CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW of NDA 217225

Application Type	NDA
Application Number	217225
Priority or Standard	Priority
Submit Date	December 19, 2022
Received Date	December 19, 2022
PDUFA Goal Date	August 19, 2023
Division/Office	DO/OND/OSM
Reviewer Name	Lucious Lim, MD, MPH
Review Completion Date	May 12, 2023
Established/Proper Name	Avacincaptad pegol intravitreal solution, 20 mg/mL
(Proposed) Trade Name	IZERVAY
Applicant	Iveric Bio, Inc.
Dosage Form(s)	Intravitreal solution for intravitreal injection
Applicant Proposed Dosing Regimen	Avacincaptad pegol is recommended to be administered by intravitreal injection. The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) once monthly (approximately 28 ± 7 days).
Applicant Proposed Indication	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Recommended Regulatory Action	Approval
Recommended Dosing Regimen	Avacincaptad pegol is recommended to be administered by intravitreal injection. The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) once monthly (approximately 28 ± 7 days) for up to 12 months.

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Glossary

AC	advisory committee
AE	adverse event
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CNV	choroidal neovascularization
COVID-19	Coronavirus Disease 2019
CRF	case report form
CS	clinically significant
CSR	clinical study report
DA	disc area
DSMC	data safety monitoring committee
ECG	electrocardiogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	fluorescein angiogram
FAF	fundus autofluorescence
FDA	Food and Drug Administration
FE	fellow eye
GA	geographic atrophy
GCP	good clinical practice
GRMP	good review management practice
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IOP	intraocular pressure
IRB	institutional review board
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IVT	intravitreal
LOCF	last observation carried forward
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MRM	Model for Repeated Measures
nAMD	neovascular age-related macular degeneration

NDA	New Drug Application
OCT	optical coherence tomography
PK	pharmacokinetics
PP	per-protocol
PMC	postmarketing commitment
PMR	postmarketing requirement
PRO	patient reported outcome
PT	preferred term
QOL	quality of life
RC	reading center
REMS	risk evaluation and mitigation strategy
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States
VA	visual acuity
VEGF	vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire 25

1. Executive Summary

1.1. Product Introduction

Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. This action may prevent the formation of key terminal fragments (C5a and C5b-9), regardless of which initial activation pathway (classical, alternative, or lectin) induced their generation. By inhibiting these C5-mediated inflammatory and MAC activities, avacincaptad pegol is thought to preserve the retinal architecture and slow progression of geographic atrophy secondary to AMD. Despite inhibition of C5 activation, avacincaptad pegol does not inhibit cleavage of complement component 3 (C3) to C3a and C3b.

Avacincaptad pegol drug product is a sterile, aqueous solution for intravitreal injection. It is formulated at a concentration of 20 mg/mL (oligonucleotide mass) in phosphate-buffered saline. During the clinical development avacincaptad pegol has also been referred to as ARC1905 or Zimura or Izervay.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 217225 is recommended for approval with the revised labeling identified in the CDTL review. The clinical studies contained in this submission support the use of Izervay (avacincaptad pegol ophthalmic solution) 20 mg/mL solution, intravitreal injection for the treatment of geographic atrophy secondary to age-related macular degeneration for up to one year of treatment.

Approval is recommended for Izervay 2 mg (0.1 mL of 20 mg/mL solution), intravitreal injection, to each affected eye once monthly (approximately every 28 ± 7 days) up to 12 months.

1.3. Benefit-Risk Assessment

Benefit-Risk Dimensions

Benefit-Risk Integrated Assessment

The adequate and well controlled studies (OPH2003 and ISEE2008) contained in this submission establish the efficacy of Izervay (avacincaptad pegol injection), 20 mg/mL for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) when the product is administered intravitreally monthly (approximately every 28 ± 7 days) for up to 12 months. This demonstration of efficacy is based on superiority in slowing the rate of change in geographic atrophy area at Month 12 compared to sham.

The most common significant ocular adverse events after treatment with avacincaptad pegol were conjunctival hemorrhage and choroidal neovascularization (CNV). Treatment with avacincaptad pegol 2 mg monthly is associated with development of CNV (7.2%) compared with sham (3.6%).

There is a favorable benefit-risk ratio of avacincaptad pegol injection, 20 mg/mL in the treatment of GA secondary to AMD with the proposed dosing regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GA secondary to AMD is characterized by progressive and irreversible atrophy of retinal cells and is a leading cause of severe vision loss worldwide. • Approximately 1 million people in the US are affected by GA and experience profound decrease in quality of life, including difficulty reading and recognizing faces and loss of independence	The goal of treatment of GA secondary to AMD is the preservation of retina cells (RPE, photoreceptors, and choriocapillaris) and preserving vision in the long term.
Current Treatment Options	• Syfovre (pegcetacoplan ophthalmic solution,150 mg/mL), intravitreal injection has been shown to be safe and effective and is approved to treat patients with GA secondary to AMD.	Izervay would provide practitioners with an additional drug treatment option.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Studies OPH2003 and ISEE2008 demonstrated that avacincaptad pegol was superior in slowing the rate of change in geographic atrophy area at Month 12 compared to sham in patients with GA secondary to AMD.	Adequate and well controlled studies support the efficacy of IZERVAY. Use of the product led to slowing the rate of change in geographic atrophy area.
Risk and Risk Management	• Risks associated with IZERVAY are consistent with the risks of other intravitreally administered drug products and the other approved treatment for GA. No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.	Routine monitoring and reporting of all adverse events are adequate.

2. Therapeutic Context

2.1. Analysis of Condition

GA secondary to AMD is a serious medical condition with both health and social impacts for patients. GA is a form of AMD and is characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris that leads to progressive and irreversible loss of visual function.

AMD is a progressive retinal disease that leads to central vision loss, which impairs the ability of patients to read, recognize faces, drive, and live an independent life (Ambati et al. 2013; Williams et al. 1998). AMD is a leading cause of severe vision loss in people over the age of 65 in the United States (US) and other Western countries (Rein et al. 2009). In the United States, about 1.75 million people have the late forms of AMD (Friedman et al. 2004). The forms of AMD are primarily classified into either exudative AMD (neovascular, wet or macular neovascularization) or geographic atrophy (GA).

2.2. **Analysis of Current Treatment Options**

Syfovre (pegcetacoplan ophthalmic solution,150 mg/mL), intravitreal injection was approved for the treatment of GA secondary to AMD in February 2023.

3. Regulatory Background

3.1. **U.S. Regulatory Actions and Marketing History**

Avacincaptad pegol has not been marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

- New IND filed on May 30, 2008
- Fast Track designation granted on April 1, 2020
- Special Protocol Assessment (SPA) for Protocol ISEE2008 (GATHER2) - No Agreement letter issued on May 14, 2021
- SPA Re-submission for Protocol ISEE2008 (GATHER2) - Agreement letter issued on July 2, 2021
- Type C meeting was held on September 8, 2021
- Type C meeting was held on November 16, 2021
- Type C meeting was held on December 6, 2021
- Pre-NDA meeting was held May 27, 2022

- Type C CMC WRO final response issued on July 14, 2022
- Rolling Review was granted on October 17, 2022
- Breakthrough Therapy Designation was granted on November 17, 2022
- Type B chemistry, manufacturing, and controls (CMC) Pre-NDA was held on October 18, 2022

3.3. Foreign Regulatory Actions and Marketing History

Avacincaptad pegol has not been marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A request for inspection of two clinical sites was been submitted to OSI. The clinical investigators, Drs. Cummings and Wong, as well as the sponsor, IVERIC bio, Inc., were inspected in support of this NDA. Based on the results of these inspections, the conduct of Protocols OPH2003 and ISEE2008, the data generated by these clinical sites, and the sponsor's oversight of these studies all appear to be adequate.

4.2. Product Quality

Avacincaptad pegol (20 mg/mL) drug product is a sterile, aqueous solution intended for single dose intravitreal administration. The drug product is supplied with a fill volume of (b) (4) mL per vial.

Components and Quantitative Composition of Avacincaptad pegol Drug Product- 20 mg/mL

Ingredient	Function	Quality Standard	Concentration (mg/mL)	Quantity (Per 0.1 mL dose)	Quantity (Per vial)[1]
Avacincaptad Pegol	Active ingredient	In-house	20.0 (Oligonucleotide basis)[2]	2.0 mg (Oligonucleotide basis)	(b) (4)
Dibasic Sodium Phosphate Heptahydrate	(b) (4)	USP	1.98	0.198 mg	
Monobasic Sodium Phosphate Monohydrate		USP	0.256	0.0256 mg	
Sodium Chloride		USP/Ph. Eur.	8.3	0.83 mg	
Water for injection		USP/Ph. Eur.	q.s.	q.s.	

[1] Quantity per vial (b) (4) includes (b) (4) of excess fill to deliver 0.1 mL dose. [2] (b) (4). q.s.: quantity sufficient

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

See CDTL review for complete findings.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name / Phase	Study Design	Number of Patients Enrolled	Study Drug Treatment Groups/Study Duration	Study Status/Type of Study Report
Phase 1 and 2 Studies				
OPH2001 Safety and Tolerability Module 5.3.5.2	**Study Design:** Phase 1, open-label, non-controlled study to evaluate safety and tolerability of two dose levels of avacincaptad in patients with GA secondary to AMD	Total Enrolled N=47 Avacincaptad pegol 0.3 mg (N=24) Avacincaptad pegol 1 mg (N=23)	Avacincaptad pegol (0.3 mg or 1 mg) IVT once monthly Study Duration=12 months	Completed Final CSR (7/26/2018)
OPH2002 Safety and Tolerability Module 5.3.5.2	**Study Design:** Phase 2a, open-label study to evaluate safety and tolerability of avacincaptad combined with anti-VEGF therapy in patients with IPCV	Avacincaptad pegol 1 mg (N=4)	Avacincaptad pegol (1 mg) IVT once monthly Study Duration=3 months	Completed Final CSR (10/5/2018)
OPH2004 Safety and Tolerability Module 5.3.5.2	**Study Design:** Phase 2a, open-label study to evaluate safety and tolerability of avacincaptad combined with anti-VEGF therapy in patients with nAMD	Avacincaptad pegol 2 mg (N=4)	Avacincaptad pegol (2 mg) IVT once monthly Study Duration=18 months	Completed Final CSR (3/7/2022)
OPH2005 Safety/Efficacy Tolerability	**Study Design:** Phase 2b, study to evaluate safety and efficacy of avacincaptad in patients with Stargardt Disease	Total Planned=120 Avacincaptad pegol (N=60)	Induction Phase: Avacincaptad pegol 2 mg or Sham administered every 14 days for the first 2 months and then monthly	Ongoing

Study Name / Phase	Study Design	Number of Patients Enrolled	Study Drug Treatment Groups/Study Duration	Study Status/Type of Study Report
		Sham (N=60)	thereafter Maintenance Phase: Avacincaptad pegol 4 mg (2 mg + 2 mg) or Sham + Sham administered every month through Month 17 Study Duration=18 months	
OPH2007 Safety and Tolerability Module 5.3.5.2	**Study Design:** Phase 2a, open-label study to evaluate safety and tolerability of avacincaptad combined with anti-VEGF therapy in patients with nAMD	Total Enrolled N=65 Cohort 1 (N=10) Cohort 2 (N=11) Cohort 3 (N=22) Cohort 4 (N=22)	Cohort 1: Monthly IVT injections of Lucentis 0.5 mg and 2 days later avacincaptad pegol 4 mg (2 mg + 2 mg); Cohort 2: Monthly IVT injections of Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day Cohort 3: Induction Phase (3 months): 2 IVT injections/month 14 days apart of 1. Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day; 2. avacincaptad pegol 2 mg Maintenance Phase (3 months): Monthly IVT injections of Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day Cohort 4: Induction Phase (3 months): 2 IVT injections/month 14 days apart of 1. Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day; 2. avacincaptad pegol 2 mg Maintenance Phase (3 months): Monthly IVT injections of avacincaptad pegol 2 mg and 2 days later Lucentis 0.5 mg + avacincaptad pegol 2 mg on the same day Study Duration=6 months	Completed Final CSR (7/10/2020)
Phase 2/3 Studies				
OPH2003	**Study Design:**	Total Enrolled	Avacincaptad pegol (1, 2, or 4 mg) by IVT injections	Completed

Study Name / Phase	Study Design	Number of Patients Enrolled	Study Drug Treatment Groups/Study Duration	Study Status/Type of Study Report
Safety/Efficacy Module 5.3.5.1	Phase 2/3, multicenter, randomized, double-masked, parallel-group, sham-controlled study to evaluate safety and efficacy in patients with GA secondary to AMD	N=286 Part 1: Avacincaptad pegol 1 mg (N=26) Avacincaptad pegol 2 mg (N= 25) Sham (N=26) Part 2: Avacincaptad pegol 2 mg (N=42) Avacincaptad pegol 4 mg (N=83) Sham (N=84)	or Sham injections once monthly Study Duration=18 months	Final CSR (3/31/2022)
Phase 3 Studies				
ISEE2008 (GATHER2) Safety/Efficacy Module 5.3.5.1	**Study Design:** Phase 3, multicenter, randomized, double-masked, parallel-group, sham-controlled study to evaluate safety and efficacy in patients with GA secondary to AMD	Total Enrolled N=448[a] Avacincaptad pegol 2 mg (N=225) Sham (N=223)	Avacincaptad pegol 2 mg by IVT injection or sham once monthly Study Duration=24 months	Ongoing Year 1 CSR
1SEE2009 Long Term Safety	**Study Design:** Open label extension study to assess long term safety in patients with GA secondary to AMD	Planned: approximately 400 patients who completed Study ISEE2008 through the Month 24 visit on study treatment (either avacincaptad pegol or Sham)	Avacincaptad pegol (2 mg) by IVT injection once monthly Study Duration=18 months	Ongoing

AMD=age-related macular degeneration, CSR=Clinical Study Report, GA=geographic atrophy, IPCV=idiopathic polypoidal choroidal vasculopathy, IVT=intravitreal, nAMD=neovascular age-related macular degeneration
[a] Total enrolled was 448 patients; however, total treated was 447 patients as one patient in Sham group was randomized and not treated.

