Official Study Title: A Phase 3 Multicenter, Randomized, Double-Masked, Sham-Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura™ (Complement C5 Inhibitor) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

NCT#: NCT04435366

Document: Protocol

Document Date: 24 May 2021

A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED CLINICAL TRIAL TO ASSESS THE SAFETY AND EFFICACY OF INTRAVITREAL ADMINISTRATION OF ZIMURA™ (COMPLEMENT C5 INHIBITOR) IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

PROTOCOL NO: ISEE2008

GATHER2

Global Amendment: C

Version Date: 24 May 2021

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TABLE OF CONTENTS

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
CFH	Complement Factor H
CNV	Choroidal Neovascularization
CRO	Contract Research Organization
CRF	Case Report Form
EC	Ethics Committee
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
IND	Investigational New Drug
IOP	Intraocular Pressure
IPCV	Idiopathic Polypoidal Choroidal Vasculopathy
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent to Treat Population
LLBCVA	Low Luminance Best Corrected Visual Acuity
MAC	Membrane Attack Complex
MMRM	Mixed Model Repeated Measures
NLP	No Light Perception
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OU	Both Eyes
RC	Reading Center
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral-Domain Optical Coherence Tomography
SE	Study Eye
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TN	Treatment-Naïve
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

2 SUMMARY OF PROTOCOL ISEE2008

SYNOPSIS	
TITLE:	A Phase 3 Multicenter, Randomized, Double Masked, Sham-Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura (Complement C5 Inhibitor) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration
OBJECTIVES:	The objectives of this study are to evaluate the safety and efficacy of Zimura intravitreal administration in patients with geographic atrophy secondary to age-related macular degeneration (AMD)
TRIAL DESIGN:	Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups: • Zimura 2 mg • Sham **Patients receiving monthly Zimura 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups:** • Zimura 2 mg administered monthly from Month 12 through Month 23 • Sham administered at Months 12, 14, 16, 18, 20, and 22, and Zimura 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23 All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23 All patients will have a final follow up visit at Month 24
ENDPOINTS:	<u>Primary Efficacy Endpoint:</u> • The mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation) <u>Safety Endpoints:</u> • Adverse events (AEs) • Vital signs (pulse, systolic and diastolic blood pressure) • Ophthalmic findings (best corrected visual acuity [BCVA], low luminance BCVA, intraocular pressure [IOP], and ophthalmic examination) • Electrocardiogram (ECG) (12-lead) • Laboratory variables (blood: hematology, renal function, hepatic function and electrolytes; urinalysis)

PLANNED SAMPLE SIZE:	Approximately 400 patients will be enrolled
SUBJECT SELECTION:	Patients of either gender aged 50 years or greater diagnosed with geographic atrophy secondary to AMD
FORMULATION:	[redacted]
INVESTIGATIONAL DRUG DOSAGE:	Patients will receive a minimum of 18 doses and a maximum of 24 doses of Zimura at a dose of 2 mg

3 STUDY ASSESSMENTS

Year 1

SCR = Screening

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													
[redacted]		[redacted]						[redacted]						[redacted]
Vital Signs/ Physical Exam[2]	X							X						X
Medical & Ophthalmic History[3], Performance Status	X													
12-Lead ECG	X							X						X
Protocol refraction and ETDRS Visual Acuity[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Low Luminance ETDRS Visual Acuity[3]		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
Color Fundus Photography[3]	X							X						X
Fluorescein Angiography[3]	X													X
Optical Coherence Tomography (OCT)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Autofluorescence[3]	X							X						X
Laboratory Tests	X							X						X
Serum Pregnancy / Urine Pregnancy (If Applicable)[8,9,10]	[8]X	[10]	[9]	[9]	[9]	[9]	[9]	[8]X	[9]	[9]	[9]	[9]	[9]	[8]X
Randomization		X												
Zimura 2 mg or Sham Study Drug Administration		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	
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 to be performed on **both eyes (OU)** pre injection at Screening, Month 6, Month 12, Month 18, and Month 24/Early Withdrawal. Ocular assessments at all other study visits are performed only on the study eye (SE).
[4]Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Month 6, Month 12, Month 18, and 24/Early Withdrawal. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must also be used to verify intraocular pressure (IOP) reading of ≥ 30 mmHg occurring at any time.
[5]Tonometry should be measured prior to the injection and at least 30 minutes after the injection as per Section 10, Trial Conduct.
[6]A full ophthalmic examination is performed prior to the injection and again at least 30 minutes after the injection.
[7]Adverse events are to be recorded starting after the first dose of study drug.
[8]Serum Pregnancy Test will be done at Screening, Month 6, Month 12, Month 18 and Month 24 for any female subject of childbearing potential.

[9] **Ireland, Slovakia Poland, France, Czech Republic**: a urine pregnancy test will be done at all monthly visits at which a serum pregnancy test is not done, for any female subject of childbearing potential.
[10] **Italy:** A urine pregnancy test will be done at Day 1 for any female subject of childbearing potential.

*Month 12 assessments are divided into “End of Year 1 Assessments” (shown in the table above) and the “Beginning of the Year 2 Assessments” as shown in the Year 2 Table of Assessments in the next page.
VISIT WINDOWS: It is essential that patients adhere to their prescheduled study visits within the visit window as per Section 10, Trial Conduct.

Year 2

Assessment	Month 12*	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24/EW
[redacted]							[redacted]						[redacted]
Vital Signs/ Physical Exam[2]							X						X
12-Lead ECG							X						X
Protocol Refraction and ETDRS Visual Acuity[3]		X	X	X	X	X	X	X	X	X	X	X	X
Low Luminance ETDRS Visual Acuity[3]							X						X
Tonometry[3,4,5]/Ophthalmologic Examination[3,6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography[3]							X						X
Fluorescein Angiography[3]													X
Optical Coherence Tomography (OCT)[3]		X	X	X	X	X	X	X	X	X	X	X	X
Fundus Autofluorescence[3]							X						X
Laboratory Tests							X						X
Serum Pregnancy /Urine Pregnancy (If Applicable)[8,9]		[9]	[9]	[9]	[9]	[9]	[8]X	[9]	[9]	[9]	[9]	[9]	[8]X
Re-randomization	X												
Zimura 2 mg or Sham Study Drug Administration	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	
Concomitant Medications		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

[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 to be performed on **both eyes (OU)** pre-injection at Screening, Months 6, Month 12, Month 18, and Month 24/Early Withdrawal. Ocular assessments at all Other study visits are performed only on the study eye (SE).
[4]Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Month 6, Month 12, Month 18, and 24/Early Withdrawal. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must also be used to verify intraocular pressure (IOP) reading of ≥ 30 mmHg occurring at any time.
[5]Tonometry should be measured prior to the injection and at least 30 minutes after the injection as per Section 10, Trial Conduct.
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[7]Adverse events are to be recorded starting after the first dose of study drug.
[8]Serum Pregnancy Test will be done at Screening, Month 6, Month 12, Month 18 and Month 24 for any female subject of childbearing potential.
[9] **Ireland, Slovakia, Poland, France, Czech Republic**: a urine pregnancy test will be done at all monthly visits at which a serum pregnancy test is not done, for any female subject of childbearing potential.

*Month 12 assessments are divided into “End of Year 1 Assessments” (shown in the table in the previous page) and the “Beginning of the Year 2 Assessments” (shown in the table above).
VISIT WINDOWS: It is essential that patients adhere to their prescheduled study visits within the visit window as per Section 10, Trial Conduct.

