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New Drug Evaluations: pegcetacoplan (SYFOVRE) injection, for intravitreal use
avacincaptad pegol (IZERVAY) injection, for intravitreal use

Date of Review: April 2024

End Date of Literature Search: 12/31/2023

Generic Name:
pegcetacoplan
avacincaptad pegol

Brand Name (Manufacturer):
Syfovre (Apellis Pharmaceuticals, Inc)
Izervay (IVERIC bio, Inc)

Dossier Received:
Yes (SYFOVRE)
No (IZERVAY)

Plain Language Summary:

- The United States (US) Food and Drug Administration (FDA) approved two new medicines, pegcetacoplan and avacincaptad pegol, to treat adults with age-related macular degeneration (AMD). These medicines are known as complement inhibitors.
- Age-related macular degeneration is a condition that affects older people of both sexes but is more common in fair-skinned people and those who smoke. Even though the cause is unknown, the condition often runs in families.
- There are two forms of AMD, dry and wet. The macula is part of an area near the center of the back of the eye, called the retina. The macula allows a person to see fine details and colors in the center of their vision.
- In dry AMD, the macula tissue is damaged, becomes thin, and gets a buildup of protein and fat products called drusen. As the body tries to repair damaged tissue, other cells and protein helpers cause inflammation. Over time, too much inflammation leads to additional tissue damage. Although there may not be noticeable bleeding, scarring, or pain right away, the patient's vision slowly gets worse. A doctor may notice these changes around the macula at an eye-exam even before patients has visual complaints.
- In wet AMD, abnormal blood vessels develop in the layer of tissue under the macula. The vessels often leak fluid that may cause immediate scarring and damage. Wet AMD is a medical emergency that may lead to complete blindness if not treated quickly.
- Dry AMD usually does not result in complete blindness but may lead to blind spots. However, the patient can still see around the outer edge of the visual field and see colors. When the patient has advanced dry AMD, or geographic atrophy (GA), it makes tasks of daily living difficult because it is hard to see things clearly especially in dim light.
- There is no cure for AMD but the complement inhibitors pegcetacoplan and avacincaptad pegol have been studied to stop some of the damage caused by inflammation in order to treat advanced AMD. These medicines must be injected directly into the eye with a special needle by a trained clinician.
- Evidence from one study shows that pegcetacoplan resulted in a small change in GA growth rate compared to a false (placebo) injection at 12 months, but the other study did not show any difference. Both of the studies did not show any improvement in eye function (for example, ability to see better or read better).

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- Evidence from two studies show that avacincaptad pegol resulted in a small change in GA growth rate compared to a false (placebo) injection at 12 months but did not show any improvement in eye function (for example, ability to see better or read better).
- Both pegcetacoplan and avacincaptad pegol may increase the risk of eye infection, eye bleeding, elevated eye pressure, retinal separation (detachment), or harmful blood vessel formation in the retinal area. Patients who used pegcetacoplan also had reports of eye inflammation.
- We recommend that pegcetacoplan and avacincaptad pegol be non-preferred, and that providers explain why someone needs one of these complement inhibitors before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the evidence for comparative efficacy of complement inhibitors pegcetacoplan and avacincaptad pegol for the treatment of age-related macular degeneration?
2. What is the evidence for comparative safety of complement inhibitors pegcetacoplan and avacincaptad pegol for the treatment of age-related macular degeneration?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a complement inhibitor for AMD?

Conclusions:

- The efficacy and safety of pegcetacoplan was studied in 2 parallel, phase 3 randomized, placebo-controlled trials (APL2-303 "DERBY" and APL2-304 "OAKS") in adult patients with AMD.[1-3]
- There is low quality evidence from one fair quality study (OAKS) that pegcetacoplan administered monthly (PM) or every other month (EOM) resulted in a statistically significant reduction in GA lesion growth compared to sham injection at 12 months (PM: -21% change; mean size difference -0.41 mm^2; 95% confidence interval (CI) -0.64 to -0.18; p=0.0004; and EOM: -16% change [mean size difference –0.32 mm^2, 95% CI, –0.54 to –0.09; p=0.0055).[1-3] The DERBY trial did not demonstrate a statistically significant difference in GA lesion growth for pegcetacoplan compared to sham injection.[1-3] The clinical significance of the change reported in the OAKS trial is unclear and neither trial showed benefit in functional measures or quality-of-life in pegcetacoplan-treated patients compared to sham injection.[1-3]
- The efficacy and safety of avacincaptad pegol was evaluated in 2 randomized, double-blind, sham-controlled trials. The first study was an 18-month, phase 2/3 trial (OPH2003 "GATHER1") and the second a 24-month, phase 3 trial (ISEE2008 "GATHER2").[4-8]
- There is low-quality evidence from two moderate-quality studies that avacincaptad pegol 2 mg administered monthly resulted in a statistically significant reduction in rate of GA lesion growth compared to sham injection at 12 months (GATHER1: -35% change; mean difference (MD) = 0.67mm^2/year;95% CI, 0.21 to 1.13; p <0.01 and GATHER2: -18% change; MD 0.38 mm^2/year; 95% CI, 0.12 to 0.63; p=0.0039).[4-8] The clinical significance of the change reported in GATHER1 and GATHER2 is unclear and neither trial was able to show any benefit in functional measures including visual acuity in avacincaptad pegol-treated patients.[4-8]
- Treatment with either pegcetacoplan or avacincaptad pegol has been associated with conjunctival hemorrhage and development of neovascular (wet) AMD.[1-8]
- Treatment with either pegcetacoplan or avacincaptad pegol is contraindicated in patients with ocular or periocular infections and those with active intraocular inflammation.[1,2,4,5]
- There is insufficient direct comparative evidence between the complement inhibitors pegcetacoplan and avacincaptad pegol for safety and efficacy in treating AMD.

- Evidence for pegcetacoplan and avacincaptad pegol is primarily limited to White populations at least 50 years of age or older.[1,3,4,6-8] There is insufficient evidence on efficacy or harms data for other subgroups.

Recommendations:
- Create a new preferred drug list (PDL) class: Ophthalmologic Complement Inhibitors.
- Designate pegcetacoplan and avacincaptad pegol as non-preferred on the PDL.
- Implement prior authorization (PA) criteria for complement inhibitors (pegcetacoplan and avacincaptad pegol) to ensure appropriate and safe use in FDA-approved indications.

