42,43,44] Studies and clinical experience have shown that serial ranibizumab injections reduce exudation from pathologic vessels, but frequently do not cause neovascularization to disappear.[45,46] A significant proportion of eyes receiving ranibizumab for NVAMD demonstrate incomplete resolution of exudation with monthly injections, or recurrence of growth and leakage

from neovascularization when ranibizumab is withheld, prompting search for supplemental agents offering more definitive treatment. The efficacy of combination investigational treatment of NVAMD with intravitreal injections of the VEGF-A antagonist ranibizumab and the investigational PDGF-B antagonist E10030 is presently under study in two phase 3 clinical trials (designated as OPH1002 and OPH1003 in the Ophthotech Corp. Investigator Brochure, v5.0, February 29, 2016).

The active moiety of E10030 is an aptamer, a novel class of oligonucleotide-based therapeutic agents. Specifically, E10030 is a pegylated aptamer containing 32 monomeric units (32-mer) arranged as a linear sequence of three oligonucleotide segments connected by non-nucleotide hexaethylene glycol spacers. E10030 binds to PDGF-B with high specificity and affinity and inhibits the functions of PDGF-B both in vitro and in vivo. Specifically, E10030 binds selectively to PDGF-BB and to PDGF-AB heterodimers and, with reduced affinity, to the PDGF-AA homodimer.

Vitreous humor concentrations of E10030 have been shown to decline in an apparent first order process with elimination half-lives of approximately three days in rabbits and two days in dogs. Following an IV bolus dose, E10030 was eliminated from plasma in an apparent first-order process with an elimination half-life of approximately three hours in rats, 30 to 50 minutes in rabbits and 16 minutes in dogs. The E10030 volume of distribution was approximately equal to the plasma volume of the animal.

There were no significant ocular or systemic safety issues identified during the E10030 nonclinical toxicology program. Chronic intravitreal studies in dogs (nine months) and rabbits (six months) have been completed, and no ocular or other effects of E10030 were observed at the highest dose levels tested, which were 1.5 and 3.0 mg/eye, respectively. These dose levels were the maximum that could be administered based on limitations of E10030 solution viscosity and intravitreal injection volumes for each species. When adjusted for the relative differences in vitreous volume across species (i.e., between the animal species and humans), these no-effect levels are equivalent to human doses of 4.5 mg/eye (for both species). There was also no indication of any adverse interaction with an anti-VEGF agent (i.e., pegaptanib sodium or ranibizumab) when co-administered in the intravitreal studies.

A phase 1, dose-escalating, uncontrolled, multiple-dose, multicenter clinical study (OPH1000) was completed in 0patients with subfoveal neovascular lesions secondary to age-related macular degeneration.[47] Subjects were enrolled in a dose escalation scheme to three monthly intravitreal injections of E10030 (0.03, 0.3, 1.5 or 3.0 mg/eye) in combination with ranibizumab 0.5 mg. Twenty-two subjects who met the inclusion/exclusion criteria were enrolled in this study. One additional subject who did not meet criteria was discontinued shortly after entry into the study, and therefore a total of 23 patients were included in the safety database for the study.

A progressive improvement of visual acuity and a decrease in macular thickness were noted at all time points. Visual acuity results showed 8 (36%), 10 (45%) and 13 (59%) subjects gaining ≥ 15 letters at Weeks 4, 8 and 12, respectively. Analysis of FA by independent readers revealed a mean decrease in choroidal neovascularization (CNV) area of 86% at Week 12 compared to baseline.

There was no evidence of drug-related AEs and no dose limiting toxicities were identified. Twenty-one patients (91%) experienced at least one AE and 18 patients (78%) experienced at least one ocular AE in the study eye. Almost all study eye AEs were considered to be related to the injection procedure. No study eye AEs were assessed to be related to E10030 or ranibizumab administration. The most frequently occurring study eye AEs were foreign body sensation in eyes (six patients, 26%), conjunctival hemorrhage (five patients, 22%), eye irritation (four patients, 17%) and punctate keratitis (three patients, 13%). Other ocular AEs reported by more than one patient were anterior chamber cells (trace), conjunctival edema and myodesopsia (floaters) (each reported by two patients, 9%). The majority of AEs were mild in severity. There was only one SAE (atrial fibrillation) reported by a patient in the 0.3 mg dose group; the event was unrelated to study drugs or injection procedure.

Recently, a phase 2b, randomized, prospective, double-masked, sham-controlled trial using combination investigational treatment with E10030 and ranibizumab (OPH1001) has been completed in patients with subfoveal neovascular lesions secondary to AMD. Patients received six monthly intravitreous injections of E10030 given in combination with ranibizumab. In this multicenter study, 449 patients were randomly assigned in a 1:1:1 ratio to the following dose

groups: E10030 0.3 mg/eye + ranibizumab 0.5 mg/eye, E10030 1.5 mg/eye + ranibizumab 0.5 mg/eye or E10030 sham + ranibizumab 0.5 mg/eye.

E10030 (1.5 mg) combination investigational treatment resulted in superior visual outcome compared to ranibizumab alone at the Week 24 time point. The combination of E10030 (1.5 mg) and ranibizumab (0.5 mg) met the pre-specified, alpha protected primary endpoint of superiority in mean visual acuity gain compared to ranibizumab alone (10.6 ETDRS letters at Week 24, compared to 6.5 letters, p=0.019). Fluorescein angiography and OCT studies confirmed marked disease modification (neovascular regression).

Combination investigational treatment was well tolerated. The most common ocular AEs were, as expected in intravitreal studies, related to the intravitreal preparation and injection procedure and not drug-related, e.g., conjunctival hemorrhage, punctate keratitis and eye pain. There were no events of endophthalmitis, retinal detachment, retinal tear or iatrogenic traumatic cataract after a total of 4431 intravitreal injections (1776 administrations of E10030 and 2655 administrations of ranibizumab). As expected, the mean Intraocular pressure (IOP) increased after each intravitreal injection consistent with the volume effect. However, mean IOP in all arms returned to pre-injection level at the next visit, including at the end of the study. The systemic safety profile of E10030/ranibizumab was similar to that of ranibizumab alone.

1.7 Treatment of Severe Ocular VHL Disease with Intravitreal Injections of E10030 and Ranibizumab

This is a phase I/II study designed to evaluate the safety and possible efficacy of combination intravitreal investigational treatment using E10030 and ranibizumab for severe ocular VHL disease. The prognosis for eyes with ocular VHL disease not amenable or refractory to standard therapies is poor, and the morbidities of any intervention, such as ablation of RCH in proximity to the optic nerve or macula, vitreoretinal surgery, cryotherapy or ocular radiation, are substantial. In such eyes, inexorable progression of disease leads to blindness and phthisis bulbi. Serial ranibizumab injections alone do not lead to RCH regression or any consistent decrease in tumor exudation, but have shown a reasonable safety profile in a pilot study.[21] There is a reasonable scientific rationale for the potential efficacy of combined VEGF and PDGF blockade in treatment of RCH, based on knowledge of the molecular biology of pVHL-defective cells and present

understanding of angiogenesis in the setting of neoplasia. The investigational agent E10030 has not been studied in eyes with ocular VHL, but has shown a reasonable safety profile alone and in combination with ranibizumab or pegaptanib sodium in pre-clinical studies; furthermore, no significant safety concerns were apparent in phase I and phase II studies evaluating combination investigational treatment with E10030 and ranibizumab for NVAMD.

Based on preliminary evidence for safety and efficacy in people with exudative AMD, and supportive evidence from animal studies, the 1.5 mg dose of E10030 has been selected for use in this phase 1/2 trial. The 0.5 mg dose of ranibizumab chosen for use in this trial is the same as that used in previous combinational therapy trials with E10030, and is the FDA-approved dose for treatment of neovascular AMD and macular edema following retinal vein occlusion.

2.0 STUDY OBJECTIVE

The objective of this study is to investigate the safety and possible efficacy of combination investigational treatment with serial intravitreal injections of E10030, a PDGF-B antagonist and ranibizumab, a VEGF-A antagonist, in participants with severe ocular VHL disease.

3.0 PARTICIPANTS

Three participants with severe ocular VHL disease who meet the eligibility criteria will receive the combination investigational treatment in one eye and will be followed for 104 weeks. Inclusion and exclusion criteria are listed below.

