Official Study Title: A Phase 2A Randomized Open-Label Trial to Assess the Safety of Zimura® (Anti-C5 Aptamer) Administered in Combination with Anti-VEGF Therapy in Treatment Experienced Subjects with Neovascular Age Related Macular Degeneration

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A PHASE 2A RANDOMIZED OPEN-LABEL TRIAL TO ASSESS THE SAFETY OF ZIMURA® (ANTI-C5 APTAMER) ADMINISTERED IN COMBINATION WITH ANTI-VEGF THERAPY IN TREATMENT EXPERIENCED SUBJECTS WITH NEOVASCULAR AGE RELATED MACULAR DEGENERATION

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Amendment A

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1 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AMD	Age-Related Macular Degeneration
CATT	Comparison of AMD Treatments Trials
CNV	Choroidal Neovascularization
CRF	Case Report Form
DA	Disc Area
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
EC	Endothelial Cell
ECG	Electrocardiography
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FP	Color Fundus Photograph
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
NLP	No Light Perception
NV	Neovascular
NVAMD	Neovascular Age-Related Macular Degeneration
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OGTT	Oral Glucose Tolerance Test
OU	Both eyes
PDGF	Platelet Derived Growth Factor
PDT	Photodynamic Therapy
PED	Pigment Epithelial Detachment
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SE	Study Eye
SHRM	Subretinal Hyper-Reflective Material
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

2 SUMMARY OF PROTOCOL OPH2004

SYNOPSIS	
TITLE:	A Phase 2A Randomized Open-Label Trial to Assess the Safety of Zimura® (Anti-C5 Aptamer) Administered in Combination With Anti-VEGF Therapy in Treatment Experienced Subjects with Neovascular Age Related Macular Degeneration
OBJECTIVES:	To assess the safety of intravitreal (IVT) Zimura® administered in combination with anti-VEGF Therapy (AVASTIN®, EYLEA®, OR LUCENTIS®) in anti-VEGF treatment experienced subjects with neovascular age related macular degeneration (AMD)
STUDY DESIGN:	All enrolled subjects will be anti-VEGF "treatment experienced" (with 1 prior intravitreal anti-VEGF treatment with AVASTIN®, EYLEA®, OR LUCENTIS® within the past 8 weeks for NVAMD in the study eye). For all subjects, there must be ≤ 0 letters of visual improvement in Snellen (not ETDRS Snellen equivalent) visual acuity since the start of anti-VEGF treatment. Stratified sampling will be employed to enroll equal subgroups previously treated with Lucentis® (n=15), Eylea® (n=15), or Avastin® (n=15). Treatment experienced subjects will receive the same anti-VEGF agent as administered prior to enrollment. **INDUCTION PHASE** **Subjects Previously Treated with Avastin®** Subjects will receive three monthly intravitreal Avastin® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day). **Subjects Previously Treated with Lucentis®** Subjects will receive three monthly intravitreal Lucentis® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day). **Subjects Previously Treated with Eylea®** Subjects will receive three monthly intravitreal Eylea® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day).

SYNOPSIS	
	MAINTENANCE PHASE Subjects will continue to be treated with the same anti-VEGF therapy as administered during the Induction Phase. After the Induction Phase, all subjects will receive treatment every 3 months (Month 5, 8, 11, 14, and 17), for a total of 18 months. Injection of anti-VEGF therapy will be administered first followed by Zimura® on the same day during the Maintenance Phase. All subjects will have a final follow-up visit at Month 18. **Retreatment Criteria** During the intervening visits (**Month 3, 4, 6, 7, 9,10, 12, 13, 15, 16**) subjects will be retreated with anti-VEGF therapy followed by Zimura® 2.0 mg/eye administered on the same day **if** • **The visual acuity decreases ≥ 5 ETDRS letters, compared to the previous visit** **OR** • **If there is a cumulative decrease of ≥ 5 ETDRS letters at consecutive visits since the previous injection**. Subjects should not be retreated if the visual acuity loss is solely attributed to new foveal atrophy and/or new opacified media (per investigator discretion).
	Safety Endpoints: • Visual Acuity Loss (Proportion of subjects with >0 letter loss at Month 12, 18) • Visual Acuity Loss (Proportion of subjects with >5 letter loss at Month 12, 18) • Visual Acuity Loss (Proportion of subjects with >10 letter loss at Month 12, 18) • Ophthalmic Adverse Events (AEs) • Systemic Adverse Events (AEs) • Laboratory variables
PLANNED SAMPLE SIZE:	Approximately 45 treatment experienced subjects will be enrolled: 15 will receive Avastin® and Zimura® 15 will receive Lucentis® and Zimura® 15 will receive Eylea® and Zimura®

SYNOPSIS	
SUBJECT SELECTION:	Subjects of either gender aged between 50 to 80 years diagnosed with subfoveal choroidal neovascularization secondary to AMD.
FORMULATION:	[redacted] Lucentis® (ranibizumab) Lucentis® is a preservative-free colorless to pale yellow sterile solution, supplied in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL Lucentis® aqueous solution with 10 mM histidine HCl, 10% α, α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Lucentis® should be used without further dilution and administered in accordance with the package insert. Avastin® (bevacizumab) Avastin® is a preservative-free, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution supplied in a single-use glass vial containing 100 mg in 4 mL, of which 0.05 mL will be administered for intravitreal injection. The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection, USP. Avastin is presented in a 4 mL vial and should be used without further dilution. The vial is considered single use and should not be used on any additional study subjects or non-study patients. Avastin® should be administered in accordance with the procedure described in this protocol. Eylea® (aflibercept) Eylea® is a preservative-free colorless to pale yellow sterile solution, supplied in a single-use glass vial designed to deliver 0.05 mL of Eylea® (40 mg/mL in 10mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2). Eylea® should be used without further dilution and administered in accordance with the package insert.

3 STUDY ASSESSMENTS

Year 1

Assessment	Scr	Day 1[1]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X													
Medical & Ophthalmic History	X													
Snellen visual acuity	X													
Protocol refraction and VA using ETDRS chart (OU)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[2, 3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photographs[4]	X						X						X	
Fluorescein Angiogram[4]	X						X						X	
Optical Coherence Tomography (OCT)[4]	X	X	X	X			X						X	
Laboratory Tests (hematology, chemistry) [5]	X							X						X
Serum pregnancy test (if applicable)[6]	X													
Avastin® + Zimura® Therapy (if applicable)		X	X	X	R	R	X	R	R	X	R	R	X	R
Lucentis® + Zimura® Therapy (if applicable)		X	X	X	R	R	X	R	R	X	R	R	X	R
Eylea® + Zimura® Therapy (if applicable)		X	X	X	R	R	X	R	R	X	R	R	X	R
3-Day Post-Injection Telephone Safety Check		X	X	X	R	R	X	R	R	X	R	R	X	R
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 Visit assessments should be performed within 14 days of Screening.
[2]Goldmann applanation tonometry must be performed at Screening and Month 18/Early withdrawal. The tonopen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30mm Hg occurring more than 30 min post-injection, or any IOP ≥30 mmHg at any other time.
[3]Tonometry should be measured prior to the first injection, to determine whether pressure has returned to within 5mm Hg of pre-injection IOP or ≤ 21mm Hg between the first and second injection, and after the final injection to determine that it is less than 30 mm Hg, and at any additional times as specified by the Intravitreous Administration Protocol (see Section 18.4).
[4]To be performed OU at all time points. Post injection ophthalmic exam to be performed on study eye only.
[5]Hematology and Chemistry Panels performed at Screening, Month 6, Month 12, and Month 18/Early Withdrawal.
[6]Serum pregnancy test performed at Screening and Month 18/Early Withdrawal for women of childbearing potential.
[7]Adverse events are to be recorded starting after the first dose of study drug.
R=Re-Treatment
VISIT WINDOWS: Subjects should adhere to their prescheduled study visits within the following visit windows of ± 7 days

STUDY Assessments (Continued)

Assessment	Year 2					
	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18/Early Withdrawal
Informed Consent						
Medical & Ophthalmic History						
Snellen visual acuity						
Protocol refraction and VA using ETDRS chart	X	X	X	X	X	X
Tonometry[2, 3]	X	X	X	X	X	X
Ophthalmic Examination[4]	X	X	X	X	X	X
Color Fundus Photographs[4]						X
Fluorescein Angiogram[4]						X
Optical Coherence Tomography (OCT)[4]						X
Laboratory Tests (hematology, chemistry)[5]						X
Serum pregnancy test (if applicable)[6]						X
Avastin® + Zimura® Therapy (if applicable)	R	X	R	R	X	
Lucentis® + Zimura® Therapy (if applicable)	R	X	R	R	X	
Eylea® + Zimura® Therapy (if applicable)	R	X	R	R	X	
3-Day Post-Injection Telephone Safety Check	R	X	R	R	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events[7]	X	X	X	X	X	X

