Official Study Title: A Phase 2/3 Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration

NCT#: NCT02686658

Document: Protocol

Document Date: 28 March 2018

[redacted] RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFICACY OF INTRAVITREOUS ADMINISTRATION OF ZIMURA™ (ANTI-C5 APTAMER) IN SUBJECTS WITH GEOGRAPHIC ATROPHY SECONDARY TO DRY AGE-RELATED MACULAR DEGENERATION

PROTOCOL NO: OPH2003
AMENDMENT C

Version Date: 28 March 2018

SPONSOR:
OPHTHOTECH CORP.
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EudraCT No. 2015-003991-56

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1 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
C	Complement Factor
CFH	Complement Factor H
CNV	Choroidal Neovascularization
CRO	Contract Research Organization
CRF	Case Report Form
CRP	C-reactive protein
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EC	Endothelial Cell
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FE	Fellow Eye
GA	Geographic Atrophy
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl-Transferase
hERG	human Ether-à-Go-Go-Related Gene
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IL-6	Interleukin-6
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent to Treat Population
MAC	Membrane Attack Complex
MMRM	Mixed Model Repeated Measures
NLP	No Light Perception
NV	Neovascular
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OU	Both eyes
RC	Reading Center
REML	restricted maximum likelihood
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SE	Study Eye
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

2 SUMMARY OF PROTOCOL OPH2003

SYNOPSIS	
TITLE:	[redacted] Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration
OBJECTIVES:	The objectives of this study are to evaluate the safety and efficacy of Zimura™ intravitreous administration when administered in subjects with geographic atrophy secondary to dry age-related macular degeneration (AMD).
TRIAL DESIGN:	In Part 1, approximately 77 subjects will be randomized in a 1:1:1 ratio to the following dose groups: • **Zimura™ 1 mg/eye** • **Zimura™ 2 mg/eye** • **Sham** Commencing with Amendment C, no new subjects will be enrolled in Part 1 of this trial as recruitment has been completed for Part 1. In Part 2, approximately 200 subjects will be randomized in a 1:2:2 ratio to the following dose groups: • **Zimura™ 2 mg/eye + Sham** • **Zimura™ 4 mg/eye (administered as two injections of Zimura™ 2 mg/eye)** • **Sham + Sham** Subjects will receive monthly intravitreal injections of Zimura™ and/or Sham for 18 months.
ENDPOINTS:	<u>Primary Efficacy Endpoint:</u> • Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12 <u>Secondary Efficacy Endpoints:</u> Secondary efficacy endpoints will be assessed from Baseline to Month 12: • The mean change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from Baseline to Month 12 • Mean change in low luminance best corrected visual acuity

SYNOPSIS	
	(ETDRS letters) from Baseline to Month 12 Safety Endpoints: • Adverse events (AEs) • Vital signs (pulse, systolic and diastolic blood pressure) • Ophthalmic findings (intraocular pressure [IOP], ophthalmic examination, fluorescein angiogram, FAF, and Optical Coherence Tomography [OCT]) • Electrocardiogram (ECG) (12-lead) • Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)
PLANNED SAMPLE SIZE:	Approximately 277 subjects will be enrolled.
SUBJECT SELECTION:	Subjects of either gender aged 50 years or greater diagnosed with geographic atrophy secondary to dry AMD.
FORMULATION:	[redacted]
INVESTIGATIONAL DRUG DOSAGE:	Subjects randomized to active drug will receive 18 doses of Zimura™ at a dose of 1 mg/eye, 2 mg/eye or 4 mg/eye. Commencing with Amendment C, no new subjects will be enrolled in Part 1 of this trial.

3 STUDY ASSESSMENTS

Year 1

Assessment	SCR	Day 1[1]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X													
Medical & Ophthalmic History[3], Performance Status	X													
Vital Signs/ Physical Exam[2]	X							X						X
12-Lead ECG	X							X						X
Protocol refraction and EDTRS Visual Acuity[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[3,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Low Luminance EDTRS Visual Acuity[3]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]						[redacted]						[redacted]
[redacted]		[redacted]						[redacted]						[redacted]
Color Fundus Photographs[3]	X							X						X
Fluorescein Angiogram[3]	X							X						X
Optical Coherence Tomography (OCT)[3]	X							X						X
Fundus Autofluorescence[3]	X							X						X
Laboratory Tests/Serum Pregnancy (If Applicable)	X							X						X
Randomization		X												
Zimura™/Sham Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 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 are performed at all indicated time points.
[3]Ocular assessments are performed at Baseline (Screening or Day 1), Months 6, 12, and Month 18/Early Withdrawal on both eyes (OU) pre-injection. Ocular assessments at all other study visits are performed on the study eye (SE) only. [redacted]
[4]Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Months 6, 12,18/Early Withdrawal. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify IOP ≥30 mmHg occurring at any time.
[5]Tonometry should be measured prior to the injection, and after each injection as per Section 10, Trial Conduct.
[6]A full ophthalmic exam is performed prior to the injection, and again at least 30 minutes after the last injection.
[7]Adverse events are to be recorded starting after the first dose of study drug.

VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the following visit windows – Months 1 to 18: ± 7 days. Monthly doses must be administered at least 21 days apart.

STUDY ASSESSMENTS (CONTINUED)

Year 2

Assessment	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18/EW
Vital Signs/ Physical Exam[2]						X
12-Lead ECG						X
Protocol refraction and EDTRS Visual Acuity[3]	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[3,6]	X	X	X	X	X	X
Low Luminance EDTRS Visual Acuity[3]	X	X	X	X	X	X
[redacted]						[redacted]
[redacted]						[redacted]
Color Fundus Photographs[3]						X
Fluorescein Angiogram[3]						X
Optical Coherence Tomography (OCT)[3]						X
Fundus Autofluorescence[3]						X
Laboratory Tests/Serum Pregnancy (If Applicable)						X
Zimura™/Sham Study Drug Administration	X	X	X	X	X	
3-Day Post-Injection Telephone Safety Check	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events[7]	X	X	X	X	X	X

[2]Physical examination is performed at Screening, and at the investigator's discretion thereafter. Vital Signs are performed at all indicated time points.
[3]Ocular assessments are performed at Baseline (Screening or Day 1), Months 6, 12, and at Month 18/Early Withdrawal on both eyes (OU) pre-injection. Ocular assessments at all other study visits are performed on the study eye (SE) only. [redacted]
[4]Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Months 6, 12, 18/Early Withdrawal. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify IOP ≥30 mmHg occurring at any time.
[5]Tonometry should be measured prior to the injection, and after each injection as per Section 10, Trial Conduct.
[6]A full ophthalmic exam is performed prior to the injection, and again at least 30 minutes after the last injection.
[7]Adverse events are to be recorded starting after the first dose of study drug.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the following visit windows – Months 1 to 18: ± 7 days.