3.1 Participant Eligibility Criteria

The participant must meet all of the eligibility criteria and none of the exclusion criteria below.

3.1.1 Inclusion Criteria

1. Participant must understand and sign the informed consent.
2. Participant must be 18 years of age or older.
3. Participant must have a diagnosis of VHL disease. In accordance with established criteria for diagnosis,[48,49] any one of the following will be considered sufficient evidence that VHL disease is present:

- A family history of VHL disease plus one or more of the following lesions: RCH, spinal or cerebellar hemangioblastoma, pheochromocytoma, multiple pancreatic cysts, epididymal or broad ligament cystadenomas, multiple renal cysts or renal cell carcinoma before age 60 years.
- Presence of two or more hemangioblastomas of the retina or brain or a single hemangioblastoma in association with a visceral manifestation such as kidney or pancreatic cysts; renal cell carcinoma; adrenal or extra-adrenal pheochromocytomas; endolymphatic sac tumors; papillary cystadenomas of the epididymis or broad ligament; or neuroendocrine tumors of the pancreas.
- Presence of a known disease-causing germline mutation in the VHL gene.

4. Any female participant of childbearing potential (see Appendix 1 for definition) must not be pregnant or breast-feeding, must have a negative pregnancy test at screening and must be willing to undergo pregnancy testing immediately prior to each treatment.
5. Any female participant of childbearing potential (see Appendix 1 for definition) and any male participant able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, be completely abstinent from intercourse or must agree to practice two effective methods of contraception throughout the course of the study and for at least two months following the last administration of combination investigational treatment. Acceptable methods of contraception include:
    - hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring),
    - intrauterine device,
    - barrier methods (diaphragm or condom) with spermicide, or
    - surgical sterilization (hysterectomy, tubal ligation or vasectomy).

3.1.2 Exclusion Criteria

1. Participant has a history or evidence of significant cardiac disease (for example, use of cardiac medications aside from agents to control blood pressure, past acute coronary syndrome, past myocardial infarction, past revascularization procedure or arrhythmias requiring past or present treatment).

2. Participant has a history of stroke or transient ischemic attack. *Note: cerebrovascular manifestations and/or complications of central nervous system hemangioblastomas are not exclusionary, in the absence of past stroke or transient ischemic attack.*
3. Participant has used systemic medication with significant anti-VEGF or anti-PDGF activity within 30 days of study entry or expects use of such a medication within 12 months of study entry.
4. Participant is medically unable to comply with study procedures or follow-up in the judgment of the investigator.
5. Participant has a diagnosis of diabetic mellitus (type 1 or type 2). Any one of the following will be considered sufficient evidence that diabetes is present:
    - Current regular use of insulin for the treatment of diabetes,
    - Current regular use of oral anti-hyperglycemia agents for the treatment of diabetes,
    - Hemoglobin A1C of $\geq 6.5\%$, or
    - Documented diabetes by ADA and/or WHO criteria.

3.2 Study Eye Eligibility Criteria

The participant must have at least one eye meeting all inclusion criteria and none of the exclusion criteria listed below.

3.2.1 Inclusion Criteria

1. Participant has at least one RCH secondary to VHL disease in the study eye that fulfills the following criteria:
    a. The RCH must exhibit growth potential with consequent threat to vision. Growth potential with consequent threat to vision is defined by AT LEAST ONE of the following:
        i. Associated intra- or sub-retinal exudation or lipid deposition that, in the judgment of the investigator, reflects ongoing vascular incompetence and is

not solely reflective of residual changes following previous treatment or solely secondary to coexistent retinal traction.

ii. Increased size of the tumor compared to a previous time point as assessed by fundus photography or FA.

iii. Associated intra-, sub- or pre-retinal hemorrhage not secondary to previous treatment, as assessed by fundus photography or FA.

iv. The presence of dilated and/or tortuous feeder vessels.

v. Vitreous cell or haze indicative of vitreous exudation, in the absence of other ocular features potentially responsible for such findings.

b. The RCH, in the judgment of the investigator, is NOT readily treatable using thermal laser because of its size, posterior location, poor previous response to conventional therapy, association with significant exudation, epiretinal proliferation, associated vascular abnormalities such as vascular proliferation or diffusely incompetent retinal vessels, or other factors predictive of a poor response to standard of care approaches.

2. The study eye must have clarity of ocular media and degree of pupil dilation sufficient to permit adequate fundus photography.

3.2.2 Exclusion Criteria

1. The study eye has present or chronic ocular or periocular infection (including any history of ocular herpes zoster).
2. The study eye has chronic glaucoma; OR has received anti-glaucoma medication at any time within 90 days of study entry; OR has significant ocular hypertension, defined as documented intraocular pressure of ≥ 28 mmHg on any occasion in the absence of self-limited acute glaucoma, OR ≥ 24 mmHg on at least two occasions in the absence of self-limited acute glaucoma. *Note: History of self-limited acute glaucoma in a study eye, if now resolved and not expected to recur, is not exclusionary. History of glaucoma or ocular hypertension in the fellow eye, if not felt to significantly impact risk of glaucoma in the study eye, is not exclusionary.*
3. The study eye has undergone any surgical procedure within 60 days prior to study entry (inclusive of cryotherapy or thermal laser).

4. The study eye has a history of intravitreal injection of an anti-VEGF agent (such as bevacizumab, ranibizumab or aflibercept) within 42 days prior to study entry.
5. The study eye has a history of intravitreal or periocular injection of long-acting corticosteroids (such as triamcinolone acetonide) within 90 days of study entry or history of any sustained-release ocular drug delivery device with reasonable expectation of residual activity in the study eye.

3.2.3 Choice of Study Eye in Cases of Bilateral Eligibility

If both eyes of a participant meet the criteria described in Sections 3.2.1 and 3.2.2 above, the investigator will choose to enroll one eye in consultation with the participant.

4.0 STUDY DESIGN AND METHODS

This is a phase I/II, single-center, prospective, open label, non randomized, uncontrolled, single group trial investigating the safety and potential efficacy of combined treatment of severe ocular VHL disease with serial intravitreal injections of E10030 and ranibizumab.

4.1 Recruitment

Most of the participants for this study can be recruited from the current patient population with ocular VHL disease at the National Eye Institute (NEI) and other institutes within NIH, including the National Institute of Neurologic Disorders and Stroke (NINDS) and the National Cancer Institute (NCI). The study may also rely on referrals from outside physicians at Kaiser Permanente, the support group of the VHL Alliance and other national clinical sites. If any recruitment materials are used, IRB-approval will be obtained prior to distribution. It is anticipated that all participants will be recruited within 12 months of activation.

4.2 Screening

Consent will be obtained before any study procedures are done, including any screening procedures that may be done under this current protocol.

All potential participants will undergo a screening visit in the NEI ophthalmology clinic to determine whether they meet the eligibility criteria. Potential participants will be screened under the NEI screening protocol (08-EI-0102), NEI natural history protocols such as 08-EI-0169 or

12-EI-0042, or an NCI or NINDS natural history protocol to establish eligibility. Data collected under these protocols may be shared with the current protocol. Each potential participant must have an active signed consent for one of the above-mentioned protocols on file in order to allow for screening examination. Under these protocols, potential participants may undergo a medical/ophthalmic history, concomitant medication assessment, vital sign testing, physical examination, ophthalmic examination, visual acuity testing, color fundus photography, OCT, FA and laboratory testing to determine eligibility. Screening data may be used as baseline data if performed within one month (31 days) of the baseline visit. At any time during the screening process, the participant may enroll in this current protocol by signing the protocol's consent form and may complete any remaining screening and baseline procedures under this protocol, with final determination of eligibility. Laboratory testing will include a complete blood count (CBC), hemoglobin A1C and acute care, hepatic and mineral panels, and may be done within one month (31 days) of the baseline visit. Women of childbearing potential (see Appendix 1 for definition) will have a pregnancy test to assess eligibility and must have a negative test within 24 hours prior to injection of any investigational product. If BCVA, concomitant medication assessment and vital sign testing were assessed on an earlier date under another protocol, these will be repeated as baseline examinations on the day of enrollment. All other screening procedures will not be repeated. These screening/baseline examinations are outlined in Appendix 2. Combination investigational treatment with E10030 and ranibizumab injections cannot occur until the participant has reviewed and signed this protocol's consent form.