Background:
Age-related macular degeneration (AMD) is a chronic, progressive, retinal disease that eventually leads to visual impairment.[9,10] Age-related macular degeneration is among the leading causes of blindness worldwide and the foremost cause of legal blindness is the US.[11] The incidence of AMD increases with age and is more common in fair-skinned individuals.[11] It affects approximately 2-6% of older adults in the US and is most prevalent in adults greater than 50 years of age. [11-13] The pathogenesis of AMD has not been fully elucidated; however, contemporary research has indicated advanced age and smoking are significant risk factors.[14-17] Other risk factors for AMD may include genetic predisposition, cardiovascular disease history, sedentary lifestyle, and increased BMI $\geq$30 kg/m^2.[11-13] There is no cure available for AMD, but the goal of treatment is to slow disease progression and prevent blindness.[18] Supportive therapy is used to preserve visual acuity through lifestyle modifications to help patients maintain maximum independence and quality of life.[19,20]

Age-related macular degeneration is characterized by degenerative changes in the light-sensitive retinal neurons and surrounding supportive cells referred to as the retinal pigment epithelium (RPE).[21,22] The RPE is a continuous single layer of epithelial cells situated between the retina and choroid.[23] Deterioration and dysfunction of the RPE results in hyperpigmentation, atrophy, macular thinning, and accumulation of extracellular drusen deposits between the RPE and the area known as Bruch's membrane.[21,23] Drusen are lipid- and protein-rich deposits that do not usually affect visual function unless they enlarge and coalesce.[23] Early AMD may be asymptomatic, but with chronic inflammation and infiltration of mononuclear phagocytes, disease may begin to progress toward later stages that are more conspicuous.[21,23] At the intermediate stage, clustering of drusen and waste deposits in the RPE leads to more central vision distortions.[21,-23] Since the destructive process takes place mostly in the macular region (the area with the highest spatial resolution) there may be increased difficulty with reading and facial recognition but generally little to no effects on peripheral vision.[22] As the areas of atrophy enlarge and coalesce, the patient may experience worsened overall vision with centralized blurred or blind spots, or scotoma, which typically have negative impacts on daily function.[21-23]

Late-stage AMD typically presents either as dry form AMD (nonexudative; non-neovascular) or the less common wet AMD (exudative; neovascular).[21] Although it is believed that dry and wet AMD share certain pathological mechanisms, there are also some notable contrasts. In both forms, drusen accumulates, induces RPE inflammation and causes photoreceptor degeneration.[21] In dry AMD, drusen deposition and photoreceptor degeneration occur relatively slowly and, when combined with natural aging process, cause eventual atrophy ("geographic atrophy" [GA]) of the macula.[21,24] However, in wet AMD, abnormal growth of choroidal vessels causes the vessels to break through the Burch membrane and invade the retina.[21,22,24] The newly formed choroidal vessels are not as well-established as the normal vasculature and tend to leak fluid, blood, and lipids into the surrounding tissue.[24] This leakage attracts microglia and macrophages that result in inflammatory damage, fibrovascular scar formation, and photoreceptor dysfunction.[21,23,24] As the vessels bleed into the macula, wet AMD becomes a medical emergency that, if untreated, may result in rapid, irreversible vision loss.[24] In roughly 10-15% of cases, patients with the dry form of AMD may progress to the wet form.[21] The risk of central vision loss is highest in wet-form AMD.[21]

Although the pathogenesis of AMD is poorly understood, chronic inflammation and the activation of complement have been implicated in the initiation and progression of AMD and geographic atrophy.[10,25] The complement system is a controlled network of more than 30 proteins within the innate immune system that may be activated in a cascade fashion to provide protection against tissue pathogens.[21] The complement cascade is activated in multiple interconnected proteolytic pathways and culminates in the formation of the membrane attack complex (MAC) .[10,25] All of the complement cascade pathways converge at the cleavage of C3 and C5 to bring about the MAC which leads to cell lysis.[10,22,25] Under normal conditions, complement activation and MAC formation are highly regulated by a number of cell-surface proteins and feedback loops to prevent complement-mediated intravascular hemolysis and injury to surrounding tissues.[22] Oxidative stress may leave retinal pigment epithelium cells vulnerable to injury from the complement system and is hypothesized to be a key factor in the development and progression of AMD.[22,26,27] In patients with AMD, a higher concentration of complement activation products has been observed in aqueous and vitreous humor samples.[22,26] There have been other findings that may indicate complement dysregulation in patients with AMD such as C3a observed in drusen, decreased regulatory complement protein in retinal pigment epithelium, and increased levels of membrane attack complex in the retina.[22,26,28]

Changes in drusen location, size, and growth rate may be helpful indicators of AMD progression.[23] The presence of geographic atrophy in a single eye is highly indicative that both eyes will be affected, typically within a 7-year time period.[29] However, the presence of small deposits of drusen do not automatically indicate the presence of AMD, but larger deposits of drusen have been correlated with increased risk of AMD progression.[30,31] Therefore, obtaining baseline drusen size is of clinical importance.[23] Size of drusen may be classified as small (<63 µm in diameter), intermediate >63 µm but ≤ 125 µm diameter), or large (>125 µm diameter). [23,30,31] Only the intermediate and large drusen have been correlated directly with AMD.[31] Extrafoveal lesions and faster lesion growth rates tend to result in a more rapid GA progression toward central vision loss, or blindness.[31] There is no consensus for a standard AMD classification scheme but the system frequently used by practitioners is the Age-Related Eye Disease Study (AREDS) or the Beckman Classification system.[30,31] The AREDS/Beckman stages AMD is based on the number, size, and location of drusen, as well as pigmentary changes (see **Table 1**).[30,31] AREDS scores range from 0 to 4 with higher scores indicative of more severe disease.[30] As the size and number of drusen size increases and both eyes become affected, the 5-year rate of developing advanced AMD can be calculated.[31]

Table 1. AREDS/Beckman Classification of AMD (modified)[30,31]

Beckman		**AREDS simplified score**	**AREDS classification/ categories**
No Disease	• No drusen • No AMD pigmentary abnormalities	0	No disease
Normal Aging	• Only drupelets (small ≤63 micrometer drusen) • No AMD pigmentary abnormalities	0	No disease or early stage
Early	• >63 to ≤125 micrometer drusen • No AMD pigmentary abnormalities	0	Early or intermediate
Intermediate	• >125 micrometer drusen and/or Pigmentary abnormalities	1-4	Intermediate
Advanced	• Neovascular AMD and/or Any geographic atrophy	n/a, 5	Advanced
Abbreviations: AREDS = Age-Related Eye Disease Study; AMD = age-related macular degeneration			

There are many methods employed to diagnose and monitor geographic atrophy progression. Indirect ophthalmoscopy allows for fundus examination through a dilated pupil which enables the clinician to see gross changes in the macula.[32-34] For detailed visualization of the AMD lesions, clinicians use techniques such as color fundus photography (CFP), fundus autofluorescence (FAF), and optical coherence tomography (OCT).[32,33] Each provide a unique perspective to help gain a better understanding of AMD disease mechanisms.[34] Each imaging technique is briefly described in **Table 2**.