4 INTRODUCTION

4.1 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is an aging disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina, responsible for central vision. AMD is characteristically a disease of the elderly and is the leading cause of visual loss in individuals > 50 years of age in developed countries (Van Newkirk et al., 2000). In the United States, it is estimated that approximately 11 million individuals are affected with AMD with a global prevalence of 170 million individuals (Pennington et al., 2016). 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, et al., 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, leading to a major public health challenge with significant socioeconomic implications (Mitchell et. al., 2018).

AMD, at its early stages, presents with drusen and abnormalities of retinal pigment epithelium (RPE). As the disease progresses with age to the advanced stage, it generally progresses to either the non-neovascular ("atrophic, dry") form of AMD or the neovascular ("wet or exudative") form of the disease (Mitchell et. al., 2018). In the dry, atrophic form, loss of photoreceptors, RPE cells and associated capillaries (choriocapillaris) in the macula result in marked thinning and/or atrophy of retinal tissue. This collective phenotype in the advanced stage of dry AMD is termed geographic atrophy (GA) (Holz et al, 2014). Furthermore, development or progression of geographic atrophy over time is a common cause of vision loss in patients diagnosed with the wet form of advanced AMD who are treated with anti-VEGF therapy, indicating that in many patients regardless of having the dry or the wet form of AMD, the final anatomic outcome leading to loss of vision is geographic atrophy (Bhisitkul et al., 2015; Grunwald et al., 2017; Abdelfatah et al., 2016).

Geographic atrophy is a significant cause of bilateral, irreversible and severe loss of functional vision, with a potential loss on average of 22 letters over 5 years, and is associated with a major impact on functional vision, quality of life, and independence (Mitchell et al., 2018;

Sivaprasad et al., 2019; Boyer et al. 2017, AREDS Report Number 26, 2009). The median time for development of central geographic atrophy from the time of diagnosis is 2.5 years with an expectancy of development in the fellow eye in approximately 7 years (AREDS Report Number 26, 2009).

Although anti-VEGF therapy is available for treatment of wet AMD, currently no Food and Drug Administration (FDA) or European Medicines Agency (EMA) approved treatment is available for geographic atrophy (Brown et al., 2006; Rosenfeld et al, 2006; Heier et al., 2012; Martin et al., 2012; Boyer et al. 2017).

The absence of treatment options for geographic atrophy secondary to 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

Although the etiology of AMD is not completely understood (Frederick & Kleinman, 2014), recognized risk factors include advanced age, environmental and genetic factors, ocular pigmentation, dietary factors, family history for AMD, hypertension, and smoking (Klein et al., 2004).

The scientific rationale for the role of complement in AMD is derived from genetic linkage studies, pre-clinical in vitro studies, and the presence of complement deposition in post-mortem human eyes of patients diagnosed with AMD.

The role for complement in development of AMD is highlighted by genetic linkage and association studies, which suggest that approximately 50% of AMD cases show 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. In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4 (Klein et al., 2005).

The complement cascade, which was originally described over a century ago by Paul Ehrlich, represents a critical portion of the innate immune system, involving a complex system of over 50 serum proteins (Ehrlich et al., 1899; Holers, 2014; Arbore et al., 2016; Kolev et al., 2014). In addition to its role in the innate immune system, recent studies indicate that complement

may also play a role in the adaptive immune system, cell and tissue development, homeostasis and repair (Kolev et al., 2014).

The complement cascade is activated via the classical (antibody-dependent), the alternative (antibody-independent), and the lectin pathways (Holers, 2014). The three cascades converge to generate the complement C3 convertase which cleaves complement C3 and leads to subsequent generation of complement C5 convertase which cleaves complement C5 into C5a and C5b, the main terminal effector components of the complement cascade, leading to cell death.

C5a: Inflammasome Activation and Cell Degeneration

Inflammasomes are critical components of the innate immune system (Swanson et al., 2019). NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) is an intracellular sensor that detects a broad range of endogenous danger signals and environmental irritants, resulting in the formation and activation of the NLRP3 inflammasome (Swanson et al., 2019). Inflammasome activation leads to pyroptosis, a rapid inflammatory form of lytic programmed cell death (Swanson et al. 2019). It is characterized by pore formation in the plasma membrane, increased osmotic pressure, cell swelling and subsequent plasma membrane rupture and release of pro-inflammatory intracellular contents (Fink et al., 2006). The extracellular release of pro-inflammatory content may further advance the spreading of damage in neighboring cells, leading to the progression of the pathology (Bergsbaken et al., 2009).

NLRP3 inflammasomes generally require two signals for activation: Signal 1 for priming and Signal 2 for NLRP3 assembly. Since complement system and NLRP3 inflammasomes both protect the host against danger, a functional cross talk between the two would appear to be natural.

Complement factor C5a is an important driver of Signal 1 priming for NLRP3 inflammasome activation and may regulate NLRP3 activation and assembly by increasing the generation of reactive oxygen species (ROS) (Arbore et al., 2016).

Human RPE cells express both C3a and C5a receptors which bind to C3a and C5a respectively; however, after incubation with activated complement only C5aR (and not C3aR) is upregulated (Cortight et al., 2009; Brandstetter et al., 2015). In response to lipofuscin toxicity, C5a leads to an increased IL-1ß secretion and a decrease in RPE cell viability, suggesting its role as active priming agent for inflammasomes in RPE cells (Brandstetter et al., 2015).

The potential role of inflammasome activation in the formation of geographic atrophy is further substantiated by reports demonstrating the presence of NLRP3 inflammasome and inflammasome products IL-1ß and IL-18 inside the RPE cells of post-mortem eyes of patients with geographic atrophy (Tarallo et al., 2012 and Cao et al., 2016). These findings support the rationale for therapeutic complement C5 inhibition in AMD, since C5 activation and C5a formation may serve as the link between lipofuscin accumulation, photooxidative damage and inflammasome formation leading to RPE degeneration in AMD (Brandstetter et al., 2015). The pyroptosis resulting from inflammasome activation may be a contributing factor in the progression of GA in patients with AMD.

C5b: Membrane Attack Complex (MAC) Formation and Cell Degeneration

One hallmark of AMD is the accumulation of lipofuscin granules inside the aging RPE cells (Feeney-Burns et al., 1984). Accumulation of lipofuscin may lead to the activation of complement system and accumulation of membrane attack complex (MAC) in RPE cells, potentially contributing to their deterioration over time and resulting in photoreceptor cell loss and decrease in vision (Zhou et al., 2006; Zhou et al., 2009; Lenis et al., 2017). Lipofuscin and MAC complex have a damaging effect on RPE cell function by impacting both lysosomes and mitochondria inside the cells (Georgiannakis et al., 2015).

Photo-oxidation of lipofuscin in RPE cells activates the complement cascade in vitro and potentially could contribute to complement activation in the RPE-Bruchs membrane interface (Zhou et al., 2006; Zhou et al., 2009). Bisretinoid pigments of lipofuscin other than A2E were also capable of activating the complement system in RPE cells (Zhou et al., 2009).