4.3 Study Design

This study will examine the effect of multiple E10030 and ranibizumab injections in participants with severe ocular VHL disease. A single study eye in each participant will receive combination treatment consisting of intravitreal injections of E10030 (1.5 mg in 0.05 mL) and ranibizumab (0.5 mg in 0.05 mL) (given as separate injections during the same procedure, meaning that participants will receive two intravitreal injections per visit, see Appendix 3) every four weeks from baseline through Week 16 (totaling five treatments) and then every eight weeks through Week 48 (totaling nine treatments from baseline). The primary endpoint will be assessed by tabulation of AEs reported through Week 52. During the second year, all participants will be seen at Weeks 60, 72, 84 and 104. Starting after Week 52, participants may return for additional visits

in the second year of the trial, as often as every four weeks, for evaluation and for administration of standard of care therapies, at investigator discretion. No further administration of investigational product will occur after the Week 48 visit. Participants will have a minimum of 14 study visits at the NEI outpatient clinic. The baseline study visit will require approximately five hours, and the subsequent visits will require approximately three to four hours each.

Standard of care therapies will be considered for significant clinical worsening at any time during the study, for clinical improvement starting at Week 16 (as in a case where clinical improvement makes an eye more amenable to ablative or surgical treatment), and without restriction starting at Week 40 (in anticipation of unavailability of investigational product after Week 48). Any participants who discontinue combination investigational treatment will be asked to return for all study visits and will be included in the analyses at the end of the study.

4.4 Study Procedures

The study will require a minimum of 14 visits (baseline and Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52, 60, 72, 84 and 104). All visits must be conducted within a window of ± 7 days from the target day through Week 52 and ± 30 days thereafter. It is anticipated that the study duration will not exceed 36 months if all participants are recruited within the first 12 months. Prior to treatment at each visit, the participant will undergo an AE assessment, concomitant medication review, vital sign check and ophthalmic evaluation.

Over the course of the study, participants will undergo the following ocular and systemic evaluations as outlined in the study flowsheet (see Appendix 2).

4.5 Ocular and Systemic Evaluations

1. Medical/Ophthalmic History
2. Concomitant Medications Assessment
3. Vital Signs
4. Physical Examination
5. AE Assessment
6. Best-corrected visual acuity (BCVA) and Manifest Refraction using EVA Method

7. Slit Lamp Examination
8. Dilated Fundus Examination
9. Intraocular Pressure (IOP)
10. Color Fundus Photography
11. Optical Coherence Tomography (OCT)
12. Fluorescein Angiography (FA)
13. Complete Blood Count with Differential (CBC)
14. Acute Care Panel
15. Hepatic Panel
16. Mineral Panel
17. Hemoglobin A1C
18. Pregnancy Test (for women of childbearing potential as defined in Appendix 1)

It is expected that tests at any given visit can be completed in one day. The testing schedule varies with the visit. The evaluation and testing schedule is outlined in the study flowsheet (Appendix 2).

4.5.1 Reporting of Expected Events

It is anticipated that participants in this study will occasionally miss or fail to complete an assessment, procedure, or study visit. These omissions will be considered expected events and not protocol deviations provided they are infrequent and do not include data needed to assess safety or the primary study outcome. If such an event is identified, the PI will submit a report to the IRB within two weeks using PTMS.

Cumulative proportions of these missed events in the study population will be presented to the IRB annually. In addition, these rates will be calculated and provided to the NEI SAE Review Committee regularly. The following are considered deviations:

- An individual misses more than 15% of the required study assessments/procedures,
- An individual misses more than 15% of the required study visits,
- An individual completes more than 15% of the required study visits outside of the visit window,

- Collectively, participants missed more than 15% of a specific assessment/procedure,
- Collectively, participants missed more than 15% of the required study visits, or
- Collectively, participants complete more than 15% of the required visits outside the visit window.

If total number of items (study visits or study assessments/procedures) expected is less than 16, two or more missed is reportable. If the total number expected is greater than 16, then if more than 15% are missed it is reportable. Missed items previously reported are not included in the subsequent tallies of missed items, but will be mentioned in future deviation reports. Once a deviation is identified, the PI will submit a report to the IRB within two weeks using PTMS.

4.6 Study Therapy and Concomitant Medications Administration

4.6.1 E10030 Description

E10030 is not a commercially available drug product, and will be provided by Ophthotech Corp. The drug product is provided as a sterile aqueous solution of E10030 at a concentration of 30 mg (oligo weight)/mL. The solution contains monobasic sodium phosphate monohydrate and dibasic sodium phosphate heptahydrate as buffering agents as well as sodium chloride as a tonicity adjuster. The intravitreal injection volume of E10030 is 50 μL, which correlates to 1.5 mg of dry E10030.

4.6.2 E10030 Preparation and Administration

The drug product is provided in a USP Type 1 glass vial with a halobutyl rubber stopper and an aluminum overseal. Included with E10030 solution is a filter needle for withdrawing the solution from the vial and appropriate syringes and needles for administration.

E10030 will be administered according to the injection procedures outlined in Appendix 3.

Each vial contains enough investigational product to inject one participant and each vial will be used one time only.

4.6.3 Ranibizumab Description

Ophthotech Corp. will be providing the commercially-available 10 mg/mL formulation of ranibizumab. Ranibizumab is formulated as a sterile solution (pH 5.5) with histidine, trehalose and polysorbate 20. The vial contains no preservative. Each vial contains 0.5 mL of 10 mg/mL ranibizumab aqueous solution. The intravitreal injection volume of ranibizumab is 50 µL, which correlates to 0.5 mg of dry ranibizumab.

4.6.4 Ranibizumab Preparation and Administration

Ranibizumab is supplied in aseptically filled, sterile, single use stoppered glass vials with blue caps. Included with each vial is a filter needle for withdrawing the solution from the vial and an appropriate needle for administration.

Ranibizumab will be administered according to the Lucentis® prescribing information and the injection procedures outlined in Appendix 3.

Each vial contains enough investigational product to inject one participant and each vial will be used one time only.

4.6.5 Investigational Product Storage

E10030 will be stored at 5°C (± 3°C) and protected from light, as recommended by the manufacturer.

Ranibizumab should be refrigerated at 2°C - 8°C (36°F - 46°F). It must not be frozen or used after the expiration date. It must be protected from light.

Storage temperature fluctuations that do not affect the stability of the investigational products will not be reported to the IRB.

4.6.6 Drug Accountability

The NIH Pharmacy is responsible for the accountability of all unused investigational products. Adequate drug accountability records include documentation of all investigational product shipped, received, stored and dispensed by the NIH Pharmacy. The NIH Pharmacy will dispose of unused investigational product once participants have completed through Week 48.

The investigator is responsible for the accountability for all used investigational product. Adequate drug accountability records include documentation of all investigational product administered and disposed of by the investigator. Used investigational product vials and supplies will be disposed in the hazardous waste disposal bins.

4.6.7 Concomitant Medications or Treatments

Any potential participant likely to need systemic treatment with an agent having significant anti-VEGF or anti-PDGF activity within 12 months of enrollment should not be entered in the study (see Section 3.2.2, Exclusion Criteria). However, once participants are enrolled in the study, concomitant therapies for non-ocular conditions are allowed without restriction. In the event that a participant requires systemic treatment with either anti-VEGF therapy or anti-PDGF therapy, interruption or discontinuation of combination investigational treatment will be considered and discussed with other treating physicians.

Standard care therapies for VHL disease, including laser photocoagulation, cryotherapy, photodynamic therapy, surgery, ocular radiation and any medication use associated with these treatments (such as use of systemic corticosteroids to minimize exudation from RCH undergoing ablative treatment) will be considered for significant clinical worsening at any time during the study, for clinical improvement at any time starting at Week 16 (as in a case where clinical improvement makes an eye more amenable to ablative or surgical treatment), and without restriction starting at Week 40 (in anticipation of unavailability of investigational product after Week 48).

Significant clinical worsening is defined as ANY OF THE FOLLOWING, assessed by clinical evaluation and /or clinical imaging with OCT, FA and fundus photography, as applicable, IF assessed to represent progression of ocular VHL disease in the judgment of the investigator:

1. A decrease in BCVA of ≥ 15 letters; OR
2. An increase in exudation, epiretinal proliferation or hemorrhage threatening vision in the judgment of the investigator; OR
3. New or more extensive retinal detachment; OR
4. Increase in size of RCH; OR
5. Appearance of new RCH.