[1]Day 1 Visit assessments should be performed within 14 days of Screening.
[2]Goldmann applanation tonometry must be performed at Screening and Month 18/Early withdrawal. The tonopen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30mm Hg occurring more than 30 min post-injection, or any IOP ≥30 mmHg at any other time.
[3]Tonometry should be measured prior to the first injection, to determine whether pressure has returned to within 5mm Hg of pre-injection IOP or ≤ 21mm Hg between the first and second injection, and after the final injection to determine that it is less than 30 mm Hg, and at any additional times as specified by the Intravitreous Administration Protocol (see Section 18.4).
[4]To be performed OU at all time points. Post injection ophthalmic exam to be performed on study eye only.
[5]Hematology and Chemistry Panels performed at Screening, Month 6, Month 12, and Month 18/Early Withdrawal.
[6]Serum pregnancy test performed at Screening and Month 18 for women of childbearing potential.
[7]Adverse events are to be recorded starting after the first dose of study drug.
R=Re-Treatment
VISIT WINDOWS: Subjects should adhere to their prescheduled study visits within the following visit windows of ± 7 days

4 INTRODUCTION

4.1 Age-Related Macular Degeneration (AMD)

Age-related macular degeneration is a disease characterized by progressive degenerative abnormalities in the macula of the eye, a small area in the central portion of the retina. It is characteristically a disease of individuals >50 years of age and is the leading cause of visual loss in developed countries. In the United States, it is estimated that approximately 6% of individuals 65-74 years of age and 20% of those older than 75 years of age are affected with AMD (Busbee et al., 2013; Leibowitz et al., 1980). Because of the increasing life expectancy in developed and developing countries, the elderly sector of the general population is expected to rise at a greater rate in the coming decades. While 1 of 8 Americans was considered to be elderly in 1994, it is expected that 1 of 5 will fall into this category in 2030. Using U.S. Census Bureau projections, the number of Americans over 65 years of age will more than double to 80 million by the middle of this century (Cheeseman-Day, 1993). In the absence of adequate prevention or treatment measures, the number of cases of AMD with visual loss is expected to grow accordingly.

Age-related macular degeneration is classified into one of two general subgroups**:** the non-neovascular (non-exudative or dry) form of the disease and the neovascular (exudative or wet) form of the disease. The non-neovascular form of AMD is more prevalent, accounting for approximately 90% of all AMD cases, and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years. By contrast, neovascular AMD, although less prevalent, commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of visual acuity in this disease (Vingerling, 1995). This type of AMD results when abnormal blood vessels (neovascularization) proliferate under and/or within the retina. These blood vessels leak blood and fluid into and under the retina, which results in rapid vision loss. The end stage of the disease features scarring with irreversible destruction of the central retina.

The current FDA approved pharmacologic therapies for wet AMD target and inhibit Vascular Endothelial Growth Factor (VEGF). VEGF is an endothelial cell survival factor and a mitogen. Endothelial cells are a key component of neovascular tissue. All approved anti-VEGF agents for wet AMD are administered by the intravitreal route of administration. These include Lucentis® (ranibizumab), Eylea® (aflibercept), and Macugen® (pegaptanib sodium) (Brown et al., 2006; Gragoudas et al., 2004; Heier et al.,

2012; Rosenfeld et al., 2006).

In addition, although not labeled by the FDA for the treatment of neovascular AMD, the anti-VEGF agent Avastin® (bevacizumab) is currently used to treat ~50% of the eyes with neovascular AMD in the United States. A multicenter, prospective, randomized trial, funded by the US National Eye Institute, "The Comparison of Age-Related Macular Degeneration Treatments Trials" (CATT) demonstrated that monthly dosing with Avastin® 1.25 mg (0.05 mL) was non-inferior to monthly dosing of Lucentis® for eyes with neovascular AMD (Martin et al., 2012).

Avastin®, Lucentis®, and Eylea®, on average, all improve the visual outcome in eyes with neovascular AMD. The primary functional impact of these anti-VEGF agents is to decrease intraretinal and subretinal fluid associated with abnormal blood vessels. Despite maximal therapy with intravitreal monotherapy anti-VEGF agents, majority of patients do not achieve significant visual gain (≥ 15 letters of vision), and approximately 20% to 30% lose additional vision from baseline.

4.2 The Complement Pathway and AMD

The etiology of AMD is not completely understood. In addition to advanced age, there are environmental and genetic risk factors for AMD including ocular pigmentation, dietary factors, a positive family history for AMD, high blood pressure, and smoking (Vingerling, 1995). Recent work suggests inflammation as a major contributor to the pathogenesis of the disease (Bok, 2005; Donoso et al., 2006).

There is mounting evidence that both the wet and dry forms of AMD are associated with an inflammatory process. Patients with AMD are known to have elevated systemic inflammatory biomarkers such as c-reactive protein (CRP), interleukin-6 (IL-6), and homocysteine (Bok, 2005; Seddon et al., 2005). Furthermore, surgically excised choroidal neovascular tissue in patients with AMD has been shown to contain inflammatory cells (Submacular Surgery Trials Report No. 7, 2005).

The complement pathway is part of the innate immune system and is a complex system of serum proteins that interact in a cascade. This complement cascade is activated via the classical (antibody-dependent), the alternative (antibody-independent) and the lectin pathways. Local inflammation and activation of the complement cascade has been implicated in drusen formation (Klein, 2004, Bora, 2005). Recent studies have implicated local inflammation and activation of the complement cascade in drusen formation (Donoso et al., 2006; Hageman et al., 2001; Nozaki et al., 2006). Additionally,

the complement components may induce VEGF up-regulation, a well known mediated of choroidal neovascularization (CNV). (Nozaki et al., 2006). Preclinical laser-induced CNV models have also implicated complement activation. In experimental models of CNV, membrane attack complex (MAC: C5b-9) formation has been shown to be important (Johnson et al., 2000). The MAC is responsible for causing pores in the affected cells that eventually leads to cell death. Inhibition of the alternate pathway of complement activation led to decreased pro-angiogenic factors and decreased CNV formation in experimental CNV (Bora et al., 2006; Haines et al. 2005). Evidence for complement-mediated inflammation in AMD is further reinforced by genetic linkage and association studies, which suggest that approximately 50 to 75% of AMD cases have polymorphism in complement regulatory proteins compared to age-matched controls. Furthermore, polymorphism in genes coding for complement or complement regulatory proteins have demonstrated increased risk in age-related macular degeneration (Edwards et al., 2005; Hageman et al., 2005, Haines et al., 2005; Klein et al., 2005, Naranyan et al., 2007).

4.3 Zimura®

Zimura®, a pegylated RNA aptamer, is a potent and specific inhibitor of complement activation. It inhibits C5, a central component of the complement cascade, which plays multiple roles in innate immunity and inflammatory diseases. Inhibition of this key step in the complement cascade at the level of C5 prevents the formation of key terminal fragments (C5a and C5b-9) regardless of which pathway (alternate, classical or lectin) induced their generation. The C5a fragment is an important inflammatory activator inducing vascular permeability, recruitment and activation of phagocytes. C5b is involved in the formation of membrane attack complex (MAC: C5b-9), which initiates cell lysis. By inhibiting these C5-mediated inflammatory and MAC activities, therapeutic benefit may be achieved in neovascular AMD.

4.3.1 NonClinical Efficacy

The preclinical data demonstrating the anti-C5 properties of Zimura® are described in detail in the Investigator Brochure (IB).

4.3.2 NonClinical Pharmacokinetics of Zimura®

Nonclinical pharmacology studies have been conducted with Zimura®, and, in some cases, with aptamers (Hoehlig et al., 2013). [redacted]

[redacted]

The safety pharmacology studies did not reveal any effects on cardiovascular, respiratory or neurologic function that would raise concerns for the intended ocular administration.

Further information regarding the pharmacology of Zimura® is presented in detail in the IB.

4.3.3 Toxicology

[redacted]

Additional details of the results of these studies, as well as the results of the various intravenous toxicity studies that were previously conducted, can be found in the IB.

4.4 Clinical Data

In a phase 1 ascending dose and parallel group clinical trial the safety, tolerability, and pharmacokinetic profile of multiple intravitreous injections of Zimura® in combination with Lucentis® 0.5mg was evaluated in subjects with wet AMD (OPH 2000).

Zimura® was well-tolerated and no particular safety concerns were identified. No significant evidence of intraocular inflammation, retinal vasculitis, or choroidal vasculopathy was evident. One patient was noted to develop a mild cataract, which was related to the drug by the investigator and visual acuity improved in this patient. No AEs were assessed to be related to Lucentis® administration. VA assessments were primarily safety assessments to detect any decrease in vision associated with the intravitreous injections. There were no safety issues identified through measurement of VA. Assessment of VA was focused on the treatment-naive (TN) patient subgroup of 43 patients who had received 6 injections at doses of 0.3 mg, 1 mg or 2 mg. There was a trend towards a mean increase in VA (number of ETDRS letters) from baseline at all time points for patients in the 0.3, 1 and 2 mg dose groups in the TN subgroup who received 6 injections. At Week 24, there was an improvement in mean VA from baseline of 13.6 ETDRS letters for the 0.3 mg dose group, 11.7 ETDRS letters for the 1 mg dose group and 15.3 ETDRS letters for the 2 mg dose group.

51% of patients in the TN subgroup (n=43 patients) gained ≥15 ETDRS letters at Week 24. This included 6 patients (46%) in the 0.3 mg dose group, 7 patients (47%) in the 1 mg dose group, and 9 patients (60%) in the 2 mg dose group gaining ≥15 ETDRS letters of VA.

