NCT Number	NCT03362190
Official Study Title:	A Phase 2A Open-label Trial to Assess the Safety of ZIMURA™ (Anti-C5) Administered in Combination With LUCENTIS® 0.5 mg in Treatment Naive Subjects With Neovascular Age Related Macular Degeneration
Document:	Protocol
Date of Document:	09-Aug-2017

A PHASE 2A OPEN-LABEL TRIAL TO ASSESS THE SAFETY OF ZIMURA™ (ANTI-C5) ADMINISTERED IN COMBINATION WITH LUCENTIS® 0.5 MG IN TREATMENT NAÏVE SUBJECTS WITH NEOVASCULAR AGE RELATED MACULAR DEGENERATION

PROTOCOL NO: OPH2007

Version Date:
9 August 2017

SPONSOR:
OPHTHOTECH CORP.
One Penn Plaza – 19th Floor
New York, NY 10119

FOR MEDICAL EMERGENCIES REFER TO THE "SAFETY CONTACT LIST" PROVIDED SEPARATELY

TABLE OF CONTENTS

1 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CATT	Comparison of AMD Treatments Trials
CNV	Choroidal Neovascularization
CRF	Case Report Form
CHF	Compliment Factor H
CRO	Contract Research Organization
CRP	C-reactive Protein
DA	Disc Area
EC	Ethics Committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FP	Color Fundus Photography
GA	Geographic Atrophy
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLD	Greatest Linear Diameter
hERG	Human Ether-à-Go-Go-Related Gene
IB	Investigator Brochure
ICH	International Conference on Harmonization
idT	Deoxythymidine Nucleotide
IL-6	Interleukin-6
IND	Investigational New Drug
ICG	Indocyanine Green Angiography
IPCV	Idiopathic Polypoidal Choroidal Vasculopathy
IOP	Intraocular Pressure
IRB	Institutional Review Board
MAC	Membrane Attack Complex
NLP	No Light Perception
NV	Neovascular
NVAMD	Neovascular Age-Related Macular Degeneration
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OU	Both Eyes
PED	Pigment Epithelial Detachment
PEG	Polyethylene Glycol
RAP	Retinal Angiomatous Proliferation
RC	Reading Committee
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography

GLOSSARY OF ABBREVIATIONS CONT.

SE	Study Eye
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TN	Treatment Naïve
ULN	Upper Limit of Normal
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

2 SUMMARY OF PROTOCOL OPH2007

SYNOPSIS	
TITLE:	A Phase 2A Open-Label Trial to Assess the Safety of Zimura™ (Anti-C5) Administered in Combination With Lucentis® 0.5 mg in Treatment Naïve Subjects with Neovascular Age Related Macular Degeneration
OBJECTIVES:	To assess the safety of intravitreal Zimura™ administered in combination with Lucentis® 0.5 mg in treatment naïve subjects with neovascular age related macular degeneration (NVAMD)
STUDY DESIGN:	There will be 4 dosing cohorts in this trial. Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2 and 20 subjects in cohorts 3 and 4. **Cohort 1** Administered Day 1 – Month 5, in the following sequence, 2 days apart: • D0: Lucentis® 0.5 mg/eye • D2: Zimura™ 4 mg/eye (administered as two injections of Zimura 2 mg) **Cohort 2** Administered Day 1 – Month 5, in the following sequence: • Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day **Cohort 3** **Induction Phase:** Administered Day 1 – Month 2, in the following sequence, 14 days apart: • D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day • D14: Zimura™ 2 mg/eye **Maintenance Phase**: Administered Month 3 – Month 5, in the following sequence: • Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day **Cohort 4** **Induction Phase:** Administered Day 1 – Month 2, in the following sequence, 14 days apart: • D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

SYNOPSIS	
	• D14: Zimura™ 2 mg/eye **Maintenance Phase**: Administered Month 3 – Month 5, in the following sequence, 2 days apart: • D0: Zimura™ 2 mg/eye • D2: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day All subjects will have a final follow-up visit at Month 6. The first 10 subjects will be enrolled into Cohort 1 according to the procedures noted below. The first three subjects will be assigned to Cohort 1 (Lucentis® 0.5 mg and Zimura™4 mg). Once the 3rd subject completes a safety period of one week after the first dose of Zimura™ 4 mg without the occurrence of a dose limiting toxicity as defined in Section 9.2.3 Dose Limiting Toxicity, full enrollment of Cohort 1 may commence. If a DLT occurs in one or more of the first 3 subjects assigned to Cohort 1, then the Ophthotech medical team will evaluate all available data and either discontinue Cohort 1 or enroll an additional three subjects (for a total of 6 subjects) in Cohort 1. If the three additional subjects are enrolled, and no additional DLT occurs once the second set of 3 subjects in Cohort 1 has reached one week after the first dose of Zimura™ 4 mg/eye, full enrollment of Cohort 1 may commence. If one or more DLTs occur in the second set of 3 subjects, a discussion of safety data will be held among the Ophthotech medical team to review the observed toxicities and determine whether Cohort 1 may proceed. Once Cohort 1 has been fully enrolled, or if enrollment has been stopped due to one or more DLTs, then enrollment in the remaining 3 cohorts may commence. Subjects will be randomized in a 1:2:2 ratio to Cohort 2, Cohort 3, or Cohort 4.
ENDPOINTS:	<u>Safety Endpoints:</u> Safety endpoints include adverse events, vital signs, electrocardiography readings (ECG), ophthalmic variables [visual acuity, intraocular pressure (IOP), ophthalmic examination, stereoscopic fundus photography, fluorescein angiography (FA), spectral domain optical coherence tomography (SD-OCT)], and laboratory variables.
PLANNED SAMPLE SIZE:	Approximately 60 subjects will be enrolled:

SYNOPSIS	
	Cohorts 1 and 2: 10 subjects per cohort Cohorts 3 and 4: 20 subjects per cohort
SUBJECT SELECTION:	Subjects of either gender aged 50 years or above diagnosed with NVAMD.
TEST DRUG DOSAGE:	Subjects randomized to Cohort 1 will receive 12 injections of Zimura™ 2 mg/eye, and 6 injections of Lucentis® 0.5 mg/eye. Subjects randomized to Cohort 2 will receive 6 injections of Zimura™ 2 mg/eye, and 6 injections of Lucentis® 0.5 mg/eye. Subjects randomized to Cohort 3 will receive 9 injections of Zimura™ 2 mg/eye, and 6 injections of Lucentis® 0.5 mg/eye. Subjects randomized to Cohort 4 will receive 12 injections of Zimura™ 2 mg/eye, and 6 injections of Lucentis® 0.5 mg/eye.
FORMULATION:	Zimura™ [redacted] Lucentis® 0.5 mg (ranibizumab) Lucentis® 0.5 mg is a preservative-free colorless to pale yellow sterile solution, presented in a single-use glass vial or as a pre-filled syringe designed to deliver 0.05 mL (50 µL) of 10 mg/mL Lucentis® 0.5 mg aqueous solution with 10 mM histidine HCl, 10% α, α-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Lucentis® 0.5 mg should be used without further dilution and administered in accordance with the package insert.