Clinical improvement is defined as ANY OF THE FOLLOWING, assessed by clinical evaluation and /or clinical imaging with OCT, FA and fundus photography, as applicable, IF associated with a significant improvement in chance of treatment success or significant reduction in treatment risk with standard of care therapies in the judgment of the investigator:

1. A decrease in exudation, epiretinal proliferation or hemorrhage; OR
2. Resolution or reduction of retinal detachment; OR
3. Decrease in size of RCH; OR
4. Disappearance of RCH.

Any necessary treatment of a non-study eye will be allowed without restriction.

4.7 Follow-Up/Termination Procedures

After the Week 104 study visit, follow-up care will be arranged with either an outside ophthalmologist or the participant will continue to be seen at the NIH under another protocol if the participant is eligible. The participants and their physicians will be informed of the participant's disease status during this study. Clinical data obtained during participation will be shared with participants and, with written permission from the participants, with their private physicians. Results from the overall study will be shared once the data have been analyzed.

5.0 MANAGEMENT OF DATA AND SAMPLES

No samples will be stored for this study. The clinical data will be stored in the NEI Electronic Medical Record, the Clinical Research Information System (CRIS) and The Emmes Corporation's secure database. All individual data will remain confidential.

Data will be maintained as specified in the informed consent document. The participant has a choice to limit data usage by selecting one of the following consent options:

Please initial on the line below that reflects your choice:

_____*YES, My data may be used for other research projects including those not related to VHL disease.*

_____*NO, I do not want my data used for other research projects.*

5.1 Data Sharing Plan

Data may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained. Repositories receiving data from this protocol may be open-access or restricted access.

Data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data may be shared with investigators and institutions with a Federal Wide Assurance (FWA) or operating under the Declaration of Helsinki (DoH) and reported at the time of Continuing Review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.

Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

6.0 RISKS/DISCOMFORTS

The anticipated discomforts and inconveniences of this protocol are those associated with the investigational products, intravitreal injections, the examination procedures and the time required for the participant to spend at the clinic.

6.1 Examination Risks

Possible risks and discomforts associated with ocular examinations include:

1. Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available. The participant's intraocular pressure will be obtained at each ophthalmic examination to determine whether there is an increased risk of developing glaucoma.

2. Color fundus photographs involve a bright flash to take pictures of the retina. This brief flash may cause temporary discomfort, but does not damage the eye.
3. In rare instances, the cornea may be scratched during measurement of intraocular pressure or use of a fundoscopic contact lens. A corneal abrasion of this sort may be painful, but it will heal quickly with no lasting effects.
4. The fluorescein dye used in fluorescein angiography can make a participant's skin turn yellow for several hours. This yellow color is transient and usually disappears in one day. Because the dye undergoes renal excretion, the participant's urine will turn dark orange for up to 24 hours after the examination. The study team will educate the participant regarding this urine color change. Some participants may be slightly nauseated during the examination, but their nausea usually lasts only a few seconds. If the dye extravasates during the injection, the skin around the injection site may feel mildly uncomfortable or become yellow. The discomfort usually lasts only a few minutes, and the yellow color fades in a few days. There is a chance of ecchymosis at the site of injection and a remote possibility of cellulitis from the needle track. In rare cases, participants may have an allergic reaction to the dye. Treatment typically consists of an oral antihistamine medication, but may require intravenous antihistamine administration if the symptoms are severe. Very rarely (less than one in one million people), a participant experiences anaphylaxis. This would be treated immediately by trained personnel with medications or, if necessary, intubation.
5. OCT is a non-invasive test used to document and analyze retinal pathology and has no known medical risks.

Possible risks and discomforts associated with non-ocular examinations include:

1. Blood draws can cause discomfort and bleeding/bruising at the site of venous puncture. There is a remote risk of fainting or local infection. If any of these conditions arise, they will be treated.
2. The medical/ophthalmic history, physical examination, vital sign testing and pregnancy testing entail no medical risk.

6.2 Potential Risks of E10030

The following safety data for intravitreal use of E10030 are drawn from the attached Investigator Brochure (v5.0, February 29, 2016), furnished by Ophthotech Corp. Based on animal studies, injection-related risks appear to be limited to the risks of any intravitreal injection. Specifically, vitreous hemorrhage, retinal detachment, cataract, lens capsule pigmentation, fibrosis and retinal dysplasia were observed in some animals in multiple injection studies. Post-injection ocular inflammation may also be a risk of E10030 injection, although this reaction appears to be species-specific and has not been noted in human clinical trials.

In beagle dogs, a single intravitreal injection of test article was associated with trace to 1+ cell transiently in some eyes in the 0.3 mg/eye, 1.0 mg/eye and 2.0 mg/eye dose groups. On pathologic examination of these eyes, the minimal inflammation noted microscopically at all dose levels was considered of little toxicological significance. These findings were not associated with major changes in retinal function, as assessed by electroretinography (ERG). No inflammatory reaction was noted in single dose testing of Dutch belted rabbits.

Repeat injection studies were done in Dutch belted rabbits. The animals received bilateral injections every two weeks for six weeks and experienced no drug-related adverse effects. Several rabbits in the study and control groups sustained injection-related effects, including retinal detachment, cataract, lens capsule pigmentation, fibrosis and retinal dysplasia.

Repeat E10030 injection studies were also done in beagle dogs. Like the animals in the single injection studies, intermittent vitreous cells (trace to 2+; suggestion of dose dependence) were detected. This was especially common in the group that was injected daily. Two animals also had anterior chamber cells. One dog that received E10030 at the 0.3 mg dose level developed marked ocular inflammation that was severe and persistent. Injection-related effects included vitreous hemorrhage in six eyes, of which four were in the control group. Three other eyes had retinal folds. One of these three was in the control group. ERG and histopathology studies revealed no E10030-related toxicity.

New Zealand white rabbits that received multiple E10030/ranibizumab combined injections exhibited a species-specific ocular inflammatory reaction. Clinical signs of ocular inflammation included vitreous opacities, debris and infiltrating cells, fibrin and debris on the lens capsule.

Inflammation was confirmed on histopathology. The incidence and severity of these findings tended to increase over time on study. The inflammation was attributed to the known immunogenicity of ranibizumab in rabbit eyes, and was not seen at the highest dose level of E10030 alone. No similar inflammation was seen in an identical study in beagle dogs. The maximum serum concentration of E10030 in the high intravitreal dose group (1.5 mg) was 41 ng/mL. In rat studies, IV dosing (0.1, 1, 10 or 100 mg of E10030/kg/day IV over 14 or 90 days) has been associated with significant perturbations of hematology and clinical chemistry parameters, especially in the high-dose groups. Rats were found to have decreased leukocyte, hemoglobin, platelet and reticulocyte counts after IV administration. Prothrombin time and activated partial thromboplastin time were significantly increased at times during the study. Globulin levels were decreased by the end of the study, and there was a corresponding increase in albumin/globulin ratios. In the high-dose groups, serum cholesterol, ALT, total protein and AST, ALP, triglycerides and total bilirubin concentrations were all significantly decreased. Reductions in serum concentrations ranged from approximately 30 to 70%. Serum calcium was slightly but significantly reduced. Glucose and blood urea nitrogen concentrations were significantly increased, by as much as 55 and 75%, respectively. Increased liver weights and decreased spleen weights were also observed, and the significance of these findings is unclear. In the 14-day study, histopathology findings in the high-dose animals consisted of minimal to marked infiltration of histiocytes (macrophages) in multiple organs including the liver, spleen, lymph nodes and kidneys. In the 90-day study, histopathology findings in the high-dose animals consisted of cellular vacuolation in numerous tissues, including liver, spleen and lymph nodes. A dose response was evident, with increased severity and frequency of findings occurring in the high-dose group versus the mid-dose group. These histopathologic findings may reflect stages in the drug clearance process.