5.2. Review Strategy

Clinical data for Studies OPH2003 and ISEE2008 listed in Section 5.1 were reviewed to support safety and efficacy. Clinical data from the additional studies in Section 5.1 were reviewed as appropriate to support safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study OPH2003 – A Phase 2/3 Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-C5 Aptamer) in Patients with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration Study Design

6.1.1. Study Design

Primary Objective: The objectives of this study were to evaluate the safety and efficacy of Zimura (avacincaptad pegol) 1 mg, 2 mg, or 4 mg intravitreal administration when administered in patients with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD).

List of Investigators
There were 80 study center(s) in the following countries: Croatia (1), Czech Republic (5), Estonia (2), Hungary (9), Israel (6), Latvia (1), and USA (56).

Table 6.1.1-1 Investigator(s) Who Randomized 10 or more Subjects

Site Number	Principal Investigator Site Address	Number of Subjects Enrolled
002	Sunil S. Patel Retina Research Institute of Texas, 5441 Health Center Drive Abilene, TX 79606	15
015	John Randolph Center for Retina and Macular Disease, 250 Avenue K Southwest Ste 200 Winter Haven, FL 33880	15
113	Agnes Kerenyi Bajcsy-Zsilinszky Kórház és Rendel-intézet/Szemészet, Maglódi út 89-91 Budapest, 1106 – Hungary	12
411	Brian Joondeph Colorado Retina Associates, PC, 400 Indiana Street, Ste 310 Golden, CO 80401	12
024	David Lally New England Retina Consultants, 3640 Main Street, Ste 201 Springfield, MA 01107	10
302	George Bertolucci Eye Medical Center of Fresno, 1360 East Herndon Ave., Ste 301 Fresno, CA 93720	10

Site Number	Principal Investigator Site Address	Number of Subjects Enrolled
311	Dennis Marcus Southeast Retina Center, 3685 Wheeler Road, Ste 201 Augusta, GA 30909	10
382	John Carlson Retinal Consultants of Southern California, 1895 Orange Tree Lane, Ste 204 Redlands, CA 92374	10

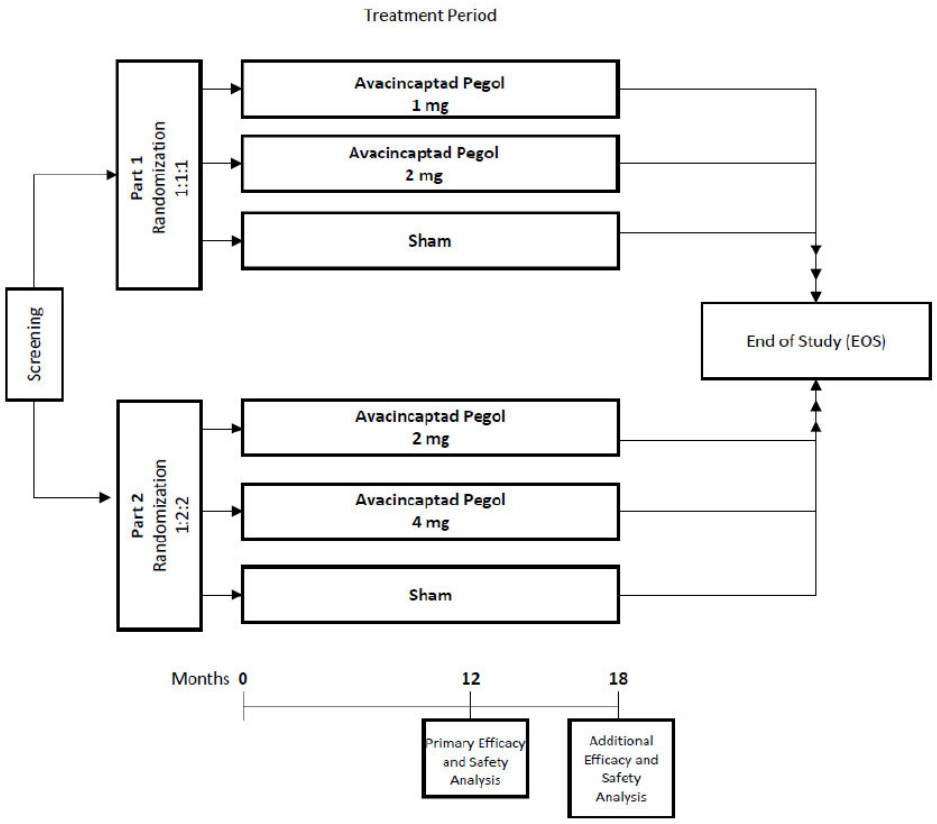
Overall Design:
This was a Phase 2/3, prospective, randomized, double-masked, sham-controlled, multicenter, 2 part study designed to compare the efficacy and safety of Zimura (avancincaptad pegol) 1, 2, and 4 mg vs Sham in patients with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD).

In Part 1, approximately 77 patients (1:1:1 randomization per treatment arm) were planned for randomization in the following dose groups:
- Zimura 1 mg/eye administered via intravitreal (IVT) injection
- Zimura 2 mg/eye administered via IVT injection
- Sham: The Sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

In Part 2, approximately 200 patients (1:2:2 randomization per treatment arm) were planned for randomization in the following dose groups:
- Zimura 2 mg/eye administered via IVT injection + Sham
- Zimura 4 mg/eye (administered as 2 IVT injections of Zimura 2 mg/eye)
- Sham + Sham

The primary efficacy and safety analyses were to be assessed at Month 12. The total study duration was 18 months.

Study Design



Patients received monthly IVT injections of Zimura and/or Sham for 18 months during Part 1 and Part 2. After the first 12 months, all parties (i.e., patients, investigator, site, Reading Center and the Sponsor) remained individually masked, and patients continued in their treatment arms until Month 18. After Day 1, monthly study visits were scheduled through Month 18.

Inclusion and Exclusion Criteria

Ophthalmic Inclusion Criteria

The following inclusion criteria applied to the study eye (SE):

1. Non-foveal GA secondary to dry AMD.
2. Total GA area ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 DA respectively), determined by Screening images of FAF.
3. If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm^2 (0.5 DA).
4. GA in part within 1500 microns from the foveal center.
5. The atrophic lesion must be able to be photographed in its entirety.
6. BCVA in the SE between 20/25 to 20/320, inclusive.
7. Clear ocular media and adequate pupillary dilatation in both eyes to allow for all imaging procedures, including good quality stereoscopic fundus photography and FAF.
8. IOP of 21 mmHg or less in the SE.

General Inclusion Criteria:

1. Patients of either gender aged ≥ 50 years.
2. Women must be using 2 forms of effective contraception, be post-menopausal for at least 12 months prior to study entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test must be performed within 14 days prior to the first injection with a negative result. The 2 forms of effective contraception must be implemented during the study and for at least 60 days following the last dose of test medication.
3. Provide written informed consent.
4. Ability to return for all study visits.

Ophthalmic Exclusion Criteria:

The following exclusion criteria applied to the SE:

1. Evidence of CNV in either eye. If CNV develops in the SE during the course of the study, the patient will be withdrawn from the study.
2. GA secondary to any condition other than AMD in either eye (e.g., drug-induced).
3. Any prior treatment for AMD or any prior IVT treatment for any indication in either eye, except oral supplements of vitamins or minerals.
4. Any ocular condition in the SE that would progress during the course of the study that could affect central vision or otherwise be a confounding factor.
5. Concomitant treatment with any ocular or non-ocular medication that is known to be toxic to the lens, retina, or optic nerve.
6. Presence of intraocular inflammation (≥ trace cell or flare), macular hole, pathologic myopia, epiretinal membrane, evidence of significant vitreo-macular traction, vitreous hemorrhage or aphakia (pseudophakia with or without an intact capsule is not an exclusion criteria).
7. Presence or history of idiopathic or autoimmune-associated uveitis in either eye.
8. Significant media opacities, including cataract, which might interfere with VA, assessment of toxicity, fundus photography, or FAF. Patients should not be entered if there is likelihood that they will require cataract surgery in the SE during the study.
9. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
10. Any intraocular surgery or thermal laser within 3 months of study entry. Any prior thermal laser in the macular region, regardless of indication.
11. Any ocular or periocular infection (including blepharitis), or ocular surface inflammation in the past 12 weeks.
12. History of any of the following procedures: Posterior vitrectomy, filtering surgery (e.g., trabeculectomy), glaucoma drainage device, corneal transplant, or retinal detachment.
13. Any sign of diabetic retinopathy in either eye.

General Exclusion Criteria:

1. Any of the following underlying diseases including:
   a. History or evidence of severe cardiac disease (e.g., New York Heart Association Functional Class III or IV, history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction, or revascularization within last 6 months, ventricular tachyarrhythmias requiring ongoing treatment.

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

2. Previous therapeutic radiation in the region of the SE.
3. Any treatment with an investigational agent in the past 60 days for any condition.
4. Women who are pregnant or nursing.
5. Known serious allergies to the fluorescein dye used in angiography or to the components of the Zimura formulation.
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.

Test and Reference Therapies
Zimura is a PEGylated ribonucleic acid (RNA) aptamer consisting of a 12,881 Da modified nucleotide aptamer that is conjugated at the 5' terminus to an ~43 kDa branched polyethylene glycol (PEG) moiety. Zimura doses were formulated in a 20 mg/mL (oligonucleotide mass) solution for injection. Zimura was supplied in single use, sterile glass vials for IVT injection.

Patients were randomized to receive Zimura 1 mg/eye (50 μL), 2 mg/eye (100 μL), 4 mg/eye (2 x 100 μL) or Sham. Zimura was administered as an IVT injection.

Treatment masking
To maintain masking when study treatments were administered, Sham injections were performed. The Sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

Prohibited Medications/Treatments
Patients enrolled were treatment-naïve (no previous treatment for AMD) in either eye except for oral supplements of vitamins or 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 study, was not permitted.

Safety Assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), Vital signs (pulse, systolic and diastolic blood pressure), Ophthalmic variables (IOP, ophthalmic examination, FA, FAF, CFP, and OCT), ECG (12-lead), and Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis).

Statistical Methods

Primary Efficacy Endpoint-Mean change from baseline in GA area at Months 12 measured by fundus autofluorescence (FAF)

Reviewer's Comment: *To determine efficacy, the best polynominal fit mean rate of change in geographic atrophy over at least 12 months measured by fundus autofluorescence (FAF) in at least three time points was requested by the Division as the primary efficacy endpoint.*

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

Analysis Populations
- Intent-to treat (ITT) population – all randomized patients and received at least one injection of study drug
- Per protocol (PP) population – all patients who received at least one injection of study drug with no significant protocol violations
- Safety population – all patients who received at least one injection of study drug with analysis based on actual dose received

The safety analyses were conducted on the safety population. Safety evaluations for the Month 12 assessment included all adverse events, vital signs (pulse, systolic and diastolic blood pressure), ophthalmic variables (IOP, ophthalmic examination, FA, FAF, CFP, and OCT), ECG (12-lead), and laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis).

Compliance with Good Clinical Practices
This study was conducted per the principles of Good Clinical Practices (GCP). There were no interim analyses.

Figure 6.1.1-2 Evaluation and Visit Schedule

Study Assessments through Month 12

Assessment	SCR	Day 1[a]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X													
Medical & Ophthalmic History[b] Performance Status	X													
Vital Signs/Physical Exam[c]	X							X						X
12-Lead ECG	X							X						X
Protocol refraction and ETDRS Visual Acuity[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[b,d,e]/Ophthalmologic Examination[b,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Low Luminance ETDRS Visual Acuity[b]		X	X	X	X	X	X	X	X	X	X	X	X	X
VFQ-25		X						X						X
Reading Rate[b]		X						X						X
Color Fundus Photographs[b]	X							X						X
Fluorescein Angiogram[b]	X							X						X
OCT[b]	X							X						X
Fundus Autofluorescence[b]	X							X						X
Laboratory Tests/Serum Pregnancy (If Applicable)	X							X						X
Randomization		X												
Zimura/Sham Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Study Protocol (Appendix 16.1.1)
ECG = electrocardiogram; ETDRS = early treatment diabetic retinopathy study; IOP = intraocular pressure; OCT = optical coherence tomography; SCR = screening; SE = study eye; VFQ-25 = Visual Function Questionnaire 25
Note: Visit Windows: It was essential that patients adhered to their pre-scheduled study visits within the following visit windows – Months 1 to 18: ± 7 days. Monthly doses must be administered at least 21 days apart.