Table 2. Common Imaging Techniques used in Diagnosis and Monitoring of Geographic Atrophy (GA) Progression [18,23,32-34,37]

Imaging Technique	Abbreviation	Description
Fluorescein Angiography	FA	Takes sequential photographs of chorioretinal circulation after fluorescein dye is injected which allows detection of leakage from neovascular lesions
Color Fundus Photography	CFP	Useful for defining GA lesion size and provides a 30- to 50-degree colored image of the macular region
Fundus Autofluorescence	FAF	Enables topographic visualization of the retina with the use of a scanning laser ophthalmoscope to detect retinal pigments and metabolic byproducts to track GA
Optical Coherence Tomography	OCT	Produces two-dimensional (2-D) views for retinal assessment, and 3-D views that can be used to compare fundus autofluorescence

Besides tracking GA lesion size and form, measuring visual function is a crucial component of monitoring geographic atrophy progression.[36] The Snellen chart is an often used test of visual acuity at a distance of 20 feet.[20] The Snellen chart has fewer letters in the upper portion of the chart and the number of letters increase as the test of visual acuity becomes finer at the lower portion of the chart.[20] With normal vision, subjects should be able to read the 20/20-foot line with each eye without correction.[20] Best-corrected VA (BCVA) is the patient's best distance vision when using optimal refraction correction.[20] Since measurement of BCVA is relatively straightforward, it is a commonly utilized endpoint for later stages of AMD.[36] Patients with a BCVA of 20/200 or worse are considered to be legally blind.[35] Low luminance BCVA (LL-BCVA) is measured by simply adding a filter to the refraction for BCVA while keeping the vision chart and lighting conditions of the room constant.[36] Clinical trials of GA have reported a difference of 20 letters between LL-BCVA and BCVA measurements is clinically significant.[38] Visual acuity may also be evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.[36] The EDTRS chart is an accurate measurement at low levels of acuity due to its flexibility in working distance and font readability.[36] The minimal clinically important difference referenced in the literature may vary, but a change of 5 letters (corresponding to 1 line on the chart or 0.1 logMAR) is typically considered to be the minimum clinically detectable change.[39] Moderate visual loss correspond to losses of 15-30 letters on the ETDRS chart and severe vision loss is typically defined as a loss of greater than 30 letters (or 6 lines on the ETDRS chart).[39,40]

The impact of GA progression on quality of life is also an important consideration for clinicians to monitor in their patients with AMD. Even with adequate visual acuity measured by BCVA, more than half of patients with GA may have compromised reading ability.[41] The functional reading independence (FRI) index score is used to measure the ability to complete everyday reading activities and has been used in various studies of patients with geographic atrophy.[18,41] The FRI Index identifies seven functional items (e.g. reading written print from books or magazines; reading to pay bills; reading a prescription bottle label, etc.) that are scored from 1 (unable to perform) to 4 (totally independent).[41] Index scores are totaled and averaged to provide a mean score.[41] The mean score is then rounded to the nearest integer (1, 2, 3, or 4) which corresponds to a functional reading independence level: Level 1 (unable to do); Level 2 (help required some or most of the time); Level 3 (moderately independent); and Level 4 (totally independent).[41]The minimal clinically important difference (MCID) on the functional reading independence index has not been established.

Anti-vascular endothelial growth factor A (anti-VEGFA) agents have been used successfully to treat vision loss in patients with wet AMD, but there are very few approved therapies for dry AMD, and new strategies and targets are currently under exploration.[22,42] Several studies with antioxidant vitamins (Vitamins C, E), minerals (zinc, copper) and other supplements (beta-carotene) have reported some benefit for slowing progression to late AMD, however evidence is inconclusive.[43] Complement inhibitors such as pegcetacoplan and avacincaptad pegol have been studied for use in AMD with GA.[44-48] Other therapeutic strategies taking place in clinical trials include visual cycle modulators, laser therapy, stem cell therapy and gene therapy.[22] With the increasing prevalence of AMD, there is a significant unmet need to find therapies that not only reduce the rate of GA progression, but also restore retinal function.[49-51]

NEW DRUG EVALUATION: Pegcetacoplan intravitreal injection

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Pegcetacoplan (SYFOVRE) received FDA approval in February 2023 for the treatment of adult patients with GA secondary to AMD.[2] Pegcetacoplan binds to complement protein C3 to prevent cleavage into its active components and also binds/inactivates C3b.[1,2] It is believed that by binding C3, pegcetacoplan may help to reduce chronic inflammation and oxidative stress to slow GA progression and enhance cell survival.[2,3] The recommended pegcetacoplan dosage is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days.[2] Pegcetacoplan must be administered by a qualified provider.[2]

Pegcetacoplan was studied in two parallel, phase 3, randomized, placebo-controlled trials (APL2-303 "DERBY" and APL2-304 "OAKS").[1-3] The OAKS and DERBY study details are described and evaluated below in **Table 5.**[1-3] Each trial was a similarly designed 24-month, multicenter study that evaluated the efficacy and safety of pegcetacoplan compared to a sham-control in patients aged 60 years and older with GA secondary to AMD.[1-3] Patients were screened for up to 28 days prior to treatment.[1-3] Eligible patients were randomized 2:2:1:1 to receive pegcetacoplan 15 mg/0.1 mL once per month (PM), once every other month (EOM), or matching sham injection (PM or EOM) procedure without actual eye penetration.[1,3] Any study eyes that developed exudative AMD were administered a VEGF inhibitor (either ranibizumab or aflibercept) in the study eye at least 30 minutes prior to but on the same day as pegcetacoplan (or sham) injection.[3] The decision to initiate VEGF therapy was at the sole discretion of the investigator.[3] The intent-to-treat (ITT) set included all randomized subjects.[1,3] Subjects were to be analyzed in the treatment arm assigned at randomization with the 2 sham treatment arms being combined into a single "control" group.[1,3] The modified ITT (mITT) set included all randomized subjects who received at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 post-baseline value of GA lesion in the study eye as assessed by fundus autofluorescence (FAF).[1,3] In both studies, the primary endpoint was change from baseline to month 12 in the total area of geographic atrophy lesions in the study eye based on FAF image analysis.[1,3] Secondary endpoints included differences in visual function endpoints of best-corrected visual acuity, functional reading independence index scores, monocular maximum reading speed, and change in mean threshold sensitivity (OAKS only). The FDA requested that the applicant provide additional 24-month follow-up data beyond the original 12 and 18-month data submission to demonstrate conclusive efficacy.[1]

A total of 2661 patients were screened in both trials of whom 1403 (53%) were excluded due to not meeting lesion size requirements (GA area ≥ 2.5 and ≤ 17.5 mm^2), evidence of choroidal neovascularization, or study noncompliance.[1,3] Of the ITT population (N=1258), 1115 (89%) completed assessment at month 12.[1,3] The mITT population used to assess the primary outcome was generally balanced with regard to baseline characteristics in both studies. Except in the DERBY trial participants in the pegcetacoplan groups had lower rates of unifocal GA and intermediate/large drusen compared to combined sham groups (roughly 27% vs

34% and 39% vs 51%, respectively).[1,3] Additionally, patients in the OAKS trial had higher rates of extrafoveal GA in the pegcetacoplan PM and EOM groups compared to the combined sham groups (43% and 36% vs 29%, respectively).[1,3] Roughly 20% of all included patients had evidence of choroidal neovascularization in the non-study eye.[3]