3 STUDY ASSESSMENTS

Cohort 1

Assessment	Scr	Day 1[1] (Baseline)		Day 9[7]	Month 1		Month 2		Month 3		Month 4		Month 5		Month 6 /EW
		D0	D2		D0	D2	D0	D2	D0	D2	D0	D2	D0	D2	
Informed consent	X														
Medical & Ophthalmic history	X														
Vital signs/Physical exam[2]	X			X											X
12-Lead ECG	X														X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[8]							X						X
Fluorescein angiography[5]	X	X[8]							X						X
SD-optical coherence tomography (SD-OCT)[5]	X	X[8]		X	X		X		X		X		X		X
Laboratory tests	X			X											X
Serum pregnancy test (if applicable)	X														
Reconfirmation of Eligibility		X													
Zimura™ 4mg/eye: two Zimura™ 2 mg/eye Injections			X			X		X		X		X		X	
Lucentis® 0.5 mg/eye Injection		X			X		X		X		X		X		
3-Day Post-Injection Telephone Safety Check			X			X		X		X		X		X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		X	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]Physical examination is performed at Screening and at the Investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen 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.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Day 9 will apply to the DLT cohort only. The DLT cohort is defined as the first 3-6 subjects (depending on if DLTs are noted) enrolled in Cohort 1.
[8]Imaging at Day 1 may be repeated if required per section 10.2.1.1 Reconfirmation of Eligibility at Day 1
EW = Early Withdrawal Visit
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.2
D0 = The first day of dosing at each monthly timepoint. D2 = The second day of dosing, 2 days after D0.

Study Assessments

Cohort 2

Assessment	Scr	Day1[1] (Baseline)	M1	Month 2	Month 3	Month 4	Month 5	Month 6/ EW
Informed consent	X							
Medical & Ophthalmic history	X							
Vital signs/Physical exam[2]	X							X
12-Lead ECG	X							X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]			X			X
Fluorescein angiography[5]	X	X[7]			X			X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]	X	X	X	X	X	X
Laboratory tests	X							X
Serum pregnancy test (if applicable)	X							
Reconfirmation of Eligibility		X						
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X	X	X	X	X	X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	
Concomitant medication assessment	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X

[1]Day 1 Visit assessments should be performed within 14 days of Screening.
[2]Physical examination is performed at Screening and at the Investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen 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.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.3.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.3.

Study Assessments

Cohort 3

Assessment	Scr	Induction Phase						Maintenance Phase			Month 6 /EW
		Day 1[1] (Baseline)		Month 1		Month 2		Month 3	Month 4	Month 5	
		D0	D14	D0	D14	D0	D14				
Informed consent	X										
Medical & Ophthalmic history	X										
Vital signs/Physical exam[2]	X										X
12-Lead ECG	X										X
Tonometry [3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]						X			X
Fluorescein angiography[5]	X	X[7]						X			X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]		X		X		X	X	X	X
Laboratory tests	X										X
Serum pregnancy test (if applicable)	X										
Reconfirmation of Eligibility		X									
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X		X		X		X	X	X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	X	X	X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X	X	X	X

[1]Day 1 Visit assessments should be performed within 14 days of Screening.
[2] Physical examination is performed at Screening and at the Investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen 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.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.4.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.4.
D0 = The first day of dosing at each monthly timepoint. D14 = The second day of dosing, 14 days after D0.

Study Assessments

Cohort 4

Assessment	Scr	Induction Phase						Maintenance Phase						Month 6 /EW
		Day 1[1] (Baseline)		Month 1		Month 2		Month 3		Month 4		Month 5		
		D0	D14	D0	D14	D0	D14	D0	D2	D0	D2	D0	D2	
Informed consent	X													
Medical & Ophthalmic history	X													
Vital signs/Physical exam[2]	X													X
12-Lead ECG	X													X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]						X						X
Fluorescein angiography[5]	X	X[7]						X						X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]		X		X		X		X		X		X
Laboratory tests	X													X
Serum pregnancy test (if applicable)	X													
Reconfirmation of Eligibility		X												
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X		X		X			X		X		X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X		X		X		X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		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]Physical examination is performed at Screening and at the Investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen 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.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.5.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.5.
D0 = The first day of dosing at each monthly timepoint. D2 = The second day of dosing, 2 days after D0. D14 = The second day of dosing, 14 days after D0

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 (Van Newkirk et al., 2000). 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 (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 (Ortma et al., 2014). While 1 of 8 Americans was aged 65 or older in 2012, it is expected that 1 of 5 will fall into this category in 2030 (US Census Bureau, 2012). Using U.S. Census Bureau projections, the number of Americans over 65 years of age will double to 80 million by the middle of this century (US Census Bureau, 2012). 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, NVAMD, 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 NVAMD 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 NVAMD are administered by the intravitreal route of administration. These include Lucentis® (ranibizumab) and Eylea® (aflibercept) (Brown

et al., 2006; Heier et al., 2012; Rosenfeld et al., 2006).

In addition, although not labeled by the FDA for the treatment of NVAMD, the anti-VEGF agent Avastin® (bevacizumab) is currently used to treat ~50% of the eyes with NVAMD in the United States (Parikh, et al, 2017). 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 NVAMD (Martin et al., 2012).

Avastin®, Lucentis®, and Eylea®, on average, all improve the visual outcome in eyes with NVAMD. 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, the 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 (Klein et al., 2004). Recent work suggests complement activation may contribute to the pathogenesis and progression of the disease (Bora at al., 2005, Donoso et al., 2006, Nozaki et al., 2006, Schnabolk G, et al., 2017)

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. Activation of the complement cascade has been implicated in drusen formation (Hageman et al., 2001, Anderson et al., 2002, Bok D, 2005). Additionally, complement components may induce up-regulation of VEGF, a well-known mediator of choroidal neovascularization (CNV) (Nozaki et al., 2006). Preclinical laser-induced CNV models have also implicated complement activation.

