CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217225Orig1s000

SUMMARY REVIEW

Summary Review of NDA 217225

Cross Discipline Team Leader, Deputy Division Director, Division Director, Office Director Review

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, MD, William Boyd, MD, Wiley Chambers, MD, Alexander Gorovets, MD
Subject	Summary Review
BLA #	217225
Applicant	IVERIC bio, Inc.
Dates of Rolling Submission	
Clinical/ Regulatory	November 3, 2022
Nonclinical	November 22, 2022
Product Quality	December 19, 2022
PDUFA Goal Date	August 19, 2023
Proprietary Name	IZERVAY
Established Name	avacincaptad pegol intravitreal solution, 20 mg/mL
Dosage Form(s)	Intravitreal solution
Proposed Indication	Treatment of Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD)
Applicant Proposed Dosing Regimen	The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection once monthly (approximately 28 ± 7 days)
Dosing Regimen being Approved	The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection once monthly (approximately 28 ± 7 days) for up to 12 months
Population	Individuals with Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD)
Regulatory Action	Approval

NDA 217225 Review Team Role	Reviewer
OND RPM	Michael Puglisi
CDTL	Rhea Lloyd
Clinical Reviewer	Lucious Lim
Pharmacology/Toxicology Reviewer	Maria Rivera
Statistical Reviewer	Abel Eshete
Clinical Pharmacology Reviewer	Amit Somani
OND Labeling Reviewer	Derek Alberding
Drug Substance	Joseph Leginus
Drug Product	Dhana Kasi
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Regulatory Business Process Manager	Shazma Aftab
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OPDP Reviewer	Carrie Newcomer
Deputy Division Director	William Boyd
Division Director	Wiley Chambers
Deputy Office Director	Alexander Gorovets
Office Director	Charles Ganley

Glossary

AC	advisory committee
AE	adverse event
BPCA	Best Pharmaceuticals for Children Act
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls review staff
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMC	data monitoring committee
eCTD	electronic common technical document
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
VAS	visual analog scale

1. Summary

Avacincaptad pegol is an RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5. This action may prevent the formation of 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 membrane attack complex (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 a phosphate-buffered saline. During the clinical development avacincaptad pegol has also been referred to as ARC1905 or Zimura or IZERVAY by the sponsor. Reference to these names is made within this review.

The data from two (OPH2003 and ISEE2008) studies contained in this application establishes the efficacy of avacincaptad pegol intravitreal solution, 2 mg (0.1 mg of 20 mg/mL solution) administered by intravitreal injection every 28 ± 7 days for the treatment of geographic atrophy secondary to age-related macular degeneration. Results in the PP population were consistent with the ITT population. Both trials while successfully demonstrating efficacy in the difference in the mean rate of change from baseline to Month 12 in geographic atrophy area by MRM analysis, square root transformation had large amounts of missing data (20-26% at month 12). Study ISEE2008 is a 24 month study, but only the first 12 months of data have been submitted. Study OPH2003 is a much smaller study than ISEE2008. While Study OPH2003 followed subjects for 18 months and was completed, 39% of the avacincaptad pegol treatment data was missing at Month 18.

Reviewers from CMC, Pharmacology/Toxicology, Statistical, Clinical Pharmacology and Labeling have not identified any deficiencies. Manufacturing facility inspections verified that the proposed manufacturing facilities are in compliance with current Good Manufacturing Practices (cGMP). The application will be approved for the use of IZERVAY (avacincaptad pegol intravitreal solution), 2 mg administered by intravitreal injection every 28 ± 7 days for up to 12 months for the treatment of geographic atrophy secondary to age-related macular degeneration. The 12 month limitation at this time is due to the limited submitted data from patients after Month 12 (i.e., Month 18 and Month 24 data from ISEE2008 has not yet been submitted.) The applicant has committed to submit this information when it becomes available.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The adequate and well controlled studies (OPH2003 and ISEE2008) contained in this application establish the efficacy of IZERVAY (avacincaptad pegol intravitreal solution), 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 over a 12 Month period compared to sham.

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

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.

Benefit-Risk Dimensions

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	• NDA 217171, SYFOVRE™ (pegcetacoplan 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 treatment option.
Benefit	• Studies OPH2003 and ISEE2008 demonstrated that IZERVAY (avacincaptad pegol intravitreal solution) has slowed the rate of change in GA area over 12 months.	IZERVAY demonstrated slower loss of photoreceptors.
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 expected to be adequate.

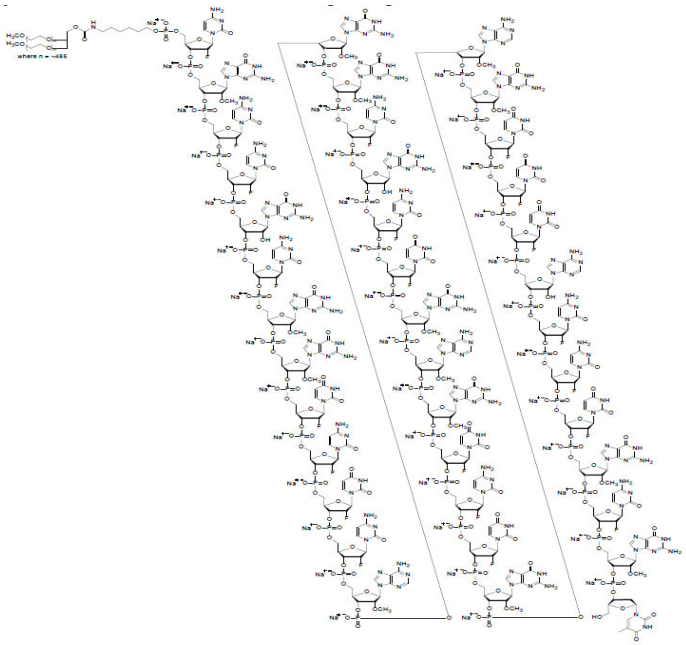
3. Patient Experience Data

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
	☒	Clinical outcome assessment (COA) data, such as		Section 7
		☒	Patient reported outcome (PRO)	Section 7
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 7
		☐	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	
☐	Patient experience data was not submitted as part of this application.			