As indicated above, the activation of complement cascade results in the formation of MAC. In RPE cells MAC is cleared by endocytic pathway and lysosomal degradation (Georgiannakis et al., 2015). Lipofuscin accumulation leads to lysosomal dysfunction in RPE cells. This prevents the clearance of MAC and leads to its further accumulation, inducing cellular distress (Schutt et al., 2002, Bergmann et al., 2004, Georgiannakis et al., 2015). These findings indicate that lipofuscin not only activates the complement system but may also prevent the clearance of MAC in RPE cells, creating a vicious cycle that makes RPE cells further susceptible to complement activation.

The accumulation of MAC not only impacts lysosomes but also leads to mitochondrial perturbation in RPE cells (Georgiannakis et al., 2015). MAC accumulation leads to a significant decrease in the quantitative number of mitochondria as a function of area and induces ultrastructural defects i.e. smaller size, rounder morphology, and fewer cristae. These changes

potentially have a deleterious impact on the energy production and subsequently the function of RPE cells. In addition, the accumulation of lipofuscin inside RPE cells impacts the mitochondria as well. Mitochondria are significantly more sensitive to lipofuscin when compared to lysosomes and their latency decreases at a lower concentration and a shorter period of time (Schutt et al., 2002). Further, accumulation of MAC leads to the complete lysis and destruction of RPE cells in a concentration-dependent manner (Li et al., 2010).

Taken together, the accumulation of lipofuscin and MAC synergistically damage both lysosomes and mitochondria inside the RPE cells, leading to their dysfunction and death. To further substantiate the role of C5 and MAC in AMD, post mortem histopathologic studies demonstrated their presence in the drusen and RPE cells of patients with AMD (Anderson et al., 2002; Bok 2005).

These findings indicate that the activation of complement pathway, contributing to the formation of inflammasome and accumulation of MAC, may play an important role in geographic atrophy, and therefore inhibition of C5 may potentially slow progression of this devastating disease. Positive efficacy results from the recently reported clinical trials assessing the impact of complement inhibition in geographic atrophy may further validate the therapeutic role of complement inhibition in GA (Liao et al., 2019; OPH2003).

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 results of these studies, as well as results from the various intravenous toxicity studies previously conducted, can be found in the IB.

4.3 Clinical Data

4.3.1 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 patients with wet AMD (OPH 2000).

Zimura was well-tolerated and no particular safety concerns were identified. [redacted] 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 [redacted] 15.3 ETDRS letters for the 2 mg dose group. [redacted]

4.3.2 Study OPH2001

An additional phase 1 study was performed in patients diagnosed with geographic atrophy

(GA). [redacted] Patients received treatment with 3 initial intravitreal injections of Zimura 0.3 mg or 1 mg, 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. Standard safety assessments were performed for ophthalmic variables that included VA, IOP, ophthalmic examination, fundus autofluorescence (FAF), fluorescein angiography (FA), and spectral-domain optical coherence tomography (SD-OCT) together with adverse events (AEs), vital signs, and laboratory variables.

[redacted] Fifteen patients (32%) had AEs, predominantly Eye Disorder AEs in the study eye, reported to be related to the injection procedure. The most frequently reported 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 2 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 and gastrointestinal inflammation, but none were related to the study drug or injection procedure. There were no discontinuations due to AEs.

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

[redacted]

4.3.3 Study OPH2002

The objectives of this study were to evaluate the safety and tolerability of Zimura intravitreal injection in combination with VEGF therapy in patients with idiopathic polypoidal choroidal

vasculopathy (IPCV). Treatment experienced patients (prior treatment with anti-VEGF monotherapy of ≥ 8 injections in the previous 12 months) diagnosed with IPCV of either gender, aged 50 years or more were enrolled in this study. Patients received 3 monthly intravitreal injections of Zimura (1 mg) in combination with intravitreal injection of anti-VEGF agent (Avastin® 1.25 mg or Lucentis® 0.5 mg or Eylea® 2 mg).

[redacted]

A total of 4 patients were enrolled in this clinical trial and all completed the study. None of the patients 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 reported 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.

4.3.4 Study OPH2003

A pivotal international, multicenter, randomized, double-masked, Sham-controlled clinical trial was performed to evaluate the safety and efficacy of Zimura in patients with geographic atrophy secondary to AMD. [redacted]

In Part 1 of the trial: [redacted] patients were randomized to receive monthly intravitreal injections of Zimura 1 mg; [redacted] Zimura 2 mg; and [redacted] Sham injections.

This trial was modified (while masked) to include a 4 mg dose group and therefore part 2 was added. In Part 2 of the trial: [redacted] patients were randomized to receive monthly intravitreal injections of Zimura 4 mg, administered as two injections of Zimura 2 mg; [redacted] Zimura 2 mg plus a Sham injection; and [redacted] Sham injections, administered as two separate Sham injections.

[redacted]

[redacted]

Safety

Zimura was generally well tolerated after 12 months of administration and there were no Zimura-related AEs, no Zimura-related inflammation, and no Zimura-related discontinuations. Further, there have been no ocular serious adverse events and no cases of endophthalmitis reported in the study eye in this clinical trial. During the first 12 months of the trial, the incidence of choroidal neovascularization (CNV) in the untreated fellow eye was 10 patients (3.5%); in the study eye of the Sham control group was 3 patients (2.7%); in the Zimura 2 mg group was 6 patients (9.0%); and in the Zimura 4 mg group was 8 patients (9.6%). These numbers were lower than reported in the literature for complement C3 inhibition (Liao et al., 2019). The most frequently reported ocular adverse events were related to the injection procedure.

Primary Efficacy Endpoint

The prespecified primary efficacy endpoint, mean rate of change in GA growth over 12 months, was measured by fundus autofluorescence (FAF) based on readings at three time points (Baseline, Month 6, and Month 12) and was calculated using the square root transformation of the GA area. The FAF images were assessed by an independent masked reading center. This trial met its prespecified primary efficacy endpoint.

The reduction in the mean rate of GA growth over 12 months was 27.38% ($p = 0.0072$) for the Zimura 2 mg group as compared to the corresponding Sham control group, and 27.81% ($p = 0.0051$) for the Zimura 4 mg group as compared to the corresponding Sham control group. These efficacy data for both dose groups were similar and statistically significant. [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]

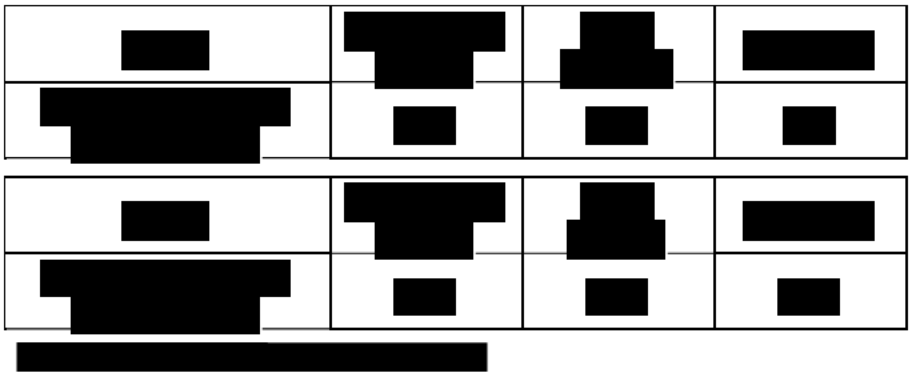
[redacted]