[a]Day 1 assessments were performed within 14 days of Screening.
[b]Ocular assessments were performed at Baseline (Screening or Day 1), Months 6, 12, and Month 18/Early Withdrawal on both eyes pre-injection. Ocular assessments at all other study visits were performed on the SE only. Reading Rate was to be performed in countries depending on language availability.
[c]Physical examination was performed at Screening and at the investigator's discretion thereafter. Vital Signs were performed at all indicated time points.
[d]Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Months 6, 12, 18/Early Withdrawal. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify IOP $\geq$ 30 mmHg occurring at any time.
[e]Tonometry was measured prior to the injection and after each injection as per Section 10 of the Study Protocol (Appendix 16.1.1), Trial Conduct.
[f]A full ophthalmic exam was performed prior to the injection and again at least 30 minutes after the last injection.
[g]Adverse events were recorded starting after the first dose of study drug.

Figure 6.1.1-2 Evaluation and Visit Schedule (continued)

Study Assessments from Month 13 through Month 18

Assessment	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18/EW
Vital Signs/Physical Exam[a]						X
12-Lead ECG						X
Protocol refraction and ETDRS Visual Acuity[b]	X	X	X	X	X	X
Tonometry[b,c,d]/Ophthalmologic Examination[b,e]	X	X	X	X	X	X
Low Luminance ETDRS Visual Acuity[b]	X	X	X	X	X	X
VFQ-25						X
Reading Rate[b]						X
Color Fundus Photographs[b]						X
Fluorescein Angiogram[b]						X
OCT[b]						X
Fundus Autofluorescence[b]						X
Laboratory Tests/Serum Pregnancy (If Applicable)						X
Zimura/Sham Study Drug Administration	X	X	X	X	X	
3-Day Post-Injection Telephone Safety Check	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events[f]	X	X	X	X	X	X

Source: Study Protocol (Appendix 16.1.1)
ECG = electrocardiogram; ETDRS = early treatment diabetic retinopathy study; EW = early withdrawal; IOP = intraocular pressure; OCT = optical coherence tomography; SE = study eye; VFQ-25 = Visual Function Questionnaire 25
Note: Visit Windows: It is essential that patients adhered to their prescheduled study visits within the following visit windows – Months 1 to 18: ± 7 days.
[a]Physical examination was performed at Screening and at the investigator's discretion thereafter. Vital Signs were performed at all indicated time points.
[b]Ocular assessments were performed at Baseline (Screening or Day 1), Months 6, 12, and at Month 18/Early Withdrawal on both eyes pre-injection. Ocular assessments at all other study visits were performed on the SE only. Reading Rate was to be performed in countries depending on language availability.
[c]Goldmann applanation tonometry was performed at Screening and pre-injection at Day 1, Months 6, 12, 18/Early Withdrawal. The Tono-Pen may have been used at other times; however, Goldmann applanation tonometry must have been used to verify IOP ≥30 mmHg occurring at any time.
[d]Tonometry was measured prior to the injection and after each injection as per Section 10 of the Study Protocol (Appendix 16.1.1), Trial Conduct.
[e]A full ophthalmic exam was performed prior to the injection and again at least 30 minutes after the last injection.
[f]Adverse events were recorded starting after the first dose of study drug.

6.1.2. Study Results

Table 6.1.2-1 Subject Disposition - ITT Population

	Part 1			Part 2			Combined[a]	
	Zimura 1 mg N=26 n (%)	Zimura 2 mg N=25 n (%)	Sham N=26 n (%)	Zimura 2 mg N=42 n (%)	Zimura 4 mg N=83 n (%)	Sham N=84 n (%)	Zimura 2 mg N=67 n (%)	Sham N=110 n (%)
Randomized and treated	77			209			177	
Month 12 Analysis								
Completed Month 12	24 (92)	20 (80)	21 (81)	35 (83)	58 (70)	75 (89)	55 (82)	96 (87)
Discontinued the study prior to Month 12	2 (7.7)	5 (20.0)	5 (19.2)	7 (17)	25 (30)	9 (11)	12 (18)	14 (13)
Reason for Discontinuation								
Adverse event	0	0	1 (3.8)	0	1 (1.2)	0	0	1 (0.9)
Protocol violation	0	0	0	0	0	0	0	0
Investigator decision	0	0	0	1 (2.4)	2 (2.4)	1 (1.2)	1 (1.5)	1 (0.9)
Sponsor decision	1 (3.8)	2 (8.0)	0	3 (7.1)	8 (9.6)	2 (2.4)	5 (7.5)	2 (1.8)
Withdrawal by patient	1 (3.8)	3 (12.0)	3 (11.5)	3 (7.1)	13 (15.7)	5 (6.0)	6 (9.0)	8 (7.3)
Lost to follow-up	0	0	1 (3.8)	0	0	0	0	1 (0.9)
Patient non-compliance	0	0	0	0	0	0	0	0
Death	0	0	0	0	1 (1.2)	1 (1.2)	0	1 (0.9)
Other	0	0	0	0	0	0	0	0
Month 18 Analysis								
Completed Month 18	22 (85)	18 (72)	17 (65)	30 (71)	46 (55)	68 (81)	48 (72)	85 (77)
Discontinued the study prior to Month 18	4 (15)	7 (28)	9 (35)	12 (29)	37 (45)	16 (19)	19 (28)	25 (23)
Reason for Discontinuation								
Adverse event	0	0	1 (3.8)	1 (2.4)	2 (2.4)	1 (1.2)	1 (1.5)	2 (1.8)
Protocol violation	0	0	0	0	0	0	0	0
Investigator decision	0	0	0	1 (2.4)	2 (2.4)	1 (1.2)	1 (1.5)	1 (0.9)
Sponsor decision	1 (3.8)	2 (8.0)	1 (3.8)	5 (11.9)	13 (15.7)	2 (2.4)	7 (10.4)	3 (2.7)
Withdrawal by patient	2 (7.7)	5 (20.0)	4 (15.4)	4 (9.5)	17 (20.5)	8 (9.5)	9 (13.4)	12 (10.9)
Lost to follow-up	0	0	2 (7.7)	0	0	1 (1.2)	0	3 (2.7)
Patient non-compliance	0	0	0	0	0	1 (1.2)	0	1 (0.9)
Death	1 (3.8)	0	0	1 (2.4)	1 (1.2)	1 (1.2)	1 (1.5)	1 (0.9)
Other	0	0	1 (3.8)	0	2 (2.4)	1 (1.2)	0	2 (1.8)
Number of patients who completed through								
Month 3 visit	25 (96)	23 (92)	23 (88)	40 (95)	76 (92)	81 (96)	63 (94)	104 (95)
Month 6 visit	25 (96)	21 (84)	21 (81)	36 (86)	68 (82)	78 (93)	57 (85)	99 (90)
Month 9 visit	24 (92)	20 (80)	21 (81)	35 (83)	62 (75)	74 (88)	55 (82)	95 (86)
Month 12 visit	23 (88)	19 (76)	19 (73)	34 (81)	56 (68)	72 (86)	53 (79)	91 (83)
Month 15 visit	22 (85)	18 (72)	18 (69)	32 (76)	50 (60)	70 (83)	50 (75)	88 (80)

Source: Study OPH2003 CSR, Tables 4 and 5
[a]Combination of Part 1 and Part 2 patients

Reviewer's Comment: *Through Month 12 (combined Parts 1 and 2), approximately 80% of patients treated with Zimura 2 mg and 90% of patients treated with Sham completed Month 12. The number of patients who discontinued the study prior to Month 12 was 12 (18%) and 14 (13%) for patients treated with Zimura 2 mg and Sham, respectively. Withdrawal from the study*

was dose dependent. Withdrawal by patient was the most common reason, 9% for Zimura 2 mg and 7% for Sham.

Through Month 18 (combined Parts 1 and 2), approximately 72% of patients treated with Zimura 2 mg and 77% of patients treated with Sham completed Month 18. The number of patients who discontinued the study prior to Month 18 was 19 (28%) and 25 (23%) for patients treated with Zimura 2 mg and Sham, respectively. Withdrawal by patient was the most common reason, 13% for Zimura 2 mg and 11% for Sham.

Table 6.1.2-2 Summary of Significant Protocol Deviations Through Months 12 and 18-ITT Population

	Part 1			Part 2			Combined[a]	
	Zimura 1 mg N=26 n (%)	Zimura 2 mg N=25 n (%)	Sham N=26 n (%)	Zimura 2 mg N=42 n (%)	Zimura 4 mg N=83 n (%)	Sham N=84 n (%)	Zimura 2 mg N=67 n (%)	Sham N=110 n (%)
Month 12 Analysis								
Number of patients with at least 1 significant protocol deviation	9 (34.6)	7 (28.0)	8 (30.8)	13 (31.0)	31 (37.3)	15 (17.9)	20 (29.9)	23 (20.9)
Baseline GA in SE not between 2.5 to 17.5(mm^2)[b]	NA	NA	NA	0	1 (1.2)	1 (1.2)	0	1 (0.9)
Prior treatment for AMD or intravitreal treatment in SE	0	0	0	0	0	0	0	0
Missed > 2 doses or >2 consecutive doses	3 (11.5)	6 (24)	6 (23)	9 (21)	26 (31)	12 (14)	15 (22)	18 (16)
Missing evaluable Month 12 FAF Assessment[c]	8 (31)	7 (28)	8 (31)	11 (26)	28 (34)	12 (14)	18 (27)	20 (18)
Month 18 Analysis								
Number of patients with at least 1 significant protocol deviation	10 (38)	10 (40)	12 (46)	18 (43)	40 (48)	22 (26)	28 (42)	34 (31)
Baseline GA in SE not between 2.5 to 17.5(mm^2)[b]	NA	NA	NA	0	1 (1.2)	1 (1.2)	0	1 (0.9)
Missed > 2 doses or >2 consecutive doses	6 (23.1)	8 (32.0)	8 (30.8)	12 (28.6)	36 (43.4)	17 (20.2)	20 (29.9)	25 (22.7)
Missing evaluable Month 18 FAF Assessment[c]	9 (34.6)	92 (36.0)	12 46.2)	17 (40.5)	38 (45.8)	20 (23.8)	26 (38.8)	32 (29.1)

Source: Study OPH2003 CSR, Tables 6 and 7
AMD = age-related macular degeneration; FAF = fundus autofluorescence; GA = geographic atrophy; ITT = intent-to-treat population; NA = not applicable; SAP = statistical analysis plan; SE = study eye
Notes: Patients with significant protocol deviations are excluded from the per-protocol population. Patients with more than one deviation of the same type will only be counted once per that category.
[a]Combination of Part 1 and Part 2 patients.
[b]Not applicable for Part 1 patients.
[c]Includes FAF assessments designated Month 18 per visit windows in SAP

Reviewer's Comment: *Through Month 12 (combined Parts 1 and 2), a total of 83 subjects, 9 (35%) in the Zimura 1 mg treatment arm, 20 (30%) in the Zimura 2 mg arm, 31 (37%) in the Zimura 4 mg arm, and 23 (21%) in the Sham arm had at least 1 significant protocol deviations during the study.*

Through Month 18 (combined Parts 1 and 2), a total of 112 subjects, 10 (39%) in the Zimura 1 mg treatment arm, 28 (42%) in the Zimura 2 mg arm, 40 (48%) in the Zimura 4 mg arm, and 34 (31%) in the Sham arm had at least 1 significant protocol deviations during the study.

Table 6.1.2-3 Analysis Populations

Analysis Population	Part 1			Part 2			Combined[a]	
	Zimura 1 mg n (%)	Zimura 2 mg n (%)	Sham n (%)	Zimura 2 mg n (%)	Zimura 4 mg n (%)	Sham n (%)	Zimura 2 mg n (%)	Sham n (%)
Randomized	26	25	26	42	83	84	67	110
Randomized but not treated	0	0	0	0	0	0	0	0
Intent-to-Treat (ITT)[b]	26	25	26	42	83	84	67	110
Per-Protocol (PP)[c]	17 (65)	18 (72)	18 (69)	29 (69)	52 (63)	69 (82)	47 (70)	87 (79)
Safety[d]	26	25	26	42	83	84	67	110

Source: Study OPH2003 CSR, Table 10
[a]Combination of Part 1 and Part 2 patients.
[b]The ITT population consisted of all randomized patients who received at least one dose of study drug, irrespective of the dose actually received. Patients were analyzed in the dose group assigned at randomization.
[c]The PP population consisted of all ITT patients without significant violation of the protocol.
[d]The Safety population included all patients who received at least one injection of the study drug. Patients who ever received an injection of Zimura were analyzed in the appropriate Zimura group according to the actual injections received.