Further, the choroid may serve as a nidus for the deposition of membrane attack complex (MAC) when compared to other tissues in the body (Chirco et al., 2016). MAC accumulation leads to mitochondrial damage and cellular dysfunction in RPE cells

(Georgiannakis et al. 2015). In experimental models of CNV, MAC formation has been shown to be important (Johnson et al., 2000). MAC is also responsible for causing pores in the affected cells that eventually leads to cell death.

Inhibition of complement activation has led to a decrease in CNV formation in experimental mouse model (Rohrer et al., 2009; Jo et al., 2017). In a CD59 knockout model, mice that were deficient in MAC inhibition developed a larger CNV size when compared to wild type mice (Schnabolk et al., 2017). Evidence for the role of complement 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 VEGF Inhibition and Complement

Avastin®, Lucentis®, and Eylea®, on average, all improve the visual outcomes in eyes with NVAMD. 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. Further, an increase in dosage or regimen did not lead to additional efficacy and it appears that a “ceiling” of anti-VEGF effect may have been reached (Busbee et al., 2013).

In addition, approximately one fifth of the patients who had received anti-VEGF therapy developed geographic atrophy (GA) within 2 years of treatment (Grunwald et al., 2014). The authors concluded that anti-VEGF therapy may play a role in the development of atrophy. At 5 years the cumulative incidence had increased to 38%, concluding that the development of GA was common after 5 years of treatment (Gruwald et al., 2017).

A meta-analysis of 13 published studies proposed that patients who are homozygous for complement factor H (CFH) polymorphism Y402H experience a reduced response to anti-VEGF treatment (Chen et al., 2015). Further, a direct relationship between VEGF and CFH was recently demonstrated where VEGF upregulated CFH expression and VEGF inhibition lead to a decrease in CFH expression in RPE cells (Keir et al., 2017). Mice that received anti-VEGF treatment, showed a significant decrease in VEGF and CFH. This led to a 200 fold increase in retinal C3 RNA and increased MAC expression, suggesting that VEGF inhibition may contribute to complement activation (Keir et al.,

2017). Further, in patients with NVAMD, aqueous humor samples collected 48 hours after intravitreal injection of bevacizumab demonstrated a decrease in VEGF levels but an increase in C3a, C4a, and C5a levels (Keir et al. 2017).

Taken together, these findings may potentially indicate that although VEGF inhibition has potent anti-permeability characteristics, it may also contribute to complement activation by reducing CFH expression and therefore limiting the full therapeutic potential of the anti-VEGF therapy in NVAMD patients.

4.4 Zimura™

Zimura™, a PEGylated RNA aptamer, is an 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 MAC: C5b-9, which initiates cell lysis. By inhibiting these C5-mediated inflammatory and MAC activities, therapeutic benefit may be achieved in NVAMD.

4.4.1 Non-Clinical Efficacy

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

4.4.2 NonClinical Pharmacokinetics of Zimura™

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

4.4.3 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.

4.5 Clinical Data

4.5.1 Study OPH2000

In a phase 1 ascending dose and parallel group clinical trial the safety, tolerability, and pharmacokinetic profile of multiple intravitreal injections of Zimura™ in combination with Lucentis® 0.5 mg was evaluated in subjects with NVAMD (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 considered to be related to study drug by the investigator; despite this event, the visual acuity improved in this patient during the study.

Visual acuity (VA) assessments were primarily safety assessments to detect any decrease in vision associated with the intravitreal injections. There were no safety issues identified through measurement of VA. Assessment of VA was focused on the treatment-naïve (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.

Fifty-one percent (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.

4.5.2 Study OPH2001

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 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 drugs 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. Intraocular pressure (IOP) showed a small mean increase following injections but no indication of any cumulative increases.

VA assessments did not show any safety signals. VA 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.

4.5.3 Study OPH2002

The objectives of this study were to evaluate the safety and tolerability of Zimura™ intravitreal injection in combination with VEGF therapy in subjects with idiopathic polypoidal choroidal vasculopathy (IPCV). Subjects included in the study were treatment experienced (prior treatment with anti-VEGF monotherapy of ≥ 8 injections in the previous 12 months) of either gender aged 50 years or above with diagnosis of IPCV. Subjects received 3 monthly intravitreal injections of Zimura™ (1 mg/eye) in combination with intravitreal injection of anti-VEGF agent (Avastin® 1.25 mg/eye or Lucentis® 0.5 mg/eye or Eylea® 2 mg/eye).

Safety endpoints included VA loss (proportion of subjects with > 15 letter loss at Month 30, ophthalmic adverse events (AEs), systemic adverse events (AEs), change in total retinal thickness (SD-OCT) at Month 3, regression and/or elimination of polyps at Month 3 compared to Screening as measured by indocyanine green angiography (ICGA) and laboratory values.

A total of 4 subjects were enrolled in this clinical trial and all the subjects completed the study. None of the subjects had a VA loss of more than 15 ETDRS letters at Month 3. There were no deaths during the study. There was one SAE of endophthalmitis reported in 1 subject. The SAE resolved and was assessed to be related to the injection procedure. None of the ocular AEs were assessed to be related to Zimura™ or anti-VEGF treatment.

The intravitreal administration of Zimura™ in combination with an anti-VEGF agent (Avastin®, Eylea®, or Lucentis®) in patients with IPCV was generally well tolerated. The data supports further investigation of the drug in larger clinical trials.

4.6 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 et al., 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 and over time patients in general lose vision with anti-VEGF monotherapy (Rakic et al. 2013, Rasmussen et al., 2013; Rofagha et al, 2013). Approximately one fifth of patients who had received anti-VEGF therapy developed GA within 2 years of treatment (Grunwald et al., 2014). The authors concluded that anti-VEGF therapy may play a role in the development of atrophy. At 5 years, the cumulative incidence was 38%, concluding that the development of GA was common after 5 years of anti-VEGF treatment (Grunwald et al., 2017).

As indicated earlier, there is mounting evidence that both the wet and dry forms of AMD may involve multiple complement 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). Evidence for the role of complement 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 gene coding for complement or complement regulatory proteins have demonstrated increased risk in AMD (Haines et al., 2005, Edwards et al., 2005, Klein et al., 2005, Hageman et al., 2005, Naranyan et al., 2007). A meta-analysis of 13 published studies proposed that patients who are homozygous for CFH polymorphism Y402H experience a reduced response to anti-VEGF treatment (Chen et al., 2015).