4 INTRODUCTION

4.1 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina. AMD is characteristically a disease of the elderly and is the leading cause of blindness in individuals >50 years of age 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 increasing life expectancy in developed and developing countries, the elderly sector of the general population is expected to increase at the greatest rate in coming decades (Ortma & Velkof, 2014). While 1 in 8 Americans was considered to be elderly in 1994, it is expected that 1 in 5 will fall into this category by 2030 (Day, 1993; Hobbs, 1996). Projections based on U.S. Census Bureau data suggest that the number of Americans over the age of 65 will more than double, increasing it to 80 million by the middle of this century (Day, 1993). In the absence of adequate prevention or treatment measures, the number of cases of AMD with visual loss is expected to grow in parallel with the aging population.

AMD is classified into one of two general subgroups; the non-neovascular ("dry") form of the disease and the neovascular ("wet") form of the disease. The non-neovascular dry form of AMD is more prevalent, accounting for approximately 90% of all AMD cases. It is characterized by degeneration of the macula, and with continued progression over multiple years, may ultimately result in atrophy of the central retina associated with central vision loss. By contrast, neovascular AMD, although less prevalent, is more likely to cause sudden, often substantial, loss of central vision (Holz et al., 2014).

Dry AMD is a significant cause of moderate and severe loss of central vision and is bilateral in most patients (Maguire & Vine, 1986; Potter & Thallemer, 1981; Sarks et al., 1988; Schatz & McDonald, 1989; Sunness et al., 1999). In dry AMD, thinning of the retinal pigment epithelial cells (RPE) in the macula develops, along with other age-related changes to the adjacent retinal tissue layers (Holz et al., 2014). Dry AMD is characterized by the presence of drusen (yellow crystalline deposits that develop within the macula) located under the RPE (Holz et al., 2014). When severe, dry AMD results in marked thinning and/or atrophy of the macula, resulting from the loss of the RPE and associated capillaries (choriocapillaris). This form of late stage

dry AMD is associated with thinning and loss of function of the neural retinal located above the affected RPE (McLeod et al., 2009). This collective phenotype in late stage dry AMD is termed geographic atrophy (GA). The progressive degeneration of light-sensitive photoreceptor cells in GA leads to severe visual loss in affected eyes. In addition, dry AMD can progress to the wet form of the disease (Holz et al., 2014).

Although dry AMD is the most common form of the disease, currently no approved therapy exists. The absence of treatment options for dry AMD represents an area of urgent unmet medical need, and a major public health concern for the rapidly increasing elderly population.

4.2 AMD and the Complement Pathway

The etiology of AMD is not completely understood (Frederick & Kleinman, 2014). In addition to advanced age, environmental and genetic risk factors for AMD are well recognized, including ocular pigmentation, dietary factors, family history for AMD, hypertension, and smoking (Klein et al., 2004). Research also indicates that inflammation is a major contributor to the pathogenesis of AMD (P.S. Bora et al., 2005).

Mounting evidence suggests that both the wet and dry forms of AMD may involve an inflammatory process (Bok, 2005; Donoso et al., 2006). Patients with AMD are known to have elevated systemic inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and homocysteine (Bok, 2005; Seddon et al., 2005). Furthermore, surgically excised choroidal neovascular tissue in patients with AMD contains inflammatory cells (Grossniklaus et al., 2005).

The role for complement (C)-mediated inflammation in AMD is highlighted by genetic linkage and association studies, which suggest that approximately 50% of AMD cases have polymorphism in complement regulatory proteins compared to age-matched controls (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005; Narayanan et al., 2007). Furthermore, polymorphism in genes coding for complement or complement regulatory proteins confer an increased risk in age-related macular degeneration.

The complement pathway involves a complex system of serum proteins as a part of the innate immune system which interacts in a cascade (Holers, 2014). The complement cascade is activated via the classical (antibody-dependent), the

alternative (antibody-independent), and the lectin pathways (Holers, 2014). Recent studies have implicated local inflammation and activation of the complement cascade in drusen formation (Hageman et al., 2001; Seddon et al., 2006). Additionally, the complement components of drusen may induce vascular endothelial growth factor (VEGF) up-regulation, and therefore contribute to the formation of neovascular AMD (Nozaki et al., 2006). Preclinical laser-induced choroidal neovascularization (CNV) models have also implicated complement activation (P.S. Bora et al., 2005). In experimental models of CNV, membrane attack complex (MAC: C5b-9) formation has been shown to be important (Nozaki et al., 2006). The MAC results in pore formation in affected cells that eventually lead to cell death (Holers, 2014). Inhibition of the alternate pathway of complement activation leads to a reduction in pro-angiogenic factors and decreased CNV formation in models of experimental CNV (N. S. Bora et al., 2006; Johnson et al., 2000).

The results from two recently completed clinical studies, with different molecules designed to block the complement pathways, have further substantiated the proof of concept for this approach in GA (Hariri et al., 2015; OPH2001).

4.2.1 Non-Clinical Efficacy

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

4.2.2 Non-Clinical Pharmacokinetics of Zimura™

The sponsor has performed supportive non-clinical pharmacology studies with Zimura™, and, in some cases, with related aptamers. [redacted]

These safety pharmacology studies did not reveal any effects on cardiovascular, respiratory or neurologic function.

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

4.2.3 Toxicology

[redacted]

Additional details regarding 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.

4.3 Clinical Data

In a phase 1 study, which enrolled patients diagnosed with geographic atrophy, subjects received treatment with three 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. Patients received two subsequent injections at Week 24 and Week 36 followed by a final follow up visit at Week 48. [redacted]

