CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217171Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leaders, Deputy Division Director, and Division Director Summary Review of NDA 217171

Review Completion Date	See DARRTS Stamp Date
From	Jennifer D. Harris, M.D., Rhea Lloyd, MD, William Boyd, M.D., Wiley Chambers, M.D.
Subject	Summary Review
NDA #	217171
Applicant	Apellis Pharmaceuticals, Inc.
Date of Submission	May 26, 2022
PDUFA Goal Date	PDUFA date amended to February 26, 2023, due to the submission of additional data during the review cycle
Proprietary Name	Syfovre
Established or Proper Name	Pegcetacoplan ophthalmic solution, 150 mg/mL
Dosage Form(s)	Intravitreal injection
Indication	Treatment of patients with geographic atrophy secondary to age-related macular degeneration
Dosing Regimen	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 25-60 days.
Regulatory Action	Approval for treatment of patients with geographic atrophy secondary to age-related macular degeneration

NDA 217171 Review Team Role	**Reviewer**
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Nonclinical Reviewer	Erin Ruhland
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Administrative Background

Syfovre (pegcetacoplan ophthalmic solution) 150 mg/mL, intravitreal injection, is a complement inhibitor developed for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. The peptide moieties bind to complement C3 and exert inhibition of the complement cascade. The 40-kDa PEG moiety is believed to impart improved solubility and longer residence time in the body after administration. Each single-use vial contains (b) (4) mg of pegcetacoplan in (b) (4) mL solution. Each vial is intended to deliver a single dose of 0.1 mL solution containing 15 mg of pegcetacoplan.

The original NDA submission was submitted with Month 12 and Month 18 data from Studies APL2-304 (OAKS) and APL2-303 (DERBY) in subjects with GA secondary to AMD. These studies were intended to provide the basis of the pegcetacoplan effectiveness and safety claims. However, this data did not demonstrate conclusive efficacy. On November 2, 2022, the Agency requested that the 24 month follow-up data be submitted for Studies APL2-304 and APL2-303. The Applicant agreed to submit the 24-month data and the PDUFA action date was extended by 3 months to permit the Agency time to review the additional data. The 24-month data set for Studies APL2-304 and APL2-303 were received by the Agency, November 17, 2022.

Benefit-Risk Assessment

Summary
Following review of the 24 Month clinical data for Studies APL2-304 and APL2-303, it has been concluded that:

1) Study APL2-304 (OAKS) demonstrated that for patients starting with geographic atrophy lesions approximately 8 mm^2 in area, dosing administered every 25-60 days leads to numerically greater slowing of geographic atrophy growth than in patients assigned to sham. While geographic atrophy lesions continue to grow in size, the area of growth in patients treated monthly was approximately 22% less than the area of growth demonstrated in the group assigned to a sham. The area of growth in patients treated every other month was approximately 18% less than the area of growth demonstrated in the group assigned to a sham. After 24 months, lesions in the group of patients assigned to sham had grown by approximately 4 mm^2, while lesions treated with Syfovre had grown approximately 3.1-3.3 mm^2.

2) Study APL2-303 (DERBY) demonstrated that for patients starting with geographic atrophy lesions approximately 8 mm^2 in area, dosing administered every 25-60 days leads to numerically greater slowing of geographic atrophy growth than in patients assigned to sham. While geographic atrophy lesions continue to grow in size, the area of continued growth in patients treated either monthly or every other month was approximately 18% less than the area of continued growth demonstrated in the group assigned to a sham. After 24 months, lesions in the group of patients assigned to sham had grown by approximately 4 mm^2, while lesions treated with Syfovre had grown approximately 3.2-3.3 mm^2.

3) Use of Syfovre increases the likelihood of developing neovascular AMD. After 24 months, 12% of patients treated monthly developed neovascular AMD, while 7% of subjects treated every other month and 3% of patients assigned to sham developed neovascular AMD.

4) The most common ocular adverse events after treatment with Syfovre (pegcetacoplan injection), 150 mg/mL, intravitreal injection for geographic atrophy (GA) secondary to age-related macular degeneration (AMD) were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage, vitreous detachment, retinal hemorrhage, punctate keratitis, posterior capsule opacification, intraocular inflammation and elevations of intraocular pressure.

There is a favorable benefit-risk ratio of pegcetacoplan injection,150 mg/mL in the treatment of GA secondary to AMD with the proposed dosing regimens.