Table 6.1.2-4 Subject Demographics – ITT Population

	Part 1			Part 2			Combined[a]	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Age (years)								
Mean	73.8	77.7	78.1	79.4	79.2	78.2	78.8	78.2
Standard Deviation	7.97	9.57	8.43	10.65	8.31	8.98	10.22	8.82
Median	75.5	80.0	79.0	83.0	80.0	78.0	82.0	79.0
Min, Max	56, 91	58, 94	57, 90	52, 94	57, 95	54, 97	52, 94	54, 97
Age group, n (%)								
< 65 years	3 (11.5)	4 (16.0)	2 (7.7)	6 (14.3)	5 (6.0)	4 (4.8)	10 (14.9)	6 (5.5)
≥ 65 years	23 (88.5)	21(84.0)	24 (92.3)	36 (85.7)	78 (94.0)	80 (95.2)	57 (85.1)	104 (94.5)
Gender, n (%)								
Male	11 (42.3)	7 (28.0)	8 (30.8)	15 (35.7)	25 (30.1)	23 (27.4)	22 (32.8)	31 (28.2)
Female	15 (57.7)	18 (72.0)	18 (69.2)	27 (64.3)	58 (69.9)	61 (72.6)	45 (67.2)	79 (71.8)
Race, n (%)								
American Indian/ Alaska Native	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	1 (1.2)	0	1 (0.9)
Asian	1 (3.8)	0	0	0	0	0	0	0
Native Hawaiian/ Pacific Islander	0	0	0	0	0	0	0	0
White	25 (96.2)	25 (100)	25 (96.2)	42 (100)	82 (98.8)	82 (97.6)	67 (100)	107 (97.3)

Other	0	0	1 (3.8)	0	1 (1.2)	1 (1.2)	0	2 (1.8)

Source: Study OPH2003 CSR, Table 11

Reviewer's Comment: *Overall, the study population (combined Parts 1 and 2) had a mean age of 79 years, was predominantly female (70%), and white (99%) which is consistent with the disease population.*

Table 6.1.2-5 Baseline Ocular Characteristics – ITT Population

	Part 1			Part 2			Combined[a]	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Lens Status, n (%)								
Aphakic	0	0	0	0	0	0	0	0
Pseudophakic	17 (65.4)	15 (60.0)	16 (61.5)	29 (69.0)	56 (67.5)	62 (73.8)	44 (65.7)	78 (70.9)
Phakic	9 (34.6)	10 (40.0)	10 (38.5)	13 (31.0)	27 (32.5)	22 (26.2)	23 (34.3)	32 (29.1)
BCVA (ETDRS Letters)								
Mean	70.5	71.6	71.3	69.4	69.5	68.3	70.2	69.0
Standard Deviation	8.04	7.48	7.48	11.25	9.81	11.03	10.01	10.35
Median	71.0	74.0	72.5	72.5	71.0	70.5	73.0	71.0
Min, Max	52, 82	50, 81	57, 82	27, 83	29, 83	28, 80	27, 83	28, 82
n	26	25	26	42	83	84	67	110
Low Luminance BCVA (ETDRS Letters)								
Mean	38.1	43.0	36.7	33.1	36.8	33.9	36.7	34.5
Standard Deviation	22.71	19.74	21.24	21.25	20.87	18.77	21.10	19.32
Median	45.0	44.5	36.0	28.0	40.0	31.0	37.5	2.0
Min, Max	0, 68	4, 77	3, 72	1, 77	1, 74	0, 69	1, 77	0, 72
n	26	24	26	42	83	84	66	110
Localization of Hypo FAF, n (%)								
Foveal[b]	2 (7.7)	5, (20.0)	4 (15.4)	0	2 (2.4)	2 (2.4)	5 (7.5)	6 (5.5)
Extrafoveal[b]	23 (88.5)	20 (80.0)	22 (84.6)	42 (100)	81 (97.6)	82 (96.7)	62 (92.5)	104 (95)
Ungradable	1 (3.8)	0	0	0	0	0	0	0
Macular Atrophy Gradable, n (%)								
Yes	25 (96.2)	25 (100)	26 (100)	42 (100)	82 (98.8)	84 (100)	67 (100)	110 (100)
If Yes, Area of GA (mm^2)								
Mean	7.37	6.60	7.33	7.77	7.90	7.45	7.33	7.42
Standard Deviation	4.321	3.346	3.728	4.010	4.179	3.893	3.793	3.838
Median	7.38	6.48	6.51	6.30	6.91	6.67	6.47	6.67
Min, Max	0.3, 16.6	0.6, 12.9	3.1, 14.3	2.8, 17.3	2.5, 17.2	2.2, 17.2	0.6, 17.3	2.2, 17.2
n	25	25	26	42	82	84	67	110
Hyper FAF, n (%)								
Yes	25 (96.2)	25 (100)	26 (100)	41 (97.6)	82 (98.8)	83 (98.8)	66 (98.5)	109 (99.1)
If Yes, Hyper FAF pattern								
Fine granular-punctate spots	7 (28.0)	6 (24.0)	8 (30.8)	1 (2.4)	9 (11.0)	17 (20.5)	7 (10.6)	25 (22.9)
Branching	1 (4.0)	4 (16.0)	3 (11.5)	3 (7.3)	4 (4.9)	1 (1.2)	7 (10.6)	4 (3.7)
Fine granular-dusty	10 (40.0)	9 (36.0)	8 (30.8)	17 (41.5)	26 (31.7)	28 (33.7)	26 (39.4)	36 (33.0)
Trickling	3 (12.0)	2 (8.0)	3 (11.5)	10 (24.4)	13 (15.9)	17 (20.5)	12 (18.2)	20 (18.3)
Reticular	2 (8.0)	1 (4.0)	1 (3.8)	6 (14.6)	15 (18.3)	8 (9.6)	7 (10.6)	9 (8.3)

	Part 1			Part 2			Combined[a]	
	Zimura 1 mg N=26	Zimura 2 mg N=25	Sham N=26	Zimura 2 mg N=42	Zimura 4 mg N=83	Sham N=84	Zimura 2 mg N=67	Sham N=110
Patchy	0	1 (4.0)	0	0	1 (1.2)	0	1 (1.5)	0
Banded	2 (8.0)	1 (4.0)	3 (11.5)	0	0	1 (1.2)	1 (1.5)	4 (3.7)
Focal	0	0	0	0	0	1 (1.2)	0	1 (0.9)
Not determinable	0	1 (4.0)	0	4 (9.8)	14 (17.1)	10 (12.0)	5 (7.6)	10 (9.2)

Source: Study OPH2003 CSR, Tables 13 and 15
FAF = fundus autofluorescence; GA = geographic atrophy; ITT = intent-to-treat population
[a]Combination of Part 1 and Part 2 patients.
[b]Foveal disease includes the foveal center point; extrafoveal includes disease in the fovea and outside the fovea but does not involve the foveal center point.

Reviewer's Comment: *Overall, the baseline ocular characteristics were comparable across treatment groups.*

Primary Efficacy Results

Table 6.1.2.6 Mean Rate of Change in Geographic Atrophy Area from Baseline to Month 18 (MRM Analysis; Square Root Transformation) – Study Eye (ITT Population)

	Zimura 2 mg[a] N=67	Sham[a] N=110	Zimura 4 mg N=83	Sham N=84
Square root area of GA (mm) at Baseline				
Mean	2.618	2.633	2.715	2.636
Standard Deviation	0.7001	0.7009	0.7320	0.7091
Median	2.544	2.583	2.629	2.583
Min, Max	0.75, 4.16	1.49, 4.15	1.57, 4.15	1.49, 4.15
N	67	110	82	84
Square root area of GA (mm) at Month 6				
Mean	2.772	2.865	2.930	2.886
Standard Deviation	0.7183	0.7154	0.7483	0.7145
Median	2.644	2.774	2.746	2.814
Min, Max	0.70, 4.33	1.60, 4.44	1.61, 4.40	1.60, 4.44
N	58	92	63	73
MRM Analysis-Rate of Change from Baseline to M6				
Least Squares Mean	0.140	0.195	0.154	0.210
Standard Error	0.044	0.044	0.040	0.039
Difference[b]		0.055		0.056
% Difference[c]		28.38		26.63
95% CI		0.007, 0.104		0.009, 0.103
p-value		0.0251		0.0199
Square root area of GA (mm) at Month 12				
Mean	3.032	3.119	3.083	3.143
Standard Deviation	0.6643	0.7182	0.7713	0.7201
Median	2.948	3.025	3.015	3.044
Min, Max	1.91, 4.52	1.67, 4.81	1.66, 4.54	1.67, 4.81
N	49	90	55	72
MRM Analysis-Rate of Change from Baseline to M12				
Least Squares Mean	0.292	0.402	0.321	0.444
Standard Error	0.077	0.075	0.074	0.072
Difference[b]		0.110		0.124

	Zimura 2 mg[a] N=67	Sham[a] N=110	Zimura 4 mg N=83	Sham N=84
% Difference[c]		27.38		27.81
95% CI		0.030, 0.190		0.038, 0.209
p-value		0.0072		0.0051
Square root area of GA (mm) at Month 18				
Mean	3.063	3.282	3.108	3.294
Standard Deviation	0.5821	0.7563	0.8158	0.7641
Median	3.006	3.251	2.874	3.281
Min, Max	2.03, 4.49	1.78, 4.96	1.61, 4.74	1.78, 4.96
N	41	78	45	64
MRM Analysis-Rate of Change from Baseline to M18				
Least Squares Mean	0.430	0.599	0.391	0.559
Standard Error	0.092	0.089	0.087	0.083
Difference[b]		0.168		0.167
% Difference[c]		28.11		29.97
95% CI		0.066, 0.271		0.062, 0.273

Source: Study OPH2003 CSR, Tables 19
CI = confidence interval, GA=geographic atrophy, ITT=Intent-to-Treat, MRM = model for repeated measures
[a]Combination of Part 1 and Part 2 subjects.
[b]Difference in least squares means between groups calculated as (Sham) minus (Zimura).
[c]% Difference is calculated by 100*(Difference)/(Least Squares Mean from Sham).

Reviewer's Comment: *At Month 12 in the ITT population, the difference in the mean rate of change from baseline in geographic atrophy area by MRM analysis, square root transformation for Zimura 2 mg (3.032 (0.664)) as compared to sham (3.119 (0.718)) was 0.110 and demonstrates a statistically reduction of 27.38% in the mean rate of GA growth compared to Sham (p=0.0072, 95% CI=0.030, 0.190).*

At Month 18 in the ITT population, the difference in the mean rate of change from baseline in geographic atrophy area by MRM analysis, square root transformation for Zimura 2 mg (3.063 (0.582)) as compared to sham (3.282 (0.756)) was 0.168 and demonstrates a 28.11% reduction in the mean rate of GA growth compared to Sham (95% CI=0.066, 0.271).

In the PP population (data not shown in this review), the difference in the mean rate of change from baseline at Month 12 in geographic atrophy area by MRM analysis, square root transformation for Zimura 2 mg (3.031(0.651)) as compared to sham (3.126 (0.713) was 0.105 and statistically significant (p=0.0181, 95% CI=0.018, 0.192). Results in the PP population were consistent with the ITT population.

As noted in the table on the previous page, there was a significant loss of participants during the course of the trial. The following tables include only subjects who had all four (baseline, month 6,12 and 18) evaluations.