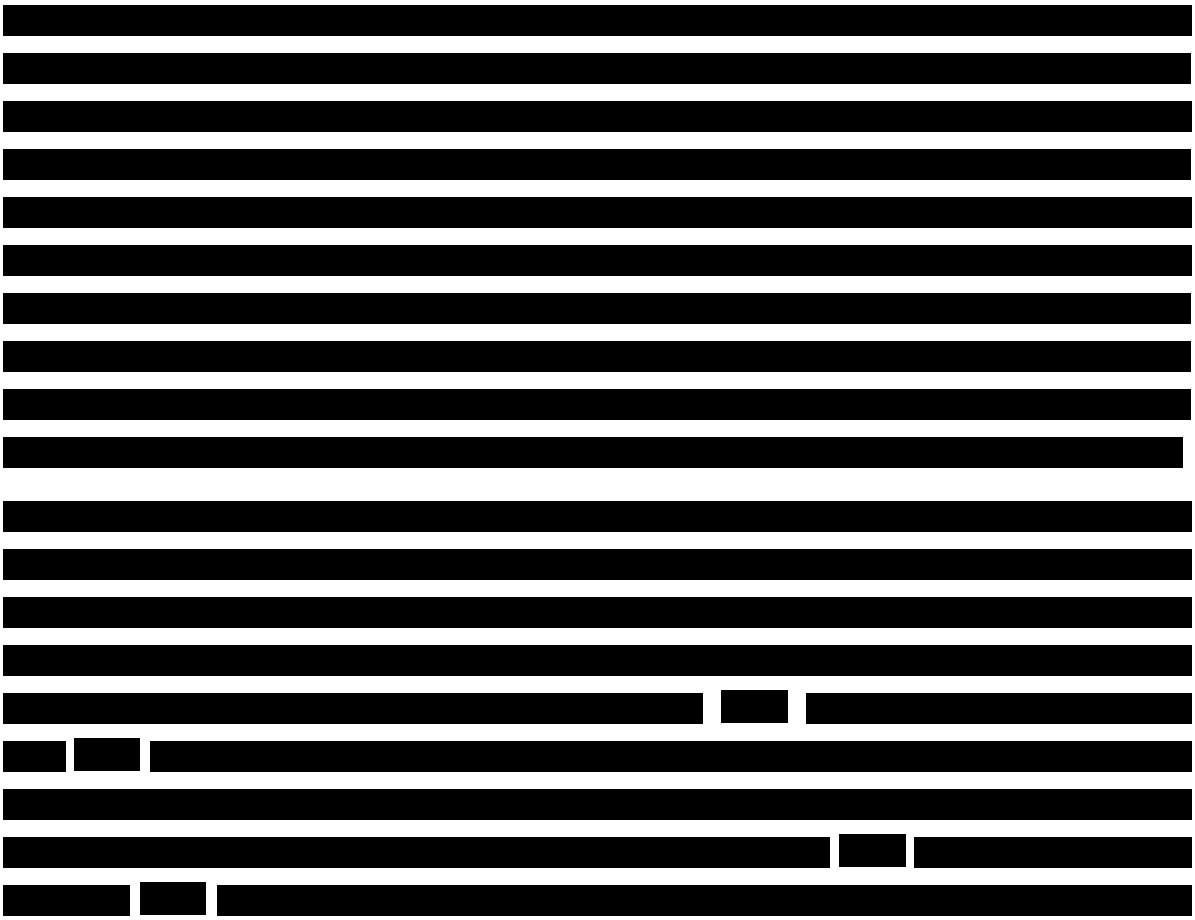
Standard safety assessments were performed for ophthalmic variables which included visual acuity (VA), intraocular pressure (IOP), ophthalmic examination, Fundus Auto-Fluorescence (FAF), Fluorescein Angiography (FA), and Spectral-Domain Optical Coherence Tomography (SD-OCT) together with adverse events (AEs), vital signs, and laboratory variables. [redacted]

[redacted] Fifteen patients (32%) had AEs, predominantly Eye Disorder AEs in the study eye (SE), assessed to be related to the injection procedure. The most frequently reported ocular AEs were

conjunctival hemorrhage (4 patients, 9%), corneal edema (4 patients, 9%), and dry eye (3 patients, 6%). No other study eye AEs were reported by more than two patients. The majority of AEs were mild or moderate in severity. There were 2 patients with AEs of severe intensity: gastrointestinal inflammation and nasopharyngitis.

Five patients experienced serious adverse events (SAEs), namely device failure, pelvic fracture, angina pectoris, chest pain, gastrointestinal inflammation, but none were related to the study drug or injection procedure. There were no discontinuations due to AEs.

Vital signs and laboratory assessments did not show any particular clinically significant patterns or changes. Study eye (SE) ophthalmic examinations were mostly normal. There were some transient findings post-injection (conjunctiva/sclera and cornea) which resolved prior to the next injection. Vitreous haze was also reported for a few patients. IOP showed a small mean increase following injections but no indication of any cumulative increase. Visual acuity (VA) assessments did not show any safety concerns.



[redacted]

In another phase 1 ascending dose and parallel group trial the safety, tolerability, and pharmacokinetic profile of multiple intravitreous injections of Zimura™ in combination with Lucentis® 0.5mg was evaluated in subjects with wet AMD (OPH 2000). In this study, 60 patients received doses of 0.03 mg, 0.3 mg, 1 mg, or 2 mg of Zimura™. Zimura™ was well tolerated and no particular safety concerns were identified.

Further, VA assessment for the treatment naïve patients who received 6 injections at the dose levels of 0.3 mg, 1 mg, or 2 mg indicated a trend towards a mean increase in VA (number of Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from baseline at all time points. At Week 24, there was an overall improvement in VA from baseline of 13.6 letters with the greatest improvement seen for the 2 mg dose group (15.3 letters).

Taken together, there is a rationale to further investigate the antagonism of C5 component of complement cascade by Zimura™ in dry AMD subjects with GA.

4.4 Trial Rationale

Multiple studies suggest that the activation of the complement system plays a major role in the pathogenesis and progression of both dry and wet AMD. These include genetic studies, histopathological studies, non-clinical *in vivo* studies, and evaluation of systemic biomarkers in patients at risk (Bok, 2005; Donoso et al., 2006; Edwards et al., 2005; Grossniklaus et al., 2005; Hageman et al., 2005; Haines et al., 2005).

Much of the scientific foundation implicating the complement system is derived from seminal studies from multiple independent labs, published in 2005 (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005; Narayanan et al., 2007). These studies infer that approximately 50% of the dry and wet forms of AMD may have underlying activation of the complement system. Further, the Y402H variant of the complement factor H (CFH) gene has been shown to be

strongly associated with geographic atrophy in the populations of various countries (United States of America, United Kingdom, Netherlands, Iceland) (Magnusson et al., 2006; Seddon et al., 2007; Sepp et al., 2006).

Histopathologic studies confirming the presence of complement activation in AMD have also been published (Grossniklaus et al., 2005). In a monkey pedigree with macular degeneration manifested by drusen that share phenotypic features with dry AMD in humans, these drusen were strongly reactive with antibodies against complement C5 (Umeda et al., 2005a) and the membrane attack complex (MAC, the terminal C5b-9 complement complex) (Umeda et al., 2005b). A study of eyes from more than 400 human donors revealed that drusen are intensely labelled using antibodies against complement C5 and MAC, and multiple complement regulatory proteins have also been shown to be present in drusen (Anderson et al., 2002).

Therefore, preclinical models, clinical and genetic studies implicate the activation of the complement cascade in AMD (Bok, 2005; Donoso et al., 2006; Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005). Inhibition of complement activation may potentially slow down or arrest the underlying pathobiology of macular degeneration. Thus, molecules involved in regulation and inhibition of complement activation are prime targets for therapeutic intervention in AMD.

