NEW DRUG APPROVAL

Brand Name	Syfovre™
Generic Name	pegcetacoplan
Drug Manufacturer	Apellis Pharmaceuticals, Inc.

Indications for Use

Syfovre™ is a complement inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

New Drug Approval

FDA Approval Date: February 17, 2023

Review Designation: Priority

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 217171

Dispensing restriction: Specialty

Therapeutic Class

Complement C3 Inhibitor; Ophthalmic Agent

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Geographic atrophy (GA) is an advanced form of dry age-related macular degeneration (commonly referred to as AMD). AMD is a disease that affects part of the back of the eye called the macula. The macula is the central part of the retina, which is the "film" lining the inside of the eye. Some patients with AMD will develop GA, an advanced form of the dry type of AMD. In GA, areas of the retina experience cell death (atrophy). These areas can grow and may result in a dim or blind spot in your vision. GA often first develops near the fovea, the center of the macula, which is the central and clearest part of your vision. Since the most center part of vision may not be affected at first, this may allow some with GA to keep a small area of central vision leading to possible delays in diagnosis of GA. GA can lead to progressive and permanent vision loss.

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment and sight loss in people 65 years of age and older in the United States, affecting approximately 11 million people. More than 2 million Americans have advanced forms of AMD, including 1 million with geographic atrophy (GA). The estimated prevalence (in at least one eye) of GA in the U.S. population over 40 years of age is 0.81%, but this prevalence increases to 3.5% in people 75 years of age and older. Since aging is the single biggest risk factor for AMD, its prevalence is anticipated to increase to 22 million by the year 2050. Caucasian race and smoking are additional risk factors for AMD, and although GA is not considered to be hereditary, certain genes increase the risk of progression of AMD to GA.

Efficacy

Syfovre was evaluated in the Phase 2 FILLY study (NCT02503332) and two Phase 3 studies, DERBY (NCT03525600) and OAKS (NCT03525613), for the treatment of GA due to AMD. The FDA approval of Syfovre was based on the Phase 3 studies. Table 1 summarizes the study design of the FILLY, DERBY, and OAKS trials.

Table 1. Syfovre™ Clinical Trials: Study Design Summary			
Study Design	**Randomized, sham-controlled clinical studies conducted in patients with GA secondary to AMD**		
	FILLY (NCT02503332) (N = 246)	**DERBY (NCT03525600) (N = 621)**	**OAKS (NCT03525613) (N = 637)**
Age	≥50 years	≥60 years (mean: 78.7, range: 60 to 100 years)	
Inclusion Criteria	• BCVA ≥24 letters ETDRS (20/320 Snellen equivalent) • GA lesion requirements: ○ Total size: ≥2.5 mm^2 and ≤17.5 mm^2 (mean: 8.23 and 8.29 in OAKS and DERBY, respectively) ○ If multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 DA) ○ Presence of perilesional hyperautofluorescence		
Exclusion Criteria	• GA secondary to a condition other than AMD, such as Stargardt disease in either eye • Ocular history of or active CNV in the study eye,* including presence of RPE tear (assessed by reading center)		
Dose	15 mg/0.1 mL monthly or EOM		
Primary Efficacy Outcome	LS mean change in square root GA lesion size at Month 12 (in mm)	Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm2) based on FAF	

Sources: NCT02503332, NCT03525600, NCT03525613.

Abbreviations: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; DA, disc area; EOM, every other month; ETDRS, Early Treatment Diabetic Retinopathy Study; FAF, fundus autofluorescence imaging; GA, geographic atrophy; LS, least squares; RPE, retinal pigment epithelial. *CNV in the fellow eye was not exclusionary.

In both trials, the discontinuation rates were significant across arms, including sham. In the OAKS trial, 31% of patients in the monthly, 21% of patients in the every-other-month (EOM) and 25% of the patients in the sham group discontinued treatment prior to Month 24. In the DERBY trial, 29% of patients in the monthly, 22% of patients in the EOM, and 21% of the patients assigned to sham discontinued treatment prior to Month 24.

While all primary endpoints were met in the OAKS and FILLY trials, results at 12 months in the DERBY trial were not statistically significant. Apellis has conducted an extensive review of baseline data in an attempt to explain the disparity in results between the DERBY and OAKS trials. Covariate analyses indicated some baseline imbalances between the groups in study eye focality, lesion location, and presence of intermediate/large drusen, which may partially explain the disparate results.

In subgroup analyses based on pooled results from the DERBY and OAKS trials, it was noted that Syfovre™ seemed to have a more significant effect on extrafoveal GA lesion growth. This could be related to greater complement activity in extrafoveal areas.

Table 2 summarizes key clinical trial results from the FILLY, DERBY, and OAKS trials.

Table 2. Syfovre™ Key Clinical Trial Results						
	12-Month Results		**18-Month Results**		**24-Month Results**	
	Monthly	**EOM**	**Monthly**	**EOM**	**Monthly**	**EOM**

Reductions in *Overall* GA Lesion Growth Compared to Sham						
OAKS	21% (*P* =0.0004)*	16% (*P* =0.0055)	22% (*P* <0.0001)	16% (*P* =0.0018)	22% (*P* <0.0001)	18% (*P* =0.0002)
DERBY	12% (*P* =0.0609)	11% (*P* =0.0853)	13% (*P* =0.0254)	12% (*P* =0.0332)	19% (*P* =0.0004)	16% (*P* =0.0030)
FILLY	20% (*P* = 0.067)**	29% (*P* =0.008)	NA	NA	NA	NA
Reductions in *Extrafoveal* GA Lesion Growth Compared to Sham						
DERBY, OAKS (Pooled)	26% (*P* <0.0001)	23% (*P* =0.0002)	26% (*P* <0.0001)	21% (*P* =0.0006)	26% (*P* <0.0001)	22% (*P* <0.0001)
Reductions in *Foveal* GA Lesion Growth Compared to Sham						
DERBY, OAKS (Pooled)	11% (*P* =0.0389)	8% (*P* = 0.1219)	26% (*P* <0.0001)	23% (*P* =0.0002)	19% (*P* <0.0001)	16% (*P* =0.0003)

Abbreviations: EOM, every other month; GA, geographic atrophy; NA, not available.
*All P values are versus sham.
**P <0.1 was the predefined threshold for statistical significance in FILLY.