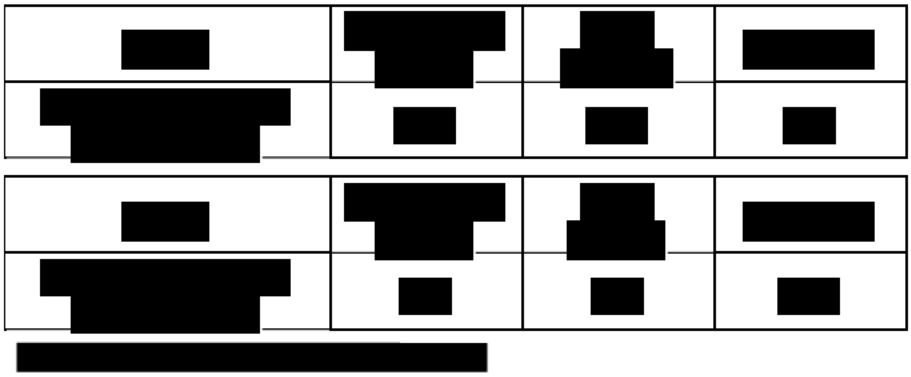
[redacted]

[redacted]

Secondary Endpoints

The prespecified secondary endpoints in this trial were the mean change in best corrected visual acuity (BCVA) (Early Treatment of Diabetic Retinopathy Study (ETDRS) letters) from Baseline to Month 12 and the mean change in low luminance best corrected visual acuity (LLBCVA) ETDRS letters from Baseline to Month 12. [redacted]





Taken together, there is rationale to further investigate the role of complement C5 inhibition by Zimura in patients with GA secondary to AMD in a second pivotal trial.

4.3.5. Study OPH2005

Study OPH2005 is a multi-center, randomized, double-masked, Sham-controlled [redacted] Phase 2b clinical trial designed to assess the safety and efficacy of Zimura compared to Sham in patients with autosomal recessive Stargardt disease.

Patients who were between 18 and 50 years of age, diagnosed with Stargardt disease with at least two pathogenic mutations of *ABCA4* gene and best corrected visual acuity in the study eye between 20/20 to 20/200 Snellen equivalent were randomized in a 1:1 ratio to Zimura or Sham group.

During the induction phase, at Day 1, Month 1, and Month 2, all patients received either Zimura 2 mg or Sham on Day 0 and Day 14; during the maintenance phase, patients received monthly Zimura 4 mg (administered as 2 intravitreal injections) or Sham (administered as 2 Sham injections).

[redacted]

4.3.6 Study OPH2007

OPH2007 was a multi-center, randomized, open-label, dose-ranging Phase 2a clinical trial designed to assess the safety of various Zimura dosing regimens in combination with anti-VEGF therapy at Month 6 for the treatment of wet AMD. [redacted]

In Cohort 1, [redacted] patients were administered monthly combination therapy consisting of Lucentis 0.5mg followed by Zimura 4mg two days later. [redacted]

In Cohort 2, [redacted] patients were administered monthly combination therapy consisting of Lucentis 0.5mg and Zimura 2 mg on the same day, which was the same dosing regimen as the best-performing group from the previously completed OPH2000. [redacted]

In Cohort 3, during the induction phase (Day 1 – Month 2), [redacted] patients were administered Lucentis 0.5mg followed by Zimura 2 mg on the same day followed by Zimura 2 mg fourteen days later. During a subsequent maintenance phase (Month 3 – Month 5), patients were administered Lucentis 0.5mg followed by Zimura 2 mg on the same day. [redacted]

In Cohort 4, during the induction phase (Day 1 – Month 2) [redacted] patients were administered Lucentis 0.5mg followed by Zimura 2 mg on the same day followed by Zimura 2 mg fourteen days later. During a subsequent maintenance phase (Month 3 – Month 5) patients were administered Zimura 2 mg followed two days later by Lucentis 0.5mg and Zimura 2 mg. [redacted]

Zimura was generally well tolerated after 6 months of administration. There was no Zimura-related AEs and no Zimura-related discontinuations from the trial. There was one ocular SAE of retinal detachment which was reported as not related to the study drugs or the injection procedure, and related to the normal aging process. There were no cases of endophthalmitis. The most frequently reported ocular adverse events were related to the injection procedure.

[redacted]

4.4 Trial Rationale

The scientific foundation implicating the role of complement in AMD is derived from genetic linkage studies, in vitro experimental studies, and post-mortem histopathologic studies performed by independent laboratories.

The seminal genetic linkage studies published in 2005 (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005; Narayanan et al., 2007) 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).

In vitro studies implicate the role of C5 in inflammasome priming and activation and MAC accumulation in RPE cells, leading to their degeneration (Brandstetter et al., 2015; Georgiannakis et al., 2015; Li et al., 2010). The presence of NLRP3 inflammasome and inflammasome products IL-1ß and IL-18 inside the RPE cells have been demonstrated in the post-mortem eyes of patients with geographic atrophy (Tarallo et al., 2012 and Cao et al., 2016). A study of eyes from more than 400 human donors revealed that drusen are intensely labelled using antibodies against complement C5 and MAC while multiple complement regulatory proteins have also been shown to be present in drusen (Anderson et al., 2002, Bok 2005).

The recent pivotal Zimura clinical trial data demonstrated a significant reduction of GA growth in patients with AMD over 12 months for both 2 mg and 4mg dose groups (OPH2003). Further, a third-party clinical trial evaluating the role of complement inhibition in GA also showed a significant reduction in GA growth in patients with AMD over 12 months, validating the potential role of complement inhibition in the treatment of GA secondary to AMD (Liao et al., 2019).

Preclinical, clinical and genetic studies implicate the potential role of the complement cascade in AMD (Bok, 2005; Donoso et al., 2006; Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005, Liao et al., 2019, Brandstetter et al., 2015, Georgiannakis et al., 2015, Liao et al., 2019, OPH2003). Inhibition of complement activation may potentially slow down or arrest the underlying pathophysiology of macular degeneration. Thus, molecules involved in regulation and inhibition of complement cascade are prime targets for therapeutic intervention in AMD.

Zimura is currently being developed by IVERIC bio for the treatment of GA secondary to AMD and Stargardt disease. Zimura is a pegylated RNA aptamer. It is a potent and specific inhibitor of complement C5. Zimura inhibits C5 cleavage, a central component of the complement

cascade, which plays multiple roles in innate immunity and cell death. Inhibition of this critical step in the complement cascade prevents the formation of key terminal fragments (C5a and C5b) regardless of the initial activation pathway (alternate, classical, or lectin). The C5a fragment plays an important role in inflammasome priming and activation leading to pyroptosis and cell death. C5b is involved in the formation of membrane attack complex (MAC: C5b-9) which also leads to cell lysis and cell death. By inhibiting these C5-mediated activities, one may slow down the progression of retinal cell degeneration and achieve therapeutic benefit in GA secondary AMD.

In this pivotal clinical trial, the safety and efficacy of Zimura 2 mg will be compared to Sham control. This is based on results of the first pivotal clinical trial (OPH2003), in which both Zimura 2 mg and Zimura 4 mg cohorts demonstrated a statistically significant reduction in the mean rate of GA growth over 12 months when compared to their corresponding Sham control cohorts with a similar efficacy, and Zimura 2 mg is administered as a single intravitreal injection vs 2 intravitreal injections for Zimura 4mg.

In the first pivotal trial, treatment with Zimura 2 mg dose, led to a 27.38% reduction in the mean rate of GA growth over 12 months as compared to the corresponding sham control group which was highly statistically significant (p-value = 0.0051). In prior clinical studies, Zimura 2 mg dose was generally well-tolerated with no drug-related AEs, drug-related inflammation, or endophthalmitis. Therefore, the sponsor believes the risk/benefit assessment is favorable.