Time period	Group Zimura: N=36 Sham: N=69	Slope (SE) (mm^2/year)	Difference (95% CI) in Slope Zimura- Sham (mm^2/year)	Percent Difference of Sham
Baseline to Month 6	Zimura 2 mg	1.74 (0.257)	-0.65(-1.27 to -0.02)	-27.1
	Sham	2.39 (0.186)		
Month 6 to Month 12	Zimura 2 mg	2.04 (0.296)	-0.63(-1.35 to 0.09)	-23.6
	Sham	2.67 (0.213)		
Month 12 to Month 18	Zimura 2 mg	1.34 (0.293)	-1.03(-1.74 to -0.31)	-43.3
	Sham	2.37 (0.208)		

Reviewer's Comments: *To evaluate the robustness of the findings, the results were recalculated using actual day of visit (as opposed to visits exactly on Day 0, Month 6, Month 12 and Month 18) and using a Square Root function. The recalculated results are shown below. The interpretation of the results is unchanged. The loss of photoreceptors as measured by the area of GA growth is less in the Zimura group than the Sham group. The difference is small, but consistent. The largest slowing occurred between months 12 and 18 in both groups. There were relatively few subjects with visits at all four evaluation timepoints. Based on the variability of lesion size at baseline, it is important to compare changes from baseline in the same group of individuals at all evaluation points.*

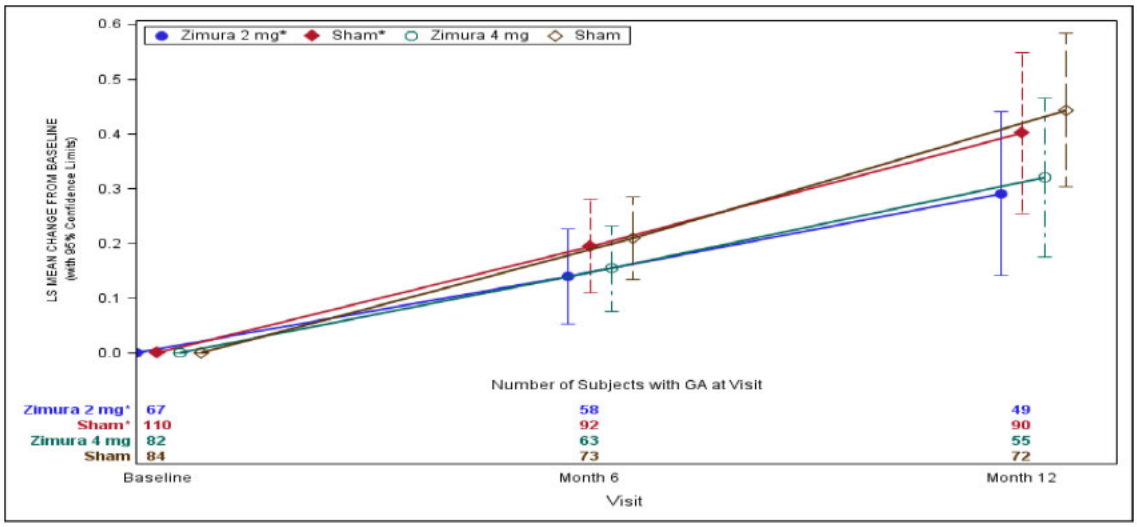
Exact Match by Days

Time Period	*Zimura 2mg mm/year*	*Sham mm/year*	*Difference (Zimura-Sham) (mm/year)*
Baseline to Month6	*1.72*	*2.39*	*-0.665*
Month 6 to Month12	*2.01*	*2.67*	*-0.662*
Month 12 to Month 18	*1.33*	*2.43*	*-1.092*

Square root transformation

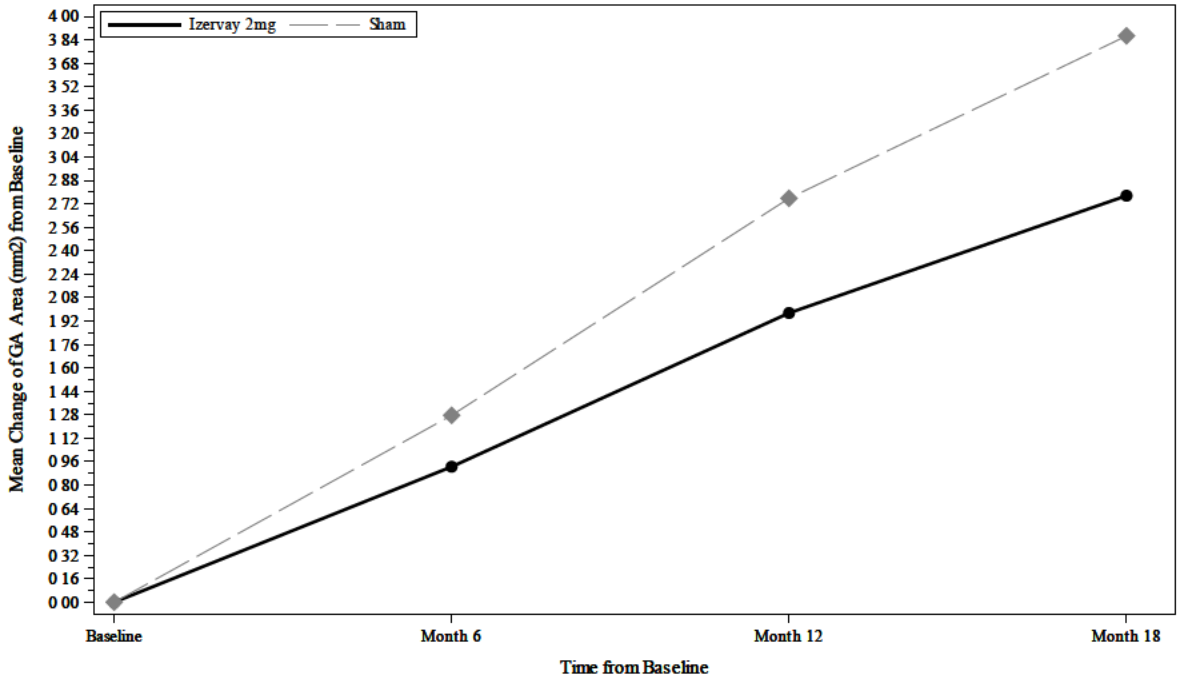
Time Period	*Zimura 2mg mm/year*	*Sham mm/year*	*Difference (Zimura-Sham) (mm/year)*
Baseline to Month6	*0.311*	*0.424*	*-0.113*
Month 6 to Month12	*0.358*	*0.440*	*-0.082*
Month 12 to Month 18	*0.220*	*0.363*	*-0.143*

Study OPH2003 Mean Rate of Change in Geographic Atrophy Area Over Time (MRM Analysis; Square Root Transformation) – Study Eye – Month 12 (ITT Population)



Source: Post-text Figure 14.2.1
GA = geographic atrophy; MRM = model for repeated measures
*Combination of Part 1 and Part 2 patients.

Reviewer's Comment: *The figure shows the mean rate of growth in geographic atrophy area over time from Baseline to Month 12 by square root transformation. The mean rate of growth for Zimura 2 mg and 4 mg are reduced as compared to their respective sham comparator.*



Reviewer's Comment: *The figure above shows the mean rate of growth in geographic atrophy area over time from Baseline to Month 18, untransformed.*

6.2. Study ISEE2008 – A Phase 3 Multicenter, Randomized, Double-Masked, Sham Controlled, Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura (Compliment C5 Inhibitor) in Patients with Geographic Atrophy secondary to Age-related Macular Degeneration (GATHER2)

6.2.1. Study Design

Primary Objective: The objective of this study was to evaluate the safety and efficacy of Zimura (avacincaptad pegol) IVT administration in patients with GA secondary to AMD.

List of Investigators
There were 205 study center(s) in the following countries: Argentina (9), Australia (3), Austria (4), Belgium (1), Brazil (3), Canada (7), Columbia (2), Croatia (1), Czech Republic (1), Estonia (2), France (13), Germany (14), Hungary (8), Israel (9), Italy (14), Latvia (1), Poland (4), United Kingdom (1), and USA (96).

Table 6.2.1-1 Investigator(s) Who Randomized 10 or More Subjects

Site Number	Principal Investigator Site Address	Number of Subjects Randomized
061	Francois Devin Centre Paradis-Monticelli, 433 Rue Paradis, 13008 Marseille, France	15
483	Edward Ysasaga Southwest Retina Specialists, 7411 Wallace Boulevard Amarillo, TX 79106	14
953	Monica Marie Lopera Clinica de Oftalmologia Sandiego, Kra 43 #29-35 Office 508 Medellin, Antioquia, ZIP 050016, Colombia	13
002	Sunil S. Patel Retina Research Institute of Texas, 5441 Health Center Drive Abilene, TX 79606	12
461	Arshad Khanani Sierra Eye Associates, 950 Ryland Street Reno, NV 89502	11
950	Francisco Rodriguez Fundacion Oftalmológica Nacional – FUNDONAL, Calle 50 # 13-50 Bogota D.C., ZIP 110311, Colombia	10
705	Giovanni Staurenghi ASST Fatebenefratelli Sacco Ospedale Luigi Sacco-Polo Univer, Via G.B. Grassi, 74 U.O. Oculistica Azienda Ospedaliera Milano 20157	10

Overall Design:

This was a Phase 3, prospective, randomized, double-masked, sham-controlled, multicenter designed to compare the efficacy and safety of Zimura 2 mg vs Sham in patients with GA secondary to AMD. Approximately 400 patients (1:1 randomization per treatment arm) were planned for randomization in the following dose groups:

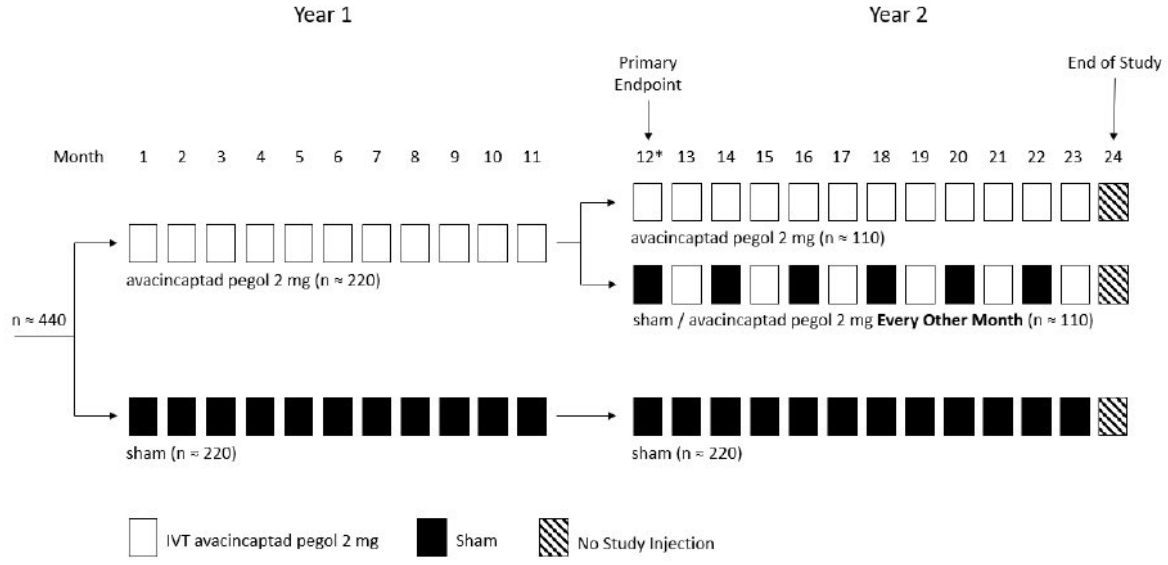
- Zimura 2 mg/eye administered via IVT injection
- Sham: The Sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

At Month 12, patients who were initially randomized to and received monthly Zimura 2 mg were re-randomized in a 1:1 ratio to the following dose groups:

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

The primary efficacy and safety analyses were to be assessed at Month 12. The total study duration was 24 months.

Study Design **Study ISEE2008**



IVT = intravitreal.

Monthly study visits and assessments were scheduled through Month 24.

Inclusion and Exclusion Criteria

Ophthalmic Inclusion Criteria

The following inclusion criteria applied to the SE:

1. Non-foveal GA secondary to dry AMD.
2. Total GA area ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 DA respectively), determined by FAF images at Screening.
3. If GA is multifocal, at least one focal lesion should measure ≥ 1.25 mm^2 (0.5 DA).
4. GA in part within 1500 microns from the foveal center.
5. The atrophic lesion must be able to be photographed in its entirety.
6. BCVA in the SE between 20/25 to 20/320, inclusive.
7. Clear ocular media and adequate pupillary dilation in both eyes to allow for all imaging procedures, including good quality stereoscopic fundus photography and FAF.
8. IOP of 21 mmHg or less in the SE.

General Inclusion Criteria

1. Patients of either gender aged ≥ 50 years.
2. For patients who were women of childbearing potential involved in any sexual intercourse that could lead to pregnancy, the patient must have used a protocol approved highly effective contraceptive method during the trial and agreed to continue the same method until at least 90 days following the last dose of test medication. Protocol approved highly effective contraceptive methods were 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 was defined as follows:
   - A woman who 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:
   - o 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)
   - o A cessation of menses for at least 24 months without FSH levels confirmed.

   If the patient was a woman of childbearing potential, she must have had 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 was male, he was expected to 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.
3. Provide written informed consent.
4. Ability to return for all study visits (24-month study duration).

Ophthalmic Exclusion Criteria

The following exclusion criteria applied to the SE:

1. Evidence of choroidal neovascularization (CNV) in either eye. If CNV developed in either eye during the course of the study, the investigator was to follow Section 10.3 'Development of Wet AMD During the Trial' in the protocol (Appendix 16.1.1).
2. GA secondary to any condition other than AMD in either eye (e.g., drug-induced).
3. Any prior treatment for AMD or any prior IVT treatment for any indication in either eye, except oral supplements of vitamins or minerals.
4. Any ocular condition in the SE that would progress during the course of the study that could affect central vision or otherwise be a confounding factor.
5. Concomitant treatment with any ocular or non-ocular medication that is known to be toxic to the lens, retina, or optic nerve.
6. Presence of intraocular inflammation (≥ trace cell or flare), macular hole, pathologic myopia, epiretinal membrane, evidence of significant vitreo-macular traction, vitreous hemorrhage or aphakia (pseudophakia with or without an intact capsule was not an exclusion criteria).
7. Presence or history of idiopathic or autoimmune-associated uveitis in either eye.
8. Significant media opacities, including cataract, which might interfere with VA, assessment of toxicity, fundus photography, or FAF. Patients should not have entered if there is likelihood that they would have required cataract surgery in the SE during the study.
9. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of -8 diopters or more, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, and multifocal choroiditis.
10. Any intraocular surgery or thermal laser within 3 months of study entry. Any prior thermal laser in the macular region, regardless of indication.
11. Any ocular or periocular infection (including blepharitis), or ocular surface inflammation in the 12 weeks prior to study entry.
12. History of any of the following procedures: Posterior vitrectomy, filtering surgery (e.g., trabeculectomy), glaucoma drainage device, corneal transplant, or retinal detachment.
13. Any sign of diabetic retinopathy in either eye.