A separate phase 1 study was also performed in subjects diagnosed with geographic atrophy (GA). In this study, a total of 47 subjects were enrolled, in the 0.3 mg dose arm (n=24) and 1 mg dose arm (n=23). Subjects received treatment with 3 initial intravitreal injections of Zimura® 0.3 mg/eye or 1 mg/eye, administered at Day 0, Week 4 and Week 8 with a follow up visit at Week 16. Subjects received 2 subsequent injections at Week 24 and Week 36 followed by a final follow up visit at Week 48. Standard safety assessments were performed for ophthalmic variables that included VA, IOP, ophthalmic examination, Fundus Autofluorescence (FAF), Fluorescein Angiography (FA), and Optical Coherence Tomography (SD-OCT) together with Adverse Events (AEs), vital signs and laboratory variables.

Zimura® was well tolerated and there were no AEs considered to be related to Zimura®. Fifteen subjects (32%) had AEs, predominantly Eye Disorder AEs in the study eye, assessed to be related to the injection procedure. The most frequently reported AEs were conjunctival hemorrhage (4 subjects, 9%), corneal edema (4 subjects, 9%), and dry eye (3 subjects (6%). No other study eye AEs were reported by more than 2 subjects. The majority of AEs were mild or moderate in severity. There were 2 subjects with AEs of severe intensity: gastrointestinal inflammation and nasopharyngitis.

Five subjects experienced Serious Adverse Events (SAEs), namely device failure, pelvic fracture, angina pectoris, chest pain and gastrointestinal inflammation, but none were related to the study drug or injection procedure. There were no discontinuations due to AEs.

Vital signs and laboratory assessments did not show any particular clinically significant patterns or changes. Study eye ophthalmic examinations did not indicate any unexpected clinical findings. There were some transient findings post-injection (conjunctiva/sclera and cornea) that resolved prior to the next injection. Vitreous haze was also reported for a few subjects. IOP showed a small mean increase following injections but no indication of any cumulative increases.

Visual acuity (VA) assessments did not show any safety signals. Visual acuity measurements are not particularly meaningful in GA given the marked irreversible atrophy of neural and supportive tissue and the variable involvement of the macular

region. There was suggestion of a drug exposure and dose related slowing of the rate of GA growth during the period of increased frequency of drug exposure (i.e. monthly dosing for 3 months) from baseline to Week 24, as well as a suggestion of stabilized VA, including VA under low light conditions. The data supported further investigation of Zimura® in larger clinical trials.

4.5 Trial Rationale

There is widespread acceptance that the therapeutic benefit of anti-VEGF monotherapy is primarily a result of its potent anti-permeability effects. Studies have shown that VEGF is the most potent inducer of permeability in biologic systems (Dvorak, Brown, Detmar, & Dvorak, 1995). Multiple investigations of currently available anti-VEGF agents (Lucentis®, Avastin® and Eylea®) suggest that they are essentially similar with respect to their safety and efficacy profiles (Brown et al., 2006; Martin et al., 2012; Rosenfeld et al., 2006; Schmidt-Erfurth et al., 2014). Furthermore, the "ceiling" of anti-VEGF mediated therapeutic benefit in NVAMD appears to have been reached as attempts at improving visual outcomes by altering the dose and regimen of anti-VEGF therapy have been unsuccessful (Busbee et al., 2013; Schmidt-Erfurth et al., 2014). Despite maximal therapy with intravitreal monotherapy anti-VEGF agents, the majority of patients do not achieve significant visual gain (≥ 15-ETDRS Letters) or achieve visual acuity of 20/40 or better. In addition, approximately 25% of the patients lose additional vision (Martin et al., 2012). Further, less than monthly regimen results in worse visual outcomes in the real world setting since over the years patients lose vision with anti-VEGF monotherapy. (Rakic et al., Rasmussen et al., 2013; Rofagha et al, 2013). Taken together, anti-VEGF resistance in connection to current anti-VEGF strategies results in a significant unmet need, related to treatment burden and sub-optimal visual outcome.

Anti-VEGF resistance may result from multiple mechanisms including involvement of cytokines other than VEGF, cell based endothelial protection (i.e. pericyte mediated), and inflammation (Bergers & Hanahan, 2008; Jain, 2001; Wang et al., 2011). As indicated earlier, there is mounting evidence that both the wet and dry forms of AMD may involve an inflammatory process. In preclinical models of CNV, inhibition of inflammatory adhesion molecules results in anti-angiogenesis (Sakurai et al., 2003). Furthermore, surgically excised choroidal neovascular tissue in patients with AMD has been shown to contain inflammatory cells (Submacular Surgery Trials Report No. 7, 2005).

The specific type of inflammation involved in AMD is yet to be definitively defined.

However, Complement mediated inflammation may play a significant role. Drusen complement components contain multiple complent pathway proteins. Preclinical laser-induced choroidal neovascularization (CNV) models have implicated complement activation as well. Complement activation has also induced the up-regulation of key mediators of angiogenesis such as VEGF (Nozaki et al., 2006) and PDGF (Benzaquen, 1994). Evidence for complement-mediated inflammation in AMD is further reinforced by genetic linkage and association studies that suggest that approximately 50 to 75% of AMD cases have polymorphism in complement regulatory proteins compared to age-matched controls. Furthermore, polymorphism in genes coding for complement or complement regulatory proteins have demonstrated increased risk in AMD (Bora et al, 2006; Donoso et al, 2006; Hageman et al., 2001; Johnson et al. 2000; Nozaki et al., 2006).

The totality of pre-clinical and genetic related evidence significantly implicates inflammation secondary to the activation of the complement cascade in AMD. Hence, inhibition of complement activation may improve outcomes in AMD patients. In addition, the potential upstream position of complement activation leading to release of VEGF and PDGF could reduce the required frequency for anti-VEGF therapy. Thus, targeting the complement pathway may result in a new therapeutic class for improvement of visual outcome and reduction of treatment burden in neovascular AMD.

Zimura® is currently being developed by Ophthotech Corporation for the treatment of dry and wet AMD. Zimura® is a pegylated RNA aptamer. It is a potent and specific inhibitor of complement activation. Zimura® inhibits C5, a central component of the complement cascade, which plays multiple roles in innate immunity and inflammatory diseases. Inhibition of this key step in the complement cascade at the level of C5 prevents the formation of key terminal fragments (C5a and C5b-9) regardless of which pathway (alternate, classical or lectin) induced their generation. The C5a fragment is an important inflammatory activator inducing vascular permeability, recruitment and activation of phagocytes. C5b is involved in the formation of membrane attack complex (MAC: C5b-9) that initiates cell lysis. By inhibiting these C5-mediated inflammatory and MAC activities, additional therapeutic benefit may be achieved in NVAMD patients receiving anti-VEGF monotherapy.

5 TRIAL OBJECTIVES

5.1 Objectives

To assess the safety of intravitreal (IVT) Zimura® administered in combination with anti-VEGF Therapy (AVASTIN®, EYLEA®, OR LUCENTIS®) in anti-VEGF treatment experienced subjects with neovascular age related macular degeneration (AMD).

5.2 Endpoints

Safety Endpoints:

- Visual Acuity Loss (Proportion of subjects with >0 letter loss at Month 12, 18)
- Visual Acuity Loss (Proportion of subjects with >5 letter loss at Month 12, 18)
- Visual Acuity Loss (Proportion of subjects with >10 letter loss at Month 12, 18)
- Ophthalmic Adverse Events (AEs)
- Systemic Adverse Events (AEs)
- Laboratory variables

6 TRIAL DESIGN

All enrolled subjects will be anti-VEGF “treatment experienced” (with 1 prior intravitreal anti-VEGF treatment with AVASTIN®, EYLEA®, OR LUCENTIS® within the past 8 weeks for NVAMD in the study eye). For all subjects, there must be ≤ 0 letters of visual improvement in Snellen (not ETDRS Snellen equivalent) visual acuity since the start of anti-VEGF treatment.

Stratified sampling will be employed to enroll equal subgroups previously treated with Lucentis® (n=15), Eylea® (n=15), or Avastin® (n=15).

Treatment experienced subjects will receive the same anti-VEGF agent as administered prior to enrollment.

INDUCTION PHASE

Subjects Previously Treated with Avastin®

Subjects will receive three monthly intravitreal Avastin® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day) .

Subjects Previously Treated with Lucentis®

Subjects will receive three monthly intravitreal Lucentis® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day).

Subjects Previously Treated with Eylea®

Subjects will receive three monthly intravitreal Eylea® treatments (Day 1, Months 1, and 2) with followed by Zimura® 2.0 mg/eye (administered on the same day).

MAINTENANCE PHASE

Subjects will continue to be treated with the same anti-VEGF therapy as administered during the Induction Phase.

After the Induction Phase, all subjects will receive treatment every 3 months (Month 5, 8, 11, 14, and 17), for a total of 18 months.

Injection of anti-VEGF therapy will be administered first followed by Zimura® on the same day during the Maintenance Phase.

All subjects will have a final follow-up visit at Month 18.

6.1 Retreatment Criteria

During the intervening visits (**Month 3, 4, 6, 7, 9,10, 12, 13, 15, 16**) subjects will be retreated with anti-VEGF therapy followed by Zimura® 2.0 mg/eye administered on the same day if

- **The visual acuity decreases ≥ 5 ETDRS letters, compared to the previous visit**

OR

- **If there is a cumulative decrease of ≥ 5 ETDRS letters at consecutive visits since the previous injection.**

Subjects should not be retreated if the visual acuity loss is solely attributed to new foveal atrophy and/or new opacified media (per investigator discretion).