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

5 TRIAL OBJECTIVES

5.1 Objectives

The objectives of this study are to evaluate the safety and efficacy of Zimura™ intravitreous administration when administered in subjects with geographic atrophy secondary to dry age-related macular degeneration (AMD).

5.2 Endpoints

Primary Efficacy Endpoint:

Mean rate of change in GA over 12 months measured by FAF at three time points: Baseline, Month 6, and Month 12

Secondary Efficacy Endpoints:

- The mean change in best corrected visual acuity (ETDRS letters) from Baseline to Month 12
- Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 12

Safety Endpoints:

- AEs
- Vital signs (pulse, systolic and diastolic blood pressure)
- Ophthalmic variables (IOP, ophthalmic examination, FA, FAF, and OCT)
- ECG (12-lead)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)

6 TRIAL DESIGN

In Part 1, approximately 77 subjects will be randomized in a 1:1:1 ratio to the following dose groups:

- **Zimura™ 1 mg/eye**
- **Zimura™ 2 mg/eye**
- **Sham**

Commencing with Amendment C, no new subjects will be enrolled in Part 1 of this trial as recruitment has been completed for Part 1.

In Part 2, approximately 200 subjects will be randomized in a 1:2:2 ratio to the following dose groups:

- **Zimura™ 2 mg/eye + Sham**
- **Zimura™ 4 mg/eye (administered as two injections of Zimura™ 2 mg)**
- **Sham + Sham**

Subjects will receive monthly intravitreal injections of Zimura™ and/or Sham for 18 months.

7 PROCEDURES

7.1 Refraction and Visual Acuity, [redacted] and Low Luminance Visual Acuity

Refraction, Vision Testing, Low Luminance, [redacted] will be performed at all time-points specified in Section 10.2 "Trial Assessments". Retroilluminated modified Ferris-Bailey ETDRS 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 ***masked to the previous visual acuity measurement and to whether or not the subject has been assigned to active treatment or Sham***. The examiner will be supplied with the previous protocol refraction only.

All necessary materials and instructions these assessments will be provided by Ophthotech Corp.

[redacted]

These assessments should always be performed in the following order; Refraction, Visual Acuity, [redacted] and then Low Luminance.

7.2 Tonometry

Tonometry will be performed at all time-points specified in Section 10.2 "Trial Assessments". On days when two injections are given, the second injection may not be administered until the IOP is ≤ 21 mmHg or within 5 mmHg of the pre-injection IOP, at which time the IOP is recorded. After the second injection and also

on days with only one injection, the IOP should be measured and recorded at least 30 minutes after the injection and IOP must be < 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 and pre-injection on Day 1, Months 6, 12, 18, and Early Withdrawal. Tono-Pen may be used at all other timepoints. Goldmann applanation tonometry must also be used to verify intraocular pressure (IOP) reading of ≥ 30 mmHg occurring at any time.

7.3 Ophthalmologic Examination

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

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

7.4 Fundus Photography, Fluorescein Angiography, and Fundus Autofluorescence

Color stereoscopic fundus photographs, FA, and FAF will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

A Reading Center (RC) will confirm eligibility of subjects prior to enrollment. All color fundus photos, FAs, and FAFs that are collected at protocol-specified time points must be sent to the RC as specified in the RC procedure manual. The RC will provide instructions for the color fundus photographs, FA, and FAF procedures.

7.5 Optical Coherence Tomography (SD-OCT)

Spectral Domain Optical Coherence Tomography (SD-OCT) will be performed at all time-points specified in Section 10.2 “Trial Assessments”. The RC will provide instructions for the OCT procedures, including which OCT reports must be sent to the RC.

7.6 Laboratory Tests

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

- Hematology: hemoglobin, platelet count, WBC and differential
- Renal Function: serum creatinine and blood urea nitrogen (BUN)
- Hepatic function: serum bilirubin, alkaline phosphatase, gamma-glutamyl-transferase (GGT), serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT)
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium and phosphate
- Complete Urinalysis (including specific gravity, protein, blood, etc.)
- Serum pregnancy test (if of child-bearing potential)

If a laboratory value outside of the normal range is judged as clinically significant by the Investigator, the Investigator should 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 should 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, Physical Examination and Performance Status (ECOG)

A physical examination will be performed at Screening and at the Investigators’ discretion thereafter. Assessment of vital signs will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

Performance Status (Eastern Cooperative Oncology Group [ECOG]) will be

assessed at Screening in accordance with Appendix 17.4.

7.8 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

7.9 [redacted]

[redacted]

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 277 subjects will be enrolled.

8.2 Inclusion Criteria

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

8.2.1 Ophthalmic Inclusion Criteria

The following inclusion criteria apply to the SE:

[redacted]

[redacted]

[redacted]

[redacted]

8.2.2 General Inclusion Criteria

8.2.2.1 Subjects of either gender aged ≥ 50 years.

8.2.2.2 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.

8.2.2.3 Provide written informed consent.

8.2.2.4 Ability to return for all trial visits.

8.3 Exclusion Criteria

Subjects will ***not be eligible for the trial*** if subjects cannot attend all trial required visits, or if any of the following criteria are present systemically or in the SE:

8.3.1 Ophthalmic Exclusion Criteria

The following exclusion criteria apply to the SE:

[redacted]

[redacted]

[redacted]

[redacted]

8.3.2 General Exclusion Criteria

8.3.2.1 Any of the following underlying diseases including:

- History or evidence of severe cardiac disease (e.g., New York Heart Association [NYHA] Functional Class III or IV - see Appendix 17.6),

history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or revascularization within last 6 months, ventricular tachyarrythmias requiring ongoing treatment.

- History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation.
- Clinically significant impaired renal (serum creatinine >2.5 mg/dl or status post renal transplant or receiving dialysis) or hepatic function. Subjects with results outside these ranges may be enrolled after consultation with Ophthotech Corp.
- Stroke (within 12 months of trial entry).
- Any major surgical procedure within 1 month of trial entry.

8.3.2.2 Previous therapeutic radiation in the region of the SE.

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

8.3.2.4 Women who are pregnant or nursing.

8.3.2.5 Known serious allergies to the fluorescein dye used in angiography or to the components of the Zimura™ formulation.

8.3.2.6 History of systemic treatment with any anti-complement agent in the past or the likelihood of treatment with any systemic anti-complement agent during the study.

9 TRIAL MEDICATION

9.1 Drug Supply

9.1.1 Zimura™

Zimura™ is a pegylated RNA aptamer [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.2 Treatment Regimen and Duration

Subjects randomized to active drug or Sham will receive monthly injections of Zimura™ or Sham for 18 months. Monthly doses should be administered at least 21 days apart.