A direct potential relationship between VEGF and CFH was recently demonstrated indicating that VEGF inhibition may lead to a decrease in CFH expression in RPE cells (Keir et al. 2017). Mice that received anti-VEGF treatment, showed a significant decrease in VEGF and CHF. This led to a 200 fold increase in retinal C3 RNA and increased MAC expression suggesting that VEGF inhibition may contribute to complement activation (Keir et al., 2017). Further, in patients with neovascular AMD, aqueous humor samples collected 48 hours after intravitreal injection of bevacizumab demonstrated a decrease in VEGF levels but an increase in C3a, C4a, and C5a levels.

The totality of pre-clinical and genetic related evidence implicates the role of complement activation in AMD. Further, the inhibition of anti-VEGF may contribute further to complement activation by decreasing CFH in RPE cells. Taken together, these findings may potentially indicate that although anti-VEGF treatment has potent anti-permeability characteristics it may also activate the complement cascade by reducing CFH expression and therefore limit the full therapeutic potential of anti-VEGF in NVAMD patients. Hence, a combination treatment which inhibits both VEGF and complement may improve visual outcome and therefore targeting the complement pathway may result in a new therapeutic class in NVAMD.

Zimura™ is currently being developed by Ophthotech Corporation for the treatment of complement mediated retinal diseases including dry AMD, NVAMD. Zimura™ is a PEGylated RNA aptamer and an 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 MAC 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.

As a dose-response relationship trend in VA gain was evident in Study OPH2000, a higher dose of Zimura 4 mg will be evaluated in this study. Additionally, it has been shown that biweekly intravitreal injections in patients with wet AMD are well tolerated (Rosenfeld et al., 2006, and Stewart et al. 2011). Further, biweekly dosing may increase the trough levels binding activity. Therefore, this study will also evaluate the biweekly

administration of Zimura 2 mg for an induction period of 3 months.

5 TRIAL OBJECTIVES

5.1 Objectives

To assess the safety of intravitreal Zimura™ administered in combination with Lucentis® in treatment naïve subjects with NVAMD.

5.2 Endpoints

Safety endpoints include:

- Adverse events (AEs)
- Vital signs (respiration, heart rate, systolic and diastolic blood pressure, etc.)
- ECG recordings
- Ophthalmic variables (visual acuity, IOP, ophthalmologic examination, stereoscopic fundus photography, fluorescein angiography, and spectral domain optical coherence tomography)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urine: urinalysis)

6 TRIAL DESIGN

There will be 4 dosing cohorts on this trial. Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2 and 20 subjects in cohorts 3 and 4.

Cohort 1

Administered Day 1 – Month 5, in the following sequence, 2 days apart:

- D0: Lucentis® 0.5 mg/eye
- D2: Zimura™ 4 mg/eye (administered as two injections of Zimura 2 mg/eye)

Cohort 2

Administered Day 1 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 3

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 4

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence, 2 days apart:

- D0: Zimura™ 2 mg/eye

- D2: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

All subjects will have a final follow-up visit at Month 6.

The first 10 subjects will be enrolled into Cohort 1 according to the procedures noted below.

The first three subjects will be assigned to Cohort 1 (Lucentis® 0.5 mg and Zimura™ 4 mg). Once the 3rd subject completes a safety period of one week after the first dose of Zimura™ 4 mg without the occurrence of a dose limiting toxicity as defined in Section 9.2.3 Dose Limiting Toxicity, full enrollment of Cohort 1 may commence.

If a DLT occurs in one or more of the first 3 subjects assigned to Cohort 1, then the Ophthotech medical team will evaluate all available data and either discontinue Cohort 1 or enroll an additional three subjects (for a total of 6 subjects) in Cohort 1. If the three additional subjects are enrolled, and no additional DLT occurs once the second set of 3 subjects in Cohort 1 has reached one week after the first dose of Zimura™ 4 mg/eye, full enrollment of Cohort 1 may commence. If one or more DLTs occur in the second set of 3 subjects, a discussion of safety data will be held among the Ophthotech medical team to review the observed toxicities and determine whether Cohort 1 may proceed.

Once Cohort 1 has been fully enrolled, or if enrollment has been stopped due to one or more DLTs, then enrollment in the remaining 3 cohorts may commence. Subjects will be randomized in a 1:2:2 ratio to Cohort 2, Cohort 3, or Cohort 4.

7 PROCEDURES

7.1 Procedures for Refraction and Vision Testing

Refraction and Vision Testing will be performed at all time-points specified in Sections 10.2 – 10.5 “Trial Assessments”.

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 Sections 10.2 – 10.5 “Trial Assessments”. On days when two injections are given tonometry should be repeated after the first injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection before the second injection is administered. After the second injection, and also on days when only one injection is administered, IOP must return to < 30 mmHg 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, Day 1, and Month 6/Early Withdrawal. Tono-Pen 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 mmHg occurring more than 30 minutes post-injection, or for a reading of ≥ 30 mmHg at any other time.

7.3 Ophthalmologic Examination

The following examinations will be performed at all time-points specified in Sections 10.2 – 10.5 “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 photography (FP) and fluorescein angiography (FA) will be performed at all time-points specified in Sections 10.2 – 10.5 “Trial Assessments”.

The Sponsor will provide the Principal Investigator with instructions for the FP and FA as well as the submission process to the Reading Committee (RC).

7.5 Spectral Domain Optical Coherence Tomography (SD-OCT)

Spectral Domain optical coherence tomography (SD-OCT) will be performed at all time-points specified in Sections 10.2 – 10.5 “Trial Assessments”.

The Sponsor will provide the Principal Investigator with instructions for the SD-OCT as well as the submission process to the RC.

7.6 Laboratory Tests

The following laboratory tests will be performed as specified in Sections 10.2 – 10.5 “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
- Complete Urinalysis (including specific gravity, protein, and blood)
- 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.

7.7 Vital Signs and Physical Examination

A physical examination will be performed at Screening and at the Investigator's discretion thereafter. Assessment of vital signs will be performed at all time points specified in Sections 10.2 – 10.5 "Trial Assessments".

7.8 12- Lead Electrocardiogram (ECG)

A 12-Lead ECG will be performed at all time points specified in Sections 10.2 – 10.5 "Trial Assessments".

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2, and 20 subjects in cohorts 3 and 4.

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

8.2.1.7 Subjects of either gender aged ≥ 50 years.

8.2.1.8 Performance Status ≤ 2 according to Eastern Cooperative Oncology Group (ECOG) / World Health Organization (WHO) scale (Appendix 17.6)

8.2.1.9 Normal electrocardiogram (ECG) or clinically non-significant changes.

8.2.1.10 Women must 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 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.