4. Product Quality

Chemical Structure



Avacincaptad pegol (20 mg/mL) drug product is a sterile, aqueous solution intended for single dose intravitreal administration which does not contain an antimicrobial preservative. The drug product is supplied with a fill volume of (b) (4) mL per vial.

Release Specifications for Avacincaptad Pegol (effective 12/19/2022)
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) mL of excess fill to deliver 0.1 mL dose.
(b) (4)

q.s.: quantity sufficient
Source: 3.2.P.1 Description and Composition of the Drug Product

Drug Product Release and Stability Specification

Quality Attribute	Method	Acceptance Criteria	Release	Stability
Appearance	Visual Inspection	Colorless to slightly yellow solution with no visible particulates	X	X
Clarity	Ph. Eur. 2.2.1	≤ Reference Solution (b) (4)	X	X
Color	Ph. Eur. 2.2.2	≤ Standard (b) (4)	X	X
Oligonucleotide Content	UV Spectrophotometry	(b) (4)	X	X
Identity by AX-HPLC (RT)	AX-HPLC	Retention time of the sample main peak is within (b) (4) of the reference standard main peak	X	NR
Purity	AX-HPLC	Main Peak Purity (b) (4)	X	X
Impurities	AX-HPLC	Specified Impurities (b) (4) Total Impurities (b) (4)	X	X
Purity	RP/IP-HPLC	Main Peak Purity	X	X
Impurities	RP/IP-HPLC	Specified Impurities Total (b) (4) (b) (4) Unspecified Impurities (individual): Total Impurities (b) (4)	X	X
Identity	GPC	Retention time of sample main peak is within (b) (4) (b) (4) of the reference standard main peak Molecular weight (Mp) of sample main peak is within (b) (4) of Reference Standard main peak	X	NR
(b) (4)			X	NR
pH	USP <791> / Ph. Eur. 2.2.3	(b) (4)	X	X
Osmolality (b) (4)	USP <785> / Ph. Eur. 2.2.35	(b) (4)	X	NR
Viscosity	USP <912> / Ph. Eur. 2.2.10	(b) (4)	X	NR
Content Uniformity	USP <905> / Ph. Eur. 2.9.40	(b) (4)	X	NR
Particulate Matter	USP <789> / Ph. Eur. 2.9.19	(b) (4)	X	X
Extractable Volume	USP <697>	(b) (4)	X	NR
Bacterial Endotoxin	USP <85> / Ph. Eur. 2.6.14	(b) (4)	X	NR
Sterility	USP <71> / Ph. Eur. 2.6.1	No Growth	X	NR
Container Closure Integrity	(b) (4)		NR	X

X: Test Required; NR: Test Not Required; RT: Retention Time; RRT: Relative Retention Time; AX-HPLC: Anion Exchange High Pressure Liquid Chromatography; RP/IP-HPLC: Reversed Phase / Ion-Pair - High Pressure Liquid Chromatography; GPC: Gel Permeation Chromatography; FLP: Full Length Product; NLT – Not Less Than

CONTAINER CLOSURE

Primary Packaging Components

Component/Material	Description	Manufacturer/Supplier	Pharmacopeial Compliance
Glass Vial	2 mL (b) (4) clear, USP Type (b) (4) glass vial	(b) (4)	USP/NF, Ph. Eur., JP
Rubber Stopper	13 mm (b) (4) rubber stopper		USP/NF, Ph. Eur., JP
Crimp Seal	13 mm aluminum seal with flip-off cap		*N/A*

Glass Vial- Specifications

Parameter	Method	Acceptance Criteria
Visual Identification	In-House	Clear glass vial
Certificate of Quality Review	Verification of vendor COA	Correct material vendor. and grade; meets manufacturer's specifications
Height	In-House	(b) (4)
Crown Outer Diameter	In-House	
Inner Diameter	In-House	
Vial Diameter	In-House	
Visual Inspection of incoming Vials	In-House	The total quantity of rejects does not meet or exceed the corresponding reject limit for that category

Facilities

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)		Drug Substance Manufacture Release and Stability Testing (b) (4)	Approve - Based on Previous History
		Color, Clarity, Bacterial Endotoxin, Sterility Testing – Release and Stability for product development Bacterial Endotoxin Testing and Bioburden Testing - Stability Testing (alternate) for product development (b) (4)	No Evaluation Necessary
		Drug Product Manufacture Drug Product Testing - Release and Stability (b) (4)	Approve - Based on Previous History
		Container Closure Integrity Testing –Stability (b) (4)	Approve - Based on Previous History
		Particulate Matter Testing – Release and Stability (b) (4)	Approve - Based on Previous History

(b) (4)	Sterility and Endotoxin Testing – Release and Stability (b) (4)	Approve - Based on Previous History
	Drug Product Labeling and Packaging (b) (4)	Approve - Based on Previous History
	Development Facility: Drug Product Manufacture Endotoxin testing – Release Drug Product Manufacturing In- Process Testing (b) (4)	No Evaluation Necessary
	Development Facility: Particulate Matter Testing – Release and Stability (b) (4)	No Evaluation Necessary
	Clinical Supplies of Drug Product: Sterility Testing – Release (b) (4)	No Evaluation Necessary
	Clinical Supplies of Drug Product: Drug Product Packaging and Labeling (b) (4)	No Evaluation Necessary

CMC Recommendations:
Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects.