For pegcetacoplan-treated subjects, there were GA lesion growth reductions over 12 months in both dosing regimens.[1,3] In the OAKS trial, pegcetacoplan given PM and EOM resulted in a reduction in extrafoveal geographic atrophy lesion area compared to sham (-21% change; mean size difference -0.41 mm^2 ; 95% CI, -0.64 to -0.18 mm^2; p=0.0004; and -16% change ; mean size difference –0.32 mm^2, 95% CI, –0.54 to –0.09 mm^2; p=0.0055, respectively).[1,3] The reported benefit was of a similar magnitude at 24 months.[1,3] However, in the DERBY trial, no statistically significant difference was demonstrated in extrafoveal geographic atrophy lesion area with pegcetacoplan administered PM or EOM versus sham-treated patients (MD: -0.23 and -0.21 mm^2; p=0.062 and 0.085, respectively).[1,3] A small, but statistically significant benefit was reported at 24 months for pegcetacoplan monthly and pegcetacoplan every other month as each slowed geographic atrophy lesion growth by 22% compared to sham (MD –0.90 mm^2, 95% CI, –1.30 to –0.50; p<0.0001) and 18% (MD –0.74 mm^2, 95% CI, –1.13 to –0.36; p=0.0002) in OAKS, and by 19% (MD –0.75 mm^2, 95% CI, –1.15 to –0.34; p=0.0004) and 16% (MD –0.63 mm^2, 95% CI, –1.05 to –0.22; p=0.0030) in DERBY, respectively.[1,3]

In the OAKS trial, the difference of GA lesion growth between the treatment groups and sham was approximately 0.3 to 0.4 mm^2. The FDA reviewers did not consider this difference clinically significant because it was less than one fifth the size of the normal blind spot.[1] In DERBY, the difference between the treatment groups and sham was approximately 0.2 mm^2, which is approximately one tenth the size of the normal blind spot.[1] The difference for the primary endpoint in DERBY was not statistically or clinically significant. At 24 months, all other secondary functional endpoint data that compared pegcetacoplan to sham did not reach statistical significance.[1,3]

Only one of two trials with pegcetacoplan met its primary endpoint and neither OAKS or DERBY reported statistically significant benefits in functional improvements or quality of life measures. With higher rates of neovascular AMD noted in pegcetacoplan treated patients compared to sham, it is uncertain whether pegcetacoplan therapy increases risk of or hastens conversion to exudative AMD in certain patient subpopulations. Routine injections or as needed use of certain anti-VEGF agents have been utilized in patients with neovascular AMD which has helped preserve (and even improve) functional outcomes such as visual acuity. Complement inhibitors do not have data to support improvements in functional outcomes, and guidelines for use while undergoing VEGF inhibitor therapy is not available. In the OAKS and DERBY studies, there were a large proportion of patients who had discontinued the study by month 24 so long-term efficacy (and safety) of pegcetacoplan treatment is unknown. The FDA review noted that at week 18, both studies reported around 26% of subjects randomized to pegcetacoplan monthly had missing efficacy data and that by Month 24, the number had increased to 30% (DERBY) and 33% (OAKS). More data is needed to determine the long-term safety of pegcetacoplan and to demonstrate that minor changes in rate of GA lesion growth correlate to a clinically significant functional benefit.

Clinical Safety:

Common adverse reactions experienced with pegcetacoplan are presented in **Table 3.**[2] Rates of intraocular inflammation were higher in pegcetacoplan-treated patients compared to sham (3% versus <1%, respectively) over 24 months in the OAKS and DERBY studies.[2] According to labeling, pegcetacoplan administration is contraindicated in patients with active intraocular inflammation or with ocular or periocular infections.[2] At 12 months, OAKS and DERBY reported new-onset exudative AMD in 5-7% of patients given pegcetacoplan monthly, 3-5% of those on EOM dosing, and from 1-3% of sham-treated patients.[3] By month 24, rates of neovascular (wet) AMD or choroidal neovascularization appeared to increase in the pegcetacoplan-treated groups compared to sham (12% when administered monthly, 7% when administered every other month and 3% in the sham group).[1-3] Roughly 96-98% of pegcetacoplan-treated patients with new wet AMD were

co-administered a VEGF inhibitor compared to about 85% of those on sham.[3] It was reported that the mean anti-VEGF injection frequency was once monthly but details regarding the number of injections in each group were not available nor the identification of which VEGF-inhibiting agent was chosen by the investigator.[3] Overall study discontinuations through month 24 were highest in the pegcetacoplan once monthly groups followed by pegcetacoplan every other month and pooled sham (29%, 22%, and 21% respectively) and mostly due to consent withdrawal and adverse events.[1,3] Patient discontinuations in both trials were mainly due to withdrawal after an adverse event and were highest in the monthly pegcetacoplan group.[1] Combined incidence of ocular inflammation was 3.8% in the PM group and 2.1% in the EOM group.[1,3] If episodes of intraocular inflammation (e.g. vitritis, iridocyclitis, uveitis, iritis, etc.) are observed during treatment, FDA prescribing information suggests holding treatment and then resuming after inflammation resolves.[2] FDA labeling warns of the possibility of an acute increase in intraocular pressure (IOP) within minutes of pegcetacoplan administration, therefore perfusion of the optic nerve head should be monitored following the injection and managed as needed.[2]

Table 3. Adverse Reactions in Study Eye Reported in ≥5% of Patients Treated with Pegcetacoplan Through Month 24 in OAKS and DERBY Studies[2]

Adverse Reactions	Pegcetacoplan once monthly (N = 419)	Pegcetacoplan every other month (N = 420)	Sham pooled (N = 417)
ocular discomfort	13%	10%	11%
neovascular (wet) AMD	12%	7%	3%
vitreous floaters	10%	7%	1%
conjunctival hemorrhage	8%	8%	4%
vitreous detachment	4%	6%	3%
retinal hemorrhage	4%	5%	3%
punctate keratitis	5%	3%	<1%

Pooled results of both studies showed there was a higher number of patient deaths in the pegcetacoplan monthly group (7%) compared to pegcetacoplan every other month (4%) or patients assigned to sham (4%) but rates and causes were reported to be consistent with the elderly population.[1] The FDA review noted that less than 20% of the subjects in the pegcetacoplan monthly treatment group received the total 24 injections allowed in the 24-month period.[1] Therefore, the actual incidence of adverse events with a full monthly treatment regimen is unknown and could be higher than what was observed in the studies. A small proportion of patients received both anti-VEGF and complement therapy.[3] Certain VEGF inhibitors as well as pegcetacoplan currently list similar warnings of intraocular inflammation and/or retinal vein occlusion (which can cause blindness) on their respective FDA labeling.[2,22] Without longer-term data, it is unclear whether anti-VEGF therapy administered with complement inhibitors have a combined increased risk of adverse effects over time.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual function
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total area of geographic atrophy lesions