8.2.1.11 Provide written informed consent.

8.2.1.12 Ability to 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]

General Exclusion Criteria

8.3.1.16 Any of the following underlying diseases including:

- 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 revascularization within last 6 months, ventricular tachyarrhythmia requiring ongoing treatment.
- History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation.
- Stroke within 12 months of trial entry.
- Any major surgical procedure within one month of trial entry.

8.3.1.17 Subjects with a clinically significant laboratory value. Laboratory tests may be repeated once before randomization.

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

8.3.1.19 Any treatment with an investigational agent in the past 60 days for any condition.

8.3.1.20 Women who are pregnant or nursing.

8.3.1.21 Known serious allergies to the fluorescein dye used in angiography, povidone iodine, to the components of the ranibizumab formulation, or to the components of the Zimura™ formulation.

9 TRIAL MEDICATION

9.1 Drug Supply

9.1.1 Zimura™

Zimura™ is a PEGylated RNA aptamer [redacted]

[redacted]

9.1.2 Lucentis® 0.5 mg

Lucentis® 0.5 mg is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Lucentis® 0.5 mg 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.

9.2 Dose and Administration

9.2.1 Preparation

Zimura™ and Lucentis® 0.5 mg will be injected without dilution.

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

Lucentis® 0.5 mg injection is a preservative-free colorless to pale yellow sterile solution, presented in a single-use glass vial or as a pre-filled syringe 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. Lucentis® should be used without further dilution and administered in accordance with the package insert.

9.2.2 Treatment Regimen and Duration

There will be 4 dosing cohorts on this trial. Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2, and 20 subjects in cohorts 3 and 4.

Cohort 1

Administered Day 1 – Month 5, in the following sequence, 2 days apart:

- D0: Lucentis® 0.5 mg/eye
- D2: Zimura™ 4 mg/eye (administered as two injections of Zimura 2 mg)

Cohort 2

Administered Day 1 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 3

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 4

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence, 2 days apart:

- D0: Zimura™ 2 mg/eye
- D2: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

All subjects will have a final follow-up visit at Month 6.

The first 10 subjects will be enrolled into Cohort 1 according to the procedures noted below.

The first three subjects will be assigned to Cohort 1 (Lucentis® 0.5 mg and Zimura™ 4 mg). Once the 3rd subject completes a safety period of one week after the first dose of Zimura™ 4 mg without the occurrence of a dose limiting toxicity as defined in Section 9.2.3 Dose Limiting Toxicity, full enrollment of Cohort 1 may commence.

If a DLT occurs in one or more of the first 3 subjects assigned to Cohort 1, then the Ophthotech medical team will evaluate all available data and either discontinue Cohort 1 or enroll an additional three subjects (for a total of 6 subjects) in Cohort 1. If the three additional subjects are enrolled, and no additional DLT occurs once the second set of 3 subjects in Cohort 1 has reached one week after the first dose of Zimura™ 4 mg/eye, full enrollment of Cohort 1 may commence. If one or more DLTs occur in the second set of 3 subjects, a discussion of safety data will be held among the Ophthotech medical team to review the observed toxicities and determine whether Cohort 1 may proceed.

Once Cohort 1 has been fully enrolled, or if enrollment has been stopped due to one or more DLTs, then enrollment in the remaining 3 cohorts may commence. Subjects will be randomized in a 1:2:2 ratio to Cohort 2, Cohort 3, or Cohort 4.

9.2.3 Dose Limiting Toxicity

9.2.3.1 Clinical Examination

- Visual acuity: loss of 4 or more lines (≥ 20 letters), Baseline through Week 1. This will not be considered a DLT if the vision loss is due to an event deemed related to the injection procedure by the investigator (e.g., vitreous hemorrhage).
- Clinically significant inflammation: defined as > 3+ according to the grading schedule as modified from the Hogan or Nussenblatt method. (Appendix 17.1 and 17.2)
- Tonometry: increase of intraocular pressure (IOP) from Baseline of ≥ 15 mmHg on two separate examinations at least one day apart excluding the day of injection, despite pharmaceutical intervention.

- Accelerated formation of cataract (not related to the injection procedure): progression of one unit from Baseline to Week 1 defined by the Age-Related Eye Disease Study (AREDS) Lens Opacity Grading Protocol as adapted from the Wisconsin Cataract Grading System where the same observer is used.
- Other severe ocular abnormalities not usually seen in subjects with NVAMD.

9.2.3.2 SD-OCT

Significant retinal abnormalities deemed related to study drugs by the investigator.

9.2.3.3 Systemic DLT

Grade III (severe), IV (life threatening) or V (death related to adverse event) toxicities as defined in the NCI Common Toxicity Criteria version 4.03, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf or any significant severe toxicity deemed related to study drug by the principal investigator.

9.2.4 Administration of Trial Drug

The method for intravitreal administration of Zimura™ and Lucentis® 0.5 mg is described in detail in Appendix 17.4.

9.2.5 Storage

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

9.3 Previous or Concomitant Therapy

Subjects enrolled must be treatment naïve except for oral supplements of vitamins and minerals. Previous treatment for AMD in the study eye prior to Screening is not permitted.

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 NVAMD 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 NVAMD, 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 NVAMD 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.

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 RC will determine eligibility of all subjects prior to enrollment. Only those subjects who fulfill all eligibility criteria will be entered into the trial.

The following assessments will be performed during the study.

10.2 Trial Assessments – Cohort 1

The following dosing days apply to subjects in Cohort 1.

D0	D0 = The first day of dosing at each monthly timepoint.
D2	D2 = The second day of dosing, 2 days after D0.

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
- Ophthalmic history (OU)
- Physical exam/Vital signs
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)
- Serum pregnancy test within 14 days of first trial injection (if applicable)
- Laboratory tests
- Concomitant medication assessment

10.2.1.1 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the following two criteria must be met:

1. There is NO SIGNIFICANT ANATOMICAL CHANGE by clinical examination between the Screening visit and Day 1 (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment).

2. VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 5 LETTERS (better or worse) of the SCREENING VA.

OR

VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 6 – 10 LETTERS (better or worse) of the SCREENING VA, and repeat clinical examination, fundus photography, fluorescein angiography, and SD-OCT imaging – together as judged and documented by the investigator – still meet the inclusion criteria.
If the patient is randomized, the repeat imaging studies must be submitted to the Reading Committee (RC) to be used as the new study Baseline.

If the clinical examination and/or the imaging studies do not meet the inclusion criteria at Day 1, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is GREATER THAN 10 ETDRS LETTERS (better or worse) different from the SCREENING VA, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is NO LONGER WITHIN THE INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200), the patient must NOT be randomized.