- Part 1 Subjects:
    - Subjects randomized to the Zimura™ 1 mg/eye treatment arm will receive Zimura™ 1 mg/eye (50 µL) intravitreal injection.
    - Subjects randomized to the Zimura 2 mg/eye treatment arm will receive Zimura™ 2 mg/eye (100 µL) intravitreal injection.

- Subjects randomized to the Sham treatment arm will receive Sham injections.
- Commencing with Amendment C, no new subjects will be enrolled in Part 1 of this trial. Subjects in Part 1 who have received greater than or equal to 18 months of Study Drug treatment will be discontinued from the study after Amendment C.

- Part 2 Subjects:
  - Subjects randomized to the Zimura™ 2 mg/eye treatment arm will receive a Zimura™ 2mg/eye injection (100 µL) and a Sham injection
  - Subjects randomized to the Zimura™ 4 mg/eye treatment arm will receive two injections of Zimura™ 2 mg/eye. The injection volume for subjects randomized to this arm will be of (100 µL) per injection.
  - Subject's randomized to the Sham treatment arm will receive 2 Sham injections.

9.1.3 Administration of Trial Drug

An (Interactive Randomization Technology) IRT system will be used to assign masked study kits to subjects throughout the duration of the trial. All study medication must be dispensed using the IRT system. At each dispensing visit the IRT system will allocate each study drug kit(s) using the kit number on the label of the study medication kit.

[redacted]

[redacted]

9.1.4 Storage

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

9.2 Previous or Concomitant Therapy

Subjects enrolled must be treatment-naïve (no previous treatment for AMD) in either eye except for oral supplements of vitamins and minerals.

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

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.

10.2 Trial Assessments

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

Ocular assessments performed at Baseline (Screening or Day 1), Month 6, Month 12, and Month 18 (and at an Early Withdrawal visit if performed) should be performed on both eyes (OU) pre-injection. Ocular assessments at all other study visits are performed on the SE only.

The following assessments will be performed during the study.

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. Screening assessments can be broken into 2 days if necessary.

- Informed consent
- Medical history
- Ophthalmologic history (OU)
- Vital Signs /Physical Examination/Performance Status (ECOG – See Appendix 17.4)
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic Examination and Goldmann Applanation Tonometry (OU)
- 12-Lead ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (OU, transit study eye)
- Optical Coherence Tomography (OU)

- Fundus Autofluorescence (OU)
- Laboratory Tests
- Serum pregnancy test (if applicable)
- Concomitant Medication Assessment

10.2.2 On-Trial Assessments

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

Note:

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

10.2.3 Reconfirmation of Eligibility at Day 1

- Subject will be **EXCLUDED** if any of the following criteria are met between Screening and Day 1;
  - A VA change of >= 5 letters

  OR
  - Significant anatomical changes (i.e. large subretinal hemorrhage, RPE rip, pigment epithelial detachment, per investigator discretion)

  OR
  - If the Snellen Equivalent is no longer between 20/25 to 20/320

10.2.3.1 Day 1 Visit

Pre-injection

- [redacted]
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- [redacted]
- Low Luminance ETDRS Visual Acuity (OU)
- Goldmann Applanation Tonometry and Ophthalmologic Examination (OU)
- Randomization
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.2 Day 3 (±1 day)

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

10.2.3.3 Month 1 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
-
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.4 Month 1 + 3 Days (±1 day)

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

10.2.3.5 Month 2 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
-
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.6 Month 2 + 3 Days (±1 day)

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

10.2.3.7 Month 3 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.8 Month 3 + 3 Days (±1 day)

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

10.2.3.9 Month 4 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.10 Month 4 + 3 Days (±1 day)

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

10.2.3.11 Month 5 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.12 Month 5 + 3 Days (±1 day)

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

10.2.3.13 Month 6 (±7 days)

Pre-Injection

- [redacted]
- Protocol refraction and Visual Acuity (4 meters) using ETDRS chart (OU)
- [redacted]
- Low Luminance ETDRS Visual Acuity (OU)
- Goldmann Applanation Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- Color fundus photographs (OU)
- Fluorescein Angiograms (OU, transit study eye)
- Optical Coherence Tomography (OU)
- Fundus Autofluorescence (OU)
- 12-Lead ECG
- Laboratory Tests
- Serum pregnancy test (if applicable)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.14 Month 6 + 3 Days (±1 day)

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

10.2.3.15 Month 7 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.16 Month 7 + 3 Days (±1 day)

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

10.2.3.17 Month 8 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.18 Month 8 + 3 Days (±1 day)

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

10.2.3.19 Month 9 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.20 Month 9 + 3 Days (±1 day)

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

10.2.3.21 Month 10 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
    - If one injection is administered: (including sham)
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.22 Month 10 + 3 Days (±1 day)

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

10.2.3.23 Month 11 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.24 Month 11 + 3 Days (±1 day)

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

10.2.3.25 Month 12 (±7 days)

Pre-Injection

- [redacted]
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- [redacted]
- Low Luminance ETDRS Visual Acuity (OU)
- Goldmann Applanation Tonometry and Ophthalmologic examination (OU)

- Vital Signs
- 12-Lead ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (OU, transit study eye)
- Optical Coherence Tomography (OU)
- Fundus Autofluorescence (OU)
- Laboratory Tests
- Serum pregnancy test (if applicable)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.26 Month 12 + 3 days (±1 day)

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

10.2.3.27 Month 13 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.28 Month 13 + 3 days (±1 day)

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

10.2.3.29 Month 14 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)

- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.30 Month 14 + 3 Days (±1 day)

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

10.2.3.31 Month 15 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
    - If one injection is administered (including sham):
        - The IOP should be recorded at least 30 minutes after the injection.
    - If two injections are administered (including sham):
        - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
        - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.32 Month 15 + 3 days (±1 day)

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

10.2.3.33 Month 16 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.34 Month 16 + 3 days (±1 day)

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

10.2.3.35 Month 17 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low Luminance ETDRS Visual Acuity (SE)
- Tonometry and Ophthalmologic examination (SE)
- Randomized Treatment: Zimura™/Sham

Post-injection

- Ophthalmologic Examination - at least 30 minutes after the last (whether first or second) injection (SE)
- Tonometry (SE):
  - If one injection is administered (including sham):
    - The IOP should be recorded at least 30 minutes after the injection.
  - If two injections are administered (including sham):
    - The second injection may NOT be administered until the IOP is ≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection, at which time the IOP will be recorded.
    - The IOP should be recorded at least 30 minutes after the 2nd injection.