Table 4. Pharmacology and Pharmacokinetic Properties.[1,2]

Parameter	
Mechanism of Action	Complement protein C3 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 1.85 L; Protein Binding N/R
Elimination	Clearance is 0.284 L/day
Half-Life	4.5 days
Metabolism	Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathway

Abbreviations: C3=complement 3; L=liters; N/A=not available; N/R=not reported

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. DERBY[1-3] (APL2-303) Phase 3, RCT, Sham-control, MC	1. Pegcetacoplan (PEG) 15 mg/0.1 ml IVI once monthly 2. Pegcetacoplan 15 mg/0.1 ml IVI once every other month 3. Sham pooled 2:2:1:1 randomization	Demographics: -Mean Age: 78 years -Female: 61% -White: 94% -Mean size GAL: 8.3 mm^2 ->20 medium to large drusen in study eye: 1. 39% 2. 39% 3. 50% -Mean number study eye BCVA, ETDRS letters: 59 -Mean number study eye LLD, ETDRS letters: 26 Key Inclusion Criteria: -Age ≥ 60 years -BCVA 24 letters or better using ETDRS charts -Clinical diagnosis of GA of the macula secondary to AMD -GA lesion criteria via FAF imaging at screening: • Total GA area ≥ 2.5 and ≤ 17.5 mm^2 • If GA multifocal, ≥ 1 focal lesion must be ≥ 1.25 mm^2	ITT: 1. 206 2. 208 3. 207 mITT: 1. 201 2. 201 3. 195 Attrition Month 12: 1. 11% 2. 10% 3. 14% Month 24: 1. 29% 2. 20% 3. 22%	Primary Endpoint: Change from baseline to month 12 in the total area of GA lesions in the study eye based on FAF image analysis. 1. 1.73 mm^2 2. 1.76 mm^2 3. 1.96 mm^2 MD PEG monthly vs sham: -0.23 mm^2 95% CI, -0.47 to 0.01, P = 0.062 MD PEG EOM vs sham: -0.21 mm^2 95% CI, -0.44 to -0.03, P = 0.085 Secondary Endpoints: Change from baseline to month 24 in the total area of GA lesions in the study eye based on FAF image analysis. 1. 3.27 mm^2 2. 3.26 mm^2 3. 3.98 mm^2 MD PEG monthly vs sham: -0.75 mm^2 95% CI, -1.15 to -0.34, P=0.0004	NA NS NS NA	TEAEs: 1. 86% 2. 87% 3. 82% Ocular TEAEs: 1. 61% 2. 52% 3. 46% Non-ocular TEAEs: 1. 79% 2. 68% 3. 71% New-onset exudative AMD: 1. 13% 2. 6% 3. 4% Intraocular inflammation: 1. 2% 2. 3% 3. 0%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Central web-based randomization with stratified permuted block by GA lesion area at screening. Eye with worst visual acuity (or right eye if same visual acuity) selected. Baseline characteristics generally similar between groups. Performance Bias: (Low) Blinded participants and investigators/care givers. External, independent data monitoring committee reviewed all data across the conduct of the studies on an ongoing basis. Sham procedure same as IVI procedure without actual injection (touch with blunt syringe). Detection Bias: (Low) FAF images evaluated in a central reading center by a minimum of two certified readers with independent manual measurements of features of the GA lesions. At 12 months, only the sponsor personnel responsible for analyzing, interpreting, and reporting data were unmasked to treatment assignment. Physicians administering treatment for active CNV were unblinded after blinded reading center provided report. Attrition Bias:(Unclear) Missing outcome data balanced at 12 months with similar TEAEs reported. At 24 months >20% did not complete trial for all groups. No imputation for missing data. Reporting Bias: (Low) Full protocol available online as supplement. No protocol deviations noted.

		• Entire GA lesion must be able to be imaged • No evidence of prior or active CNV in the study eye or presence of RPE tear Key Exclusion Criteria: -Geographic atrophy secondary to condition other than AMD -History or active CNV, associated with AMD or any other cause, including evidence of neovascularization -Active ocular disease that compromises visual function -History of intraocular surgery or laser therapy in the macular region -Contraindication to IVI injection including current ocular or periocular infection		MD PEG EOM vs sham: -0.63 mm^2 95% CI, -1.05 to -0.22, p = 0.003 Change in BCVA from baseline to month 24: 1. -7.89 2. -8.83 3. -6.94 MD PEG vs Sham: *Not statistically significant* Change from baseline in FRI composite score at month 24: 1. -0.35 2. -0.37 3. -0.32 MD PEG vs. Sham: *Not statistically significant*	NS NS			Other Bias: (Unclear) Manufacturer funded the study and contributed to report writing. Multiple authors received grants, funding, consultant fees from, or are paid employees of manufacturer. **Applicability**: Patient: Age appropriate; racial and ethnic makeup not necessarily reflective of overall Medicaid population but disease more common in fair-skinned individuals. Intervention: Pegcetacoplan 15 mg IVI every 4 or 8 weeks appropriate based on earlier phase testing. Comparator: Sham injection is appropriate. No standard available. Outcomes: Change in the GA lesion area is a surrogate marker but rational measure of photoreceptor loss. Longer term outcomes needed, particularly those that correlate with improved function. Setting: Multicenter at 110 clinical sites and 122 clinical sites worldwide, including United States, Canada, Europe, and Australia.
2. OAKS [1-3] (APL2-304) Phase 3, RCT, Sham-control, MC	1. Pegcetacoplan 15 mg/0.1 ml IVI once monthly 2. Pegcetacoplan (PEG) 15 mg/0.1 ml IVI once every other month 3. Placebo/Sham 2:2:1:1 randomization	Demographics: -Mean Age: 78 years -Female: 61% -White: 93% -Mean size GAL: 8.3 mm^2 -Extrafoveal GAL: 39% -Unifocal GAL: 30% ->20 medium to large drusen in study eye: -Mean BCVA, ETDRS letters baseline: 59 -Mean number study eye ETDRS letters: Key Inclusion Criteria: -see DERBY Key Exclusion Criteria: -see DERBY	ITT: 1. 213 2. 212 3. 212 mITT: 1. 202 2. 205 3. 207 Attrition: Month 12 1. 10% 2. 10% 3. 10% Month 24 1. 32% 2. 20% 3. 25%	Primary Endpoint: CFB to month 12 in the total area of GALs in the study eye based on FAF image analysis. 1. 1.56 mm^2 2. 1.65 mm^2 3. 1.97 mm^2 MD PEG monthly vs sham: -0.411 mm^2 95% CI, -0.640 to -0.183 P=0.0004 -21% difference vs sham MD PEG EOM vs sham: -0.318 95% CI, -0.542 to -0.094 P = 0.0055 -16% difference vs sham Secondary Endpoints:	NA NA NA NA	TEAEs: 1. 90% 2. 88% 3. 83% Ocular TEAEs: 1. 62% 2. 58% 3. 46% Non-ocular TEAEs: 1. 82% 2. 78% 3. 73% New-onset exudative AMD: 1. 11% 2. 8% 3. 2%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see DERBY Performance Bias: see DERBY Detection Bias: see DERBY Attrition Bias; see DERBY Reporting Bias: see DERBY Other Bias: see DERBY **Applicability**: Patient: see DERBY Intervention: see DERBY Comparator: see DERBY Outcomes: see DERBY Setting: see DERBY