(b) (4) Needles and syringes are 510k-cleared or 510k exempt, and CDRH confirmed a consult was not necessary on January 25, 2023. OPMA has issued an overall acceptable recommendation for all the facilities on May 2, 2023. Therefore, NDA 217225 is recommended approval from Product Quality perspective.

5. Nonclinical Pharmacology/Toxicology

From the Nonclinical Pharmacology/ Toxicology review finalized on May 30, 2023:

Repeat-dose intravitreal (IVT) toxicity studies were conducted in New Zealand White rabbits (0, 0.15, 0.5, and 1.5 mg/eye) and Beagle dogs (0, 0.3, 1, and 3.0 mg/eye). The studies included a combination arm of the high dose plus Lucentis® (ranibizumab for IVT injection), a recombinant humanized monoclonal antibody that binds and inhibits vascular endothelial growth factor (VEGF). The main finding in both species was vacuolation of the ganglion cell layer of the retina observed upon microscopic evaluations. In the dog, vacuolation of the optic tract in the brain was also observed. Coadministration with Lucentis® did not impact these findings.

In the rabbit, based on the retinal vacuolation, the NOEL for avacincaptad pegol is 0.5 mg/eye for single and repeated IVT injections (0.66X the recommended clinical dose). The vacuolation was mostly of mild severity, reversible, and not associated with histopathological adverse changes (i.e., retinal degeneration, inflammation, necrosis, etc.) or noticeable effects on electroretinography (ERG) measurements. Therefore, it appeared not to be adverse. In the absence of adverse effects at the doses examined, the NOAEL for avacincaptad pegol is considered to be ≥ 1.5 mg/eye (2X the recommended clinical dose).

In the dog, the finding of retinal vacuolation was observed at all dose levels (0.3 to 3 mg/eye). There was no NOEL following single or repeated IVT injections. Given the more diffuse retinal vacuolation observed at 3.0 mg and extension of the finding to the optic tract, a conservative approach was used to select the NOAEL. The NOAEL is considered to be 1.0 mg/eye (0.66X the recommended clinical dose) even though optic tract vacuolation at 3.0 mg/eye was not associated with any adverse histopathology or significant ERG findings.

The presence of the vacuoles most likely reflects uptake of the PEGylated aptamer within the retinal cells (i.e., the vacuoles may occur due to the presence of the PEG polymer conjugated to the aptamer). These findings were not considered adverse as there were no histopathology findings consistent with tissue damage or inflammation or noticeable ERG changes. These vacuolation findings were reversible or partially reversible in both species. The retinal vacuolation was not observed in the clinical trials as monitored by optical coherence tomography (OCT).

After IVT administration in NZW rabbits and beagle dogs, there were no adverse systemic effects up to the highest dose evaluated. In the dog, there were marginally increased Activated Partial Thromboplastin Clotting Time (APTT) values at the high dose (ARC1905 3 mg/eye ± Lucentis 0.5 mg/eye) from Week 13 onward. The finding was not present following a 4-week recovery period. Per the Applicant, effects on coagulation (APTT and prothrombin time (PT)) were monitored in the clinic (Study OPH2000; doses of 0.3, 1, and 2 mg for at least 6 months) with no adverse effects observed.

In intravenous (IV) toxicity studies in rats and monkeys of up to 7-day duration, adverse effects included mortalities (attributed to cardiopulmonary failure resulting from hemorrhage and edema in the heart and lungs in monkeys), increased incidence of rouleaux formation, anemia, thrombocytopenia, hypoproteinemia, and/or various clinical chemistry changes. Vacuolation of macrophages in multiple tissues and prolongation of APTT and PT was observed in both species. Most clinical pathology findings were reversible or partially reversible. Vacuolation in macrophages was still present in multiple tissues at the end of the recovery period. A NOAEL was not identified in the 7- day IV toxicity studies. At the low dose in each study (367 mg/kg/day in rats and 141 mg/kg/day in monkeys), exposure margins are over 1000X (rat) and 540X (monkey) the systemic exposure observed in humans at the recommended clinical dose of 2 mg (AUC_{0-t} of 999.9 ng.day/mL or 23.99 µg.hr/mL). Therefore, it is considered unlikely that systemic tissue vacuolization and other adverse effects identified in the 7-day continuous IV dose studies will occur at the systemic exposures expected to be observed in humans at the intended dosing regimen.

Avacincaptad pegol was negative for genotoxicity based on a standard battery of studies including the bacterial reverse mutation assay, chromosomal aberration in mammalian cells and in vivo mouse bone marrow micronucleus assays.

The Applicant submitted a justification not to conduct carcinogenicity, fertility/early embryonic development, and pre-/postnatal development studies. The Pharmacology/Toxicology team

concluded that the weight of evidence supports that the studies are not necessary for the intended dosing regimen and indication.