10.2.2 Day 1 (D0 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and Ophthalmologic Examination (SE)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.3 Day 1 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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 Day 9 Visit – Subjects in the DLT cohort only. The DLT cohort is defined as the first 3-6 subjects (depending on if DLTs are noted) enrolled in Cohort 1.

- Vital signs
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Ophthalmologic examination and Goldmann applanation tonometry (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)
- Laboratory tests

10.2.5 Month 1 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.6 Month 1 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.2.7 Month 2 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.8 Month 2 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.

- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.2.9 Month 3 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.10 Month 3 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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 4 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.12 Month 4 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.2.13 Month 5 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

  Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.2.14 Month 5 (D2 Visit)

Pre-injection

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

Injection

- Zimura™ 2 mg/eye – **dose 1**
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.

- Zimura™ 2 mg/eye – **dose 2**

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after each injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.2.15 Month 6 (± 7 days)/Early Withdrawal

- Vital signs
- Laboratory tests
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann applanation Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein Angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

10.3 Trial Assessments – Cohort 2

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.***

10.3.1 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
- Ophthalmic history (OU)
- Physical exam/Vital signs
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral domain optical coherence tomography (SD-OCT) (OU)
- Serum pregnancy test within 14 days of first trial injection (if applicable)
- Laboratory tests
- Concomitant medication assessment

10.3.1.1 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the following two criteria must be met:

1. There is NO SIGNIFICANT ANATOMICAL CHANGE by clinical examination between the Screening visit and Day 1 (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment).

2. VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 5 LETTERS (better or worse) of the SCREENING VA.

   OR

VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 6 – 10 LETTERS (better or worse) of the SCREENING VA, and repeat clinical examination, fundus photography, fluorescein angiography, and SD-OCT imaging – together as judged and documented by the investigator – still meet the inclusion criteria.
If the patient is randomized, the repeat imaging studies must be submitted to the RC to be used as the new study baseline.

If the clinical examination and/or the imaging studies do not meet the inclusion criteria at Day 1, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is GREATER THAN 10 ETDRS LETTERS (better or worse) different from the SCREENING VA, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is NO LONGER WITHIN THE INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200), the patient must NOT be randomized.

10.3.2 Day 1 Visit

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and ophthalmologic examination (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.3 Month 1 (± 7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Spectral domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.4 Month 2 (± 7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.5 Month 3 (± 7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral domain optical coherence tomography (SD-OCT) (OU)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye– administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.6 Month 4 (± 7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.7 Month 5 (± 7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.3.8 Month 6 (± 7 days)/Early Withdrawal

- Vital signs
- Laboratory tests
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann applanation Tonometry and Ophthalmologic examination (OU)

- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral domain optical coherence tomography (SD-OCT) (OU)

10.4 Trial Assessments – Cohort 3

The following dosing days apply to subjects in Cohort 3.

D0	D0 = The first day of dosing at each monthly timepoint.
D14	D14 = The second day of dosing, 14 days after D0.

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.***

10.4.1 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
- Ophthalmic history (OU)
- Physical exam/Vital signs
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)

- Spectral Domain optical coherence tomography (SD-OCT) (OU)
- Serum pregnancy test within 14 days of first trial injection (if applicable)
- Laboratory tests
- Concomitant medication assessment

10.4.1.1 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the following two criteria must be met:

1. There is NO SIGNIFICANT ANATOMICAL CHANGE by clinical examination between the Screening visit and Day 1 (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment).

2. VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 5 LETTERS (better or worse) of the SCREENING VA.

   OR

   VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 6 – 10 LETTERS (better or worse) of the SCREENING VA, and repeat clinical examination, fundus photography, fluorescein angiography, and SD-OCT imaging – together as judged and documented by the investigator – still meet the inclusion criteria.
   If the patient is randomized, the repeat imaging studies must be submitted to the RC to be used as the new study baseline.

   If the clinical examination and/or the imaging studies do not meet the inclusion criteria at Day 1, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is GREATER THAN 10 ETDRS LETTERS (better or worse) different from the SCREENING VA, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is NO LONGER WITHIN THE INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200), the patient must NOT be randomized.

10.4.2 Day 1 (D0 Visit) – Induction Phase

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and Ophthalmologic Examination (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.3 Day 1 (D14 Visit ±1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.4 Month 1 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.5 Month 1 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.6 Month 2 (±7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.

- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.7 Month 2 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.8 Month 3 (± 7 days) (D0 Visit) - Maintenance Phase

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.9 Month 4 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.10 Month 5 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) - 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.4.11 Month 6 (±7 days)/Early Withdrawal

- Vital signs
- Laboratory tests
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann applanation Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein Angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

10.5 Trial Assessments – Cohort 4

The following dosing days apply to subjects in Cohort 4.

D0	D0 = The first day of dosing at each monthly timepoint.
D2	D2 = The second day of dosing, 2 days after D0.
D14	D14 = The second day of dosing, 14 days after D0.

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.***

10.5.1 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
- Ophthalmic history (OU)
- Physical exam/Vital signs
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)
- Serum pregnancy test within 14 days of first trial injection (if applicable)
- Laboratory tests
- Concomitant medication assessment

10.5.1.1 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the following two criteria must be met:

1. There is NO SIGNIFICANT ANATOMICAL CHANGE by clinical examination between the Screening visit and Day 1 (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment).

2. VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 5 LETTERS (better or worse) of the SCREENING VA.

   OR

   VISUAL ACUITY at Day 1 is WITHIN INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200) and WITHIN 6 – 10 LETTERS (better or worse) of the SCREENING VA, and repeat clinical examination, fundus photography, fluorescein angiography, and SD-OCT imaging – together as judged and documented by the investigator – still meet the inclusion criteria.
   If the patient is randomized, the repeat imaging studies must be submitted to the RC to be used as the new study baseline.

   If the clinical examination and/or the imaging studies do not meet the inclusion criteria at Day 1, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is GREATER THAN 10 ETDRS LETTERS (better or worse) different from the SCREENING VA, the patient must NOT be randomized.

If the Snellen VA equivalent at Day 1 is NO LONGER WITHIN THE INCLUSION CRITERIA (Snellen equivalent 20/63 to 20/200), the patient must NOT be randomized.