No drug-specific adverse effects of E10030 have been identified in limited human use. The only serious AE in the phase 1 clinical trial of E10030 was new onset atrial fibrillation reported by a patient in the 0.3 mg dose group. The event was assessed as unrelated to study drugs or injection procedure. In the phase 1 clinical trial of E10030 and ranibizumab for choroidal neovascularization in age-related macular degeneration (n=23) (OPH1000), AEs were almost exclusively mild and related to the injection procedure. The most frequently occurring (≥ 3 subjects) AEs were all events that occurred in the study eye, including foreign body sensation in the eye, conjunctival

hemorrhage, eye irritation and punctate keratitis. The only other ocular AEs reported in the study eye of more than one patient were conjunctival edema, anterior chamber cells (trace) and myodesopsia (floaters) (each reported in two patients, 9%). In a phase 2b randomized, prospective, double-masked, controlled trial of 449 patients with subfoveal neovascular lesions secondary to AMD (OPH1001), combination investigational treatment with E10030 and ranibizumab was well tolerated. Patients received six monthly intravitreous injections of E10030 given in combination with ranibizumab. In this randomized, sham-controlled, multicenter study, 449 patients were randomly assigned in a 1:1:1 ratio to the following dose groups: E10030 0.3 mg/eye + ranibizumab 0.5 mg/eye, E10030 1.5 mg/eye + ranibizumab 0.5 mg/eye or E10030 sham + ranibizumab 0.5 mg/eye.

The most common ocular AEs were, as expected in intravitreal studies, related to the intravitreal preparation and injection procedure and not drug-related, e.g., conjunctival hemorrhage, punctate keratitis and eye pain. There were no events of endophthalmitis, retinal detachment, retinal tear or iatrogenic traumatic cataract after a total of 4,431 intravitreal injections (1,776 administrations of E10030 and 2,655 administrations of ranibizumab). As expected, the mean IOP increased after each intravitreal injection consistent with the volume effect. However, mean IOP in all arms returned to pre-injection level at the next visit, including at the end of the study. The systemic safety profile of E10030/ranibizumab was similar to that of ranibizumab alone. In the phase 2b trial above (OPH1001), the incidence of SAEs was similar among treatment arms. The percentage of subjects with at least one systemic SAE was 8.7% in the group getting E10030 0.3 mg + ranibizumab 0.5 mg; 5.9% in the group getting E10030 1.5 mg + ranibizumab 0.5 mg; and 7.4% in the group getting sham + ranibizumab 0.5 mg. Systemic exposure to E10030 following intravitreous injection is extremely low. Pharmacokinetic studies have been performed in rats, rabbits and dogs and are described in the Investigator Brochure, but the most meaningful data comes from a dose-escalating, multiple-dose phase 1 study involving 23 participants with exudative AMD involving three monthly injections of E10030 (0.03, 0.3, 1.5 and 3.0 mg) plus ranibizumab (0.5 mg). In this study, plasma levels of E10030 were measured at days 0, 1, 3 and 7 and at week 4 and 8. E10030 was detectable in all participants receiving 1.5 mg or 3.0 mg doses. The mean maximum plasma concentration was calculated to be 15.9 ng/mL for those receiving 1.5 mg and 34.4 ng/mL for those receiving 3.0 mg, with an estimated terminal half-life of 8-14 days. By comparison, in animal studies, vitreous levels of E10030 were consistently more

than 1000-fold higher than systemic values. Further information is contained in the Investigator Brochure.

After intravitreal injection, transient increases in intraocular pressure should be anticipated in the immediate post-injection time period. Subjects should be cautioned on the potential risks associated with intravitreal injection procedures, which include retinal detachment, traumatic cataract, vitreous hemorrhage and intraocular infection, particularly endophthalmitis.

Present cumulative experience in completed and ongoing human trials described in the Ophthotech Corp. Investigator Brochure involves use of E10030 in combination with an anti-VEGF agent (ranibizumab, bevacizumab or aflibercept) in approximately 1,245 subjects. To date, serious AEs have been reported in 225 participants, including four suspected unexpected serious adverse reactions: one case of uveitis in the OPH1001 trial; one case of cerebral hemorrhage in the OPH1002 trial; one case of retinal pigment epithelial tear in the OPH 1003 trial; and one case of left facial numbness with negative neurologic work-up, resolving within a day, in the OPH 1004 trial, none of which has been considered to be likely to be related to E10030 administration by the Sponsor. Only one other case of uveitis (not designated a suspected unexpected SAE by investigators) has been reported across existing studies to date.

No evidence was observed for a toxic or pharmacokinetic interaction between E10030 and the anti-VEGF agent ranibizumab when the combinations were administered by the intravitreal route to dogs and rabbits. Although no systematic studies of interactions have been conducted with other drugs to date, no interactions of E10030 with other drugs are anticipated. E10030 is metabolized by nucleases in vitreous humor and plasma; therefore, cytochrome P450- mediated drug interactions are unlikely.

To date, no specific studies have been conducted to assess the effects of E10030 on the reproductive ability of adult animals or developmental parameters of fetuses or pups; therefore, E10030 must not be used during pregnancy or lactation. All women of childbearing potential must use two forms of effective contraception.

6.3 Potential Risks of Ranibizumab

Ranibizumab (Lucentis®) is made by Genentech, Inc. and approved by the FDA as an intravitreal injection for the treatment of neovascular age-related macular degeneration, macular edema secondary to retinal vein occlusion, diabetic macular edema (DME) and diabetic retinopathy in people with DME. Ranibizumab may cause allergic reactions although, to date, none have been reported. Several thousand patients have been treated with ranibizumab for different therapeutic indications in clinical trials. Serious AEs possibly or probably attributed to intravitreal injection of ranibizumab include severe uveitis, endophthalmitis, retinal tears, retinal detachment, vitreous hemorrhage, lens damage and central retinal vein occlusion. Non-serious AEs possibly or probably attributed to intravitreal injection of ranibizumab include anterior chamber and vitreal inflammation, mild transient increases in IOP, posterior vitreal detachment, retinal hemorrhage, injection site pain, subconjunctival hemorrhage and transient decrease in visual acuity. Other ocular non-serious events included a foreign body sensation in the eye after intravitreal injection, conjunctivitis, dry eye and pruritus. Some of these ocular side effects may cause decreased vision and a possibility of causing blindness. Although there was a low rate of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction or vascular death (including deaths of unknown cause).

The safety of ranibizumab in pregnant or lactating women has not been tested.

6.4 Potential Risks of Any Intravitreal Injection

Potential risks of any injection are related to the mechanics of manipulating the eye. Potential risks associated with intravitreal injection itself are similar to those associated with the injection of other approved drugs delivered via the same route and include endophthalmitis, retinal tear, retinal detachment, lens trauma, intraocular hemorrhage and elevated intraocular pressure. Such risks can lead to irreversible vision loss or blindness. These risks will be minimized by restricting performance of the treatment to clinicians with experience in intravitreal injection and by use of a standardized injection procedure. Appendix 3 describes the injection procedure that will be used.

7.0 PARTICIPANT SAFETY MONITORING

Participants will be assessed for AEs during all study visits by the study investigators. At each visit, the participant will be asked about any new ocular or systemic symptoms including hospitalizations or new/changed medications. Participants will be instructed to contact a study investigator at any time if they experience any problems.

Participants will be monitored at each visit for injection-related complications such as endophthalmitis, retinal tear/detachment, intraocular hemorrhage, cataract and glaucoma and for any progression of ocular VHL disease. They will also be monitored at each visit for intraocular inflammation (as assessed by presence of anterior chamber or vitreous cell on ophthalmoscopy), which was noted in some pre-clinical models using doses of E10030 higher than the human equivalent dose planned for this study.

7.1 Treatment of Endophthalmitis, Retinal Tear/Detachment, Intraocular Hemorrhage, Cataract and Glaucoma

The decision to treat a participant for endophthalmitis, suspected endophthalmitis, retinal tear/detachment, intraocular hemorrhage, cataract or glaucoma will be guided by the clinical judgment of the investigator. Clinical management is also at the discretion of the investigator and should follow current standard practice patterns. A decision regarding whether discontinuation of combination investigational treatment is warranted will be made by the investigator in consultation with the participant.

7.2 Individual Withdrawal Criteria

Participants may choose to withdraw from this study for any reason at any time without penalty, loss of benefits or prohibition from enrolling in other clinical protocols. Reasons for participant discontinuation of combination investigational product or withdrawal may include, but are not limited to, the following:

- Visual acuity loss of ≥ 30 letters from baseline;
- Investigator determination that it is not in the best medical interest of the participant to continue participation;
- Findings in the course of the trial that may affect willingness to participate;

- Inability to keep study visits or to comply with study requirements;
- Participant requires ocular surgery which cannot safely be postponed until the end of the study;
- Pregnancy;
- An adverse reaction to the study treatment or a serious complication associated with or aggravated by continuation of one or both investigational products;
- Cardiovascular event or stroke; or
- Other safety concerns.