10.2.3.36 Month 17 + 3 Days (±1 day)

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

10.2.3.37 Month 18 (±7 days)

- [redacted]
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- [redacted]
- Low Luminance ETDRS Visual Acuity (OU)
- Goldmann Applanation Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- 12-Lead ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (OU, transit study eye)
- Optical Coherence Tomography (OU)
- Fundus Autofluorescence (OU)
- Laboratory Tests
- Serum pregnancy test (if applicable)

10.2.3.38 Early Withdrawal

- [redacted]
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- [redacted]
- Low Luminance ETDRS Visual Acuity (OU)
- Goldmann Applanation Tonometry and Ophthalmologic examination (OU)
- Vital Signs
- 12-Lead ECG
- Color fundus photographs (OU)
- Fluorescein Angiograms (OU, transit study eye)
- Optical Coherence Tomography (OU)
- Fundus Autofluorescence (OU)
- Laboratory Tests
- Serum pregnancy test (if applicable)

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

10.3 Withdrawal from Trial

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

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

Subjects who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule.

10.4 Trial Discontinuation

The reason for a subject discontinuing from the trial will be recorded in the source documentation and 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 12.3). 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

The following summarizes the statistical approaches that will be employed in this trial designed to compare the effects of 2 mg and 4 mg doses of Zimura™ against the Sham control arm, regarding geographic atrophy secondary to Dry AMD.

11.1 Study Design

This is a randomized, double-masked, Sham controlled [redacted] study that will obtain evidence regarding the effects of multiple dose levels of Zimura™ in reducing the rate of GA growth over 12 months, when compared with the Sham control.

This [redacted] trial will provide evidence suggesting that a dose of Zimura™:

- Is not plausibly more efficacious than the Sham control, and should be discarded in its current formulation in this indication;
- Is plausibly more efficacious than the Sham control and should be evaluated definitively in a subsequent Phase 3 clinical trial; or
- Is more efficacious than the Sham control, with strength of evidence meeting the standard requirement of a 0.0125 one-sided false-positive error rate, adjusting for the multiple comparisons of 2 mg and 4 mg doses against the Sham control. A confirmatory trial likely would be required for regulatory approval.

Eligible subjects that consent to participate will be randomized to Zimura™ or Sham control in two parts of the trial. In Part 1, approximately 77 subjects are randomized to Zimura™ 1 mg vs Zimura™ 2 mg vs Sham control, in a 1:1:1 allocation. In Part 2, approximately 200 subjects are randomized to Zimura™ 2 mg vs Zimura™ 4 mg vs Sham control, in a 1:2:2 allocation. A total of approximately 277 subjects are to be randomized.

11.2 Endpoints

11.2.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint:

- Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, Month 12

Secondary Efficacy Endpoints:

Secondary efficacy endpoints will be assessed from Baseline to Month 12:

- Mean change in best corrected visual acuity (ETDRS letters) from Baseline to Month 12

- Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 12

11.2.2 Safety and Tolerability Endpoints

Safety and tolerability endpoints:

- All adverse events reported, whether or not deemed related to the injection procedure or study treatment
- All SAEs, whether or not deemed related to the injection procedure or study treatment
- Laboratory data (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)
- Ophthalmic variables (IOP, ophthalmic examination, fluorescein angiograms, FAF, and OCT)
- Vital sign measurements
- 12-lead ECG

11.3 Determination of Sample Size and Statistical Rationale

The sample size determination for this study is based on [redacted] screening methodology presented in Fleming and Richardson (2004). The power calculations are based on the recently released results from a clinical trial of a complement inhibitor, including the estimated precision of the estimated effects on rate of GA growth over 12 months, and including the plausible effect size for Zimura™.

A total of approximately 277 subjects will be enrolled. When follow-up is complete for the primary analysis based on 12-month follow-up, the data base will be locked. Information post-12 months will remain fully confidential until completion of 18-month follow-up. By pre-specification, a hierarchical analysis will be performed where the treatment effect on the rate of GA growth over 18 months will be statistically assessed if statistical significance is achieved on the rate of GA growth over 12 months.

[redacted] the primary analyses will be based on comparisons of Zimura™ 2 mg vs the Sham control, and Zimura™ 4 mg vs Sham control. For the comparison of Zimura™ 2 mg vs Sham control, the 26 subjects randomized to Zimura™ 2 mg and 26 subjects randomized to Sham control from Part 1 will be combined with the 40 subjects randomized to Zimura™ 2 mg and 80 subjects randomized to Sham control from Part 2, where the analysis will be stratified by Part 1 vs Part 2. The comparison of Zimura™ 4 mg vs Sham control will be based on the 80 subjects randomized to each of these two arms in Part 2.

The primary analysis [redacted] for each of the two pairwise comparisons of an active dose of Zimura™ vs the Sham control is formally based on a three-category decision guideline. To be specific, the decision guideline for this trial is based on whether the estimated reduction in rate of GA growth over 12 months for a dose of Zimura™ versus Sham control is less than 14%, is from 14% up to 24.5%, or is at least 24.5%.

Note that these categories should not be interpreted as providing strict decision rules but rather as guidelines that will be factored into a broader scientific assessment of the benefit to risk profile of the Zimura™ dose regimen. This broader assessment will include consideration of safety, of supportive efficacy endpoints, and of relevant information external to this trial. Specifically, the decision guidelines for this trial are:

1. If the estimated reduction in the rate of GA growth over 12 months is less than 14%, then this dose of Zimura™ is not plausibly more efficacious than the Sham control; its utility in this indication should be reconsidered.
2. If the estimated reduction in the rate of GA growth over 12 months is from 14% to up to 24.5%, then this dose of Zimura™ is plausibly more efficacious than the Sham control and should be evaluated in a subsequent Phase 3 clinical trial.

   In planning the design of the confirmatory Phase 3 trials, this trial (and other information that emerges during the conduct of this trial) will provide important insights through consideration of:

   a. The estimated benefit-to-risk profile of this dose of Zimura™;

   b. Possible refinements in the dose/schedule of Zimura™

   c. Approaches to improve adherence to the Zimura™ regimen;

   d. Modifications to defining eligibility criteria to enhance enrichment;

   e. Approaches to achieving timely accrual of study participants at centers with established ability to provide high quality implementation of the trial and high quality data.
3. If the estimated reduction in the rate of GA growth over 12 months is at least 24.5%, then this dose of Zimura™ would be statistically significantly more effective than the Sham control, with strength of evidence meeting the standard requirement of a 0.0125 one-sided false positive error rate (incorporating an adjustment for multiplicity arising from comparing each dose with the Sham control).

The operating characteristics for this three-category decision guideline are:

1. The false-positive error rate of the screening procedure is low. In particular, if a given dose of Zimura™ truly provides no improvement in the rate of GA growth over 12 months, then there is only a 10% chance of bringing that dose forward to a Phase 3 trial and only a 1.25% chance of reaching the false positive conclusion that that dose regimen provides a statistically significant improvement in efficacy relative to a Sham control. Given that there will be two pairwise comparisons, if both doses of Zimura™ truly provide no improvement in the rate of GA growth over 12 months, then the probability of achieving a false positive conclusion for further study for at least one dose regimen likely would be in the range of 15% to 17% (when one takes into account the positive correlation between these two

assessments), and the probability of reaching a conclusion that at least one dose regimen provides a statistically significant improvement in efficacy relative to a Sham control is only 2.5%.