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. Individuals affected by GA experience decreases 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).
Current Treatment Options	None.	N/A
Benefit	In each of two studies, while geographic atrophy lesions continued to grow in size, the area of growth in treated patients was slowed.	Slowing of geographic atrophy slows the development of visual field defects.
Risk and Risk Management	The most common significant ocular adverse events after treatment with Syfovre were an increase chance of exudative AMD, vitreous floaters, and intraocular inflammation.	Routine monitoring and reporting of all adverse events are adequate.

Product Quality

Composition of Pegcetacoplan, Solution for Intravitreal Injection, 150 mg/mL

Ingredient	Quality Standard	Function	Quantity per mL	Quantity per vial[a]
Pegcetacoplan	In-house standard	Drug Substance	150.0 mg[b]	15.0 mg[b]
Trehalose dihydrate	NF/Ph.Eur./JP	(b) (4)	59.5 mg	5.95 mg
Glacial acetic acid	USP/Ph.Eur./JP		0.895 mg	0.0895 mg
Sodium acetate trihydrate	USP/Ph.Eur./JP		0.353 mg	0.0353 mg
Sodium hydroxide	NF/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Glacial acetic acid	USP/Ph.Eur./JP	pH adjustment	q.s. to pH 5.0	q.s. to pH 5.0
Water for Injection	USP/Ph.Eur.	Solvent	q.s. to 1.0 mL	q.s. to 0.1 mL

[a] Based on the label claim, does not reflect the overfill
[b] Actual quantity adjusted based on drug substance assay to achieve 150 mg/mL pegcetacoplan.
NF- National Formulary; USP - United States Pharmacopoeia; Ph.Eur. - European Pharmacopoeia; JP – Japanese Pharmacopoeia

Specifications - P.5.1 Specification

Regulatory Specification for Pegcetacoplan, Solution for Intravitreal Injection, 150 mg/mL

Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Visual	(b) (4)
Degree of coloration	Ph. Eur. 2.2.2	
pH[a]	USP <791>/Ph. Eur. 2.2.3	
Identity[a]	RP-HPLC	
Identity[a]	SE-HPLC	
Assay	RP-HPLC	
Degradation products	RP-HPLC	
Degradation products	SE-HPLC	
Degradation products	SCX-HPLC	
(b) (4) content	RP-HPLC	
Bioassay[a]	ELISA	
Particulate matter	USP <789> Method 2, Microscopic Particle Count Test	
Minimum fill[a]	USP <755>	
Osmolality[a]	USP <785>/Ph. Eur. 2.2.35 Vapor Pressure	
Viscosity[a]	USP <912>/Ph. Eur. 2.2.10	
Bacterial endotoxins[a]	USP <85>/Ph. Eur. 2.6.14	
Sterility[a]	USP <71>/Ph. Eur. 2.6.1	
Container/closure integrity[b]	USP <1207> by Helium Leak Detection	

Abbreviations: area% = percentage by area; ELISA = enzyme linked immunosorbent assay; EU = endotoxin units; HMW = high molecular weight; HPLC = high-performance liquid chromatography; RP-HPLC = reversed phase HPLC; SCX-HPLC = strong cation exchange HPLC; SE-HPLC = size-exclusion HPLC; USP = US Pharmacopeia; Ph. Eur. = European Pharmacopoeia

[a] Test performed only at release.

[b] Test performed only on stability.

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The Quality Assessment Team recommended approval of the application in a review finalized 10/26/2022.

Nonclinical Pharmacology/Toxicology

From the Nonclinical review dated 10/27/22: The nonclinical studies conducted by the Applicant support the approval the NDA. The NDA is approvable from nonclinical pharmacology/toxicology standpoint.

Brief Discussion of Nonclinical Findings

- APL-2 is only pharmacologically relevant in monkeys and humans due to the species specificity of compstatin (the active moiety in APL-2) and its inhibitory effect on complement C3. Although only monkeys were used in ocular toxicity studies, both rabbits and monkeys were used in repeat-dose systemic toxicology studies.
- In systemic toxicity studies, subcutaneous administration of APL-2 in rabbits and monkeys resulted in findings of histiocytic infiltrates and macrophage vacuolation in several tissues, most notably the renal tubules and brain choroid plexus. It is thought that these effects are mediated by the PEG moiety in APL-2 since similar findings were reported in a PEG control group. In the monkey, minimal renal tubular degeneration was observed at the high dose.
- Intravitreal injection of APL-2 in monkeys resulted in low systemic exposure and no adverse ocular or systemic toxicity.
- The Applicant markets a systemic formulation of pegcetacoplan at a much higher systemic dose of pegcetacoplan (Empaveli®). Empaveli® is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Nonclinical sections of the labeling for Syfovre® are based on the same studies conducted for the approval of Empaveli®.