10.5.2 Day 1 (D0 Visit) – Induction Phase

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and Ophthalmologic Examination (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.3 Day 1 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.4 Month 1 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.5 Month 1 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.6 Month 2 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.7 Month 2 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Zimura™ 2 mg/eye

Post-injection

- Indirect Ophthalmoscopy (SE) - 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.8 Month 3 (± 7 days) (D0 Visit) - Maintenance Phase

Pre-Injection

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

- Color fundus photography (FP) (OU)
- Fluorescein angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

Injection

- Zimura™ 2 mg/eye

Post Injection

- Indirect Ophthalmoscopy (SE) - 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

  Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.5.9 Month 3 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.10 Month 4 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Zimura™ 2 mg/eye

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

  Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.5.11 Month 4 (D2 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Lucentis® 0.5 mg/eye – administered 1st

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.

- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.12 Month 5 (± 7 days) (D0 Visit)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic examination (SE)
- Spectral Domain optical coherence tomography (SD-OCT) (SE)

Injection

- Zimura™ 2 mg/eye

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

  Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

10.5.13 Month 5 (D2 Visit)

Pre-injection

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

Injection

- Lucentis® 0.5 mg/eye – administered 1st
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Ophthalmologic exam/Tonometry (SE) – After the injection, to confirm perfusion of the optic nerve and return of IOP to ≤ 21 mmHg or within 5 mmHg of pre-injection.
- Zimura™ 2 mg/eye – administered 2nd

Post 2nd Injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg 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.

10.5.14 Month 6 (± 7 days)/Early Withdrawal

- Vital signs
- Laboratory tests
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann applanation Tonometry and Ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)

- Fluorescein Angiography (FA) (OU, transit SE)
- Spectral Domain optical coherence tomography (SD-OCT) (OU)

10.6 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 NVAMD is initiated before completing the study dosing, the subject will no longer be evaluated according to this protocol.

10.7 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

There will be 4 dosing cohorts in this trial. Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2, and 20 subjects in cohorts 3 and 4.

Cohort 1

Administered for a total of 6 times (Day 1 – Month 5), in the following sequence, 2 days apart:

- D0: Lucentis® 0.5 mg/eye
- D2: Zimura™ 4 mg/eye (administered as two injections of Zimura 2 mg)

Cohort 2

Administered for a total of 6 times (Day 1 – Month 5), in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 3

Induction Phase: Administered for a total of 3 times (Day 1 – Month 2), in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered for a total of 3 times (Month 3 - Month 5), in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 4

Induction Phase: Administered for a total of 3 times (Day 1 - Month 2), in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered for a total of 3 times (Month 3 - Month 5) in the following sequence, 2 days apart:

- D0: Zimura™ 2 mg/eye
- D2: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

All subjects will have a final follow-up visit at Month 6.

The first 10 subjects will be enrolled into Cohort 1 according to the procedures noted below.

The first three subjects will be assigned to Cohort 1 (Lucentis® 0.5 mg and Zimura™ 4 mg). Once the 3rd subject completes a safety period of one week after the first dose of Zimura™ 4 mg without the occurrence of a dose limiting toxicity as defined in Section 9.2.3 Dose Limiting Toxicity, full enrollment of Cohort 1 may commence.

If a DLT occurs in one or more of the first 3 subjects assigned to Cohort 1, then the Ophthotech medical team will evaluate all available data and either discontinue Cohort 1 or enroll an additional three subjects (for a total of 6 subjects) in Cohort 1. If the three additional subjects are enrolled, and no additional DLT occurs once the second set of 3 subjects in Cohort 1 has reached one week after the first dose of Zimura™ 4 mg/eye, full enrollment of Cohort 1 may commence. If one or more DLTs occur in the second set of 3 subjects, a discussion of safety data will be held among the Ophthotech medical team to review the observed toxicities and determine whether Cohort 1 may proceed.

Once Cohort 1 has been fully enrolled, or if enrollment has been stopped due to one or more DLTs, then enrollment in the remaining 3 cohorts may commence. Subjects will be randomized in a 1:2:2 ratio to Cohort 2, Cohort 3, or Cohort 4.

11.2 Randomization

Once all subjects have been enrolled in cohort 1, subjects will be centrally allocated to one of the three remaining treatment cohorts using a randomization list generated by a block randomization.

11.3 Endpoints

Safety Endpoints:

Safety endpoints include adverse events, vital signs, electrocardiography readings (ECG), ophthalmic variables [visual acuity, intraocular pressure (IOP), ophthalmic

examination, stereoscopic fundus photography, fluorescein angiography (FA), spectral domain optical coherence tomography (SD-OCT)], and laboratory variables.

11.4 Number of Subjects

Approximately 60 subjects will be enrolled, 10 subjects in cohorts 1,2 and 20 subjects in cohorts 3, 4.

11.4.1 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 variables of the proposed regimen and to improve upon the study design prior to performance of controlled trials that may be initiated in the future.

11.4.2 Statistical Analyses

No formal hypothesis testing will be performed.

11.4.3 Descriptive Statistics

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

11.4.4 Safety Analysis

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

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

All laboratory data will be listed and values falling outside normal ranges will be identified. Summary statistics (i.e., mean, median, standard deviation, minimum, and maximum) will be presented for all continuous variables.

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.

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 intravitreal injection procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, subconjunctival injection of anesthetic, intravitreal injection), termed "injection procedure-related", or to study drug (Zimura™ or Lucentis® 0.5 mg).

The relationship to the intravitreal 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 promptly 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.

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

Anderson D.H., Mullins R.F., Hageman G.S., Johnson L.V. (2002). A role for local inflammation in the formation of drusen in the aging eye. Am J Ophthalmol., 134(3):411-31.

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.

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., Kaliappan, S., Kaplan, H., 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.

Brown, D. M., Kaiser, P. K., Michels, M., Soubrane, G., Heier, J. S., Kim, R. Y., SY J.P., Schneider S., Anchor Study Group (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med, 355(14), 1432-1444.

Busbee, B. G., Ho, A. C., Brown, D. M., Heier, J. S., Suner, I. J., Li, Z., Rubio R.G., Lai P.; HARBOR Study Group (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.

Chen, G., Tzekov, R., Li, W., Jiang, F., Mao, S., & Tong, Y. (2015) Pharmacogenetics of Complement Factor HY402H Polymorphism and Treatment of Neovascular AMD with Anti-VEGF Agents: A Meta-Analysis. Scientific Reports, 5:14517.

Chirco, K., Tucker, B., Stone, E., Mullins, R. (2015) Selective Accumulation of the Complement Membrane Attack Complex in Aging Choriocapillaris. Experimental Eye Research, 146:393-397.

Day, J. (1993). Population Projections of the United States, by Age, Sex, Race, and Hispanic Origin: 1993 to 2050. Government Printing Office, P25-110 (Current Population Reports).