7 PROCEDURES

7.1 Procedures for Refraction and Vision Testing

Refraction and Vision Testing will be performed at all time-points specified in Section 10.2"Trial Assessments".

For Snellen testing at SCREENING ONLY, standard Snellen clinic charts will be utilized to assess, for "treatment experienced" subjects, that there must be ≤ 0 letters of improvement in Snellen (not ETDRS Snellen equivalent) visual acuity since the start of anti-VEGF treatment.

For ETDRS testing, retroilluminated modified Ferris-Bailey ETDRS (Early Treatment Diabetic Retinopathy Study) charts are used starting at 4 meters (see Appendix 17.3).

When protocol refraction and best-corrected visual acuity measurement is required by the trial protocol, this will be performed only by certified visual acuity examiners. The examiner will be supplied with the previous protocol refraction only.

7.2 Tonometry

Tonometry will be performed at all time-points specified Section 10.2 "Trial Assessments". When Zimura® is given on the same day as anti-VEGF, tonometry should be performed before the first injection to confirm that IOP is ≤21 mm Hg. Tonometry should be repeated after the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection IOP must return to <30 mm Hg before the subject leaves the clinic. For the post-injection tonometry, proper care should be taken to minimize the risk of contamination.

Goldmann applanation tonometry must be performed at Screening and at Month 18/Early Withdrawal. Tonopens may be used at all other time-points, but Goldmann applanation tonometry must be used to verify IOP for a post-injection reading of ≥ 30 mm Hg occurring more than 30 minutes post-injection, or for a reading of ≥ 30 mm Hg at any other time.

7.3 Ophthalmologic Examination

The following examinations will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

- Inspection of the eyelids
- Examination of the extra-ocular muscle movement
- Inspection of the cornea
- Examination of the anterior chamber for inflammation (Appendix 17.1)
- Examination of the pupils
- Examination of the iris
- Inspection of the lens
- Inspection of the vitreous body (Appendix 17.2)
- Inspection of the retina and optic disc

7.4 Fundus Photography and Fluorescein Angiography

Color fundus photographs (FP) and fluorescein angiography (FA) will be performed at all time-points specified in Section 10.2 “Trial Assessments”. Investigators will determine eligibility based on findings from diagnostic imaging.

7.5 Optical Coherence Tomography (SD-OCT)

Spectral Domain Optical Coherence Tomography (SD-OCT) will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

Investigators will determine eligibility based on findings from diagnostic imaging.

7.6 Laboratory Tests

The following laboratory tests will be performed as specified in Section 10.2 “Trial Assessments”:

• Hematology: hemoglobin, platelet count, WBC and differential

• Renal Function: serum creatinine and BUN

• Hepatic function: serum bilirubin, alkaline phosphatase, GGT, SGOT/AST and SGPT/ALT

• Electrolytes: sodium, potassium, chloride, bicarbonate, calcium and

phosphate

• Serum pregnancy test (for women of child-bearing potential)

If the Investigator judges a laboratory value outside of the normal range as clinically significant, the Investigator will repeat the laboratory determination as judged appropriate to ensure the validity of the abnormal result. If any clinically significant abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered clinically significant by the investigator, or an explanation for the change is obtained.

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 45 treatment-experienced subjects will be enrolled:
15 will receive Avastin® and Zimura
15 will receive Lucentis® and Zimura
15 will receive Eylea® and Zimura

8.2 Inclusion Criteria

Subjects **must meet the following criteria** to be eligible to participate in this study:

Ophthalmic Inclusion Criteria

The following inclusion criteria apply to the study eye:

[redacted]

General Inclusion Criteria

8.2.8 Subjects of either gender aged 50 to 80 years.

8.2.9 Women must agree to be using two forms of effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test must be performed within 14

days prior to the first injection of trial medication with a negative result. The two forms of effective contraception must be implemented during the trial and for at least 60 days following the last dose of test medication.

8.2.10 Provide written informed consent.

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

8.3 Exclusion Criteria

Subjects will ***not be eligible for the trial*** if any of the following criteria are present in the study eye or systemically:

Ophthalmic Exclusion Criteria

[redacted]

[redacted]

General Exclusion Criteria

8.3.18 Any of the following underlying conditions or diseases including:

- History of other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
- History or evidence of severe cardiac disease (e.g., NYHA Functional Class III or IV - see Appendix 17.5), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or coronary artery revascularization within 6 months, or ventricular tachyarrythmias requiring ongoing treatment.
- Stroke (within 12 months of trial entry).

- Any major surgical procedure within one month of trial entry.

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

8.3.20 Known serious allergies to the fluorescein dye used in angiography (mild allergy amenable to treatment is allowable), or iodine, or to the components or formulation of either Zimura®, Avastin®, Lucentis®, Eylea®.

9 TRIAL MEDICATION

9.1 Drug Supply

9.1.1 Zimura®

Zimura® is a pegylated RNA aptamer [redacted]

9.1.2 Lucentis®

Lucentis® is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Lucentis® has a molecular weight of approximately 48 kilodaltons and is produced by an E. coli expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.

9.1.3 Avastin®

Avastin® is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Avastin® contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin® has an approximate molecular weight of 149 kD. Avastin® is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product and the solution is preservative free.

9.1.4 Eylea®

Eylea® is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, consisting of an additional 15% of the total molecular mass, resulting in a total

molecular weight of 115 kDa. Eylea® is produced in recombinant Chinese Hamster Ovary (CHO) cells.

9.2 Dose and Administration

9.2.1 Preparation

Zimura®, Lucentis®, Avastin®, and Eylea® will be injected without dilution.

Zimura® is supplied in a single-use glass vial as noted in Section 9.1.1 above. [redacted]

Lucentis® injection is a preservative-free colorless to pale yellow sterile solution, supplied in a single-use glass vial designed to deliver 0.05 mL of 10 mg/mL ranibizumab injection aqueous solution with 10 mM histidine HCl, 10% α, α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Using aseptic technique, all (0.2 mL) of the Lucentis® injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

Avastin® injection is a preservative-free, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution supplied in a single-use glass vial containing 100 mg in 4 mL, of which 0.05 mL will be administered for intravitreal injection. The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. Using aseptic technique, 0.2 mL of the Avastin® injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-cc tuberculin syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

The Avastin® vial is for single use. Any Avastin® remaining in the vial is non-sterile and may not be used to treat any additional study subjects or non-study patients.

Eylea® is a sterile, clear, and colorless pale yellow solution. Eylea® is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of Eylea® (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2). Using aseptic technique, all (0.28 mL) of the Eylea® injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-cc syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with a sterile 30-gauge × 1/2-inch needle for the intravitreal injection. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

9.2.2 Treatment Regimen and Duration

Enrolled subjects will receive 8-18 injections of Zimura® 2.0 mg/eye and 8-18 injections of anti-VEGF therapy.

9.2.3 Administration of Trial Drug

The method for intravitreous administration of Zimura®, Lucentis®, Avastin® and Eylea® is described in detail in Appendix 17.4.

9.2.4 Storage

The investigator, or an approved representative (e.g. pharmacist), will ensure that all trial drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. [redacted]

9.3 Previous or Concomitant Therapy

Previous treatment for AMD in the study eye prior to Day 1 is not permitted with the exception of two prior anti-VEGF treatments or any oral supplements or vitamins and minerals.

Any treatment with any investigational agent for any condition in the 60 days prior to Screening, or treatment with an investigational agent for any condition during the trial, is not permitted.

Treatment for AMD in the fellow eye during the study with an approved product is permitted at any time. ***If intravitreal treatment in the fellow eye is administered on the same day as study drug, the injection(s) in the study eye should be administered first (before the injection in the fellow eye).***

Although not labeled for the treatment of wet AMD, Avastin® is also allowed in the fellow eye at the discretion of the investigator.

10 TRIAL CONDUCT

10.1 Subject Enrollment

Before recruitment of subjects into the trial, written Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol and informed consent must be obtained.

Subjects who meet the eligibility criteria and have provided written informed consent will be enrolled in the trial. If any inclusion or exclusion criteria are not met, treatment with trial drug should not commence without prior written approval from Ophthotech Corp. or its designee.

Written informed consent must be obtained before any of the Screening procedures listed below are performed. However, if a routine office procedure (e.g. FA, OCT) is performed to diagnose AMD independent of this clinical trial, and subsequently the subject provides informed consent for this study, these procedures performed prior to informed consent may be used as screening assessments for this study, provided the 14-day period of screening evaluations is respected and provided the assessments are acceptable to the standards of the study. An explanation of the trial and discussion of the possible risks and discomforts will be given by the investigator. Only those subjects who fulfill all eligibility criteria will be entered into the trial.

For the Screening visit only, assessments can be broken into 2 days if necessary. For all other visits, all assessments indicated must be performed on the same day.

The following assessments will be performed during the study.