In the embryofetal development (EFD) toxicity studies in rats and rabbits, there was no avacincaptad pegol-related adverse effects on any measured maternal or fetal parameter at doses up to 1.2 mg/kg/day (NOAEL). In the rats, a dose-dependent increase in the incidence of a skeletal variation (short thoracolumbar supernumerary rib) was observed at all avacincaptad pegol dose levels. In the rabbits, there was an increased incidence of full thoracolumbar supernumerary ribs at the high dose. Supernumerary rib is one of the most common skeletal variants in rodent and rabbit developmental toxicity studies. This abnormality was considered a non-adverse variation (would not be expected to affect long-term survival).

The Pharmacology/Toxicology team recommends approval of avacincaptad pegol solution for the proposed indication of treatment of geographic atrophy secondary to age-related macular degeneration. The nonclinical studies were adequate to inform risk.

6. Clinical Pharmacology

From the Clinical Pharmacology review finalized on May 19, 2023:

Pharmacokinetic (PK) data for proposed to-be-marketed (TBM) avacincaptad pegol was collected in phase 1 study OPH2000. The clinical pharmacology review was focused on reviewing PK and Population (Pop) PK information for avacincaptad pegol from Study OPH2000.

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant and recommends approval of this NDA. The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

Clinical Pharmacology Recommendations and Comments

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness is derived from two Phase 3 studies: Studies OPH2003 and ISEE2008. See clinical review for additional details.
General dosing instructions	2 mg (0.1 mL of 20 mg/mL solution) administered by IVT injection once monthly (approximately 28 ± 7 days). The proposed dosing regimen was evaluated in two pivotal phase 3 studies (OPH2003 and ISEE2008).
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments based on any intrinsic or extrinsic factors are recommended.
Bridge between the to-be-marketed (TBM) and clinical trial formulations	A bridging pharmacokinetic (PK) study between the TBM and clinical trial formulation is not warranted since no change in formulation was made throughout the development program as per the Applicant.

7. Clinical Efficacy

Study OPH2003 was an 18-month study, and consisted of two parts, Part I and Part 2. In Part 1, 77 subjects were randomized in an approximately 1:1:1 ratio to receive monthly injections with Izervay 1mg, Izervay 2mg or sham. In Part 2, 209 subjects were randomized in a 1:2:2 ratio to receive monthly injections with Izervay 2mg, Izervay 4mg (administered as 2 IVT injections of Izervay 2mg) or sham. For the comparison of Izervay 2mg versus sham, subjects randomized to these two arms in Part 1 and 2 were combined. For the comparison of Izervay 4mg versus sham, only subjects randomized to the sham arm in Part 2 were included. Per the Applicant, although the Izervay 1mg arm was included in the study, there was no plan to evaluate the efficacy of this dose.

OPH2003 Study Results

Subject Demographics – ITT Population

	Part 1			Part 2			Combined[a]	
	Izervay 1 mg N=26	Izervay 2 mg N=25	Sham N=26	Izervay 2 mg N=42	Izervay 4 mg N=83	Sham N=84	Izervay 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)
Sex, 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.*

Baseline Ocular Characteristics – ITT Population

	Part 1			Part 2			Combined[a]	
	Izervay 1 mg N=26	Izervay 2 mg N=25	Sham N=26	Izervay 2 mg N=42	Izervay 4 mg N=83	Sham N=84	Izervay 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 Dev	8.0	7.5	7.5	11.2	9.8	11.0	10.0	10.4
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 Dev	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 (8)	5 (20)	4 (15)	0	2 (2)	2 (2)	5 (7)	6 (5)
Extrafoveal[b]	23 (89)	20 (80)	22 (85)	42 (100)	81 (98)	82 (97)	62 (93)	104 (95)
Ungradable	1 (4)	0	0	0	0	0	0	0
Macular Atrophy Gradable, n (%)								
Yes	25 (96)	25 (100)	26 (100)	42 (100)	82 (99)	84 (100)	67 (100)	110 (100)
No	1 (3.8)	0	0	0	1 (1.2)	0	0	0
If Yes, Area of GA (mm^2)								
Mean	7.4	6.6	7.3	7.8	7.9	7.5	7.3	7.4
Standard Dev	4.3	3.3	3.7	4.0	4.2	3.9	3.8	3.8
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)	25 (100)	26 (100)	41 (98)	82 (99)	83 (99)	66 (99)	109 (99)
No	0	0	0	0	0	0	0	0
Ungradable	1 (3.8)	0	0	1 (2.4)	1 (1.2)	1 (1.2)	1 (1.5)	1 (0.9)
If Yes, Hyper FAF pattern								
Fine granular-punctate spots	7 (28)	6 (24)	8 (31)	1 (2)	9 (11)	17 (20)	7 (11)	25 (23)
Branching	1 (4)	4 (16)	3 (12)	3 (7)	4 (5)	1 (1)	7 (11)	4 (4)
Fine granular-dusty	10 (40)	9 (36)	8 (31)	17 (42)	26 (32)	28 (34)	26 (39)	36 (33)
Trickling	3 (12)	2 (8)	3 (12)	10 (24)	13 (16)	17 (21)	12 (18)	20 (18)
Reticular	2 (8)	1 (4)	1 (4)	6 (15)	15 (18)	8 (10)	7 (11)	9 (8)
Patchy	0	1 (4)	0	0	1 (1)	0	1 (1)	0
Banded	2 (8)	1 (4)	3 (12)	0	0	1 (1)	1 (1)	4 (4)
Focal	0	0	0	0	0	1 (1)	0	1 (1)
Not determinable	0	1 (4)	0	4 (10)	14 (17)	10 (12)	5 ()	10 (9)