<u>General Exclusion Criteria</u>

1. Any of the following underlying diseases including:
   a. History or evidence of severe cardiac disease (e.g., New York Heart Association Functional Class III or IV- see Appendix 17.6 of the protocol in Appendix 16.1.1), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction, or revascularization within last 6 months prior to study entry, ventricular tachyarrhythmias requiring ongoing treatment.
   b. History or evidence of clinically significant peripheral vascular disease, such as intermittent claudication or prior amputation.
   c. Clinically significant impaired renal (serum creatinine >2.5 mg/dL or status post-renal transplant or receiving dialysis) or hepatic function.
   d. Stroke (within 12 months of study entry).
   e. Any major surgical procedure within 1 month of study entry.
2. Previous therapeutic radiation in the region of the SE.
3. Any treatment with an investigational agent in the 60 days prior to study entry for any condition.
4. Women who are pregnant or nursing.

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.
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.

Test and Reference Therapies
Zimura is a PEGylated ribonucleic acid (RNA) aptamer consisting of a 12,881 Da modified nucleotide aptamer that is conjugated at the 5' terminus to an ~43 kDa branched polyethylene glycol (PEG) moiety. Zimura doses were formulated in a 20 mg/mL (oligonucleotide mass) solution for injection. Zimura was supplied in single use, sterile glass vials for IVT injection. Patients were randomized to receive Zimura 2 mg/eye (100 μL) or Sham. Zimura was administered as an IVT injection.

Treatment masking
To maintain masking when study treatments were administered, Sham injections were performed. The Sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

Prohibited Medications/Treatments
Patients enrolled were treatment-naïve (no previous treatment for AMD) in either eye except for oral supplements of vitamins or 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 study, was not permitted.

Safety Assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), Vital signs (pulse, systolic and diastolic blood pressure), Ophthalmic variables (IOP, ophthalmic examination, FA, FAF, CFP, and OCT), ECG (12-lead), and Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis).

Statistical Methods

Primary Efficacy Endpoint-Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at 3 time points: Baseline, Month 6, and Month 12

Reviewer's Comment: *To determine efficacy, the best polynominal fit mean rate of change in geographic atrophy over at least 12 months measured by fundus autofluorescence (FAF) in at least three time points was requested by the Division as the primary efficacy endpoint.*

Secondary Endpoints:

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

Analysis Populations

- Intent-to treat (ITT) population – all randomized patients and received at least one injection of study drug
- Per protocol (PP) population – all patients who received at least one injection of study drug with no significant protocol violations
- Safety population – all patients who received at least one injection of study drug with analysis based on actual dose received

The safety analyses were conducted on the safety population. Safety evaluations for the Month 12 assessment included all adverse events, vital signs (pulse, systolic and diastolic blood pressure), ophthalmic variables (IOP, ophthalmic examination, FA, FAF, CFP, and OCT), ECG (12-lead), and laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis).

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP). There were no interim analyses.

Schedule Year 1

Assessment	Screening	D1[1]	M1[1]	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12*
Informed Consent	X													
Visual Function Questionnaire (VFQ-25)		X						X						X
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

Year 2 Schedule

Assessment	M12*	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24/ EW
Visual Function Questionnaire (VFQ-25)							X						X
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

[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, 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 ≥ 30mmHg 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.

6.2.2. Study Results Table 6.2.2-1 Subject Disposition - ITT Population

	Zimura 2 mg N=225 n (%)	Sham N=222 n (%)
Month 12 Analysis		
Randomized	225 (100.0)	223 (100.0)
Randomized and treated	225 (100.0)	222 (99.6)
Completed through Month 12	200 (88.9)	205 (92.3)
Discontinued the study prior to Month 12	25 (11.1)	17 (7.7)
Reason for Discontinuation		
Adverse event	3 (1.3)	2 (0.9)
Withdrawal by subject	17 (7.6)	13 (5.9)
Lost to follow-up	2 (0.9)	1 (0.5)
Subject non-compliance	1 (0.4)	0
Death	2 (0.9)	1 (0.5)

Source: Study ISEE2008 CSR, Table 5

Reviewer's Comment: *The number of subjects who discontinued the study prior to Month 12 was 25 (11%) and 17 (8%) for the Zimura 2 mg, and sham treatment groups, respectively. Withdrawal by subject was the most common reason, 8% for Zimura 2 mg, and 6% for sham.*

Table 6.2.2-2 Summary of Significant Protocol Deviations Through Month 12 - ITT Population

Type of Deviation	Zimura 2 mg N=225 n (%)	Sham N=222 n (%)
Number of patients with at least one major protocol deviation	45 (20.0)	45 (20.3)
Deviation of ICF procedure	5 (2.2)	5 (2.3)
Deviation of IOP monitoring procedures	4 (1.8)	3 (1.4)
Incorrect assessment	3 (1.3)	1 (0.5)
Laboratory	2 (0.9)	1 (0.5)
Masking	2 (0.9)	4 (1.8)
Medication deviation	2 (0.9)	0
Missed assessment	12 (5.3)	18 (8.1)
Missed visit	3 (1.3)	5 (2.3)
Potential unmasking	2 (0.9)	3 (1.4)
Reconfirmation of eligibility error	4 (1.8)	4 (1.8)
SAE reporting	4 (1.8)	3 (1.4)
Treatment not per protocol	5 (2.2)	1 (0.5)
Violation of eligibility criteria	7 (3.1)	8 (3.6)

Source: Study ISEE2008 CSR, Table 6; ICF = informed consent form; IOP = intraocular pressure; SAE = serious adverse event.

Reviewer's Comment: *A total of 90 subjects, 45 (20%) in the Zimura 2 mg and 45 (20%) in the sham arm had significant protocol deviations during the study.*

Table 6.2.2-3 Analysis Populations

Analysis Population	Zimura 2 mg	Sham
Randomized	225	223
Number of patients randomized but not treated	0	1
Intent-to-Treat (ITT)	225	222
Per-Protocol (PP)	220	217
Safety	225	222

Source: Study ISEE2008 CSR, Table 7

Table 6.2.2-4 Subject Demographics – ITT Population

	Zimura 2 mg N=225	Sham N=222
Age (years)		
Mean	76.3	76.7
Standard deviation	8.61	8.82
Median	77.0	77.0
Min, Max	51, 93	51, 96
Age group, n (%)		
< 65 years	19 (8.4)	20 (9.0)
65-74 years	72 (32.0)	65 (29.3)
75-84 years	91 (40.4)	91 (40.0)
≥ 85 years	43 (19.1)	46 (20.7)
Gender, n (%)		
Male	71 (31.6)	66 (29.7)
Female	154 (68.4)	156 (70.3)
Race, n (%)		
American Indian/Alaska Native	1 (0.4)	0
Black or African American	0	1 (0.5)
Asian	1 (0.4)	1 (0.5)
Native Hawaiian/Pacific Islander	0	0
White	182 (80.9)	186 (83.8)
Other	10 (4.4)	13 (5.9)
Not reported	31 (13.8)	21 (9.5)

Source: Study ISEE2008 CSR, Table 8

Reviewer's Comment: *Overall, the study population had a mean age of 77 years, was majority female (69%), and white (82%) which is consistent with the disease population.*

Table 6.2.2-5 Baseline Ocular Characteristics – ITT Population

Baseline Characteristic	Zimura 2 mg N=225	Sham N=222
Lens Status, n (%)		
Aphakic	0	0
Pseudophakic	123 (54.7)	128 (57.7)
Phakic	102 (45.3)	94 (42.3)
BCVA (ETDRS Letters)		
Mean	70.9	71.6
Standard deviation	8.93	9.35
Median	73.0	74.0
Min, Max	34, 83	8, 88
N	225	222
Low Luminance BCVA (ETDRS Letters)		
Mean	41.0	39.6
Standard deviation	19.70	19.58
Median	42.0	41.5
Min, Max	0, 76	0, 79
n	224	220
Localization of Hypo FAF[a], n (%)		
Foveal	0	0
Extrafoveal	225 (100.0)	222 (100.0)
Ungradable	0	0
Macular Atrophy Gradable, n (%)		
Yes	225 (100.0)	222 (100.0)
No	0	0
If Yes, Area of GA (mm^2)		
Mean	7.48	7.81
Standard deviation	4.005	3.885
Median	6.36	7.04
Min, Max	2.3, 17.6	2.4, 17.2
n	225	222
Size of Baseline GA		
≥ 4 disc areas	54 (24.0)	64 (28.8)
< 4 disc areas	171 (76.0)	158 (71.2)
Hyper FAF, n (%)		
None/Focal	8 (3.6)	4 (1.8)
Banded/Diffuse	217 (96.4)	218 (98.2)
If Banded/Diffuse, is there diffuse trickling?		
Yes	77 (35.5)	90 (41.3)
No	140 (64.5)	128 (58.7)
Ungradable	0	0

Source: Study ISEE2008 CSR, Tables 10 and 12
FAF = fundus autofluorescence; GA = geographic atrophy; ITT = intent-to-treat population
[a] Foveal disease includes the foveal center point; extrafoveal includes disease in the fovea and outside the fovea but does not involve the foveal center point.

Reviewer's Comment: *Overall, the baseline ocular characteristics were comparable across treatment groups.*

Primary Efficacy Results

Table 6.2.2-6 Mean Rate of Change in Geographic Atrophy Area from Baseline to Month 12 (MMRM Analysis, Square Root Transformation) – Study Eye (ITT Population)

	Zimura 2 mg N=225	Sham N=222
Square Root Area of GA (mm) at Baseline		
Mean	2.641	2.707
Standard Deviation	0.7142	0.6961
Median	2.521	2.653
Min, Max	1.50, 4.19	1.53, 4.15
N	225	222
Square Root Area of GA (mm) at Month 6		
Mean	2.839	2.950
Standard Deviation	0.7152	0.6950
Median	2.751	2.900
Min, Max	1.65, 4.41	1.75, 4.42
N	204	206
MMRM Analysis- Rate of Change from Baseline to Month 6		
Mean	0.168	0.196
Standard Error	0.016	0.016
Difference[a]		0.028
Standard Error of the Difference		0.010
% Difference[b]		14.25
95% CI		0.008, 0.048
p-value		0.0064
Square root area of GA (mm) at Month 12		
Mean	2.991	3.112
Standard Deviation	0.7205	0.7108
Median	2.860	3.064
Min, Max	1.65, 4.65	1.79, 4.65
N	181	186
MMRM Analysis- Rate of Change from Baseline to Month 12		
Mean Change	0.336	0.392
Standard Error	0.032	0.033
Difference[a]		0.056
Standard Error of the Difference		0.020
% Difference[b]		14.25
95% CI		0.016, 0.096
p-value		0.0064

Source: Study ISEE2008 CSR, Table 14
CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MMRM = mixed model for repeated measures
[a] Difference in growth rate between groups calculated as (Sham) minus (Zimura 2 mg).
[b] % Difference is calculated by 100*(Difference)/(Growth rate from Sham).

Reviewer's Comment: *At Month 12 in the ITT population, the difference in the mean rate of change from baseline in geographic atrophy area by MMRM analysis, square root transformation for Zimura 2 mg (2.991 (0.7205)) as compared to sham (3.112 (0.7108)) was 0.056 (0.020) and demonstrates a statistically reduction of 14.25% in the mean rate of GA growth compared to Sham (p=0.0064, 95% CI=0.016, 0.096).*

Table 6.2.2-7 Mean Rate of Change in Geographic Atrophy Area from Baseline to Month 12 (MMRM Analysis, Square Root Transformation) – Study Eye (PP Population)

	Zimura 2 mg N=220	Sham N=217
Square Root Area of GA (mm) at Baseline		
Mean	2.641	2.710
Standard Deviation	0.7167	0.6975
Median	2.519	2.655
Min, Max	1.50, 4.19	1.53, 4.15
n	220	217
Square Root Area of GA (mm) at Month 6		
Mean	2.839	2.952
Standard Deviation	0.7167	0.6945
Median	2.760	2.911
Min, Max	1.65, 4.41	1.75, 4.42
n	199	201
MMRM Analysis- Rate of Change from Baseline to Month 6		
Mean	0.169	0.196
Standard Error	0.016	0.016
Difference[a]		0.027
Standard Error of the Difference		0.010
% Difference[b]		13.69
95% CI		0.006, 0.047
p-value		0.0099
Square root area of GA (mm) at Month 12		
Mean	2.992	3.116
Standard Deviation	0.7221	0.7138
Median	2.887	3.081
Min, Max	1.65, 4.65	1.79, 4.65
n	176	184
MMRM Analysis- Rate of Change from Baseline to Month 12		
Mean Change	0.337	0.391
Standard Error	0.032	0.033
Difference[a]		0.054
Standard Error of the Difference		0.021
% Difference[b]		13.69
95% CI		0.013, 0.094
p-value		0.0099

Source: Study ISEE2008 CSR, Table 14.2.1.4
CI = confidence interval; GA = geographic atrophy; ITT = intent-to-treat population; MMRM = mixed model for repeated measures
[a] Difference in growth rate between groups calculated as (Sham) minus (Zimura 2 mg).
[b] % Difference is calculated by 100*(Difference)/(Growth rate from Sham).