Currently there are no treatments available for patients with geographic atrophy.

5 TRIAL OBJECTIVES

5.1 Objectives

The objectives of this study are to evaluate the safety and efficacy of Zimura intravitreal administration in patients with geographic atrophy secondary to age-related macular degeneration (AMD).

5.2 Endpoints

Primary Efficacy Endpoint:

The mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation)

Safety Endpoints:

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

6 TRIAL DESIGN

Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups:

- Zimura 2 mg
- Sham

Patients receiving monthly Zimura 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups

- Zimura 2 mg administered monthly from Month 12 - Month 23
- Sham administered at Months 12, 14, 16,18, 20, and 22, and Zimura 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23

All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23

All patients will have a final follow up visit at Month 24

7 PROCEDURES

7.1 Refraction, Visual Acuity, and Low Luminance Visual Acuity

Refraction, Vision Testing, and Low Luminance Vision testing will be performed at all time-points specified in Section 10.2 “Trial Assessments”. Retro-illuminated modified Ferris-Bailey ETDRS charts are used starting at 4 meters (see Appendix 17.3).

When protocol refraction and best-corrected visual acuity measurement are required by the study protocol, this will be performed only by certified visual acuity examiners masked to the previous visual acuity measurement and masked 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 for these assessments will be provided by IVERIC bio.

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

7.2 Tonometry

Tonometry will be performed at all time-points specified in Section 10.2 “Trial Assessments”. 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, pre-injection on Day 1, Month 6, Month12, Month18, Month 24 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 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, Fundus Autofluorescence, and Optical Coherence Tomography (SD-OCT)

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

An independent and masked Reading Center (RC) will confirm eligibility of patients prior to enrollment. All color fundus photos, FAs, FAFs, and SD-OCTs 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 photography, FA, FAF, and SD-OCT procedures. **During the eligibility assessment, if the FAF images were reviewed to be ungradable per the independent Reading Center, the FAF images must be repeated within 72 hours. The eligibility decision by the Reading Center is final.**

7.5 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 woman of child-bearing potential): These laboratory tests will be performed at the Screening, Month 6, Month 12, Month 18, and Month 24/EW visit. The total blood volume collected per patient for this study is approximately 35 mL. Additionally, a serum or urine pregnancy test will be performed for women of childbearing potential at the visits as indicated in Section 3, “Study Assessments”, and in Section 10.2 “Trial Assessments” in specified countries.

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.

7.6 Vital Signs, Physical Examination and Performance Status (ECOG)

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 Section 10.2 “Trial Assessments”.

Performance Status (Eastern Cooperative Oncology Group [ECOG]) will be assessed at Screening in accordance with Appendix 17.4.

7.7 12-Lead Electrocardiogram

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

[redacted]

[redacted]

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 400 patients will be enrolled.

8.2 Inclusion Criteria

Patients 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 study eye (SE), one study eye per patient. If both eyes satisfy the inclusion criteria, it is in the investigator's discretion to determine the SE.

[redacted]

8.2.2 General Inclusion Criteria

8.2.2.1 Patients of either gender aged ≥ 50 years.

8.2.2.2 For patients who are women of childbearing potential involved in any sexual intercourse that could lead to pregnancy, the patient has used a protocol approved highly effective contraceptive method during the trial and agrees to continue the same method until at least 90 days following the last dose of test medication. Protocol approved highly effective contraceptive methods are hormonal

contraceptives (i.e., combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, abstinence as defined by refraining from heterosexual intercourse during the entire period of the study and until at least 90 days following the last dose of study medication, vasectomy, and tubal ligation.

A woman of non-childbearing potential is defined as follows:

- A woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
- A woman ≥ 60 years of age
- A woman ≥ 40 and < 60 years of age who fulfills at least one of the following:
    - A cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming non-childbearing potential (refer to laboratory reference ranges for confirmatory levels)
    - A cessation of menses for at least 24 months without FSH levels confirmed

If the patient is a woman of childbearing potential, she must have a negative serum pregnancy test within 14 days prior to the first injection and have no plans to donate ova during the duration of the trial and at least 90 days following the last dose of test medication.

Ireland, Slovakia, United Kingdom, Czech Republic, Poland, France, Italy: If the patient is male, he should use a condom and not donate sperm during the time of study drug exposure and for 90 days following the last exposure of study drug.

8.2.2.3 Provide written informed consent.

8.2.2.4 Ability to return for all trial visits for the 24-month duration of the study.

8.3 Exclusion Criteria

Patients will ***not be eligible for the trial*** if patients 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]

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 tachyarrhythmias 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.
- 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.

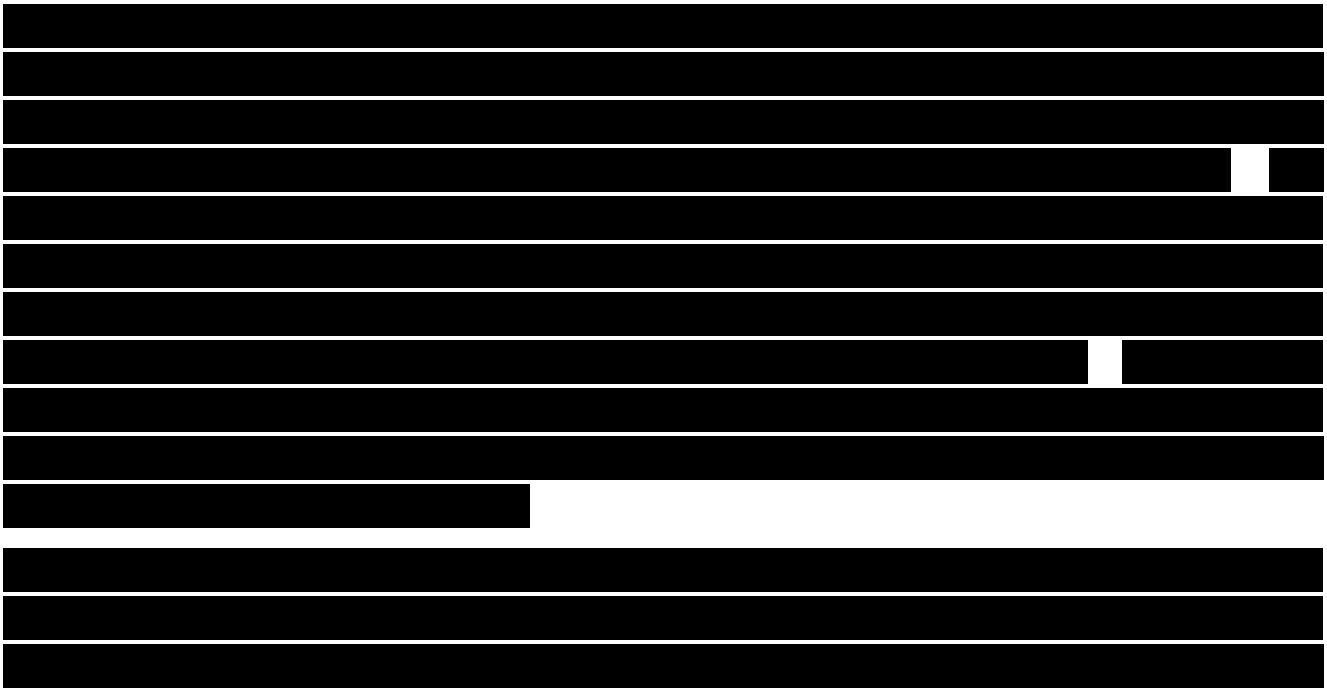
8.3.2.5 Known serious allergies to the fluorescein dye used in angiography, povidone iodine, or hypersensitivity to the active substance or any of the excipients or components of the Zimura formulation.