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

Time period	Group Izervay: N=36 Sham: N=69	Slope (SE) (mm^2/year)	Difference (95% CI) in Slope Izervay- Sham (mm^2/year)	Percent Difference of Sham
Baseline to Month 6	Izervay 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	Izervay 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	Izervay 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 Izervay 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.*

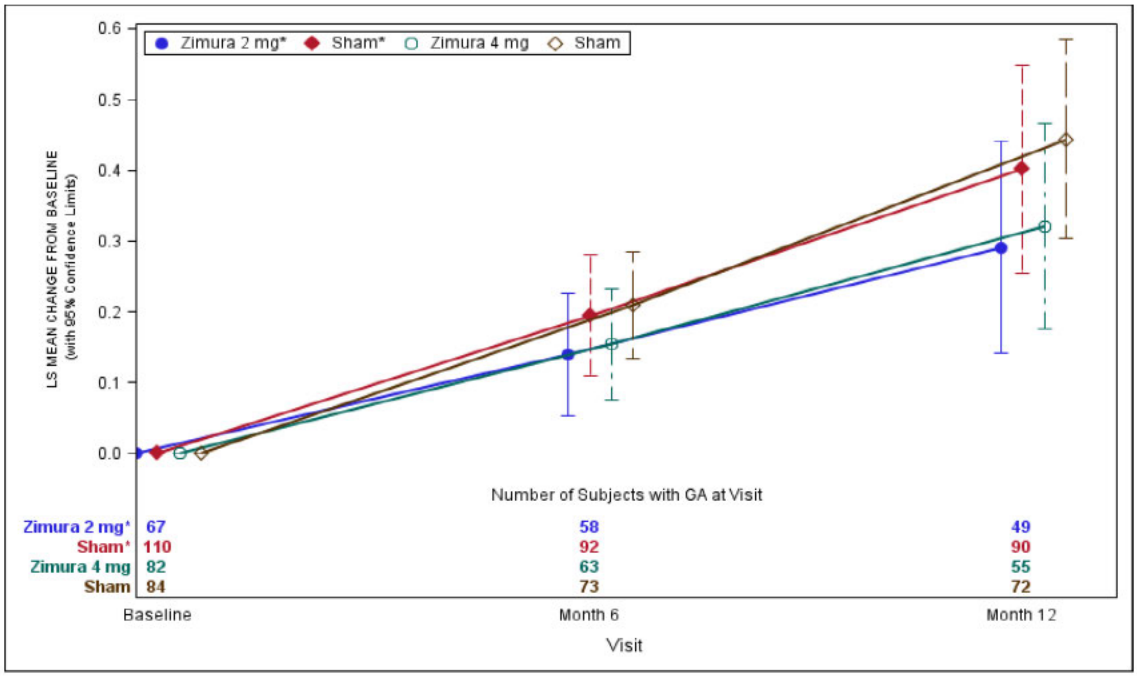
Exact Match by Days

Time Period	*Izervay 2mg mm/year*	*Sham mm/year*	*Difference (Izervay-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*

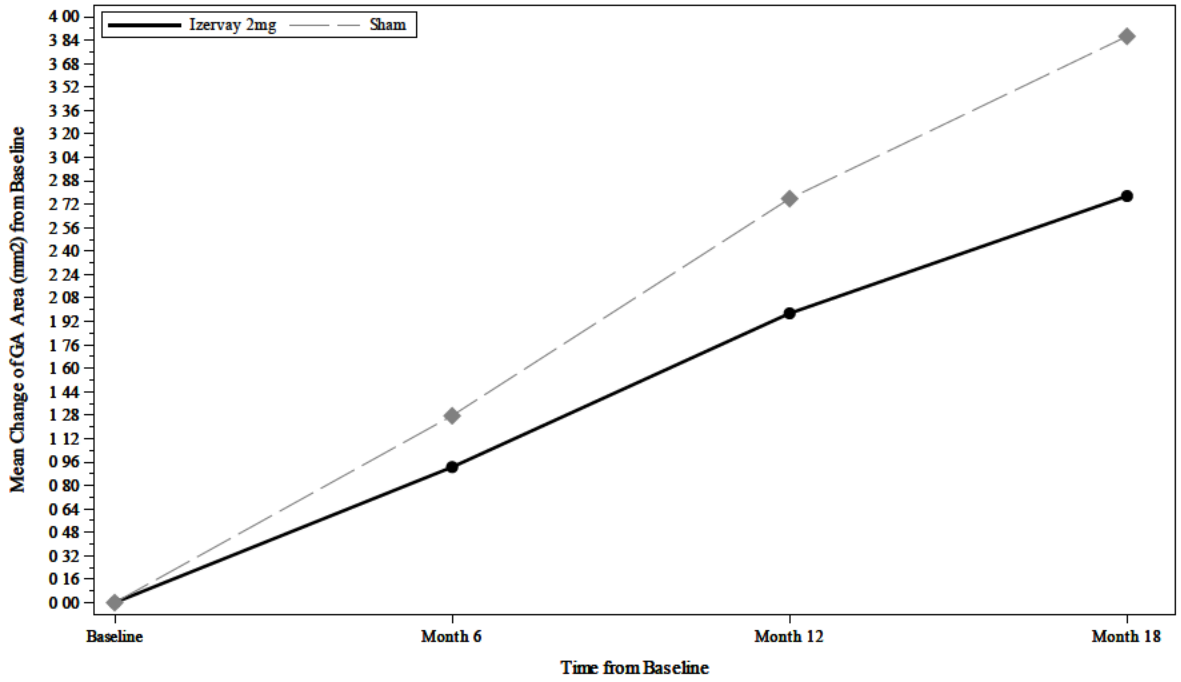
Square root transformation

Time Period	*Izervay 2mg mm/year*	*Sham mm/year*	*Difference (Izervay-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*

Applicant's Analysis: 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.