Discontinuation of the combination investigational treatment does not necessitate study withdrawal. Whenever possible, investigators will ask study participants discontinuing combination investigational treatment to continue to return for study visits.

7.3 Pregnancy Monitoring

If an investigator becomes aware that a female study participant has become pregnant during the study, no further intravitreal injections of combination investigational treatment will be administered. The investigator and participant will determine whether to continue any remaining study visits or to exit the study.

If an investigator becomes aware that a male study participant has impregnated his partner during the study, the investigator will remind the participant of the potential risks to the unborn fetus.

In either case of reported pregnancy, participant (or partner) will be referred to the NIH OB/GYN consultation service for evaluation and counseling. The investigator must follow the participant (or partner) until the pregnancy outcome.

8.0 OUTCOME MEASURES

8.1 Primary Outcome

The primary outcome for the study will be safety of the combination investigational treatment, assessed by tabulation of AEs reported through Week 52.

8.2 Secondary Outcomes

Secondary outcomes will include tabulation of AEs reported through Week 104 and the following measures in the study eye at Week 52 and 104: the proportion of participants experiencing reduction in size of at least one RCH in the absence of other ablative treatment (assessed by fundus photography and FA); the proportion of participants experiencing moderate vision loss (defined as a loss of ≥ 15 letters from baseline on EVA testing); mean change in visual acuity; change in size of RCH (measured by fundus photography and FA); change in exudation (measured by fundus photography, OCT and FA); change in epiretinal proliferation, fibrosis or retinal traction (assessed by OCT and fundus photography); proportion of participants undergoing ablative treatment of RCH or ocular surgery; proportion of participants with successful ablative treatment of RCH; and the proportion of participants with appearance of one or more new RCH.

9.0 STATISTICAL ANALYSIS

All participants will be included in the analyses.

9.1 Primary Outcome Analysis

In this open-label, prospective study, analyses will be primarily descriptive and by participant. All ocular and systemic AEs reported through Week 52 will be tabulated by participant. AE frequencies will be presented by body system, severity and whether they are considered related to the study treatment.

9.2 Secondary Outcome Analysis

The proportion of participants experiencing reduction in size of at least one RCH, in the absence of other ablative treatment, will be assessed by fundus photography and FA images taken at Week 52 and 104 compared to baseline. OCT, fundus photograph and FA findings will be presented by participant to indicate increases/decreases in lesion size and exudation from baseline. Change in epiretinal proliferation, fibrosis or retinal traction will be assessed by fundus photography and OCT and will be reported descriptively for each participant. The proportion of participants experiencing moderate vision loss (defined as a loss of ≥ 15 letters from baseline on EVA testing); undergoing ablative treatment of RCH or ocular surgery; achieving successful

ablative treatment of RCH; and showing appearance of one or more new RCH in the study eye will be reported. Mean change in visual acuity will be tabulated.

9.3 Sample Size/Accrual Rate

The accrual goal is three participants. This is an appropriate sample size for the study objectives, since this preliminary investigation will not attempt to definitively determine the safety or efficacy of this treatment.

10.0 HUMAN PARTICIPANTS PROTECTION

10.1 Equitability

Accrual will be equitable among patients with VHL disease meeting the enrollment criteria for this study.

10.1.1 Justification for Exclusion of Children

Children are not eligible for this study, as the safety of E10030 and ranibizumab has not been investigated in children. Furthermore, it is unlikely that young participants will be able to comply with all examinations and with intravitreal injections.

10.1.2 Justification for Exclusion of Pregnant or Lactating Women

Women who are pregnant or breastfeeding are excluded from this study because of the unknown risks of E10030 or ranibizumab on a fetus or nursing baby and the uncertainty with respect to whether E10030 or ranibizumab is excreted in human milk. Given the known and unknown effects on pregnancy outcomes, two forms of contraception will be required for female participants of childbearing potential (see Appendix 1 for definition). In addition, female participants of childbearing potential will undergo pregnancy tests throughout the study.

10.1.3 Justification for Exclusion of Individuals without Consent Capacity

Vulnerable subjects who lack consent capacity or are cognitively impaired are excluded from this study because they are frequently unable to cooperate with evaluation and testing in the manner standardized for other adult participants.

10.2 Qualifications of Investigators

The physicians who will be performing study procedures are experienced in caring for patients with VHL. In addition, they are experienced in conducting studies similar to this protocol. Credentialed NEI staff physicians and clinical fellows may also conduct procedures under the direction of these investigators.

The Principal Investigator (PI) has verified that all individuals working on this protocol required to take HRPP training under OHSRP SOP 25 (Training requirements for the NIH Human Research Protections Program) have completed all required training, or will do so before assuming any duties for this protocol.

Henry Wiley, MD, is the PI with the ability to obtain informed consent. He is responsible for the conduct and oversight of the study. Specifically, Dr. Wiley is responsible for obtaining medical history, performing ophthalmic examinations, administering combination investigational treatment, completing regulatory documentation and IRB submissions, generating clinical source documents, entering data and resolving data queries and overseeing the entire study. Dr. Wiley is a staff clinician, medical and surgical retina, at NEI with experience in clinical management of ocular VHL disease.

Emily Chew, MD, is the Lead Associate Investigator with the ability to obtain informed consent. She is responsible for obtaining medical history, performing ophthalmic examinations, administering combination investigational treatment and generating clinical source documents. Dr. Chew is the deputy clinical director (CD) and director of the medical retina fellowship program at NEI. Dr. Chew has been PI on previous studies of ocular VHL disease and has written articles, contributed to book chapters and presented on VHL disease.

Wai T. Wong, MD, PhD is an Associate Investigator with the ability to obtain informed consent. He is responsible for obtaining medical history, performing ophthalmic examinations, administering combination investigational treatment and generating clinical source documents. Dr. Wong is a staff clinician and the head of the unit of neuron-glial interactions in retinal diseases at NEI. He has written articles, contributed to book chapters and presented on VHL disease.

Catherine Cukras, MD, PhD is an Associate Investigator with the ability to obtain informed consent. She is responsible for obtaining medical history, performing ophthalmic examinations, administering combination investigational treatment and generating clinical source documents. Dr. Cukras is a staff clinician at NEI and is a graduate of the medical retina fellowship program at NEI.

Tiarnan Keenan, MD, PhD, Alexander Kaplan, MD, Munir Iqbal, MD, FRCSC, and Christopher Hwang, MD are Associate Investigators with the ability to obtain informed consent. They are responsible for obtaining medical history, performing ophthalmic examinations, administering combination investigational product and generating clinical source documents. They are clinical fellows at the NEI.

Angela Kibiy, MPH, BSN, RN is an Associate Investigator and Referral Contact participating in the consent process but without the ability to obtain informed consent. She is responsible for assisting the PI with study visits, generating clinical source documents, entering data and resolving data queries.

Prashant Chittiboina, MD, Karel Pacak, MD, PhD, DSc and W. Marston Linehan, MD are Associate Investigators without the ability to obtain informed consent. Dr. Chittiboina is a Clinical Investigator at the National Institute of Neurological Disorders and Stroke (NINDS). His laboratory focuses on neurosurgical disorders of the pituitary gland and inheritable tumor syndromes. Dr. Pacak is a Senior Investigator in Medical Neuroendocrinology at the National Institute of Child Health and Human Development (NICHD). His work focuses on the etiology, pathophysiology, genetics, diagnosis and treatment of pheochromocytoma and paraganglioma. Dr. Linehan is a Senior Investigator in the Urologic Oncology Branch of the National Cancer Institute (NCI). Dr. Linehan and his colleagues identified the VHL gene and his work has led to the development of new therapeutic strategies for kidney cancer associated with VHL disease. They are responsible for assisting the PI with the systemic evaluation of ER-VHL patients for screening and offering scientific input.

11.0 BENEFITS

Participants may benefit directly from this study if combined E10030 and ranibizumab treatment causes regression of RCH and preserves visual acuity. The study will also lead to generalizable knowledge that will enhance our understanding of using E10030 and ranibizumab as treatment for patients with RCH associated with VHL.

12.0 SUMMARY/CLASSIFICATION OF RISK

Risk is classified as more than minimal risk. The risks will be minimized with careful monitoring and are reasonable given that the participants are experiencing or are at risk of experiencing visual loss due to VHL disease.