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



[redacted]

9.1.2 Treatment Regimen and Duration

Patients randomized to active drug or Sham may receive monthly injections of Zimura or Sham for up to 24 months. Monthly doses should be administered at least 21 days apart.

Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups:

- Zimura 2 mg
- Sham

Patients receiving monthly Zimura 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups:

- Zimura 2 mg administered monthly from Month 12 - Month 23
- Sham administered at Months 12, 14, 16,18, 20, and 22, and Zimura 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23

All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23

All patients will have a final follow up visit at Month 24

9.1.3 Administration of Study Drug

An Interactive Randomization Technology (IRT) system will be used to assign masked study kits to patients 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 the appropriate study medication kit(s) based upon randomized treatment assignment. Study medication kits will be assigned by the unique identifier (kit number) printed on the label.

[redacted]

9.1.4 Drug Accountability

A Drug accountability log will be provided by the Sponsor and must be maintained by the clinical site. The drug accountability log must be kept current and must contain the date and drug units [kit number(s) dispensed (as indicated by the IRT system), subject number, date of dispensation and initials of the dispenser].

At the end of the study or when indicated by the Sponsor, all unused study medication should be destroyed locally by the study site. Where local laws or site procedures do not permit local site destruction the Sponsor will provide instructions for the return of unused medication to a local depot. Sites that destroy study medication locally must be able to produce a certificate of destruction upon request of the Sponsor.

9.1.5 Storage

The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study 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

Patients enrolled must be treatment-naïve (no previous treatment for dry or wet 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.

If wet AMD were to develop during the study, in either the Study Eye or the Fellow Eye, please refer to section 10.3 for guidance on the use of concomitant treatment.

10 TRIAL CONDUCT

10.1 Subject Enrollment

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

Patients 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 study drug should not commence without prior written approval from IVERIC bio 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 patients who fulfill all eligibility criteria will be entered into the trial.

A trained and qualified professional will take the laboratory samples (hematology, renal function, hepatic function, electrolytes, complete urinalysis) as well as the serum pregnancy test.

Ocular assessments performed at Baseline (Screening or Day 1), Month 6, Month 12, Month 18, and Month 24 (and at an Early Withdrawal visit if performed) should be performed pre-injection on both eyes (OU). Ocular assessments at all other study visits are performed only on the SE.

The following assessments will be performed during the study:

10.2.1 Screening Assessments - Year 1

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**
- **Vital signs /physical examination/performance status (ECOG – see appendix 17.4)**
- **Medical history**
- **Ophthalmologic history (OU)**
- **12-lead ECG**
- **Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)**
- **Goldmann applanation tonometry and ophthalmologic examination (OU)**
- **Color fundus photography (OU)**
- **Fluorescein angiography (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 study drug.***
- ***Ireland, Slovakia, Poland, France, and the Czech Republic:*** *A urine pregnancy test will be performed for any woman of childbearing potential at all monthly study visits at which a serum pregnancy test is not done.*

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 - 20/320

10.2.3.1 Day 1 Visit

Pre-injection

- [redacted]
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Low luminance ETDRS visual acuity (OU)
- Goldmann applanation tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- **Italy**: Urine pregnancy test for any women of childbearing potential.
- Confirmation of Day 1 eligibility
- Randomization
- Randomized treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection

- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.4 Month 1 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.6 Month 2 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.8 Month 3 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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]
- Vital signs
- 12-Lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Low luminance ETDRS visual acuity (OU)
- Goldmann applanation tonometry and ophthalmologic examination (OU)
- Color fundus photography (OU)
- Optical coherence tomography (OU)
- Fundus autofluorescence (OU)
- Laboratory tests
- Serum pregnancy test (if applicable)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.16 Month 7 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.18 Month 8 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.20 Month 9 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)

- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.24 Month 11 + 3 Days (±1 day)

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

10.2.3.25 Month 12 (±7 days)

Pre-Injection: End of Year 1 Assessments

- [redacted]
- Vital signs
- 12-lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Low luminance ETDRS visual acuity (OU)
- Goldmann applanation tonometry and ophthalmologic examination (OU)
- Color fundus photography (OU)
- Fluorescein angiography (OU, transit study eye)
- Optical coherence tomography (OU)
- Fundus autofluorescence (OU)
- Laboratory tests
- Serum pregnancy test (if applicable)

Beginning of the Year 2 Assessments

- **Re-randomization**
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.28 Month 13 + 3 days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.30 Month 14 + 3 Days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)

- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.32 Month 15 + 3 days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.34 Month 16 + 3 days (±1 day)

- Telephone call to patient 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)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.36 Month 17 + 3 Days (±1 day)

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

10.2.3.37 Month 18 (±7 days)

Pre-Injection

- [redacted]
- Vital signs
- 12-lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Low luminance ETDRS visual acuity (OU)
- Goldmann applanation tonometry and ophthalmologic examination (OU)
- Color fundus photography (OU)
- Optical coherence tomography (OU)
- Fundus autofluorescence (OU)
- Laboratory tests
- Serum pregnancy test (if applicable)
- Assigned treatment: Zimura/Sham

Post-Injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.38 Month 18 + 3 Days (±1 day)

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

10.2.3.39 Month 19 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection

- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.40 Month 19 + 3 days (±1 day)

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

10.2.3.41 Month 20 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.42 Month 20 + 3 days (±1 day)

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

10.2.3.43 Month 21 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.44 Month 21 + 3 days (±1 day)

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

10.2.3.45 Month 22 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.46 Month 22 + 3 days (±1 day)

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

10.2.3.47 Month 23 (±7 days)

Pre-Injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Assigned treatment: Zimura/Sham

Post-injection

- Ophthalmic exam (SE): Must be performed at least 30 minutes after the injection
- Tonometry (SE): The IOP should be recorded at least 30 minutes after the injection (including Sham)

10.2.3.48 Month 23 + 3 days (±1 day)

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

10.2.3.49 Month 24/Early Withdrawal

- [redacted]
- Vital signs
- 12-lead ECG
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)

- Low luminance ETDRS visual acuity (OU)
- Goldmann applanation tonometry and ophthalmologic examination (OU)
- Color fundus photography (OU)
- Fluorescein angiography (OU, transit study eye)
- Optical coherence tomography (OU)
- Fundus autofluorescence (OU)
- Laboratory tests
- Serum pregnancy test (if applicable)

Adverse events are recorded 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 Development of Wet AMD During the Trial

If the investigator suspects the development of CNV in the study eye, or if the subject has > 5 EDTRS letters of VA loss between the current visit and the immediate past visit, the diagnosis must be assessed with FP, FA and OCT and **confirmed by the Duke Reading Center prior** to initiating anti-VEGF treatment in the study eye.

For patients who develop CNV in the *study eye* **and the diagnosis is confirmed by the Duke Reading Center** during the trial, the study eye should be treated with either Lucentis® (ranibizumab) or Eylea® (aflibercept) per their label.