				CFB to month 24 in the total area of GALs in the study eye based on FAF image analysis: 1. 3.12 mm^2 2. 3.28 mm^2 3. 4.03 mm^2 MD PEG monthly vs sham: -0.90 mm^2 95%CI, -1.30 to -0.50; P < 0.0001 MD PEG EOM vs sham: -0.74 mm^2 95% CI, -1.13 to -0.36; p= 0.0002		<u>Intraocular inflammation:</u> 1. 5% 2. 1% 3. 0% <u>Infectious endophthalmitis</u> 1. 1% 2. 1% 3. 0%		
<u>Abbreviations</u>: AMD = Age-related macular degeneration; ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = Fundus Autofluorescence; FRI = functional reading independence; GA = geographic atrophy; ITT = intention to treat; IVI = intravitreally; MC = multicenter; MD = mean difference; mITT = modified intention to treat; mm = millimeters; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PEG = pegcetacoplan; PM = per month; PP = per protocol; TEAE = treatment emergent adverse event; RCT = randomized controlled trial								

NEW DRUG EVALUATION: Avacincaptad pegol intravitreal injection

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Avacincaptad pegol (IZERVAY) received FDA approval in August 2023 for the treatment of adult patients with GA secondary to AMD.[4,5] Avacincaptad pegol binds to complement protein C5 to prevent cleavage into its active components of C5a and C5b.[4] It is believed that C5a fragments may contribute to formation of the membrane attack complex and cell apoptosis.[4] The recommended dose of avacincaptad pegol intravitreal solution is 2 mg (0.1 mL) into affected eye(s) once monthly (or every 21 to 35 days) for up to 12 months administered by a qualified health provider.[4]

Avacincaptad pegol was studied in two randomized, double-blind, sham-controlled trials.[4-8] The first study was an 18-month, phase 2/3 trial (OPH2003 "GATHER1") and the second a 24-month, phase 3 trial (ISEE2008 "GATHER2").[4-8] Both were multicenter studies that evaluated the efficacy and safety of avacincaptad pegol in patients aged 50 years and older with GA secondary to AMD.[4,6-8] Inclusion and exclusion criteria were similar for both trials.[4,6-8] In GATHER2, patients who developed confirmed macular neovascularization in the study eye were treated with either ranibizumab or aflibercept per their label and remained in the trial.[8] Study details for GATHER1 and GATHER2 are described and evaluated below in **Table 8.**[4-8] For the purposes of this review, only the FDA-approved dose of avacincaptad pegol 2 mg compared to sham will be highlighted in the evidence table.

In Part 1 of GATHER1, 77 patients were randomized 1:1:1 to receive monthly avacincaptad pegol 1 mg, 2 mg, or sham administered via intravitreal (IVI) injection.[4,6,7] In Part 2, patients were then randomized 1:2:2 to receive avacincaptad pegol 2 mg once monthly (plus sham), 4 mg monthly (2 x 2 mg injections), or monthly (2x) sham injection.[4,6,7] In GATHER2 (N=448) patients were randomized 1:1 to avacincaptad pegol 2 mg monthly (2 injections: 1 drug, 1 sham) or sham monthly (2 injections: both sham) for 12 months. The primary endpoint of GATHER1 and GATHER2 was the mean rate of change in GA from baseline over 12 months (as measured by FAF).[4,8] Secondary endpoints included the mean change in BCVA (ETDRS letters) from baseline to month 12 and the mean change in low luminance BCVA (ETDRS letters) from baseline to month 12.[4,6-8]

Baseline demographics were similar between treatment and sham groups in both trials.[4,6-8] In GATHER1, the mean patient age was 78 years, about 71% were female, and almost all patients (97–100%) were White.[4,6,7] The mean total GA area was about 7.3 – 7.4 mm^2.[4,6,7] Mean baseline BCVA was about 70 letters and the mean low luminance BCVA at baseline was roughly 35 letters.[4,6,7] In GATHER2 the mean patient age was 76 years, 68% were female, and roughly 81% were White.[4,8] The mean GA area at baseline was 7.48 mm^2 in avacincaptad pegol group (compared to 7.81 mm^2 for sham), while the mean BCVA and low luminance BCVA were roughly 71 and 41 letters, respectively.[4,8]

The mean rate of change in GA area was reduced for both avacincaptad pegol treatment cohorts compared to sham.[4-8] At 12 months, GATHER1 reported a reduced mean rate of square-root-transformed GA growth in the avacincaptad pegol 2 mg compared to sham (0.292 mm and 0.402 mm, respectively) with a MD 0.110 mm (95% CI 0.030–0.190; p = 0.0072).[4-7] In a mixed model repeated measures (MMRM) analysis of observed data at 12 months, the treatment difference was 0.67 mm^2/year (95% CI 0.21–1.13; p < 0.01), corresponding to a relative reduction of 35% compared with sham.[5] In GATHER2, similar results were observed from baseline to month 12 with a lower mean rate of square-root-transformed geographic atrophy growth in the avacincaptad pegol 2 mg group compared to sham (0.34 mm/year and 0.39 mm/year, respectively) and an absolute difference of 0.06 mm/year [(95% CI, 0.02–0.1); 14% difference, P=0.0064].[4,7,8] The

MMRM analysis of observed data for GATHER2 at 12 months reported a reduced rate of GA growth in avacincaptad pegol 2 mg compared to sham (1.75 mm^2/year and 2.12 mm^2/year, respectively) with a mean difference of 0.38 mm^2/year [(95% CI, 0.12 to 0.63); 18% relative difference, p<0.01].[5]

Although the surrogate marker of reduced GA growth showed a very modest but statistically significant difference, the clinical significance of such a minor difference has not been established. There was no correlation of reduced GA growth rate and functional outcome studied as both functional measures, BCVA and LL-BCVA, showed no benefit in either GATHER1 or GATHER2.[4,6-8] GATHER1 and GATHER2 excluded patients with fellow-eye choroidal neovascularization so the benefit of therapy in patients with this history is unknown. Longer term data is needed to demonstrate that minor changes in rate of GA lesion growth correlate to a clinically significant functional benefit.