13.0 CONSENT DOCUMENTS AND PROCESS

Study investigators with consenting privileges will obtain informed consent. All NIH study investigators obtaining informed consent have completed the National Institute of Mental Health (NIMH) Human Subject's Protection Unit (HSPU) "Elements of Successful Informed Consent" training. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study. The participants must have the ability to understand and sign an informed consent form, which must be signed prior to enrollment. The participants will have an opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves.

If the participant requires the consent to be in larger font in order to read it well, this will be provided. If participants are visually impaired to the point of being unable to read the consent, they can take the consent back with them to read it over with a family member or with the use of magnifying devices. If the participant chooses, the investigator can also read the consent verbatim to the participant and answer any questions that may arise.

An investigator present during the consent process will document the consent process in the participant's medical record. A copy of the signed informed consent form will be provided to the participant to take home.

13.1 Unanticipated Enrollment of Non-English Speaking Participants

If a non-English speaking participant is eligible for enrollment, the participant will be provided with the Clinical Center (CC) Short Written Consent Form for Non-English Speaking Research Subjects in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study. The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is not related to the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will interpret the IRB-approved English consent form and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent documents as the witness and, in this case, will note "Interpreter" with his/her signature. If not also serving as the witness, the interpreter will be separately identified on the short form in the space provided. A copy of both signed forms (the long form serving as the script and the short form) will be provided to the participant. The short form process, including the use of an interpreter, will be documented in the medical record in accordance with NIH policy.

All instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language within an IRB approval period, this will be reported to the IRB immediately.

Interpreters will also be present for other protocol procedures as necessary.

14.0 DATA AND SAFETY MONITORING

The NEI SAE Review Committee is responsible for monitoring data and safety, and will exercise oversight of the clinical investigation independently from the study investigators.

14.1 Coordinating Center

The Emmes Corporation (Emmes) has been assigned as the Coordinating Center for this trial to conduct data collection, protocol monitoring, data analysis and reporting. The Coordinating Center provides routine monitoring of study participants' data. More frequent monitoring visits will be performed at the beginning of the study when enrollment is open. Monitoring will decrease as enrollment closes and as participant follow-up continues.

Although the Coordinating Center advises the NEI CD and PI on data and statistical activities, the Coordinating Center staff does not have direct access to or interaction with participants.

14.2 NEI Serious Adverse Event Review Committee

The NEI SAE Review Committee, which consists of the NEI CD and three other NEI physicians, will be responsible for reviewing any reported serious safety events, if they occur under this protocol. The Committee will review data on a semiannual basis to determine whether the study should continue. If changes to the protocol are indicated, recommendations will be made to the NEI CD and Institutional Review Board (IRB) who will consider and act on such recommendations in a timely manner. Should any suspected serious adverse reactions occur, the NEI CD may, at his discretion, assemble the Committee before the scheduled date to consider if the study should go forward. In addition, if three or more participants experience non-serious suspected adverse reactions that require temporary or permanent cessation of the combination investigational treatment, the PI shall report this to the NEI CD. The NEI CD may convene the Committee before the scheduled time to consider the cessation of the study as a whole.

14.3 Criteria for Stopping the Study

The NEI SAE Review Committee or IRB may recommend temporarily suspending or closing enrollment, or stopping the study at any time due to safety concerns, lack of efficacy or slow recruitment.

15.0 QUALITY ASSURANCE

The NEI and Emmes maintain quality control by adhering to standard operating procedures (NEI QA program and NEIS standard operating procedures). These procedures cover the full protocol cycle beginning with staff credentialing and training, and protocol development and

approval, through database development, data collection, monitoring and analysis and finally manuscript preparation at the conclusion of the study. Data quality assurance is of the utmost importance to the NEI and Emmes. The two groups use a quality assurance system that relies on real-time data checks and reports throughout the course of a study to ensure the accuracy of information. This system is a secure and confidential data management system that stores data and provides quality assurance and reporting. Emmes has developed a number of routine reports specifically designed for monitors (e.g., listings of SAEs, etc.).

Additionally, Emmes has developed summary reports of discrepancies, as well as reports of the exceptions databases, which include requests and reasons for exceptions. The results of the reports are communicated back to site staff, and, along with protocol compliance issues, to the DSMC (if applicable).

Following the monitoring plan for this study, Emmes will perform monitoring activities, including on-site audits, review of database entries and the resolution of study issues. In addition to monitoring, Emmes performs various detailed automated and manual data quality checks. The results from these checks and any protocol compliance issues are communicated back to site staff and to the NEI Project Officer, NEI CD and applicable regulatory bodies.

16.0 REPORTING OF UNANTICIPATED PROBLEMS, PROTOCOL DEVIATIONS AND ADVERSE EVENTS

The PI is responsible for detecting, documenting and reporting unanticipated problems, AEs, including SAEs and deviations in accordance with NIH policy, IRB requirements and federal regulations. Relatedness to the research of all SAEs will be determined by the PI in consultation with the NEI CD.

Serious unanticipated problems, SAEs (including deaths) that are not unanticipated problems and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than seven days after the PI first learns of the event, unless immediate reporting is waived for specific SAEs as noted below. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing not more than 14 days after the PI first learns of the event. Written reports will be submitted in PTMS.

All AEs, deviations and unanticipated problems will be summarized and reported at the time of Continuing Review.

The PI will immediately report SAEs to the Sponsor according to the requirements of 21 CFR 312.64(b). The PI will record non-serious AEs and report them to the Sponsor.

Unexpected serious suspected adverse reactions will be reported to the FDA as soon as possible by facsimile or e-mail within seven days if life-threatening or resulting in death with a follow-up report within 15 days, and with a written report within 15 days otherwise.

All SAEs or unanticipated problems will be reported to Ophthotech Corp. as soon as possible.

17.0 ALTERNATIVES TO PARTICIPATION

Standard care for RCH in VHL ocular disease includes ablative therapies such as laser photocoagulation and trans-scleral cryotherapy. Other therapies include verteporfin photodynamic therapy, episcleral brachytherapy and external beam radiotherapy. Vitreoretinal surgery is used as an adjunct to ablative therapy in order to address vision-threatening epiretinal proliferation, tractional or rhegmatogenous retinal detachment or vitreous hemorrhage.

Participants may receive standard care treatment for RCH (laser photocoagulation and cryotherapy) and complications of RCH (vitreoretinal surgery) when indicated for significant clinical worsening during this study. If a participant achieves clinical improvement during the study that allows for standard care treatment that was not previously feasible, this treatment may be administered anytime starting at the Week 16 visit.

18.0 PRIVACY

All research activities will be conducted in as private a setting as possible.

19.0 CONFIDENTIALITY

No blood, tissue or other samples will be stored in this study. All medical records will be kept confidential and will only be reviewed by the participating investigators. Data will be kept in password-protected computers held at the NEI and Emmes. Only study investigators and Emmes staff will have access to the study data. The participants' names will not appear on any of the data forms reported to the Coordinating Center. A unique, coded identifier and study registration

number will identify the participant if his or her information is shared with the Coordinating Center or Ophthotech Corp. for research purposes. Participants' personal information will be kept as private as possible. However, records can be inspected by organizations for quality assurance and data analysis. These include the members of the IRB, the Coordinating Center and the NEI SAE Review Committee. Ophthotech Corp. will supply the investigational products, but will have neither control of the data nor access to identifiable information in order to ensure research integrity and participant privacy.

20.0 CONFLICT OF INTEREST

The NIH guidelines were distributed to all of the investigators, and none of the investigators had conflicts of interest. Ophthotech Corp. will provide the investigational products and provide travel and per diem reimbursement.

21.0 TECHNOLOGY TRANSFER

Ophthotech Corp. will provide the investigational products and provide travel and per diem reimbursement through a cooperative research and development agreement (CRADA) with the NEI. They will receive coded summary data after completion of the study as outlined in the CRADA. The company will receive any reports submitted to the FDA.

22.0 RESEARCH AND TRAVEL COMPENSATION

There is no compensation for participation in this study. This protocol offers travel and per diem reimbursement for participants, paid by Ophthotech Corp.

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APPENDIX 1: DETERMINING CHILDBEARING POTENTIAL

A female participant who is considered non-childbearing due to a medical condition (i.e., participant has previously undergone a hysterectomy) does not need a pregnancy test, Follicle-stimulating Hormone (FSH) test or contraception.