ISEE2008 Study Results

Study ISEE2008 was a 24-month study. This study first randomized 448 subjects in an approximately 1:1 ratio to receive monthly Izervay 2mg or sham monthly injections for 12 months. At Month 12, subjects who were initially randomized to the monthly Izervay 2mg arm were re-randomized in a 1:1 ratio to receive Izervay 2mg administered monthly from Month 12 to Month 23 or Izervay 2mg administered every other month at Months 13, 15, 17, 19, 21, and 23. For Months 12-24, sham was administered at Months 12, 14, 16, 18, 20, and 22 to ensure masking. Note, subjects who were initially randomized to sham continued to receive monthly sham injections through Month 23. All patients had a final follow-up visit at Month 24.

Subject Demographics – ITT Population

	Izervay 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)
Sex, 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.*

Baseline Ocular Characteristics – ITT Population

Baseline Characteristic	Izervay 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)
Ungradable	0	0
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

Time period	Group Izervay: N=175 Sham: N=180	Slope (SE) (mm^2/year)	Difference (95% CI) in Slope Izervay- Sham (mm^2/year)	Percent Difference of Sham
Baseline to Month 6	Izervay 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	Izervay 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 Izervay 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.*

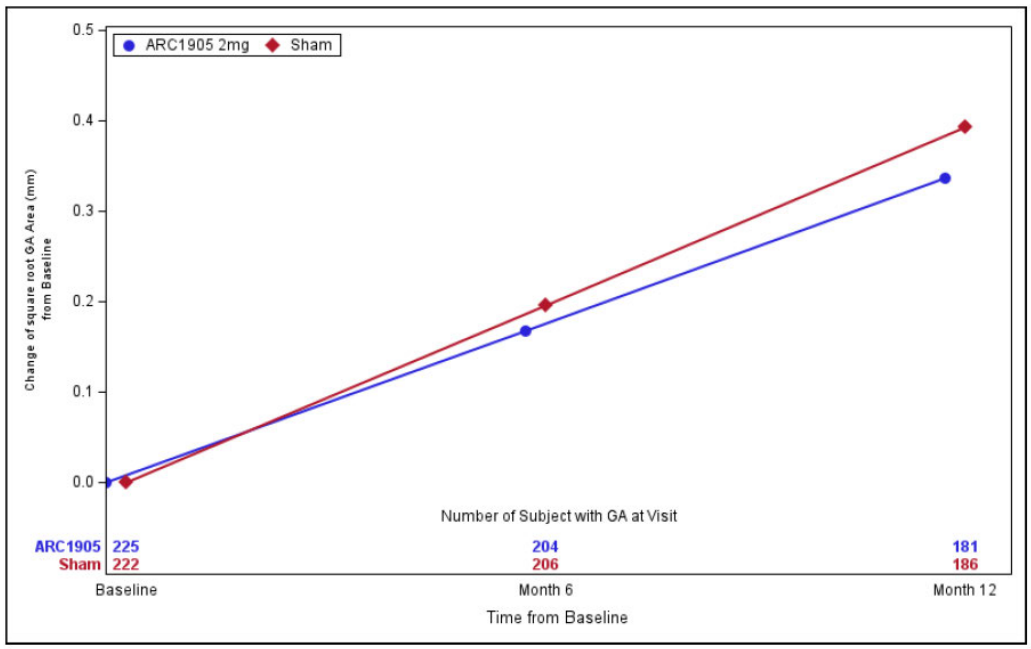
Exact match by days

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

Applicant's Results 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=Izervay 2 mg

Reviewer's Comment: *The mean rate of growth in geographic atrophy area over time from Baseline to Month 12 by square root transformation is shown above. The mean rate of growth for Izervay 2 mg is reduced as compared to sham. Although the study will be of 24 month duration, results have only been submitted for the first 12 months. A post-marketing commitment has been made to submit the 24 month data when available.*

8. Safety

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)

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
	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.*

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%).*

Blurred vision was reviewed as a composite. The following events were combined for this category.