Incremental GA Lesion Area Growth

When analyzed in 6-month increments, the change in rate of GA lesion area growth compared to sham seems to increase with increasing time of treatment. Table 3 highlights results from Month 0 to Month 6 and Month 18 to Month 24 in both trials. Additional details are available in the prescribing information. Of note, previous Apellis publications expressed the difference in growth rate from sham as a positive percentage, while the prescribing information expresses this difference as a negative percentage.

Table 3. Analysis of Change from Baseline in Study Eye GA Lesion Area Measured by FAF in OAKS and DERBY Studies

Time Period	Group	Rate of GA Lesion Area Growth (mm^2)[a]		
		Slope (SE)	Difference (95% CI) in Slope from Sham Period	Percent Difference from Sham Pooled
OAKS (SM: n = 202; SEOM: n = 205; Sham Pooled: n = 207)				
Baseline to Month 6	**SM**	0.76 (0.046)	−0.22 (−0.35 to −0.09)	−22.7%
	SEOM	0.82 (0.043)	−0.16 (−0.29 to 0.04)	−16.4%
	Sham Pooled	0.98 (0.047)	NA	
Month 18 to Month 24	**SM**	0.76 (0.067)	−0.23 (−0.41 to −0.06)	−23.5%
	SEOM	0.75 (0.044)	−0.25 (−0.39 to −0.10)	−24.7%
	Sham Pooled	1.00 (0.058)	NA	
DERBY (SM: n = 201; SEOM: n = 201; Sham Pooled: n = 195)				
Baseline to Month 6	**SM**	0.91 (0.048)	−0.05 (−0.19 to 0.08)	−5.7%
	SEOM	0.88 (0.047)	−0.08 (−0.21 to 0.05)	−8.2%
	Sham Pooled	0.96 (0.050)	NA	

Table 3. Analysis of Change from Baseline in Study Eye GA Lesion Area Measured by FAF in OAKS and DERBY Studies				
Time Period	**Group**	**Rate of GA Lesion Area Growth (mm^2)[a]**		
		Slope (SE)	**Difference (95% CI) in Slope from Sham Period**	**Percent Difference from Sham Pooled**
Month 18 to Month 24	**SM**	0.63 (0.068)	−0.35 (−0.52 to −0.18)	−36.1%
	SEOM	0.69 (0.053)	−0.28 (−0.43 to −0.14)	−29.1%
	Sham Pooled	0.98 (0.055)	NA	

Abbreviations: CI, confidence interval; FAF, fundus autofluorescence; GA, geographic atrophy; NA, not applicable; SE, standard error; SEOM, Syfovre™ every other month; SM, Syfovre™ monthly.

[a] Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18. The model included effects for treatment, baseline GA lesion area (<7.5 mm^2 or ≥ 7.5 mm^2), time terms, presence of choroidal neovascularization in the fellow eye (yes or no), time terms by treatment interactions, and time terms by baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) interactions. Time terms include a linear effect of time for each 6-month time period.

Apellis also analyzed the trial data for study eyes versus fellow (untreated) eyes in the study population with bilateral disease. In patients with bilateral disease, GA tends to progress at a similar rate in both eyes. In the Apellis analysis, progression of GA in fellow eyes occurred at approximately 2 mm2 per year, which is comparable to the rate of progression seen in natural history studies.

No Change in Visual Function

At 24 months, there was no statistically significant difference in measures of visual function, including normal luminance best-corrected visual acuity (BCVA), maximum reading speed, Functional Reading Independence Index, and microperimetry: mean threshold sensitivity (OAKS only), between either treatment group (monthly or EOM) and the sham group. BCVA in the treatment groups continued to decline at a rate similar to the sham group.

Safety

ADVERSE EVENTS

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions ≥5%) reported in patients receiving Syfovre™ were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 3. Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with Syfovre™ Through Month 24 in Studies OAKS and DERBY			
Adverse Reactions	**PM (N = 419) %**	**PEOM (N = 420) %**	**Sham Pooled (N = 417) %**
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1

Table 3. Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with Syfovre™ Through Month 24 in Studies OAKS and DERBY			
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: Syfovre™ monthly; PEOM: Syfovre™ every other month
*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

WARNINGS & PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with Syfovre™, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering Syfovre™ in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

In clinical trials, use of Syfovre™ was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving Syfovre™ should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from Syfovre™ administration.

Intraocular Inflammation

In clinical trials, use of Syfovre™ was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with Syfovre™.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with Syfovre™. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

CONTRAINDICATIONS

- Ocular or Periocular Infections
- Active Intraocular Inflammation

Clinical Pharmacology

MECHANISMS OF ACTION

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

Dose & Administration

ADULTS

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.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 150 mg/mL in a single-dose vial.