10.2 Trial Assessments

The following evaluations, as outlined in the Study Assessments Chart (see Section 3), will be performed on the days specified below:

Note:

- ***Concomitant Medications should be assessed at every study visit.***
- ***Adverse events (AEs) should be assessed starting at Day 1 after the first dose of trial drug.***

10.2.1 Screening Assessments

The following Screening evaluations, as outlined in the Study Assessments Chart (see Section 3), will be performed ***within 14 days*** prior to Day 1.

- Informed consent
- Medical history
- Ophthalmologic history (OU)
- Snellen visual acuity (comparable standard Snellen chart used previously in clinic for "treatment experienced" subjects)
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic Examination and Goldmann Applanation Tonometry (OU)
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Serum pregnancy test within 14 days of first trial injection (if applicable)
- Laboratory Tests
- Concomitant Medication Assessment

10.2.2 Day 1 Visit

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic Examination (OU)
- Optical Coherence Tomography (OCT) (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.3 Month 1 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Optical Coherence Tomography (OCT) (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.4 Month 2 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Optical Coherence Tomography (OCT) (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed

with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.5 Month 3 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (Only if Retreatment Criteria is Met)

- Anti-VEGF– administered 1st
- Zimura® 2.0 mg/eye– administered 2nd

Post-injection– if subject is retreated Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check – (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.6 Month 4 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (Only if Retreatment Criteria is Met)

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection– if subject is retreated Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion

must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)– if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.7 Month 5 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.8 Month 6 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Laboratory Tests
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met)*

- Anti-VEGF – administered 1st

- Zimura® 2.0 mg/eye – administered-2nd

Post-injection – if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.9 Month 7 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met)*

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection – if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.10 Month 8 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)

Injection

- Anti-VEGF – administered 1st

- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.11 Month 9 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met)*

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection – if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.12 Month 10 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (Only if Retreatment Criteria is Met)

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection– if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.13 Month 11 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.14 Month 12 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)

- Tonometry and Ophthalmologic examination (OU)
- Laboratory Tests
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met)*

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection – if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.15 Month 13 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (Only if Retreatment Criteria is Met)

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection – if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) – if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.16 Month 14 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered-2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.17 Month 15 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met*)

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection- if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) - if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.18 Month 16 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Assessment if Retreatment is necessary (refer to Section 6.1)

Injection (*Only if Retreatment Criteria is Met)*

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered 2nd

Post-injection - if subject is retreated

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day) - if subject is retreated

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.19 Month 17 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)

Injection

- Anti-VEGF – administered 1st
- Zimura® 2.0 mg/eye – administered-2nd

Post-injection

- Ophthalmic Exam/Tonometry (SE) - After the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤21 mm Hg or within 5 mm of pre-injection. After the second injection, the optic nerve perfusion must be confirmed with indirect ophthalmoscopy and IOP must be <30 mm Hg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.20 Month 18/Early Withdrawal (±7 days)

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann Applanation Tonometry and Ophthalmologic examination (OU)
- Color fundus photographs (OU)
- Fluorescein Angiograms (FA) (OU, transit study eye)
- Optical Coherence Tomography (OCT) (OU)
- Serum pregnancy test (if applicable)
- Laboratory Tests

10.3 Withdrawal from Trial

Subjects have the right to withdraw from the trial at any time for any reason. The Investigator (after consultation with the Sponsor) or Sponsor also have the right to withdraw subjects from the trial in the event of concurrent illness, adverse events, treatment-failure after a prescribed procedure, protocol violations, cure, administrative or other reasons.

Final trial assessments as outlined in the Study Assessments Chart, Section 3, should be performed on all subjects who withdraw. Subjects who withdraw due to an adverse event should be followed until resolution of the adverse event, or an adequate explanation for the event is obtained.

Subjects who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule. If an alternative treatment for AMD is initiated, the subject will no longer be evaluated according to this protocol.

10.4 Trial Discontinuation

The reason for a subject discontinuing from the trial will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. A discontinuation must be reported immediately to the clinical monitor or his/her designated representative if it is due to a serious adverse event (SAE) (see Section 12). The final evaluation required by the protocol will be performed at the time of trial discontinuation. The investigator will record the reason for trial discontinuation, provide or arrange for

appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Ophthotech Corp.

11 STATISTICAL METHODS

11.1 Experimental Design

All enrolled subjects will be anti-VEGF "treatment experienced" (with 1 prior intravitreal anti-VEGF treatment with AVASTIN®, EYLEA®, OR LUCENTIS® within the past 8 weeks for NVAMD in the study eye). For all subjects, there must be ≤ 0 letters of visual improvement in Snellen (not ETDRS Snellen equivalent) visual acuity since the start of anti-VEGF treatment.

Stratified sampling will be employed to enroll equal subgroups previously treated with Lucentis® (n=15), Eylea® (n=15), or Avastin® (n=15).

Treatment experienced subjects will receive the same anti-VEGF agent as administered prior to enrollment.

INDUCTION PHASE

Subjects Previously Treated with Avastin®

Subjects will receive three monthly intravitreal Avastin® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye(administered on the same day) .

Subjects Previously Treated with Lucentis®

Subjects will receive three monthly intravitreal Lucentis® treatments (Day 1, Months 1, and 2) followed by Zimura® 2.0 mg/eye (administered on the same day).

Subjects Previously Treated with Eylea®

Subjects will receive three monthly intravitreal Eylea® treatments (Day 1, Months 1, and 2) with followed by Zimura® 2.0 mg/eye (administered on the same day).

MAINTENANCE PHASE

Subjects will continue to be treated with the same anti-VEGF therapy as administered during the Induction Phase.

After the Induction Phase, all subjects will receive treatment every 3 months (Month 5, 8, 11, 14, and 17), for a total of 18 months.

Injection of anti-VEGF therapy will be administered first followed by Zimura® on the same day during the Maintenance Phase.

All subjects will have a final follow-up visit at Month 18.

Retreatment Criteria

During the intervening visits (**Month 3, 4, 6, 7, 9,10, 12, 13, 15, 16**) subjects will be retreated with anti-VEGF therapy followed by Zimura® 2.0 mg/eye administered on the same day if

- T**he visual acuity decreases ≥ 5 ETDRS letters, compared to the previous visit**

OR

- **If there is a cumulative decrease of ≥ 5 ETDRS letters at consecutive visits since the previous injection.**

Subjects should not be retreated if the visual acuity loss is solely attributed to new foveal atrophy and/or new opacified media (per investigator discretion).

11.2 Endpoints

Safety Endpoints:

- Visual Acuity Loss (Proportion of subjects with >0 letter loss at Month 12, 18)
- Visual Acuity Loss (Proportion of subjects with >5 letter loss at Month 12, 18)
- Visual Acuity Loss (Proportion of subjects with >10 letter loss at Month 12, 18)
- Ophthalmic Adverse Events (AEs)
- Systemic Adverse Events (AEs)
- Laboratory variables

11.3 Number of Subjects

Approximately 45 treatment-experienced subjects will be enrolled:

15 will receive Avastin® and Zimura®

15 will receive Lucentis® and Zimura®

15 will receive Eylea® and Zimura®

11.3.1 Sample Size Required

As this study is not designed to perform formal hypothesis testing, there is no formal sample size calculation. The sample size selected is based on a reasonable number of subjects to understand the safety and of the proposed regimen and to improve upon the study design prior to performance of controlled trials that may be initiated in the future.

11.3.2 Statistical Analyses

No formal hypothesis testing will be performed.

11.3.3 Descriptive Statistics

Descriptive statistics will be provided to document baseline and on-trial comparability, including demographic information, treatment administration, and protocol violations.

11.3.4 Safety Analysis

The safety analysis will be conducted on all subjects who had at least one administration of trial drug.

Adverse events will be summarized using MedDRA terms. The incidence and severity of adverse events will be listed and grouped by body system.

Summary statistics will be given on the number of subjects for whom the trial medication had to be permanently stopped.

12 ADVERSE EVENTS

12.1 Definition of Adverse Events

An Adverse Event (AE) is defined as follows: Any untoward medical occurrence in a patient or subject including unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product and which does not necessarily have to have a causal relationship to this treatment.

Adverse events include illnesses with onset during the trial, or exacerbations of pre-existing illnesses. Exacerbation of pre-existing illness is defined as a significant increase in the severity of the illness as compared to the start of the trial, and should be considered when a subject requires new or additional treatment for that illness. Lack of or insufficient clinical response or efficacy should not be recorded as an adverse event.

In addition, clinically significant changes in objective findings (e.g., laboratory, ECG, X-ray, physical examination) should also be considered as to whether they are adverse events. The criteria for determining whether an objective finding should be reported as an adverse event are as follows:

1. Associated with accompanying symptoms; and/or
2. Requires medical/surgical intervention; and/or
3. Leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy; and/or
4. Leads to any of the outcomes included in the definition of a serious adverse event; and/or
5. Is considered to be an adverse event by the investigator or Sponsor.

Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

12.2 Assessment and Reporting of Adverse Events

Adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. An adverse event that is ongoing at the last follow up study visit is required to be followed up until the event resolves or stabilizes at a level acceptable to the investigator and/or Sponsor.

All adverse events spontaneously reported, elicited or observed by the investigators will be recorded. The events will be recorded in the source documents and onto the adverse event pages of the case report form, including date of onset and resolution, severity, relationship to trial treatment and determination of “serious”.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

The investigator will take all therapeutic measures necessary for resolution of the adverse event. Any medication necessary for treatment of the adverse event must be recorded in the subject’s source documents and on the appropriate pages of the subject’s case report form.