2. The false-negative error rate is low. If a given dose of Zimura™ truly provides a 28% reduction in the rate of GA growth over 12 months, then there is only a 10% chance that that dose of Zimura™ would be discarded, and thus a 90% chance that it would be evaluated in a subsequent confirmatory Phase 3 trial. Given that there will be two pairwise comparisons, if both doses of Zimura™ truly provide a 28% reduction in the rate of GA growth over 12 months, then it is likely (when one takes into account the positive correlation between these two assessments) that there is at least a 95% chance that at least one dose would be evaluated in a subsequent confirmatory Phase 3 trial. If a given dose of Zimura™ truly provides a 28% reduction in the rate of GA growth over 12 months, there is a 63% chance that that regimen will have a statistically significant improvement in efficacy (at one-sided $p<0.0125$) relative to the Sham control.

11.4 Randomization Procedure

Subjects will be centrally allocated to one of the three treatment groups stratified by factors known to be of prognostic importance in dry AMD:

- Baseline visual acuity < 50 ETDRS letters (20/100 Snellen equivalent) vs $\geq$ 50 ETDRS letters
- Size of baseline geographic atrophy (< 4 disc areas vs $\geq$4 disc areas)
- Pattern of Fundus Auto Fluorescence (FAF) at the junctional zone of GA (None/focal vs banded/diffuse)

Randomization will be performed using an IRT system based on the stratification information above to randomize each subject and assign a treatment arm.

The IRT system will be used to assign masked study kits to subjects throughout the duration of the trial. All study medication must be dispensed using the IRT system. At each dispensing visit the IRT system will allocate each study drug kit(s) using the kit number on the label of the study medication kit.

11.5 Masking Procedures

It is the responsibility of the Principal Investigator to ensure that the physician assessing adverse events, the VA examiner, all masked study personnel, and the subject remain masked to the subject's treatment assignment.

For subjects receiving both Zimura™ and Sham injections, the Zimura™ injection must be administered first. To maintain masking, the IRT system will provide instructions as to which kit is to be administered first at each dispensing visit. These instructions are located on the IRT confirmation of drug assignments, which is provided for each dispensing visit. This information must be communicated to the unmasked injector and stored with subject's study documentation.

Within each study drug kit there is a dosing label which indicates the amount of medication to be administered to the subject, based upon the randomized treatment arm of the subject. This dosing label may only be seen by unmasked study personnel.

In the case of a rare emergency where, in the Investigators opinion, unmasking the treatment is necessary to evaluate a further course of action, the Investigator should access the IRT and follow the instructions to initiate unmasking. Every effort should be made to contact the sponsor prior to unmasking a subject. Any unmasking should be reported to the unmasked contact at the sponsor immediately.

In the event of an unmasking, the Investigator will be informed of the subjects randomized treatment assignment. Any unmasking information must be stored separately from the subject's study files in a secure location to ensure the treatment assignment remains masked to other site, CRO and sponsor personnel as required. The IRT system will generate an email notification that does not contain unmasking information, which will be sent to the Investigator and appropriate Sponsor personnel.

11.5.1 Visual Acuity Assessments

Since this is a double-masked study, subjects and staff at the investigational site, particularly the visual acuity examiners, will be masked to study treatment. All VA assessments will be performed by the trial refractionist/ophthalmologist, who will be masked to the subject's treatment as well as previous visual acuity assessments. The trial refractionist/ophthalmologist will be supplied only with the subject's most recent protocol refraction.

11.5.2 Injections

Each clinical site is required to have a minimum of two ophthalmologists – the unmasked injector and the masked assessor. The unmasked injector will perform the Zimura™/Sham injection as well as the post-injection ophthalmic exam and tonometry measurements. The unmasked injector and designated unmasked assistants (if needed) are not permitted to be involved in the conduct of the study in

any other manner and are not to communicate with any other personnel or subjects regarding the treatment assignment. The masked assessor will perform all other physician assessments including the relationship of all adverse events to study drug, including those noted by the unmasked injector.

11.5.3 Statistical Analyses

All statistical analyses will be performed by a statistical office independent of the study Sponsor. The Sponsor and the subjects will remain masked to treatments until the end of the study, except if safety considerations justify breaking the code for individual subjects.

11.6 Analytical Considerations

11.6.1 Analytical Plan

A Statistical Analysis Plan (SAP) will provide the details necessary for the statistical analyses to be explicitly pre-specified prior to unmasking. The methods for imputation of post-baseline, missing data will be specified in the Statistical Analysis Plan.

11.6.2 Significance Levels

The overall (one-sided) false positive error rate in this trial, accounting for the conduct of two pairwise comparisons with Sham control, is 0.025 for the analysis of the primary endpoint.

11.6.3 Descriptive Statistics

Descriptive statistics will be provided on demographic information, treatment administration, baseline characteristics, and protocol deviations, as well as for selected endpoints at relevant time points. No tests of significance will be carried out to compare treatment groups on baseline data because any observed differences between them must be attributed to chance.

11.6.4 Efficacy Analysis

The efficacy analysis will be conducted on all randomized and treated subjects according to the intention-to-treat principle.

For normal endpoints, treatment groups will be compared through an analysis of variance including stratification factors.

For binary endpoints, treatment groups will be compared through Mantel-Haenszel or Cochran-Mantel-Haenszel χ^2 tests adjusting for strata as above.

11.6.5 Subset Analyses

The trial is not sized to test for the presence of treatment by subset interactions. Thus, true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone. With these caveats in mind, exploratory subset analyses will be performed to identify any major effect that might be worth testing in future trials. Clinically meaningful subsets will be looked at, including stratification factors.

11.6.6 Safety Analysis

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

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

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 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 whether the event qualifies as a “serious” adverse event (Section 12.3).

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

The relationship to the intravitreous injection procedure or to study drug will be assessed using the following definitions:

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

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

12.3 Definition of Serious Adverse Events

A serious adverse event is any event that:

1. Results in death;
2. Is life-threatening (immediate risk of death);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;

4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect.

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

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

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

Hospitalization is defined as any inpatient admission. 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 by the site
to the Sponsor or Designee within 24 hours.
Refer to the "Safety Contact List" provided separately

12.5 Independent Data Monitoring Committee

An Independent Data Monitoring Committee will review subject safety data during the course of the trial.

12.6 Exposure in Utero

If any trial subject becomes or is found to be pregnant while receiving trial drug, the investigator must contact the Sponsor. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The Sponsor will inform the site of the information to be provided.