If the investigator plans to administer the anti-VEGF agent on the day of the diagnosis, the Duke Reading Center will confirm the diagnosis within 1 hour after receiving the images. If the anti-VEGF agent and Zimura/Sham are administered in the SE on the same day, Zimura/Sham should be administered first, and the anti-VEGF administered second. The anti-VEGF agent may NOT be administered after the Zimura/Sham injection until the IOP is ≤ 21 mmHg or within 5 mmHg of the baseline IOP on that day (i.e., the “baseline” IOP is the pre-injection IOP before the Zimura/Sham administration on that day). If the IOP is **not** ≤ 21 mmHg or within 5 mmHg of the baseline IOP, the IOP should continue to be monitored until it is ≤ 21 mmHg or within 5 mmHg of the baseline IOP before proceeding to the anti-VEGF injection.

For the anti-VEGF agent administration, it is ***mandatory*** that, the same injection preparation and administration protocol specified for the Zimura administration be followed by an unmasked ophthalmologist. Please refer to **Appendix 17.5 Intravitreous Administration Protocol**; for example, the use of aseptic technique, sterile gloves, anesthesia, eye speculum and povidone-iodine are required.

The subject will continue with the study treatment (Zimura or Sham) as scheduled.

For patients who develop CNV in the *fellow eye* during the study, the fellow eye should be treated with either Lucentis® (ranibizumab) or Eylea® (aflibercept) per their label, with no change to study conduct regarding the study eye. **However, if the study eye is treated on the same day as the fellow eye, the study eye should be treated before the fellow eye.**

10.4 Withdrawal from Trial

Patients 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 patients from the trial in the event of concurrent illness, adverse events (including pregnancy in female patients), 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 patients who withdraw. Patients 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.

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

10.5 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 patients, 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 IVERIC bio.

The study will be considered completed when the last subject completes the final study visit.

11 STATISTICAL METHODS

The following summarizes the statistical methods that will be employed in this trial designed to compare the effects of Zimura 2 mg dose against the Sham control arm in patients with geographic atrophy secondary to AMD.

11.1 Study Design

This is a randomized, double-masked, Sham-controlled pivotal study that will obtain evidence regarding the effects of Zimura 2 mg in reducing the mean rate of GA growth over 12 months, when compared with Sham control.

Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups:

- Zimura 2 mg
- Sham

Patients receiving monthly Zimura 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups:

- Zimura 2 mg administered monthly from Month 12 - Month 23
- Sham administered at Months 12, 14, 16,18, 20, and 22, and Zimura 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23

All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23.

All patients will have a final follow up visit at Month 24.

11.2 Endpoints

11.2.1 Primary Efficacy Endpoint

Primary Efficacy Endpoint:

- The mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation)

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 drug
- All SAEs, whether or not deemed related to the injection procedure or study drug
- Laboratory data (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)
- Ophthalmic variables (best corrected visual acuity, low luminance best corrected visual acuity, IOP, and ophthalmic examination)
- Vital sign measurements
- 12-lead ECG

11.3 Determination of Sample Size and Statistical Rationale

The sample size for this study is based on recently obtained 12-month results of the OPH2003 pivotal international, multicenter, randomized, double masked, sham-controlled clinical trial that was performed to evaluate the safety and efficacy of Zimura in patients with geographic atrophy secondary to AMD. The prespecified primary endpoint, mean change in GA growth over 12 months, equivalent to the mean rate of GA growth used in this study, was measured by fundus autofluorescence (FAF) based on readings at three time points (Baseline, Month 6, and Month 12) and was calculated using the square root transformation of the GA area. The FAF images were assessed by an independent masked reading center. The reduction in the mean rate of GA growth over 12 months was 0.11 mm ($p = 0.0072$) for the Zimura 2 mg group compared to the Sham control group.

In this Phase 3 trial, the primary analyses will be based on the comparison of the estimated reduction in the mean rate of GA growth over 12 months for Zimura 2 mg group versus the Sham control group. By pre-specification, this study will obtain evidence regarding the effect of Zimura on the mean rate of growth (slope) estimated based on GA area measured by fundus autofluorescence (FAF) in at least 3 time points over 12 months, when compared with Sham (square root transformation). The FAF images will be assessed by an independent masked reading center. The effect of treatment on the square root transformation of the GA area will be assessed using a mixed model for repeated measures model (MMRM) including stratification factors.

A total of approximately 400 patients will be randomized. If the 2 mg dose of Zimura truly provides a 0.11 mm reduction in the mean rate of GA growth over 12 months, then the trial will have 97% power to detect that effect at the two-sided significance level of 0.05. **Statistical**

significance at the two-sided significance level of 0.05 will be achieved for an estimated 0.057 mm reduction in the mean rate of GA growth over 12 months.

11.4 Year 2 Data Analysis

When the 12-month follow-up is complete for the primary analysis, the database will be locked. Post-12 month information will remain fully masked until completion of 24-month follow-up.

11.5 Randomization Procedure

Patients will be centrally allocated to one of the two treatment groups by a dynamic minimization procedure using clinical site in a 1:1 ratio stratified by factors known to be of prognostic importance in 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)

Patients initially randomized to Zimura 2 mg at Day 1 will be re-randomized at Month 12 in 1:1 ratio to Zimura 2 mg monthly vs every other month (please see 11.1 Study Design) using the same minimization procedure as for the initial randomization (i.e. using the same factors at Baseline).

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 patients 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.

11.6 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.

To maintain masking, the IRT system will provide instructions as to which kit is to be administered 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.

In the case of a rare emergency where, in the Investigator's 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. 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 patient's randomized treatment assignment. Any unmasking information must be stored separately from the patient'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.

11.6.1 Visual Acuity Assessments

Since this is a double-masked study, patients 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.

11.6.2 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 patients 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.

11.6.3 Statistical Analyses

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

11.7 Analytical Considerations

11.7.1 Analytical Plan

A Statistical Analysis Plan (SAP) will provide the details necessary for the statistical analyses to be explicitly pre-specified prior to unmasking, both at Month 12 and at Month 24. The methods for imputation of post-baseline, missing data will be specified in the SAP.

11.7.2 Significance Levels

The overall two-sided false positive error rate in this trial is 5%.

11.7.3 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 since the lack of a well-defined sampling context would render corresponding p-values to be uninterpretable.

11.7.4 Efficacy Analysis

The efficacy analysis will be conducted on all randomized and treated patients 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 stratification factors.

11.7.5 Subset Analyses

The trial is not sized to test for the presence of treatment by Baseline covariate interactions. Thus, true treatment by Baseline covariate interactions likely will not be rigorously established, unless they are quite substantial. In particular, should any subset of patients seem to benefit more or less from therapy than the total population, this will not be taken as reliable evidence of a true treatment by Baseline covariate interaction, given the likelihood that such an observation readily could be due to chance alone. With these caveats in mind, exploratory subset analyses will be performed as descriptive evidence regarding the generalizability of trial results.

11.7.6 Safety Analysis

The safety analysis will be conducted on all patients who had at least one administration of 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 patients 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 patient 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 study 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 "not related" or "related" to one of the following: (1) the intravitreous injection procedure (including eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine, subconjunctival injection of anesthetic, intravitreous injection of Zimura or anti-VEGF), or (2) related to the study drug (Zimura/sham), or (3) related to anti-VEGF treatment (if administered).