Adverse events are recorded up until 30 days after the last dose of study drug or until the last follow up visit of the trial, whichever comes later. An adverse event that is ongoing at the last follow-up study visit is required to be followed up until the event resolves or stabilizes at a level acceptable to the Investigator and/or Sponsor. If the subject still presents with any treatment-related toxicity, the follow-up period will be extended until return to baseline status or until the condition has stabilized.

To assist with grading of adverse event severity, the following definitions are provided:

Mild = Aware of sign or symptom, but easily tolerated;

Moderate = Discomfort enough to cause interference with usual activity;

Severe = Incapacitating with inability to work or do usual activity;

Adverse events are assessed as either related to the intravitreous injection procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, subconjunctival injection of anesthetic, intravitreous injection), termed “injection procedure-related”, or to study drug (Zimura®, Lucentis®, Avastin® or Eylea®).

The relationship to the intravitreous injection procedure or to study drug will be

assessed using the following definitions:

Not Related = There is not a reasonable possibility that the adverse event is related to the injection procedure or to the study drug.

Related = There is a reasonable possibility that the adverse event is related to the injection procedure or to the study drug.

12.3 Definition of Serious Adverse Events

A serious adverse event is any event that:

1. Results in death;
2. Is life-threatening (immediate risk of death);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A life-threatening adverse event is any event that places the patient/subject at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

Hospitalization is defined as any formal inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit).

- Inpatient admission does not include the following:
    - Emergency Room/Casualty Department visits
    - Outpatient/same-day/ambulatory procedures and observation/short-stay units
    - Hospice facilities and Respite care (e.g., caregiver relief)
    - Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities
- Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse event and thus is not subject to immediate reporting to the Sponsor. For example:
    - Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)
    - Social admission (e.g., subject has no place to sleep)
    - Optional admission not associated with a precipitating clinical adverse event (e.g., yearly physical, elective cosmetic surgery)

12.4 Assessment and Reporting of Serious Adverse Events

Serious adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. Any serious adverse event occurring at any other time after completion of the trial must be promptly reported if a causal relationship to trial drug is suspected.

If a serious adverse event occurs, the Sponsor is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to the Sponsor must be made regardless of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

All Serious Adverse Events must be reported to the
Sponsor or Designee within 24 hours.
Refer to the "Safety Contact List" provided separately

12.5 Exposure in Utero

Ophthotech Drug Safety or contracted CRO must be notified of any patient who becomes pregnant or their partner who becomes pregnant, while participating in a clinical trial. The Investigator must immediately notify the Sponsor's Medical Monitor of any pregnancy associated with study medication exposure (at least 6 half-lives after drug administration) and record the event using sponsor provided pregnancy report form. Protocol-required procedures for study discontinuation must be performed on the patient unless contraindicated by pregnancy. All pregnancies must be followed to conclusion to determine their outcome. Infants should be followed for a minimum of 8 weeks.

13 RESPONSIBILITIES

13.1 Emergency Equipment

All participating sites should have emergency resuscitation equipment available, including at a minimum, an Ambu bag, IV tubing, D5W IV fluid, oxygen, and epinephrine 1:1000, and Diphenhydramine Hydrochloride (Benadryl). It is each center's responsibility to ensure that all equipment is within specifications for the duration of the trial. Each center should have written policies regarding resuscitation procedures.

13.2 Case Report Forms and Trial Documentation

The Investigator or designee will complete the appropriate case report form pages within 3 business days following completion of each procedure or evaluation.

All data recorded on case report forms will be supported by source documents. For certain trial parameters, with prior written agreement by the trial sponsor and monitor, the case report form may be used to record source data.

All source documents will be made available to Ophthotech Corp. clinical monitors during scheduled monitoring visits, to auditors during any audits requested by Ophthotech Corp., and to regulatory agencies during inspections.

The investigator will maintain a Trial File containing all trial related documentation required by Good Clinical Practice (GCP). This Trial File will be reviewed periodically for completeness by Ophthotech Corp.'s clinical monitors and must be made available to auditors and regulatory agencies.

All case report forms and original source documents including ocular images should be stored for a minimum of two years after a marketing application has been approved, or two years after formal discontinuation of development of the investigational drug, or five years after completion of the trial, whichever is longer. Documents should not be destroyed without the permission of Ophthotech Corp. In the event of the Principal Investigator leaving the clinical site, it is the Principal Investigator's responsibility to notify Ophthotech Corp. in writing and to designate which trial material will be transferred at the clinical site.

13.3 Drug Accountability/Storage Conditions

The investigator is responsible for the accountability of all used and unused trial medication and for recording and documenting the drug storage temperature at arrival and throughout the trial. Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all trial drug supplies received, dispensed to trial subjects, and returned to Ophthotech Corp.

At the end of the trial, all drug supplies and documentation will be reviewed and verified by the trial monitors. The sites will be instructed to destroy unused trial drug supplies when the trial is completed, or the site may choose to return the drug to an Ophthotech Corp. contracted drug management facility for destruction. If the drug is destroyed at the site, the drug accountability form must be completed and sent to Ophthotech Corp. for archiving.

13.4 Protocol Compliance

Ophthotech Corp. will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

Under certain circumstances, individual protocol criteria may be waived by Ophthotech Corp. and in agreement with the investigator. Any such waiver will be documented in writing and provided to the investigator by Ophthotech Corp.

13.5 Ethical Aspects

Local Regulations/Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (May 9th 1997) and with local law if it affords greater protection to the subject. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

13.6 Institutional Review Board (IRB) or Ethics Committee (EC) Approval and Informed Consent

The investigator is responsible for obtaining approval of the trial protocol, informed consent, and any advertising used for subject recruitment from the appropriate IRB/EC prior to initiating the trial. The investigator will forward the following documents prior to commencement of subject enrollment:

- IRB/EC approval documentation
- Approved trial subject informed consent
- A list of IRB/EC members, or statement of compliance

Prior to enrollment, written informed consent must be obtained from each subject or his/her legally authorized representative. The informed consent must contain all of the elements prescribed by the relevant regulatory authorities and must be appropriately signed, dated and witnessed. **Any changes by the Investigator or local IRB/EC to the sample consent provided by the Sponsor must be approved by the Sponsor before initiating enrollment.**

13.7 Clinical Trial Insurance

Ophthotech Corp. has insurance coverage for medicine-induced injury and other liabilities incurred during clinical trials with its compounds.

13.8 Trial Report and Publications

The trial will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or investigator may publish or present any results from the trial until a joint, multi-center publication of the trial results is made by Sponsor in conjunction with various participating investigators and appropriate sites contributing data and comments. Subsequently, individual investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the clinical trial agreement will prevail.

14 MONITORING

The investigator will permit representatives of Ophthotech Corp. to review all case report forms, trial documentation, and subject medical records at regular intervals throughout the trial. These monitoring visits are for the purpose of verifying protocol compliance, subject safety, and the adequacy of data collected.

15 REFERENCES

Benzaquen, L. R., Nicholson-Weller, A., & Halperin, J. A. (1994). Terminal complement proteins C5b-9 release basic fibroblast growth factor and platelet-derived growth factor from endothelial cells. *The Journal of experimental medicine*, *179*(3), 985-992.

Bergers, G., & Hanahan, D. (2008). Modes of resistance to anti-angiogenic therapy. *Nature Reviews Cancer*, *8*(8), 592-603.

Bok, D. (2005). Evidence for an inflammatory process in age-related macular degeneration gains new support. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(20), 7053-7054.

Bora, P. S., Sohn, J. H., Cruz, J. M., Jha, P., Nishihori, H., Wang, Y., ... & Bora, N. S. (2005). Role of complement and complement membrane attack complex in laser-induced choroidal neovascularization. *The Journal of Immunology*,*174*(1), 491-497.

Bora, N. S., Kaliappan, S., Jha, P., Xu, Q., Sohn, J. H., Dhaulakhandi, D. B., ... & Bora, P. S. (2006). Complement activation via alternative pathway is critical in the development of laser-induced choroidal neovascularization: role of factor B and factor H. The Journal of Immunology, 177(3), 1872-1878.

Brown, D. M., Kaiser, P. K., Michels, M., Soubrane, G., Heier, J. S., Kim, R. Y., . . . Group, A. S. (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med, 355*(14), 1432-1444. doi: 10.1056/NEJMoa062655

Busbee, B. G., Ho, A. C., Brown, D. M., Heier, J. S., Suner, I. J., Li, Z., . . . Group, H. S. (2013). Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology, 120*(5), 1046-1056. doi: 10.1016/j.ophtha.2012.10.014

Cheeseman-Day, J. (1993). *Population projection of the United States by age, sex, race, and Hispanic origin: 1993 to 2050.* . Government Printing Office.

Comparison of Age-related Macular Degeneration Treatments Trials [CATT] Research Group, C. R., Martin, D. F., Maguire, M. G., Ying, G. S., Grunwald, J. E., Fine, S.