If a female participant is considered non-childbearing due to menopause, it must be in accordance with the CNS IRB/NIH Ob-Gyn guidance on the definition of menopause. This guidance defines menopause as:

- Women over age 55 who have not had a period for one year will be considered menopausal and do not need a pregnancy test, FSH test or contraception.
- Women between 50 and 55, who have not had a period for one year, should have an FSH test. If their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and do not need pregnancy testing or contraception. If their FSH level is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.
- Women between 45 and 50 who have not had a period for one year will need both an FSH test and a pregnancy test. If they are not pregnant and their FSH level is ≥ 20 mIU/mL, they will be considered menopausal and will not require contraception or additional pregnancy testing. If their FSH test is < 20 mIU/mL, they will need pregnancy testing and contraception as required by the protocol.

APPENDIX 2: STUDY FLOWSHEET

VISIT SCHEDULE*	0	4	8	12	16	24	32	40	48	52
Visit Number (week)	000	004	008	012	016	024	032	040	048	052
Target Day From Baseline	0	28	56	84	112	168	224	280	336	364
STUDY INTERVENTION										
Intravitreal injections of E10030 and Ranibizumab	X	X	X	X	X	X	X	X	X	
GENERAL ASSESSMENTS										
Medical/Ophthalmic History	X[2]									
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Physical Examination	X[2]									
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X
OCULAR ASSESSMENTS (BOTH EYES)										
BCVA (EVA)	X	X	X	X	X	X	X	X	X	X
Manifest Refraction[1]	X				X					X
Slit Lamp Examination	X	X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure (IOP)	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography	X[2]				X					X
Optical Coherence Tomography (OCT)	X[2]	X	X	X	X	X	X	X	X	X
Fluorescein Angiography (FA)	X[2]				X					X
LABORATORY										
Complete Blood Count (CBC)	X[2]				X					
Acute Care Panel	X[2]				X					
Hepatic Panel	X[2]				X					
Mineral Panel	X[2]				X					
Hemoglobin A1C	X[2]									
Pregnancy Test[3]	X	X	X	X	X	X	X	X	X	X

* All visits during the first year must be conducted within a window of ±7 days from the target visit day. After Week 52, visits are conducted within a window of ±30 days from the target visit day.

[1] Manifest refraction must be performed when scheduled and when there is a change in visual acuity of ≥ 10 E-ETDRS letters (≥ 0.20 logMAR) as compared with testing at the last visit.

[2] These procedures may be completed under another NEI/NCI/NINDS protocol if performed within 31 days prior to the baseline visit.

[3] Only for women of childbearing potential. See Appendix 1 for guidance on determining whether a female is considered to be of childbearing potential. Some women may require a follicle-stimulating hormone (FSH) test to determine childbearing potential. Participants who meet this definition must have a negative test within 24 hours prior to injection of any investigational product.

APPENDIX 2: STUDY FLOWSHEET, CONTINUED: EXTENSION PHASE

Visit Schedule*	(Y2 Extra**)	60	72	84	104
Visit Number (week)	N/A	060	072	084	104
Target Day From Baseline	N/A	420	504	588	728
GENERAL ASSESSMENTS					
Medical/Ophthalmic History					
Concomitant Medications Assessment	X	X	X	X	X
Vital Signs		X	X	X	X
Physical Examination					
Adverse Event Assessment	X	X	X	X	X
OCULAR ASSESSMENTS (BOTH EYES)					
BCVA (EVA)	X	X	X	X	X
Manifest Refraction[1]					
Slit Lamp Examination	X	X	X	X	X
Dilated Fundus Examination	X	X	X	X	X
Intraocular Pressure (IOP)	X	X	X	X	X
Color Fundus Photography					
Optical Coherence Tomography (OCT)	X	X	X	X	X
Fluorescein Angiography (FA)					
LABORATORY					
Complete Blood Count (CBC)					
Acute Care Panel					
Hepatic Panel					
Mineral Panel					
Hemoglobin A1C					

* All visits during the first year must be conducted within a window of ±7 days from the target visit day. After Week 52, visits are conducted within a window of ±30 days from the target visit day.

** Additional, discretionary visits may occur during the second year as often as every four weeks between Week 56 and Week 104

[1] Manifest refraction must be performed when scheduled and when there is a change in visual acuity of ≥ 10 E-ETDRS letters (≥ 0.20 logMAR) as compared with testing at the last visit.

Appendix 3: Injection Procedures for All Participants

The following procedures will be implemented to minimize the risk of potential AEs associated with serial intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation and investigational product administration. In addition to the procedures outlined below, specific institutional policies associated with the safety of intravitreal injections will be observed. Included in these safety procedures are use of a mask and sterile gloves by staff preparing and administering intravitreal injections and instruction to the patient to minimize talking during preparation and administration of the injection.

- The technician or nurse assembles the supplies and prepares a sterile field.
- The investigator physician and/or nurse prepare the investigational product in sterile fashion as described in Section 4.6, with loading of ranibizumab and E10030 in separate, sterile, labeled syringes, with appropriate needles for injection affixed, on the sterile field.
- The technician or nurse instills 1 drop of 0.5% tetracaine or proparacaine solution into the study eye. This is repeated one or two more times.
- The technician or nurse instills 5% povidone iodine ophthalmic solution in the study eye. Anesthesia can be supplemented with additional drops of 0.5% tetracaine or proparacaine if the participant is uncomfortable. If additional topical anesthetic is delivered, then 2-3 additional drops of 5% povidone iodine ophthalmic solution is instilled in the study eye.
- The technician or nurse disinfects the periocular skin and eyelid of the study eye in preparation for injection. The technician or nurse cleanses the eyelid, lashes and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin.
- The investigator physician may opt to supplement the topical anesthetic regimen for the study eye with subconjunctival administration lidocaine 1% or 2%, in order to maximize comfort. Lidocaine 1% or 2% may be injected before or after the lid and periorbital preparation with povidone iodine and the insertion of the lid speculum described below, but only after pre-treatment with tetracaine or proparacaine and 5% povidone iodine on the ocular surface. A sterile cotton swab or sterile cotton pledget soaked in tetracaine or proparacaine may be used to supplement topical analgesia before the subconjunctival injection. Administration of lidocaine 1% or 2% consists of injecting between 0.1 and 1.0 mL to raise a subconjunctival bleb in the quadrant of the study eye planned for injection, using a 30 gauge 0.5 inch needle, with care taken to maintain the needle as tangential to the globe as possible.
- The investigator physician gloves and inserts an eye speculum into the study eye.

- The investigator physician saturates a sterile cotton-tipped applicator with 0.5% proparacaine or tetracaine drops and holds the swab against the planned intravitreal injection site for 20 to 40 seconds. Analgesia may be supplemented with 3.5% lidocaine gel at investigator discretion. If lidocaine gel is used, any additional 5% povidone iodine solution (see below) should be applied prior to gel application, and residual gel should be irrigated from the eye surface before the end of the procedure.
- The investigator physician uses a caliper to mark the planned injection site, usually 3.5 to 4 mm from the limbus.
- The investigator physician applies another drop of 5% povidone iodine solution to the planned injection site.
- The investigator physician injects 50 µL of ranibizumab using a 30-gauge 0.5-inch needle into the vitreous cavity and then removes the needle.
- The investigator physician applies another drop of 5% povidone iodine solution to the injection site.
- The investigator physician injects 50 µL of E10030 with a 27-gauge needle into the vitreous cavity and then removes the needle.
- Sterile saline drops may be used in between steps above to keep the cornea lubricated as warranted, but should not be used immediately after application of povidone iodine solution.
- The investigator physician removes the speculum.
- The investigator physician performs pain assessment, visual testing (hand-motion testing) and assessment of retinal perfusion (by ophthalmoscopy) immediately after injections. Any severe pain, absence of hand-motion vision, or absence of perfusion of the retinal arterioles immediately following injection should prompt standard care assessment and intervention. Intraocular pressure should be measured and documented in such a circumstance, and should be treated with appropriate standard care options including medical management and/or surgical paracentesis when warranted.
- Intraocular pressure is measured by Tono-Pen within 20 minutes after injection. Elevated intraocular pressure is monitored, and if necessary, managed using standard of care measures. A participant may be discharged from clinic when intraocular pressure measures ≤ 24 mmHg.