Clinical Safety:

Common adverse reactions experienced by patients in the 2 trials are presented in **Table 6.**[4,5] In GATHER1, ocular treatment emergent adverse events (TEAEs) in the treated eye were reported in 52% of avacincaptad pegol 2 mg recipients (*n* = 67), 69% of avacincaptad pegol 4 mg recipients (*n*= 83) and 35% of sham recipients (*n* = 110).[4,5] In GATHER2, ocular TEAEs occurred in 49% and 37% of avacincaptad pegol and sham recipients, respectively.[4] In a pooled analysis of GATHER1 and GATHER2, the most frequent ocular adverse events occurring in more than 2% of subjects and at a higher rate with avacincaptad pegol 2 mg compared to sham were conjunctival hemorrhage (13% vs. 9%), increased intraocular pressure (9% vs. 1%), blurred vision (8% vs. 5%), and choroidal neovascularization (7% vs. 4%).[4,5] In GATHER1 there were systemic TEAEs reported in 58% and 55% of the avacincaptad pegol 2 mg versus sham-treated patients, respectively.[4,5] The most common systemic TEAEs in avacincaptad pegol 2 mg compared to sham, respectively, were urinary tract infection (10% vs. 8%), falls (9% vs. 5%), nasopharyngitis (9% vs. 4%), and atrial fibrillation (6 vs. <1%).[4,5] No patients discontinued treatment due to an AE in GATHER1.[4,5] In GATHER2, TEAEs were more common in the avacincaptad pegol group compared to sham (79% and 71%, respectively), and discontinuations due to TEAEs were reported in 3% of the avacincaptad pegol patients and <1% of sham recipients.[4,5] No serious ocular AEs were reported in either eye in all treatment groups for the GATHER1 trial.[4,5] Although avacincaptad pegol is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation, no cases of endophthalmitis or intraocular inflammation were observed in the trials.[4,5] There were 3 deaths (2 in the avacincaptad pegol 2 mg group and one in the sham group) to month 12, none of which was determined by the investigator to be related to injection procedure or the study drug.[4] No deaths were reported in GATHER1.[4,6,7] More studies are needed to assess long-term safety of avacincaptad pegol.

Table 6. Common Ocular Adverse Reactions (>2%) and greater than Sham in Study Eye [4,5]

Adverse Reactions	**avacincaptad pegol (N = 292)**	**Sham pooled (N = 332)**
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

*****Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual symptom improvement
2) Visual function
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total area of geographic atrophy lesions

Table 7. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	RNA aptamer, a PEGylated oligonucleotide that binds to and inhibits complement protein C5.
Oral Bioavailability	N/A
Distribution and Protein Binding	Max concentration in vitreous humor 500 µg/mL after first injection; Protein Binding N/R
Half-Life	12 days
Metabolism/Elimination	Avacincaptad pegol is catabolized by endonucleases and exonucleases to oligonucleotides of shorter lengths and excreted renally

Abbreviations: C5=complement 5; µg/mL=micrograms per milliliter; N/A=not applicable; N/R=not reported

Table 8. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. GATHER1[4-7] (OPH2003) Phase 2/3, RCT, PC (Sham), MC	1. avacincaptad pegol (AP) 2 mg IVI once monthly 2. Sham 1:2 randomization* (* = part 2 excluded 4 mg dose)	Demographics: -Mean Age: 78 years -Female: 70% -White: 98% -Mean size GAL: 7.4 mm^2 -Active smoker: 34% -Mean BCVA, ETDRS letters baseline: 70 -Mean LL-BCVA: 35 Key Inclusion Criteria: -Age 50 years or greater -BCVA between 20/25 and 20/320 in study eye -GA secondary to AMD -Total GA area ≥2.5 and ≤17.5 mm^2 -For multifocal GA lesions ≥1 focal lesion ≥1.25 mm^2 Key Exclusion Criteria: -GA secondary to condition other than AMD -Active or history of CNV in either eye -Prior treatment for AMD -Intraocular inflammation -Uveitis in either eye -Significant media opacities, including cataract -Diabetic retinopathy in either eye -History of intraocular surgery or laser therapy in the macular region -Contraindication to IVI injection including current ocular or periocular infection -Hx of stroke (prior 12 months), PAD, cardiac dysfunction -Pregnant or nursing women	ITT: 1. 67 2. 110 Attrition (month 12): 1. 18% 2. 13%	Primary Endpoint: Change in the (square root transformed) GA lesion area from baseline to month 12: 1. 0.292 mm 2. 0.402 mm MD = 0.110 mm 95% CI, 0.030 to 0.190; P = 0.0072 -27% difference from sham FDA label: Change in the mean rate of GA lesion area growth from baseline to month 12: 1. 1.22 mm^2/year 2. 1.89 mm^2/year MD = 0.67 mm^2/year (95% CI, 0.21 to 1.13); P <0.01 -35% difference from sham Secondary Endpoint: Mean change from baseline to month 12 in BCVA: 1. -7.9 2. -9.3 MD = 1.4 (95% CI, -1.5 to 4.3) Mean Change from baseline to month 12 in LL-BCVA (ETDRS Letters): 1. -1.0 2. -1.4 MD = 0.4 (95% CI, -3.3 to 4.1)	NA NS NS	Ocular TEAEs: 1. 52% 2. 35% Systemic TEAEs: 1. 58% 2. 57% Systemic SAEs: 1. 10% 2. 18% p-value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Central web-based randomization with minimization method used to maintain balance between groups and for each stratification criterion. Baseline characteristics similar between groups. Performance Bias: (Low) Blinded participants, investigators, reading center personnel and sponsor personnel. Method of blinding not described but masking reported to be preserved through trial. Detection Bias: (Low) Masked, trained readers independently analyzed and graded the FAF images. More than a 10% discrepancy in results measurements were arbitrated by Reading Center Director. Attrition Bias (Unclear) Substantial overall attrition with a slightly larger proportion of patients in treatment group unable to complete the trial. Treatment effects compared with MMRM using only observed data. Multiple prespecified imputation methods used to replace missing values and treatment effects remained statistically significant. Reporting Bias: (Unclear) No CIs or p-values reported in secondary outcome data tables. Other Bias: (High) Manufacturer funded the study and contributed to study design, data collection, data management, data analysis, data interpretation, and report writing. **Applicability**: Patient: Study population was mostly older, white females. Racial and ethnic makeup not necessarily reflective of overall Medicaid population but disease more common in fair-skinned individuals. Mean age appropriate as condition largely affects adults >50 yrs Intervention: Lower monthly dose (2 mg) consistent with FDA approval. Comparator: Sham control appropriate for safety and efficacy comparisons. Outcomes: Change in the GA lesion area is a surrogate marker but rational measure of photoreceptor loss. Longer term outcomes needed notably those that correlate with improved function. Setting: Multicenter at 63 sites in United States, Europe, and Israel.