Reviewer's Comment: *In the PP population, the difference in the mean rate of change from baseline at Month 12 in geographic atrophy area by MMRM analysis, square root transformation for Zimura 2 mg (2.992(0.7221)) as compared to sham (3.116 (0.7138) was 0.054 and statistically significant (p=0.0099, 95% CI=0.013, 0.0942). Results in the PP population were consistent with the ITT population.*

Reviewer's Comments: *There was a loss of participants during the course of the trial. The following tables include only subjects who had all three (baseline, month 6,and 12) evaluations. While treatment continued through Month 24, the results beyond Month 12 have not been submitted.*

Time period	Group Zimura: N=175 Sham: N=180	Slope (SE) (mm^2/year)	Difference (95% CI) in Slope Zimura- Sham (mm^2/year)	Percent Difference of Sham
Baseline to Month 6	Zimura 2 mg	2.15 (0.115)	-0.31(-0.62 to 0.01)	-12.5
	Sham	2.46 (0.113)		
Month 6 to Month 12	Zimura 2 mg	2.07 (0.127)	-0.44(-0.79 to -0.09)	-17.7
	Sham	2.51 (0.125)		

Reviewer's Comments: *To evaluate the robustness of the findings, the results were recalculated using actual day of visit (as opposed to visits exactly on Day 0, Month 6, and Month 12) and using a Square Root function. The recalculated results are shown below. The interpretation of the results is unchanged. The loss of photoreceptors as measured by the area of GA growth is less in the Zimura group than the Sham group. The difference is small, but consistent. The larger slowing occurred between months 6 and 12 in both groups. There were relatively few subjects with visits at all three evaluation timepoints. Based on the variability of lesion size at baseline, it is important to compare changes from baseline in the same group of individuals at all evaluation points.*

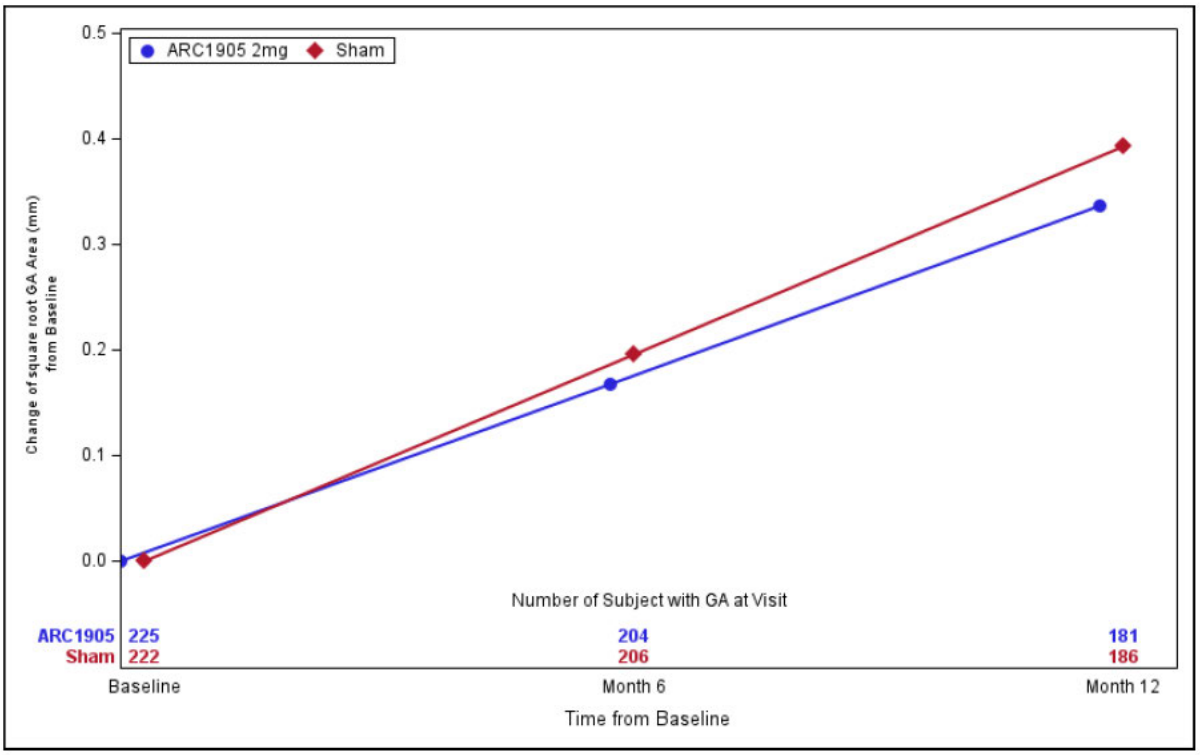
Exact match by days

Time Period	*Zimura 2mg mm/year*	*Sham mm/year*	*Difference (Zimura-Sham) (mm/year)*
Baseline to Month6	*2.12*	*2.44*	*-0.32*
Month 6 to Month12	*2.11*	*2.48*	*-0.38*

Square Root Transformation

Time Period	*Zimura 2mg mm/year*	*Sham mm/year*	*Difference (Zimura-Sham) (mm/year)*
Baseline to Month6	*0.392*	*0.436*	*-0.044*
Month 6 to Month12	*0.354*	*0.406*	*-0.052*

Study ISEE2008 Mean Rate of Change in Geographic Atrophy Area Over Time (MRM Analysis, Square Root Transformation) – Study Eye – Month 12 (ITT Population)



Source: Post-text Figure 14.2.1.1
GA = geographic atrophy; ITT = intent-to-treat; MMRM = mixed model for repeated measures.
ARC1905=Zimura 2 mg

Reviewer's Comment: *Figure 2 shows the mean rate of growth in geographic atrophy area over time from Baseline to Month 12 by square root transformation. The mean rate of growth for Zimura 2 mg is reduced as compared to sham.*

Reviewer's Effectiveness Conclusions:
The data from two (OPH2003 and ISEE2008) studies contained in this submission establishes the efficacy of avacincaptad pegol ophthalmic solution, 2 mg (0.1 mg of 20 mg/mL solution) administered by intravitreal injection every 28 ± 7 days for up to 12 months in the treatment of geographic atrophy secondary to age-related macular degeneration.

7. Review of Safety

7.1. Safety Review Approach

The review focuses on the safety database from Studies OPH2001, OPH2003 and ISEE2008 which evaluated patients with GA secondary to AMD and are characterized by the following:

- A study duration of 12 months for Study OPH2001, 18 months for Study OPH2003 and 24 months for ISEE2008.
- Studies OPH2001 and OPH2003 have been completed
- Study ISEE2008 is ongoing
- Treatment groups with avacincaptad pegol 0.3 mg or 1 mg in Study OPH2001
- Treatment groups with avacincaptad pegol 2 mg or 4 mg in Study OPH2003
- A treatment group with avacincaptad pegol 2 mg in Study ISEE2008

Supportive safety data are provided from studies evaluating avacincaptad pegol in patients with nAMD (Studies OPH2000 and OPH2007) and Stargardt's disease (Study OPH2005 ongoing).

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Table 8.2.1-1 Exposure to Study Drug at Month 12 – Safety Population

Extent of Exposure	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 4 mg[c] N=83
Number of injections received per patient, n (%)				
1-3 injections	9 (2.7)	2 (4.1)	14 (4.8)	10 (12.0)
4-6 injections	13 (3.9)	22 (44.9)	15 (5.1)	6 (7,2)
7-9 injections	15 (4.5)	1 (2.0)	12 (4.1)	7 (8.4)
10-12 injections	295 (88.9)	24 (49.0)	251 (86.0)	60 (72.3)
Number of injections received				
Mean (± SD)	11.1 (2.17)	8.2 (3.64)	10.8 (2.59)	9.8 (3.40)
Median	12.0	7.0	12.0	12.0
Min, Max	1, 12	1, 12	1, 12	1, 12
Treatment duration (days)[d]				
Mean (± SD)	344.8 (61.97)	313 (70.31)	336.5 (77.35)	306.3 (103.33)
Median	365.0	296.0	365.0	361.0
Min, Max	31, 384	31, 377	31, 387	31, 377
Total number of injections	3692	403.0	3155	815.0

Source: ISS, Table 2.7.4.1.-6
[a] Data from Studies OPH2003 and ISEE2008
[b] Data from Studies OPH2001 and OPH2003
[c] Data from Studies OPH2003
[d] Treatment duration (days) is defined as (Last injection – First injection + 30)

Reviewer's Comment: *The mean number of intravitreal injections of active study treatment were 8.2, 10.8, and 9.8 for the avacincaptad pegol 1 mg, 2 mg, and 4 mg treatment groups, respectively.*

Table 8.2.1-2 Subject Disposition at Month 12

Disposition	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 4 mg[c] N=83
Number of patients who completed, n (%)				
Month 3 visit	324 (97.6)	47 (95.9)	279 (95.5)	76 (91.6)
Month 6 visit	314 (94.6)	47 (95.9)	266 (91.1)	68 (81.9)
Month 9 visit	301 (90.7)	46 (93.9)	259 (88.7)	62 (74.7)
Month 12 visit	288 (86.7)	45 (91.8)	246 (84.2)	56 (67.5)
Number of patients ongoing in the clinical trial	12 (3.6)	1 (2.0)	8 (2.7)	2 (2.4)
Number of patients who discontinued early	32 (9.6)	3 (6.1)	38 (13.0)	25 (30.1)
Adverse event	3 (0.9)	0	3 (1.0)	1 (1.2)
Protocol violation	0	0	0	0
Investigator decision	1 (0.3)	0	1 (0.3)	2 (2.4)
Sponsor decision	3 (0.9)	1 (2.0)	6 (2.1)	8 (9.6)
Patient request	21 (6.3)	2 (4.1)	23 (7.9)	13 (15.7)
Lost to follow-up	2 (0.6)	0	2 (0.7)	0
Patient non-compliance	0	0	1 (0.3)	0
Death	2 (0.6)	0	2 (0.7)	1 (1.2)
Other	0	0	0	0

Source: ISS, Table 2.7.4.1.-2
[a] Data from Studies OPH2003 and ISEE2008
[b] Data from Studies OPH2001 and OPH2003
[c] Data from Studies OPH2003

Reviewer's Comment: *Ninety-two percent (92%), 84%, and 68% of subjects in the avacincaptad pegol 1 mg, 2 mg and 4 mg treatment groups, respectively completed the Month 12 study visit. Six percent (6%) of subjects from the 1 mg treatment group, 13% of subjects from the 2 mg treatment group, and 30% of subjects from the 4 mg treatment group discontinued from the study before the Month 12 study visit. The most common reasons for discontinuation were "patient request."*

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

7.3.2. Categorization of Adverse Events

Adverse events were categorized as ocular and non-ocular.

7.3.3. Routine Clinical Tests

Clinical laboratory parameters were as expected for the subject population under study. No clinically significant differences between treatment groups were observed for any of the analyzed laboratory parameters.