L., & Jaffe, G. J. (2011). Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med, 364*(20), 1897-1908. doi: 10.1056/NEJMoa1102673

Comparison of Age-related Macular Degeneration Treatments Trials [CATT] Research Group., Martin, D. F., Maguire, M. G., Fine, S. L., Ying, G. S., Jaffe, G. J., Ferris, F. L., 3rd. (2012). Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology, 119*(7), 1388-1398. doi: 10.1016/j.ophtha.2012.03.053

Donoso, L. A., Kim, D., Frost, A., Callahan, A., & Hageman, G. (2006). The role of inflammation in the pathogenesis of age-related macular degeneration.*Survey of ophthalmology*, *51*(2), 137-152.

Dvorak, H. F., Brown, L. F., Detmar, M., & Dvorak, A. M. (1995). Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. *Am J Pathol, 146*(5), 1029-1039.

Edwards, A. O., Ritter, R., Abel, K. J., Manning, A., Panhuysen, C., & Farrer, L. A. (2005). Complement factor H polymorphism and age-related macular degeneration. Science, 308(5720), 421-424.

Fett, A. L., Hermann, M. M., Muether, P. S., Kirchhof, B., & Fauser, S. (2012). Immunohistochemical localization of complement regulatory proteins in the human retina. *Histol Histopathol, 27*(3), 357-364.

Gragoudas, E. S. (2004). VEGF Inhibition Study in Ocular Neovascularization–1 (VISION–1): Efficacy Results From Phase II/III Macugen™ (Pegaptanib Sodium) Clinical Trials. Investigative Ophthalmology & Visual Science, 45(13), 2364-2364.

Hageman, G. S., Luthert, P. J., Chong, N. V., Johnson, L. V., Anderson, D. H., & Mullins, R. F. (2001). An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Progress in retinal and eye research*, *20*(6), 705-732.

Hageman, G. S., Anderson, D. H., Johnson, L. V., Hancox, L. S., Taiber, A. J., Hardisty, L. I. & Allikmets, R. (2005). A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular

degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(20), 7227-7232.

Haines, J. L., Hauser, M. A., Schmidt, S., Scott, W. K., Olson, L. M., Gallins, P., & Pericak-Vance, M. A. (2005). Complement factor H variant increases the risk of age-related macular degeneration. *Science*, *308*(5720), 419-421.

Han, D. P., & Sievers, S. (2009). Extensive drusen in type I membranoproliferative glomerulonephritis. Arch Ophthalmol, 127(4), 577-579. doi: 10.1001/archophthalmol.2009.38

Heier, J. S., Brown, D. M., Chong, V., Korobelnik, J. F., Kaiser, P. K., Nguyen, Q. D., ... & Schmidt-Erfurth, U. (2012). Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*, *119*(12), 2537-2548.

Helwick, C. (2013), MAHALO Finds New Biomarker for Dry Macular Degeneration, Retrieved from: http://www.medscape.com/viewarticle/814822

Hoehlig, K., Maasch, C., Shushakova, N., Buchner, K., Huber-Lang, M., Purschke, W. G., ... & Klussmann, S. (2013). A novel C5a-neutralizing mirror-image (l-) aptamer prevents organ failure and improves survival in experimental sepsis. *Molecular Therapy*, *21*(12), 2236-2246.

Holekamp, N. M., Liu, Y., Yeh, W. S., Chia, Y., Kiss, S., Almony, A., & Kowalski, J. W. (2014). Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. *Am J Ophthalmol, 157*(4), 825-833 e821. doi: 10.1016/j.ajo.2013.12.018

Jain, R. K. (2001). Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nature medicine*, *7*(9), 987-989.

Johnson, L. V., OZAKI, S., STAPLES, M. K., ERICKSON, P. A., & ANDERSON, D. H. (2000). A potential role for immune complex pathogenesis in drusen formation. *Experimental eye research*, *70*(4), 441-449.

Khandhadia, S., Cipriani, V., Yates, J. R., & Lotery, A. J. (2012). Age-related macular degeneration and the complement system. Immunobiology, 217(2), 127-146. doi: 10.1016/j.imbio.2011.07.019

Klein, R., Peto, T., Bird, A., & Vannewkirk, M. R. (2004). The epidemiology of age-related macular degeneration. American journal of ophthalmology, 137(3), 486-495.

Klein, R. J., Zeiss, C., Chew, E. Y., Tsai, J. Y., Sackler, R. S., Haynes, C., ... & Hoh, J. (2005). Complement factor H polymorphism in age-related macular degeneration. *Science*, *308* (5720), 385-389.

Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., . . . Dawber, T. R. (1980). The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Surv Ophthalmol, 24*(Suppl), 335-610.

Magnusson, K. P., Duan, S., Sigurdsson, H., Petursson, H., Yang, Z., Zhao, Y., ... & Gulcher, J. R. (2006). CFH Y402H confers similar risk of soft drusen and both forms of advanced AMD. PLoS medicine, 3(1), 109.

Maguire, P., & Vine, A. K. (1986). Geographic atrophy of the retinal pigment epithelium. Am J Ophthalmol, 102(5), 621-625.

Martin, D. F. and the Comparison of Age-related Macular Degeneration Treatments Trials Research Group. (2012). Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology, 119(7), 1388-1398. doi: 10.1016/j.ophtha.2012.03.053

Nozaki, M., Raisler, B. J., Sakurai, E., Sarma, J. V., Barnum, S. R., Lambris, J. D., Ambati, J. (2006). Drusen complement components C3a and C5a promote choroidal neovascularization. *Proc Natl Acad Sci U S A, 103*(7), 2328-2333. doi: 10.1073/pnas.0408835103

Narayanan, R., Butani, V., Boyer, D. S., Atilano, S. R., Resende, G. P., Kim, D. S., ... & Kenney, M. C. (2007). Complement factor H polymorphism in age-related macular degeneration. *Ophthalmology*, *114*(7), 1327-1331.

Parmeggiani, F., Romano, M. R., Costagliola, C., Semeraro, F., Incorvaia, C., D'Angelo, S., Sebastiani, A. (2012). Mechanism of inflammation in age-related macular degeneration. Mediators Inflamm, 2012, 546786. doi: 10.1155/2012/546786

Peden, M. C., Suñer, I. J., Hammer, M. E., & Grizzard, W. S. (2015). Long-Term Outcomes in Eyes Receiving Fixed-Interval Dosing of Anti–Vascular Endothelial Growth Factor Agents for Wet Age-Related Macular Degeneration.Ophthalmology, 122(4), 803-808.

Rakic, J. M., Leys, A., Brié, H., Denhaerynck, K., Pacheco, C., Vancayzeele, S., & Abraham, I. (2013). Real-world variability in ranibizumab treatment and associated clinical, quality of life, and safety outcomes over 24 months in patients with neovascular age-related macular degeneration: the HELIOS study.Clinical ophthalmology (Auckland, NZ), 7, 1849.

Rasmussen, A., Bloch, S. B., Fuchs, J., Hansen, L. H., Larsen, M., LaCour, M., & Sander, B. (2013). A 4-year longitudinal study of 555 patients treated with ranibizumab for neovascular age-related macular degeneration.Ophthalmology, 120(12), 2630-2636.

Regillo, C. D., Brown, D. M., Abraham, P., Yue, H., Ianchulev, T., Schneider, S., & Shams, N. (2008). Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol, 145*(2), 239-248. doi: 10.1016/j.ajo.2007.10.004

Rofagha, S., Bhisitkul, R. B., Boyer, D. S., Sadda, S. R., Zhang, K., & Group, S.-U. S. (2013). Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology, 120*(11), 2292-2299. doi: 10.1016/j.ophtha.2013.03.046

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y., . . . Group, M. S. (2006). Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med, 355*(14), 1419-1431. doi: 10.1056/NEJMoa054481

Sakurai, E., Taguchi, H., Anand, A., Ambati, B. K., Gragoudas, E. S., Miller, J. W., & Ambati, J. (2003). Targeted disruption of the CD18 or ICAM-1 gene inhibits choroidal neovascularization. *Investigative ophthalmology & visual science*, *44*(6), 2743-2749.

Sarks, J. P., Sarks, S. H., & Killingsworth, M. C. (1988). Evolution of geographic atrophy of the retinal pigment epithelium. *Eye*, *2*(Pt 5), 552-577.

Seddon, J. M., George, S., Rosner, B., & Rifai, N. (2005). Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin 6, and other cardiovascular biomarkers. *Archives of Ophthalmology*,*123*(6), 774-782.

Seddon, J. M., Francis, P. J., George, S., Schultz, D. W., Rosner, B., & Klein, M. L. (2007). Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. *JAMA, 297*(16), 1793-1800. doi: 10.1001/jama.297.16.1793

Sepp, T., Khan, J. C., Thurlby, D. A., Shahid, H., Clayton, D. G., Moore, A. T., ... & Yates, J. R. (2006). Complement factor H variant Y402H is a major risk determinant for geographic atrophy and choroidal neovascularization in smokers and nonsmokers. *Investigative ophthalmology & visual science*, *47*(2), 536-540.

Skeie, J. M., Fingert, J. H., Russell, S. R., Stone, E. M., & Mullins, R. F. (2010). Complement component C5a activates ICAM-1 expression on human choroidal endothelial cells. *Invest Ophthalmol Vis Sci, 51*(10), 5336-5342. doi: 10.1167/iovs.10-5322

Submacular Surgery Trials Research Group. (2005). Histopathologic and ultrastructural features of surgically excised subfoveal choroidal neovascular lesions: submacular surgery trials report no. 7. *Archives of ophthalmology*,*123*(7), 914.