2. GATHER2[4,5,8] (ISEE2008) Phase 3, RCT, PC (Sham), MC	1. avacincaptad pegol 2 mg IVI once monthly 2. Sham 1:1 randomization*	Demographics: -Mean Age: 76 years -Female: 69% -White: 82% -Active Smoker: 48% -Mean size GAL: 7.65 mm^2 -Mean BCVA, ETDRS letters baseline: 71 -Mean LL-BCVA: 40 Key Inclusion Criteria: -see GATHER1 Key Exclusion Criteria: -see GATHER1	ITT: 1. 225 2. 222 Attrition: 1. 11% 2. 8%	Primary Endpoint: Change in GA lesion from baseline to month 12 (slope analysis of square-root-transformed data): 1. 0.336 mm/year 2. 0.392 mm/year MD 0.056 mm/year 95% CI, 0.016 to 0.096 P = 0.0064 Change in the mean rate of GA lesion area growth from baseline to month 12: 1. 1.75 mm^2/year 2. 2.12 mm^2/year MD 0.376 mm^2/year 95% CI, 0.122 to 0.63 P = 0.0039 -18% difference from sham Secondary Endpoints: Mean change in BCVA (ETDRS letters) in the study eye from baseline to month 12: 1. 1.34 2. 0.96 MD 0.38 95% CI, -1.43 to 2.19 P = 0.68 Mean change in LL-BCVA (ETDRS letters) in the study eye from baseline to month 12: 1. -4.35 2. -2.29 MD -2.06 95% CI, -4.86 to 0.75 P = 0.15	NA NS NS	TEAEs: 1. 79% 2. 71% Conjunctival hemorrhage 1. 12% 2. 8% Increased ocular pressure 1. 9% 2 1% Choroidal neovascularization 1. 7% 2. 4% Serious TEAEs 1. 13% 2. 17% Discontinuations due to TEAE: 1. 3% 1. 1% Death: 1. 0.9% 2. 0.5%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: see GATHER1 Performance Bias: see GATHER1 Detection Bias: see GATHER1 Attrition Bias: see GATHER1 Reporting Bias: Protocol was available. Also see GATHER1. Other Bias: see GATHER1 **Applicability**: Patient: see GATHER1 Intervention: see GATHER1 Comparator: see GATHER1 Outcomes: see GATHER1 Setting: see GATHER1

Abbreviations: AMD = Age-related macular degeneration; ARR = absolute risk reduction; BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; EOM = every other month; ETDRS = Early Treatment Diabetic Retinopathy Study; GA = geographic atrophy; ITT = intention to treat; IVI = intravitreally; LL-BCVA = low luminance best-corrected visual acuity MC = multicenter; MD = mean difference; mm = millimeters; MMRM = mixed model repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PAD = peripheral arterial disease; PEG = pegcetacoplan; PM = per month; PP = per protocol; SAE = serious adverse event; TEAE = treatment emergent adverse event; RCT = randomized controlled trial

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYFOVRE safely and effectively. See full prescribing information for SYFOVRE.

SYFOVRE ™ (pegcetacoplan injection), for intravitreal use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Retinal Vasculitis and/or Retinal Vascular Occlusion (5.2) 11/2023

----------INDICATIONS AND USAGE----------
SYFOVRE is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dose for SYFOVRE is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 150 mg/mL in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
- Ocular or Periocular Infections (4.1)
- Active Intraocular Inflammation (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and Retinal Detachments (5.1)
- Retinal Vasculitis and/or Retinal Vascular Occlusion (5.2)
- Neovascular AMD (5.3)
- Intraocular inflammation (5.4)
- Increased Intraocular Pressure (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Appendix 2: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IZERVAY safely and effectively. See full prescribing information for IZERVAY.

IZERVAY™ (avacincaptad pegol intravitreal solution)
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
IZERVAY is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) (1).

----------DOSAGE AND ADMINISTRATION----------
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately 28 ± 7 days) for up to 12 months (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Intravitreal solution: 20 mg/mL in a single-dose vial (3).

----------CONTRAINDICATIONS----------
- Ocular or periocular infections (4.1).
- Active intraocular inflammation (4.2).

----------WARNINGS AND PRECAUTIONS----------
- Endophthalmitis and Retinal Detachments (5.1).
- Neovascular AMD (5.2)
- Increase in Intraocular Pressure (IOP) (5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions were conjunctival hemorrhage (13%), increased IOP (9%), blurred vision (8%) and neovascular age-related macular degeneration (7%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact IVERIC bio, Inc. at 1-800-707-4479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2023

FULL PRESCRIBING INFORM ATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

Ophthalmic Complement Inhibitors

Goal(s):

- To ensure appropriate use of complement inhibitors in patients with geographic atrophy (GA) due to age-related macular degeneration (AMD).

Length of Authorization:

Initial 12 months with total cumulative lifetime treatment period not to exceed 24 months* per affected eye
(*=12 months maximum for avacincaptad pegol).

Requires PA:

- Pegcetacoplan (SYFOVRE); Avacincaptad Pegol (IZERVAY); (applies to both physician-administered and pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Dosage and Administration per FDA Labeling.

	Pegcetacoplan (SYFOVRE)	**Avacincaptad pegol (IZERVAY)**
Dose (per single affected eye)	15 mg (0.1 mL of 150 mg/mL solution)	2 mg (0.1 mL of 20 mg/mL solution)
Route of Administration	Intravitreal Injection	Intravitreal Injection
Frequency	Once every 25 to 60 days	Once monthly (approximately 28 ± 7 days)
Maximum Lifetime Limit	Unknown	12 months

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the patient an adult with a diagnosis of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) supported by clinical documentation of appropriate testing (e.g. fundus autofluorescence (FAF), optical coherence tomography (OCT))?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have any of the following: • active intraocular inflammation? • active ocular or periocular infections? • history of intraocular surgery or laser therapy in the macular region?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for continuation of therapy for a patient who has received ≥ 6 months of initial therapy with the requested agent?	**Yes:** Go to **Renewal Criteria**.	**No:** Go to #5
5. Is the agent being prescribed and administered by or under the supervision of an ophthalmologist?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient have a best corrected visual acuity (BCVA) in the affected eye of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there evidence that the patient is currently receiving therapy with a different ophthalmic complement inhibitor or medication for GA treatment?	**Yes:** Go to #8	**No:** Go to #9
8. Is this a switch in GA therapy due to intolerance, allergy or ineffectiveness and has therapy with the previous agent been discontinued?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have active choroidal neovascularization or wet age-related macular degeneration?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10

Approval Criteria		
10. Is the dose, route, and frequency consistent with the FDA-labeling for the requested agent?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this a request for avacincaptad pegol?	**Yes**: Go to #2	**No:** Go to #3
2. Has the patient already received 12 months of cumulative therapy in the affected eye(s)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #3
3. Does the patient exhibit any evidence of the following: • Unacceptable toxicity or adverse events (e.g. endophthalmitis, retinal detachment, or conversion to wet AMD)? • Significant decline in visual acuity (loss of 10 or more letters on EDTRS chart)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Has the prescriber documented a positive patient response to therapy such as disease stabilization or slowing in the growth rate of geographic atrophy lesions compared to pre-treatment baseline?	**Yes**: Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/24 (DE)
Implementation: 5/1/24