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.

Georgiannakis, A., Burgoyne, T., Lueck, K., Flutter, C., Greenwood, J., Moss, S. (2015) Retinal Pigment Epithelial Cells Mitigate the Effects of Complement Attack by Endocytosis of C5b-9. J of Immunol, 195:3382-3389.

Grunwald, J., Daniel, E., Huang, J., Ying, G., Maguire, M., Toth, C., Jaffe, G., Fine, S., Blodi, B., Klein, M., Martin, A., Hagstrom, S., Martin, D., (2014). Risk of Geographical Atrophy in the Comparison of Age-related Macular Degeneration Treatment in Trials. Ophthalmology 121:150-161.

Grunwald, J., Pistilli, M., Daniel, E., Ying, G., Pan, W., Jaffe, G., Toth, C., Hagstrom, S., Maguire, M., Martin, D., (2017). Incidence and Growth of Geographic Atrophy during 5 Years of Comparison of Age-Related Macular Degeneration Treatments in Trials. Ophthalmology, 124:97-104.

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.

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.

Hobbs, F. B. (1996). The elderly population. Retrieved 10 Oct 2015, 2015.

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.

Jo, D., Kim, J., Yang, W., Kim, H., Chang, S., Kim, D., Chang, M., Lee, K., Chung, J., Kim, J. (2017) Anti-complement Component of 5 Antibody Targeting MG4 Domain Inhibits Choroidal Neovascularization. Oncotarget. 11;8(28):45506-45516.

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.

Keir, L., Firth, R., Aponik, L., Feitelberg, D., Sakimoto, S., Aguilar, E., Welsh, G., Richards, A., Yoshihiko, U., Satchell, S., Kuzmuk, V., Coward, R., Goult, J., Bull, K., Sharma, R., Bharti, K., Westenskow, P., Michael, I., Saleem, M., Friedlander, M., (2017) VEGF Regulates Local Inhibitory Complement Proteins in the Eye and Kidney. J Clin Invest, 127(1) 199-214.

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., Henning, A., SanGiovanni, J., Mane, S., Mayne, S., Bracken, M., Ferris, F., Ott, J., Barnstable,

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 Sataract, Glaucoma, Diabetic Retinopathy, Macular Degeneration, and Visual Acuity in a General Population of 2631 Adults, 1973-1975. Surv Ophthalmol, 24(Suppl), 335-610.

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.

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.

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.

Ortma, J. M., & Velkof, V. A. (2014). An Aging Nation: The Older Population in the United States. Current Population Reports, (May).

Parikh, R., Ross, J. S., Sangaralingham, L. R.,Adelman, Ron A., Shah, N. D., Barkmeier, A. J.(2017). Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients. Ophthalmology, 2017;124:352-358.

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.

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.

Rohrer, B., Long, Q., Coughlin, B., Wilson, R., Huang, Y., Qiao, F., Tang, P., Kunchithapautham, K., Gilkeson, G., Tomlinson, S. (2009). A Targeted Inhibitor of the Alternative Complement Pathway Reduces Angiogenesis in a Mouse Model of Age-Related Macular Degeneration. Investigative Ophthalmology & Visual Science, 50(7):3056-64.

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y., Kim, R., MARINA Study Group (2006). Ranibizumab for Neovascular Age-related Macular Degeneration. N Engl J Med, 355(14), 1419-1431.

Rosenfeld, R., Heier, J., Hantsbarger, G., Shams, N. (2006) Tolerability and Efficacy of Multiple Escalating Doses of Ranibizumab (Lucentis) for Neovascular Age-Related Macular Degeneration. Ophthalmology 113:623-632.

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.

Schmidt-Erfurth, U., Kaiser, P., Korobelnik J-K., Brown, D., Chong, V., Nguyen, Q., Ho, A., Ogura, Y., Simader, C., Jaffe, G., Slakter, J., Yancopoulos, G., Stahl, N., Vitti, R., Berliner, A., Soo, Y., Anderesi, M., Sowade, O., Zeitz, O., Norenberg, C., Sandbrink, R., Heier, J. (2014) Ophthalmology;121:193-201.

Schnabolk, G., Beon, M. K., Tomlinson, S., Rohrer, B. (2017). New Insights on Complement Inhibitor CD59 in Mouse Laser-Induced Choroidal Neovascularization: Mislocalization After Injury and Targeted Delivery for Protein Replacement. J Ocul Pharmacol Ther, 33(5): 400-411.

Stewart, M.W., Rosenfeld, P., Penha, F. M., Wang, F., Yehoshua, Z., Bueno-Lopez, E., Lopez, P. F. (2012). Pharmacokinetic Rationale for Dosing Every 2 Weeks

Versus 4 Weeks with Intravitreal Ranibizumab, Bevacizumab, and Aflibercept (Vascular Endothelial Growth Factor Trap-eye). Retina, 32(3):434-57.

Van Newkirk, M. R., Nanjan, M. B., Wang, J. J., Mitchell, P., Taylor, H. R., & McCarty, C. A. (2000). The Prevalence of Age-related Maculopathy: The Visual Impairment Project. Ophthalmology, 107(8), 1593-1600.

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.

U.S. Census Bureau. International Database. Washington, DC. 2012

16 SIGNATURE PAGE

Signatures confirm that this protocol OPH2007 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 OPH2007: A Phase 2A Open-Label Trial to Assess the Safety of Zimura™ (Anti-C5) Administered in Combination with Lucentis® 0.5 mg in Treatment Naïve Subjects with Neovascular Age Related Macular Degeneration

Trial Sponsor: **Ophthotech Corporation**

Principal Investigator: _____ _____

Name (Print) ***(Signature)***

_____

(Date)

17 APPENDICES

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

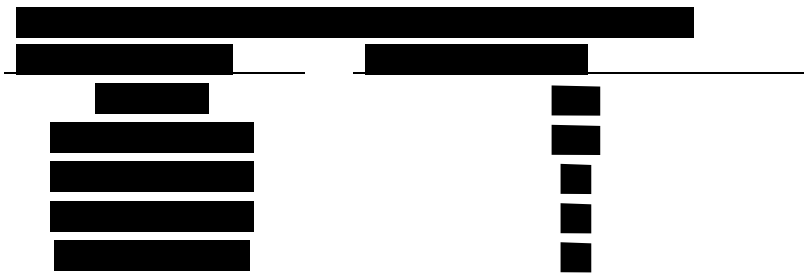
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]							
[redacted]	[redacted]		[redacted]			[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	

[redacted])

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]