Tranos, P., Vacalis, A., Asteriadis, S., Koukoula, S., Vachtsevanos, A., Perganta, G., & Georgalas, I. (2013). Resistance to antivascular endothelial growth factor treatment in age-related macular degeneration. *Drug design, development and therapy*, *7*, 485.

Tsutsumi, C., Sonoda, K. H., Egashira, K., Qiao, H., Hisatomi, T., Nakao, S., . . . Ishibashi, T. (2003). The critical role of ocular-infiltrating macrophages in the development of choroidal neovascularization. *J Leukoc Biol, 74*(1), 25-32.

Umeda, S., Ayyagari, R., Allikmets, R., Suzuki, M. T., Karoukis, A. J., Ambasudhan, R., ... & Iwata, T. (2005). Early-onset macular degeneration with drusen in a cynomolgus monkey (Macaca fascicularis) pedigree: exclusion of 13 candidate genes and loci. *Investigative ophthalmology & visual science*,*46*(2), 683-691.

Umeda, S., Suzuki, M. T., Okamoto, H., Ono, F., Mizota, A., Terao, K., ... & Iwata, T. (2005). Molecular composition of drusen and possible involvement of anti-retinal autoimmunity in two different forms of macular degeneration in cynomolgus monkey (Macaca fascicularis). *The FASEB journal*, *19*(12), 1683-1685.

van Lookeren Campagne, M., LeCouter, J., Yaspan, B. L., & Ye, W. (2014). Mechanisms of age-related macular degeneration and therapeutic opportunities. The Journal of pathology, 232(2), 151-164.

Vingerling, J. R., Dielemans, I., Hofman, A., Grobbee, D. E., Hijmering, M., Kramer, C. F., & de Jong, P. T. (1995). The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology, 102(2), 205-210.

Wang, Y., Wang, V. M., & Chan, C. C. (2011). The role of anti-inflammatory agents in age-related macular degeneration (AMD) treatment. Eye, 25(2), 127-139.

Ying, G. S., Kim, B. J., Maguire, M. G., Huang, J., Daniel, E., Jaffe, G. J., & Martin, D. F. (2014). Sustained visual acuity loss in the comparison of age-related macular degeneration treatments trials. JAMA ophthalmology, 132(8), 915-921.

16 SIGNATURE PAGE

Signatures confirm that this protocol OPH2004 Amendment A has been carefully read and fully understood, and that there is agreement to comply with the conduct and terms of the trial specified herein in compliance with Good Clinical Practice and all other regulatory requirements.

PROTOCOL OPH2004 Amendment A: A Phase 2A Randomized Open-Label Trial to Assess the Safety of Zimura® (Anti-C5 Aptamer) Administered in Combination With Anti-VEGF Therapy in Treatment Experienced Subjects with Neovascular Age Related Macualr Degeneration.

[redacted]

Principal Investigator:

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17 APPENDICES

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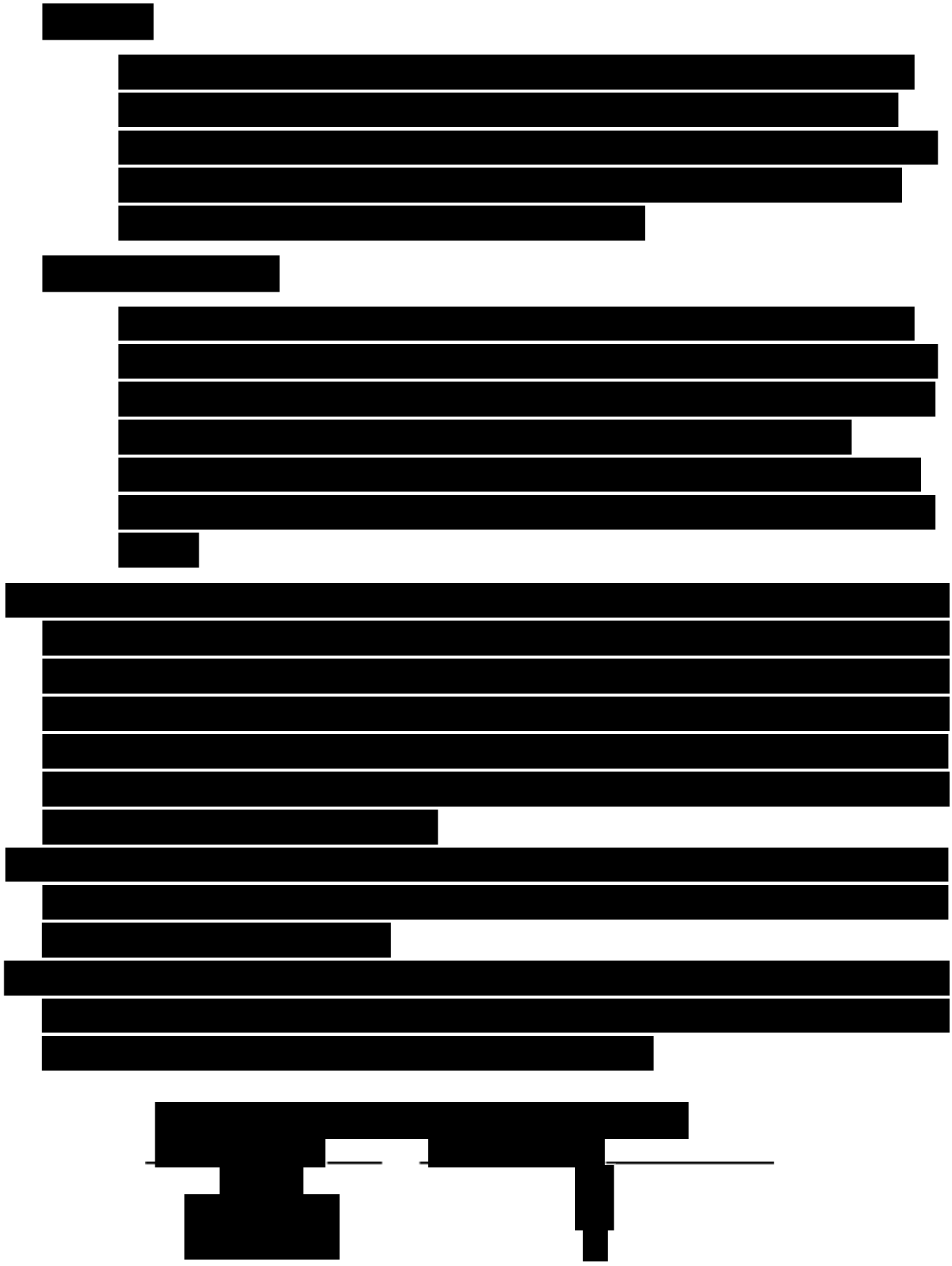

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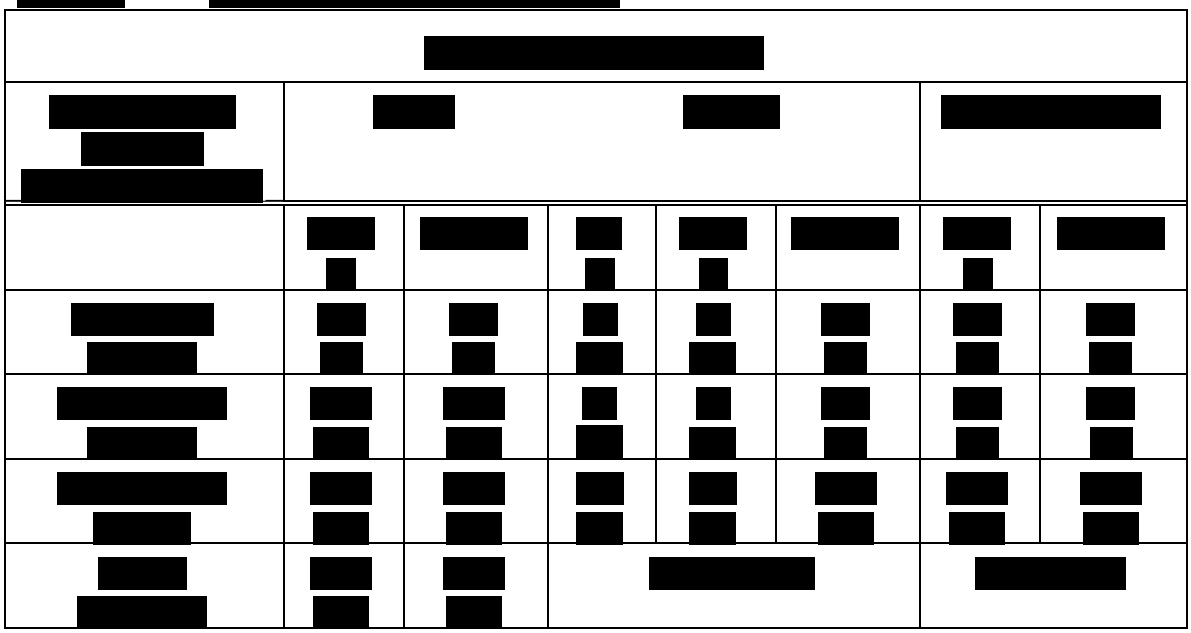

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