USUBJID	TRTSDT	TRTEDT	TRT01P	AETERM
(b) (6)			Izervay	Big drop in vision
			Izervay	Blurred vision
			Izervay	Blurred vision
			Izervay	Blurred vision
			Izervay	Blurred vision (S/P Injection)
			Izervay	Blurred vision post-injection
			Izervay	Decrease in BCVA
			Izervay	Decrease in BCVA due to CNV
			Izervay	Decrease in visual acuity
			Izervay	Decrease of visual acuity
			Izervay	Decrease of visual acuity
			Izervay	Loss of visual acuity transient
			Izervay	Subjective complaint of decreased vision
			Izervay	Temporary loss of vision
			Izervay	Transient blurred vision
			Izervay	Transient blurred vision
			Izervay	Transient decrease in visual acuity
			Izervay	Transient decrease of visual acuity
			Izervay	Transient loss of vision
			Izervay	Transient loss of vision
			Izervay	Transient loss of visual acuity
			Izervay	Transitory 12 letter loss in BCVA
			Sham	23 Letters worsening of visual acuity since screening visit
			Sham	Blurred vision
			Sham	Blurry vision
			Sham	Blurry vision
			Sham	Decrease in visual acuity due to geographic atrophy
			Sham	Decrease visual acuity
			Sham	Decreased visual acuity
			Sham	Decreased visual acuity
			Sham	Decreased visual acuity in the study eye
			Sham	Foggy vision appeared after injection
			Sham	Loss of 10 letters since last BCVA test
			Sham	Subjective decrease in visual acuity
			Sham	Transient decrease in BCVA
			Sham	Transient decreased vision
			Sham	VA decrease
			Sham	Vision decreased from worsening dry AMD
			Sham	Visual acuity decrease
			Sham	Visual acuity reduced

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%).*

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
NOTE: 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% compared to 4% for patients treated with sham.*

9. Advisory Committee Meeting

There were no issues that were thought to benefit from a discussion at an Advisory Committee Meeting. No Advisory Committee Meeting was held for this supplemental application.

10. Pediatrics

This NDA triggered PREA because IZERVAY is a new active ingredient. The applicant requested a full product specific waiver for all pediatric age groups (i.e., birth to < 18 years) for the treatment of geographic atrophy secondary to age-related macular degeneration on the grounds that the condition does not occur in pediatric patients. The Agency agrees.

11. Biostatistics

In both studies, the main efficacy outcome of interest was the total area of GA lesions in the study eye measured by fundus autofluorescence (FAF) images. The protocol defined primary efficacy endpoint in Study OPH2003 was the mean change from baseline in GA area at Month 12 and is estimated as the least squares mean change from baseline based on a mixed effects model for repeated measures (MMRM). For Study ISEE2008, the protocol defined primary efficacy endpoint was the mean rate of GA growth and was estimated as a slope of a linear mixed effects model fitted using GA data collected at Baseline, Month 6 and Month12. For this indication, the Clinical Group expects the mean rate of growth (Slope) to be the primary efficacy endpoint.

The Applicant's findings for the protocol defined primary efficacy endpoints are presented below. Both studies met the primary objective of demonstrating the efficacy of Izervay compared to sham. However, the percentage of patients with missing primary outcome data was relatively

very high in both studies. Sensitivity analyses to assess the impact of missing data yield consistent findings with the primary analysis. Analyses across various patient subgroups are also presented. Results from these analyses are generally consistent with the primary analysis findings.

Key secondary endpoints analyzed in this review are best corrected visual acuity (BCVA) and low luminous visual acuity (LL-BCVA). The analysis results for these endpoints provided treatment differences between Izervay and sham that were not statistically significant.

Summary of Efficacy at Month 12 (Study OPH2003)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)[c]	
	Izervay 2mg [a] N=67	Sham [a] N=110	Izervay 4mg N=82	Sham [b] N=84	Izervay 2mg vs Sham	Izervay 4mg vs Sham
Mean Change[1]	0.292 (0.077)	0.402 (0.075)	0.321 (0.074)	0.444 (0.072)	0.110 (0.030, 0.190)	0.124 (0.038, 0.209)
Slope[2]	0.283 (0.070)	0.392 (0.068)	0.307 (0.069)	0.416 (0.066)	0.109 (0.031, 0.186)	0.109 (0.027, 0.192)

Source: [1]Table 18 of the Applicant's study report. [2]Table 14.2.1.5 and Table 14.2.1.1 of the Applicant's integrated summary of efficacy (ISE).
[a] Combination of Part 1 and Part 2 patients. [b] Sham from part 2 only. [c] Differences are taken as sham-Izervay.

Summary of Efficacy at Month 12 (Study ISE2008)

Study	LS mean (SE)		Difference (95% Confidence Interval)[c]
	Izervay 2mg N=225	Sham N=222	
Slope[1]	0.336 (0.032)	0.392 (0.033)	0.056 (0.016, 0.096)
Mean Change[2]	0.333 (0.034)	0.392 (0.035)	0.059 (0.017, 0.100)

Source: [1]Table 14 of the Applicant's study reports. [2]Table 14.2.3.6 of the Applicant's study report. [c] Differecnes are taken as sham-Izervay.

Per the study results, the treatment difference between sham and the Izervay 2mg arm is roughly 50% lower in Study ISEE2008 compared to Study OPH2003. This appears mainly because of the difference in the growth rate in subjects treated with Izervay 2mg arms across the two studies. Subjects treated with Izervay 2mg in Study OPH2003 appear to have slower GA growth rate compared to similar subjects in Study ISEE2008. There does not appear to be notable difference in the demographic characteristics of age, sex and ethnicity among subjects randomized to the Izervay 2mg arms across the two studies. However, differences in some baseline and disease characteristics, missing data and treatment compliance rates were observed. Therefore, the difference in GA progression across the Izervay 2mg arms of the two studies could be partly attributed to the differences discussed above.