12.7 Abnormal Laboratory Results

If a clinically significant laboratory value occurs, the investigator will repeat the laboratory determination as judged appropriate until the abnormality is resolved, is no longer considered clinically significant by the investigator, or an explanation for the change is obtained.

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

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

All source documents will be made available to Ophthotech Corp. clinical monitors, or its representatives, 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, or its representatives, and must be made available to auditors and regulatory agencies.

All case report forms and original source documents including ocular images should be stored for a minimum of two years after a marketing application has been approved, or two years after formal discontinuation of development of the investigational drug, or five years after completion of the trial, whichever is longer.

Documents should not be destroyed without the permission of Ophthotech Corp. In the event of the Principal Investigator leaving the clinical site, it is the Principal Investigator's responsibility to notify Ophthotech Corp. in writing and to designate which trial material will be transferred at the clinical site.

13.3 Drug Accountability/Storage Conditions

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

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

13.4 Protocol Compliance

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

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

13.5 Ethical Aspects

Local Regulations/Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the

individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (May 9th 1997) and with local law if it affords greater protection to the subject. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

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

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

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

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

13.7 Clinical Trial Insurance

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

13.8 Trial Report and Publications

The trial will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or investigator may publish or present any results from the trial until a joint, multi-center publication of the trial results is made by Sponsor in conjunction with various participating

investigators and appropriate sites contributing data and comments. Subsequently, individual investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the clinical trial agreement will prevail.

14 MONITORING

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

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16 SIGNATURE PAGE

Signatures confirm that this protocol OPH2003 Amendment C 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 OPH2003: "[redacted] Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration"

Trial Sponsor: Ophthotech Corporation

[redacted]

Principal Investigator: _____ _____

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

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17 APPENDICES

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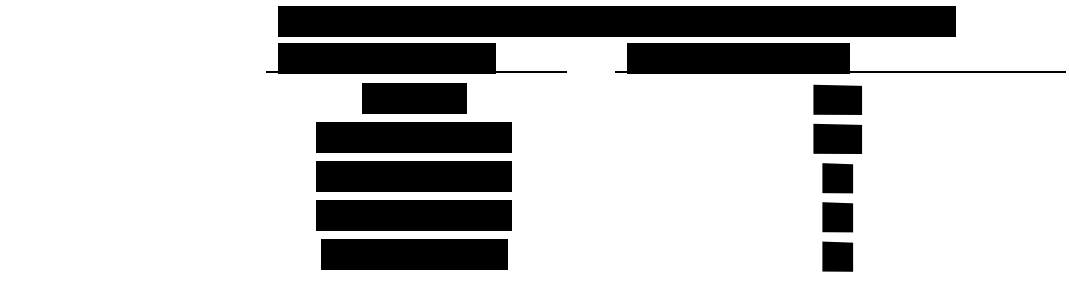

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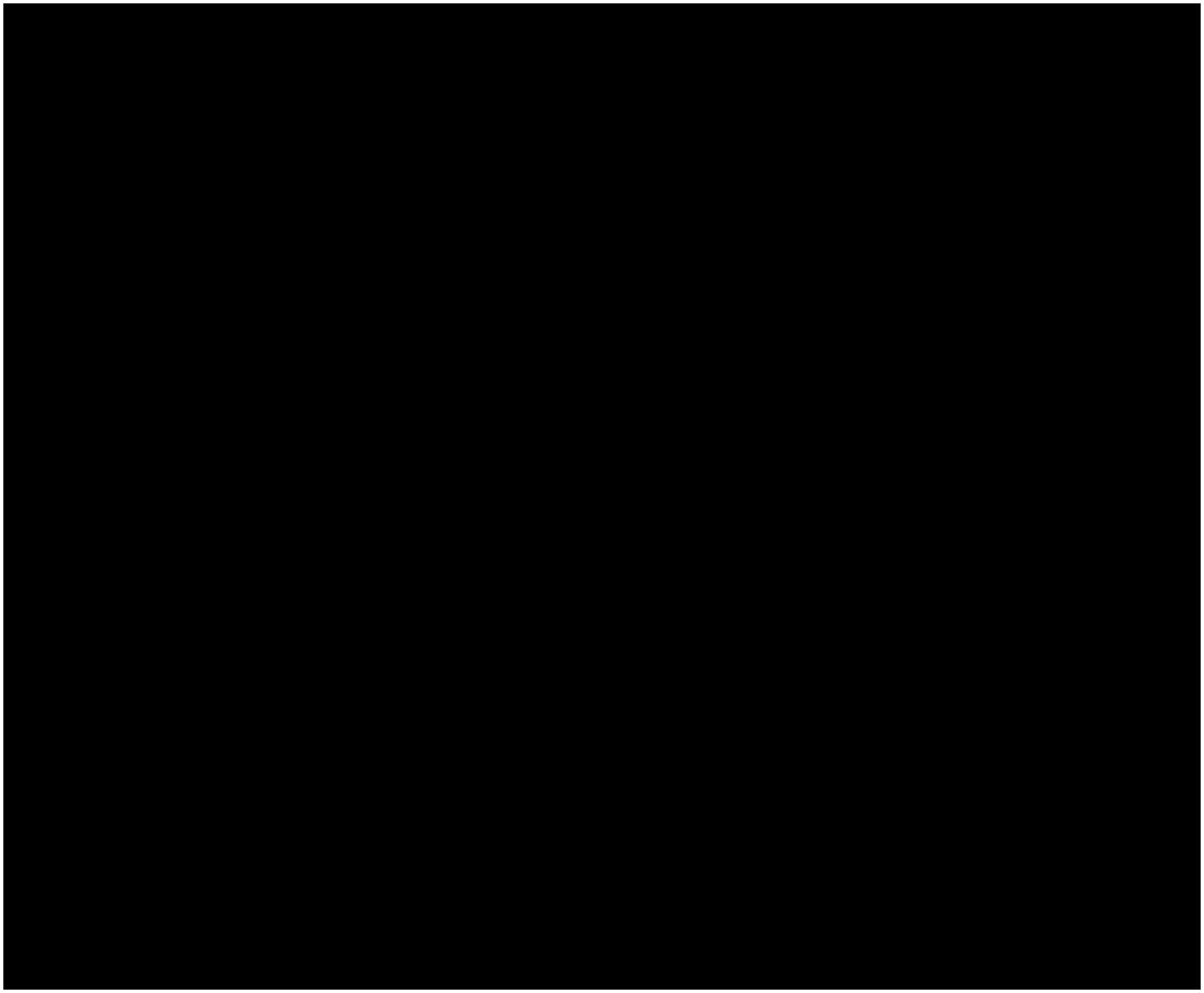

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