7.4. Safety Results

7.4.1. Deaths

Patient Number	Age/ Gender	Cause of Death	Last Injection Date/ Death Date	Study
Avacincaptad pegol 1 mg				
(b) (6)	75 M	Esophageal varices rupture	(b) (6)	OPH2003
Avacincaptad pegol 2 mg				
(b) (6)	84 M	Cerebral infarction/pulmonary thromboembolism/ hypostatic pneumonia/acute renal failure		OPH2003
	87 M	Neurogenic shock due to a fall		ISEE2008
	80 M	Pneumonia		ISEE2008
	64 M	Pneumonia		ISEE2008
Avacincaptad pegol 4 mg				
(b) (6)	80 F	Injuries due to motor vehicle accident		OPH2003
Sham				
(b) (6)	78 F	COPD/Chronic respiratory failure		OPH2003
	74 F	Metastatic ovarian carcinoma		ISEE2008

Source: ISS Listing 14.3.3.CI

Reviewer's Comment: *The deaths which occurred during the studies are consistent with the age and past medical history of the subjects enrolled.*

7.4.2. Serious Adverse Events

Table 8.4.2-1 Serious Adverse Events – Ocular and Non-ocular

Preferred Term	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 4 mg[c] N=83
Ocular				
Number of patients with at least one adverse event, n (%)	2 (0.6)	0	2 (0.7)	0
Eye disorders	2 (0.6)	0	2 (0.7)	0
Choroidal neovascularization	1 (0.3)	0	2 (0.7)	0
Visual acuity reduced	1 (0.3)	0	0	0
Visual acuity reduced transiently	1 (0.3)	0	0	0
Non-ocular				
Number of patients with at least one adverse event	3 (0.9)	0	4 (1.4)	1 (1.2)
Cardiac disorders	9 (2.7)	1 (2.0)	6 (2.1)	2 (2.4)
Gastrointestinal disorders	11 (3.3)	2 (4.1)	4 (1.4)	2 (2.4)
Infections and Infestations	10 (3.0)	0	9 (3.1)	7 (8.4)
Injury, poisoning, and procedural complications	7 (2.1)	0	8 (2.7)	3 (3.6)
Nervous system disorders	7 (2.1)	1 (2.0)	2 (0.7)	3 (3.6)
Respiratory, thoracic and mediastinal disorders	7 (2.1)	0		1 (1.2)

Source: ISS, Tables 2.7.4.2-12 and 2.7.4.2-13; [a] Data from Studies OPH2003 and ISEE2008; [b] Data from Studies OPH2001 and OPH2003; [c] Data from Studies OPH2003

Reviewer's Comment: *The most frequently reported serious ocular adverse event was choroidal neovascularization for subjects in the avacincaptad pegol 2 mg treatment group (0.7%). The most frequently reported serious non-ocular adverse event was infections and infestations for subjects in the avacincaptad pegol 2 mg treatment groups (3%).*

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 8.4.3-1 Adverse Events Leading to Study Discontinuation

Preferred Term	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 4 mg[c] N=83
Ocular				
Number of patients with at least one adverse event, n (%)	0	0	2 (0.7)	1 (1.2)
Eye disorders	0	0	1 (0.3)	1 (1.2)
Macular degeneration	0	0	0	1 (1.2)
Vitreous detachment	0	0	1 (0.3)	0
Investigations	0	0	1 (0.3)	0
Intraocular pressure increased	0	0	1 (0.3)	0
Non-ocular				
Number of patients with at least one adverse event	3 (0.9)	0	4 (1.4)	1 (1.2)
Infections and Infestations	0	0	2 (0.7)	0
Pneumonia	0	0	2 (0.7)	0
Injury, poisoning, and procedural complications	0	0	0	0
Road traffic accident	0	0	0	0
Neoplasm benign, malignant, and unspecified (incl cysts and polyps)	0	0	1 (0.3)	0
Acute leukemia	0	0	1 (0.3)	0
Nervous system disorders	3 (0.9)	0	0	0
Cerebrovascular accident	1 (0.3)	0	0	0
Dementia	1 (0.3)	0	0	0
Transient ischemic attack	1 (0.3)	0	0	0
Vascular disorders	0	0	1 (0.3)	0
Neurogenic shock	0	0	1 (0.3)	0

Source: ISS, Tables 2.7.4.2-14; [a] Data from Studies OPH2003 and ISEE2008; [b] Data from Studies OPH2001 and OPH2003; [c] Data from Studies OPH2003

Reviewer's Comment: *The most frequently reported ocular adverse events which led to discontinuation were vitreous detachment (0.3%) and increased intraocular pressure (0.3%) for the avacincaptad pegol 2 mg treatment group.*

The most frequently reported non-ocular adverse event which led to discontinuation was pneumonia (0.7%) for the avacincaptad pegol 2 mg treatment group.

7.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.4-1 Ocular Adverse Events Occurring in ≥ 2% of Subjects

Preferred Term		Studies OPH2001, OPH2003 and ISEE2008 Pooled		
	Sham[a] N=332	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 4 mg[c] N=83
Ocular				
Number of patients with at least one adverse event, n (%)	121 (36.4)	149 (51.0)	23 (46.9)	59 (71.1)
Eye disorders	117 (35%)	140 (48%)	22 (45%)	52 (63%)
Conjunctival hemorrhage	30 (9%)	37 (13%)	5 (10%)	27 (33%)
Intraocular pressure increased	3 (1%)	25 (9%)	2 (4%)	16 (19%)
Blurred vision [1]	18 (5%)	22 (8%)	2 (4%)	6 (7%)
Choroidal neovascularization	12 (4%)	21 (7%)	1 (2%)	8 (10%)
Conjunctival hyperemia	17 (5%)	15 (5%)	0	8 (10%)
Punctate keratitis	22 (7%)	15 (5%)	0	6 (7%)
Eye pain	9 (3%)	11 (4%)	1 (2%)	6 (7%)
Vitreous detachment	11 (3%)	9 (3%)	4 (8%)	3 (4%)
Dry eye	10 (3%)	8 (3%)	0	1 (1%)
Vitreous floaters	2 (0.6%)	7 (2%)	0	1 (1%)
Blepharitis	1 (0.3%)	6 (2%)	0	3 (4%)
Cataract	8 (2%)	6 (2%)	1 (2%)	0
Conjunctival edema	5 (1.5%)	5 (2%)	0	5 (6%)
Eye irritation	9 (3%)	5 (2%)	1 (2%)	2 (2%)
Retinal hemorrhage	7 (2%)	4 (1%)	1 (2%)	2 (2%)
Lacrimation increased	6 (2%)	3 (1%)	0	3 (4%)
Conjunctivitis	3 (1%)	2 (1%)	1 (2%)	2 (2%)
Conjunctivitis viral	1 (0.3%)	2 (1%)	0	2 (2%)
Cataract nuclear	0	1 (0.3%)	2 (4%)	0
Dermatochalasis	3 (1%)	0	0	2 (2%)

Source: ISS, Tables 2.7.4.2-5;[1] Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently; [a] Data from Studies OPH2003 and ISEE2008; [b] Data from Studies OPH2001 and OPH2003; [c] Data from Studies OPH2003

Reviewer's Comment: *The most frequent ocular adverse events occurring with avacincaptad pegol 2 mg at a higher rate than sham were conjunctival hemorrhage (13%), intraocular pressure increased (9%), blurred vision (8%), choroidal neovascularization (7%), and eye pain (4%). The adverse event rate for choroidal neovascularization for avacincaptad pegol 2 mg (7%) was nearly two times higher than that reported for the sham group (3.6%).*

Table 8.4.4-2 Non-Ocular Adverse Events Occurring in ≥ 2% of Subjects

Non-ocular Preferred Term	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	Avacincaptad pegol 2 mg[a] N=292	Avacincaptad pegol 1 mg[b] N=49	Avacincaptad pegol 4 mg[c] N=83
Number of patients with at least one adverse event	185 (56%)	164 (56%)	25 (51%)	45 (54%)
Injury, poisoning and procedural complications	45 (14%)	43 (15%)	1 (2%)	11 (13%)
Cardiac disorders	25 (8%)	26 (9%)	1 (2%)	5 (6%)
Gastrointestinal disorders	25 (8%)	21 (7%)	7 (14%)	8 (10%)
Fall	24 (7%)	20 (7%)	0	5 (6%)
Nervous system disorders	39 (12%)	19 (7%)	4 (8%)	7 (8%)
Urinary tract infection	21 (6%)	18 (6%)	5 (10%)	6 (7%)
Vascular disorders	18 (5%)	15 (5%)	1 (2%)	2 (2%)
Hypertension	10 (3%)	11 (4%)	0	2 (2%)
Nasopharyngitis	10 (3%)	10 (3%)	1 (2%)	3 (4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (7%)	10 (3%)	0	5 (6%)
COVID-19	9 (3%)	9 (3%)	0	0
Atrial fibrillation	6 (2%)	8 (3%)	0	2 (2%)
Back pain	9 (3%)	7 (2%)	2 (4%)	2 (2%)
Pneumonia	3 (1%)	7 (2%)	1 (2%)	2 (2%)
Basal cell carcinoma	6 (2%)	6 (2%)	0	2 (2%)
Edema peripheral	0	6 (2%)	0	0
Headache	10 (3%)	6 (2%)	1 (2%)	2 (2%)
Influenza	3 (1%)	6 (2%)	0	0
Arthralgia	1 (0.3%)	5 (2%)	2 (4%)	2 (2%)
Contusion	7 (2%)	5 (2%)	1 (2%)	2 (2%)
Osteoarthritis	2 (0.6%)	5 (2%)	3 (6%)	0
Sinusitis	6 (2%)	5 (2%)	4 (8%)	2 (2%)
Cystitis	5 (2%)	4 (1%)	2 (4%)	1 (1%)
Spinal stenosis	2 (0.6%)	2 (0.7%)	2 (4%)	0
Arthritis	2 (0.6%)	1 (0.3%)	0	2 (2%)
Diverticulitis	3 (1%)	1 (0.3%)	0	2 (2%)
Sepsis	0	1 (0.3%)	0	3 (4%)
Pain in extremity	1 (0.3%)	0	2 (4%)	0
Pancreatitis	1 (0.3%)	0	0	2 (2%)

Source: ISS, Tables 2.7.4.2-9; [a] Data from Studies OPH2003 and ISEE2008; [b] Data from Studies OPH2001 and OPH2003; [c] Data from Studies OPH2003

Reviewer's Comment: *Overall, there were no significant differences in the non-ocular adverse event rates between sham and the avacincaptad pegol treatment groups (2 mg and 4 mg). The most frequent non-ocular adverse events for avacincaptad pegol 2 mg were fall (7%) and urinary tract infection (6%).*

7.4.5. Laboratory Findings

No notable trends or clinically significant changes between treatment groups were observed for any of the analyzed laboratory parameters.

7.4.6. Vital Signs

No clinically significant differences in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) through Month 12 were observed between treatment groups.

7.4.7. Electrocardiograms (ECGs)

No significant effects were observed for any ECG parameter and no trends were observed in ECGs collected between treatment groups.

7.4.8. Immunogenicity

No studies have been conducted to assess immunogenicity.

7.5. Analysis of Submission-Specific Safety Issues

Table 8.5-1 Development of CNV Through Month 12 – Safety Population

Number of Patients n (%)	Studies OPH2001, OPH2003 and ISEE2008 Pooled			
	Sham[a] N=332	**Avacincaptad pegol 2 mg[a] N=292**	**Avacincaptad pegol 1 mg[b] N=49**	**Avacincaptad pegol 4 mg[c] N=83**
Patients with CNV at anytime				
No	320 (96%)	271 (93%)	48 (98%)	75 (90%)
Yes	12 (3.6%)	21 (7.2%)	1 (2%)	8 (10%)
Time to onset				
0 – 3 months	2	4	1	0
>3 – 6 months	5	4	0	4
>6 – 9 months	1	7	0	1
>9 – 12 months	4	6	0	3

Source: ISS, Tables 2.7.4.2-22; CNV=choroidal neovascularization; [a] Data from Studies OPH2003 and ISEE2008; [b] Data from Studies OPH2001 and OPH2003; [c] Data from Studies OPH2003; Events of CNV (in the study eye) that were reported based on findings at the Month 12 visit and confirmed by the reading center (RC) were included regardless of AE cut-off date.

Reviewer's Comment: *The percentage of patients treated with avacincaptad pegol 2 mg who developed CNV during the study was 7.2% compared to 3.6% for patients treated with sham.*

7.6. Safety Analyses by Demographic Subgroups

No clinically significant differences in adverse events were identified related to age (<65, 65-74, 75-84, and ≥ 85 years) or gender in patients treated with avacincaptad pegol 2 mg.

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies were conducted. The Applicant submitted a request for a waiver of nonclinical carcinogenicity studies.

7.7.2. Human Reproduction and Pregnancy

Avacincaptad pegol not been tested in pregnant women. Ninety percent of subjects in the clinical

trials were greater than 65 years of age.

7.7.3. Pediatrics and Assessment of Effects on Growth

Avacincaptad pegol has not been tested in pediatric patients. There are no proposed pediatric indications.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Avacincaptad pegol is not a narcotic and does not have abuse potential.

7.8. Safety in the Postmarket Setting

Avacincaptad pegol is not a marketed drug product. There are no Postmarketing data to report.

7.9. Integrated Assessment of Safety

On April 21, 2023, the Applicant submitted the 120-day Safety Update report. The submission included masked data up to the cut-off date from Study ISEE2008, which is ongoing. No new safety signals were identified for avacincaptad pegol 2 mg.

The safety database contained in this submission supports the relative safety of avacincaptad pegol, 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection once monthly for the treatment of geographic atrophy secondary to age-related macular degeneration.

8. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

See labeling in CDTL Review.

10. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

11. Post-marketing Requirements and Commitments

A post-marketing commitment has been made by the application to submit the pending 18 and 24 month data for ongoing Clinical Studies ISEE2008 and ISEE2009 is planned.

12. Appendices

12.1. Literature Search

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

12.2. **Financial Disclosure**

Clinical Investigator Financial Disclosure

Application Number: NDA 217225
Submission Date(s): June 26, 2019
Applicant: Iveric bio, Inc.
Product: Izervay (avacincaptad pegol injection) 2 mg (0.1 mL of 20 mg/mL solution)
Reviewer: Lucious Lim, MD
Covered Clinical Studies (Name and/or Number): OPH2003; ISEE2008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: OPH2003 80 investigators ISEE2008 205 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): OPH2003 0 investigators ISEE2008 5 investigators		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

12.3. Patient Experience Data

Studies OPH2003 and ISEE2008
Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sec 6 Study endpoints
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LUCIOUS LIM
07/31/2023 03:03:41 AM

RHEA A LLOYD
07/31/2023 09:19:20 AM