Regarding safety, a higher percentage of subjects in the Izervay arms of both studies reported at least one ocular adverse event compared to the corresponding subjects in the sham arms. The most frequently reported ocular adverse events in subjects randomized to the Izervay arms were conjunctival hemorrhage, conjunctival hyperemia, punctate keratitis, choroidal neovascularization (CNV) and visual acuity reduced. In addition, in both studies, a higher percentage of subjects discontinued the Izervay arms compared to the sham arm. In the two studies combined, 8 deaths, 6 of which were in the Izervay arms, are reported. Note, based on the drug exposure summary ion Error! Reference source not found.), approximately between 60-71% of the subjects randomized to the Izervay arms received the total allowed 12 injections during the 12-month period. Therefore, it is possible that the actual annual incidence of adverse events with a full treatment regimen might be higher.

In conclusion, the results of the primary efficacy analyses in the two pivotal studies demonstrated the efficacy of Izervay for the treatment of GA secondary to AMD. Because the incidence of adverse events was higher in the Izervay arms compared to sham, the final determination for the approval of this drug should be made based on the totality of evidence taking the potential safety issues into account.

12. Financial Disclosure

Clinical Investigator Financial Disclosure

Submission Date(s): June 26, 2019

Applicant: Iveric bio, Inc.

Product: Izervay (avacincaptad pegol intravitreal solution) 2 mg (0.1 mL of 20 mg/mL solution)

Covered Clinical Studies (Name and/or Number): OPH2003 and 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)

13. Study Integrity

From the OSI Clinical Investigation Summary finalized June 23, 2023: 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.

14. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized their review on 3/25/2023. DMEPA identified medication error issue concerns, described below. The clinical staff agreed with some of the recommendations and disagreed with others.

Identified Issues and Recommendations for Iveric Bio. Inc.				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	Clinical Conclusion
Professional Sample and Trade Container Label(s) and Carton Labeling				
1.	As currently presented, we note the use of the package type term [redacted] (b) (4)	[redacted] (b) (4) is not considered an appropriate package type term.[c]	Revise the package type term to "Single Dose."	Agree with recommendation
Trade and Professional Sample Carton Labeling				
1.	As currently presented the strength statement of the professional sample and trade container labels reads "2 mg 0.1 mL of 20 mg/mL."	Per USP General Chapter <7> Labeling, for container that hold a volume of less than 1 mL, the quantity per fraction of milliliter should be the only expression of strength.[d]	Revise the strength statement to remove 20 mg/mL such that the strength statement appears as "2 mg/0.1 mL" only.	There is a concern for confusion in labeling concentrations other than x/mL. 20mg/mL will be maintained.
2.	The usual dosage statement is not included.	21 CFR 201.55 requires that labels for prescription drug bear a statement of the recommended or usual dosage.	Add your intended "Recommended Dosage" statement. For example, "Recommended Dosage: See prescribing information."	Agree with recommendation
	As currently presented, the storage requirement is not included.	Appropriate storage information can help mitigate the risk of wrong storage medication errors.	Include the storage information as described in the Prescribing Information. For example: Must be refrigerated at 2°C to 8°C (26°F to 46°F)	Agree with recommendation
	As currently presented, the product identifier is missing.	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human- readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[e] The DSCSA guidance on product identifiers recommends that the human- readable portion be located near the 2D data matrix barcode and recommends the following format: NDC: [insert product's NDC]	Agree with recommendation
			SERIAL: [insert product's serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]	Agree with recommendation

			If you determine that the product identifier requirements apply to your product's labeling, we request you include product identifier along with the 2-D data matrix barcode. Additionally, ensure that there is sufficient white space between the linear barcode and 2-D data matrix barcode to allow barcode scanners the ability to correctly read each barcode.	
5.	The lot number and expiration date are missing.	The lot number and expiration date are required per 21 CFR 203.38(a) and 21 CFR 211.137, respectively.	Include the lot number and expiration date. Additionally, ensure the lot number is clearly differentiated from the expiration date. See previous recommendation.	Agree with recommendation

15. Post-marking Risk Management

There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

16. Regulatory Action

Reviewers from CMC, Pharmacology/Toxicology, Statistical, Clinical Pharmacology and Labeling have not identified any deficiencies. Manufacturing facility inspections verified that the proposed manufacturing facilities are in compliance with current Good Manufacturing Practices (cGMP). NDA 217225 for IZERVAY (avacincaptad pegol intravitreal solution) will be approved for the use of avacincaptad pegol intravitreal solution, 2 mg administered by intravitreal injection every 28 ± 7 days for up to 12 months for the treatment of geographic atrophy secondary to age-related macular degeneration. The 12 month limitation at this time is due to the limited submitted data from patients after month 12 (i.e., Month 18 and Month 24 data from ISEE2008 has not yet been submitted.) The applicant has committed to submit this information when it becomes available:

PMC 4477-1
Submit 24 Month safety and efficacy data from ISEE2008 (GATHER2), a randomized, double-masked, controlled trial to assess the safety and efficacy of intravitreal administration of avacincaptad pegol in approximately 330 patients with geographic atrophy secondary to dry age-related macular degeneration (AMD).

Trial Completion:	8/2023
Final Report Submission:	2/2024

PMC 4477-2
Submit 18 Month long-term safety data from ISEE2009, an open-label extension trial to assess the safety of intravitreal administration of avacincaptad pegol in approximately 230 patients with geographic atrophy who completed ISEE2008 (GATHER2) through Month 24.

Trial Completion:	2/2025
Final Report Submission:	8/2025

The agreed upon package insert is included below, submitted by the applicant on August 3, 2023.

22 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

RHEA A LLOYD
08/04/2023 12:54:38 PM

WILLIAM M BOYD
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WILEY A CHAMBERS
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