The adverse relationship will be assessed using the definitions below. The investigator will choose either "not related", or chose the most likely cause of the AE (i.e., only one of the relationships noted in the above paragraph may be chosen):

Not Related = There is not a reasonable possibility that the adverse event is related to the intravitreous injection procedure, or to the study drug (Zimura/sham), or to the anti-VEGF treatment.

Related = There is a reasonable possibility that the adverse event is related to the intravitreous injection procedure or to the study drug (Zimura/sham), or to the anti-VEGF treatment.

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 study 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 study 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, consisting of persons who are independent of the Sponsor, trial coordination center, data coordination center, regulatory agencies, IRB/EC and investigators, and who have no financial, scientific, or other conflict of interest with the clinical trial, will meet approximately every 6 months to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial, and provide recommendations to continue, modify, or terminate the trial depending upon the analyses. The safety data provided to the Committee will be prepared by an independent statistician.

The Sponsor will ensure the proper conduct of the study, collection of accurate and timely data, and promptly report potential safety concerns to the Data Monitoring committee, and communicate with regulatory authorities, IRB/EC, and investigators in a manner that maintains integrity of the data as necessary.

12.6 Exposure in Utero

If any trial patient becomes or is found to be pregnant while receiving study 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

Each center must adhere to their policies regarding emergency equipment and resuscitation procedures that may be in effect at the individual site or institution.

The sponsor recommends, if applicable for the participating sites, to 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) and to ensure that all equipment is within specifications for the duration of the trial. If applicable, each center should follow their written policies regarding resuscitation procedures. In addition to the above, any additional measures in adherence to specific site or institutional policies should be followed.

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 IVERIC bio clinical monitors, or its representatives, during scheduled monitoring visits, to auditors during any audits requested by IVERIC bio, 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 IVERIC bio'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 IVERIC bio. In the event of the Principal Investigator leaving the clinical site, it is the Principal Investigator's responsibility to notify IVERIC bio 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 study. Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all study drug supplies received, dispensed to trial patients, and returned to IVERIC bio.

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

13.4 Protocol Compliance

IVERIC bio 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 IVERIC bio and in agreement with the Investigator. Any such waiver will be documented in writing and provided to the Investigator by IVERIC bio.

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 Patients", and part 56, "Institutional Review Boards".

Expedited reporting will be conducted in accordance with local legislation.

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 patient informed consent
- A list of IRB/EC members, or statement of compliance

Prior to enrollment, written informed consent must be obtained from each patient 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

IVERIC bio 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 IVERIC bio 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 **GATHER2 (ISEE2008)-Global 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 GATHER2 (ISEE2008): "A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM CONTROLLED CLINICAL TRIAL TO ASSESS THE SAFETY AND EFFICACY OF INTRAVITREAL ADMINISTRATION OF ZIMURA (COMPLEMENT C5 INHIBITOR) IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION"

Trial Sponsor: **IVERIC bio, Inc**

[redacted]

Principal Investigator: _____ _____

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

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(Date)

17 APPENDICES

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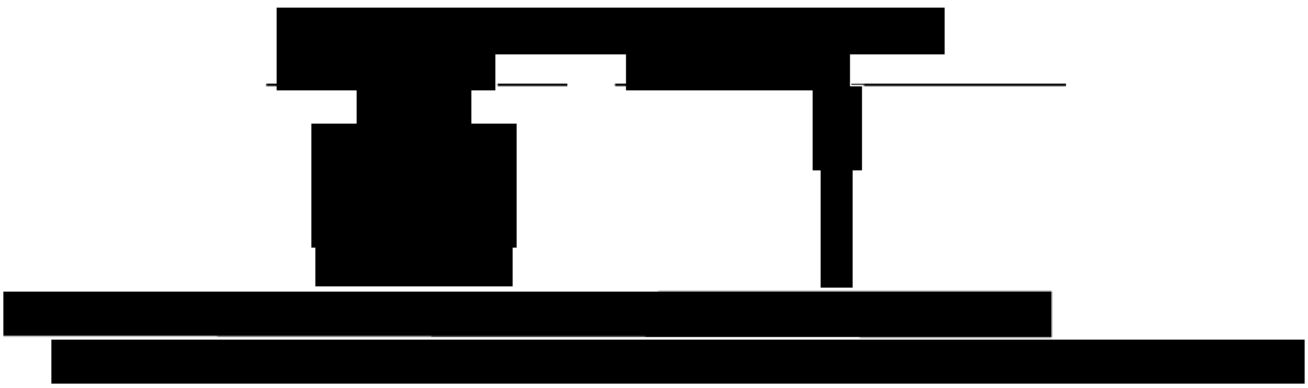

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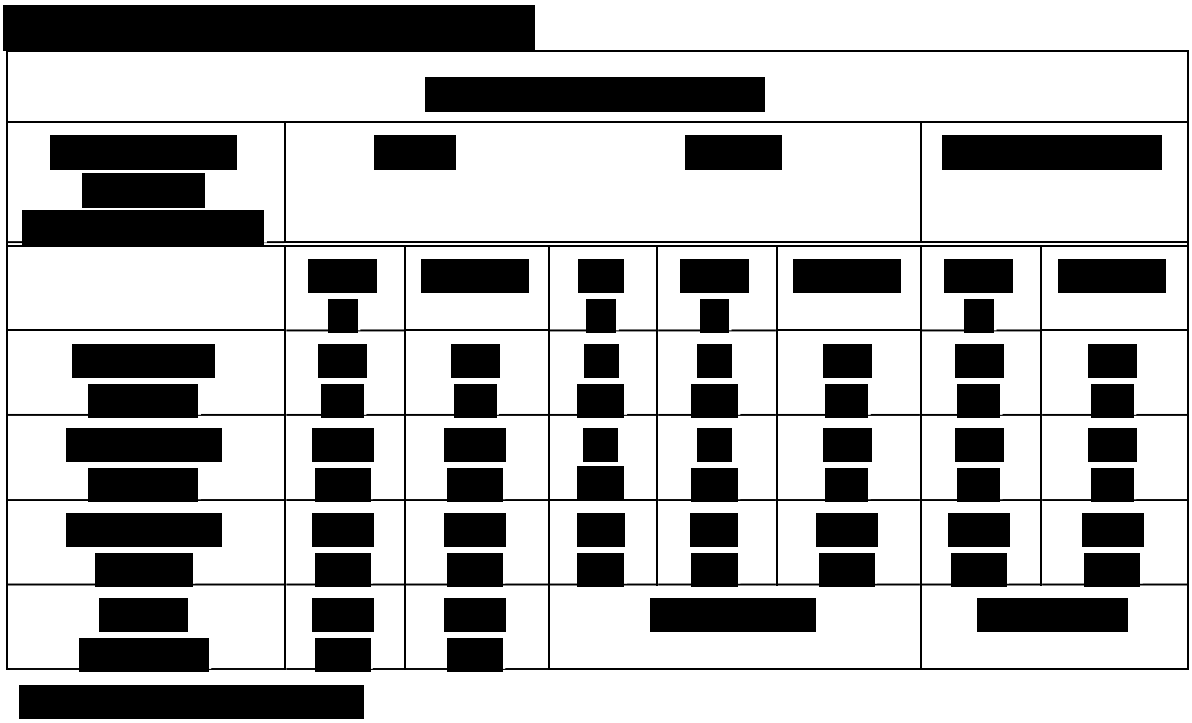

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