Clinical Pharmacology

From the original Clinical Pharmacology reviews dated 10/26/22 and 1/9/23:

The clinical pharmacology assessment of IVT pegcetacoplan for GA secondary to AMD was based on 2 clinical pharmacology studies in subjects with nAMD (Studies POT-CP043014 and APL2-203) and 3 clinical studies in subjects with GA secondary to AMD (Studies POT-CP121614, APL2-303, and APL2-304). The to-be-marketed formulation was used in the pivotal clinical studies. The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen for the treatment of adult patients with GA secondary to AMD.

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant in NDA 217171 for GA secondary to AMD and recommends approval of this NDA from a clinical pharmacology perspective. In this initial NDA, the Applicant focused on the up to Month 12 endpoints, for which the clinical pharmacology review was completed and placed in DARRTS on October 26, 2022.

The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of IVT pegcetacoplan, administered either monthly or EOM, in patients with GA secondary to AMD was established in three randomized and sham-controlled studies based on change from baseline to Month 12 in total area of GA lesion(s) in the study eye (Study APL2-303 and Study APL2-304) or the change from baseline to Month 12 in square root of total area of GA lesion in the study eye (Study POT-CP121614).
General dosing instructions	Pegcetacoplan is recommended to be administered by intravitreal injection at 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4) .
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment in any patient subgroups (e.g., age, sex or baseline C3 concentration) is needed.
Labeling	Refer to Section 2.4.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical studies.

On November 15, 2022, the Applicant submitted the 24-month efficacy and safety data from the Phase 3 APL2-303 (DERBY) and APL2-304 (OAKS) studies (eCTD Sequence Number 0019). [A second memo was completed and] focused on reviewing the updated PK, PD and immunogenicity data at Month 24. The updated PK, PD and immunogenicity data at Month 24 are consistent with those in the initial NDA.

Clinical Efficacy

Clinical data for Studies APL2-303 (DERBY) and APL2-304 (OAKS) were reviewed to support safety and efficacy for the treatment of geographic atrophy secondary to age-related macular degeneration indication.

Efficacy Results – Primary Endpoint

The Applicant's planned primary endpoint was the change from baseline (CFB) to Month 12 in total area of GA lesion(s) in the study eye, based on FAF images read by an independent central reading center, for pegcetacoplan treated eyes compared to sham. The Agency disagreed with the planned primary endpoint because the change from baseline in the control group would not reach a clinically significant change and therefore it would be impossible to achieve a clinically significant finding. The Agency recommended evaluating the rate of change. If the product demonstrated a slower rate of change, the clinical effect would eventually become clinically significant.

Analyses of CFB in Total Area of GA Lesion(s) (mm^2) (FAF) of the Study Eye With MMRM at Month 12 in Studies APL2- 304 and APL2-303 - mITT Population

	Study APL2-304			**Study APL2-303**		
	PM (N = 202)	**PEOM (N = 205)**	**Sham pooled (N = 206)**	**PM (N = 201)**	**PEOM (N = 200)**	**Sham pooled (N = 194)**
Number of subjects included in model	202	204	205	200	199	193
LS mean (SE) CFB in GA lesion area, mm^2	1.557 (0.0835)	1.651 (0.0812)	1.969 (0.0823)	1.734 (0.0792)	1.756 (0.0745)	1.964 (0.0959)
95% CI of LS mean CFB in GA lesion area, mm^2	1.394-1.722	1.491-1.810	1.807-2.130	1.578-1.890	1.610-1.903	1.776-2.152
Difference in LS mean (95% CI) CFB in GA lesion area vs sham pooled group, mm^2	−0.411 (−0.640,−0.183)	−0.318 (−0.542,−0.094)	NA	−0.230 (−0.471, 0.011)	−0.208 (−0.445, 0.029)	NA
Percentage difference in LS mean CFB in GA lesion area vs sham pooled group	−20.9%	−16.2%	NA	−11.7%	−10.6%	NA
P value vs sham pooled group	.0004	.0055	NA	.0609	.0853	NA

Abbreviations: CFB = change from baseline; CNV = choroidal neovascularization; CSR = clinical study report; FAF = fundus autofluorescence; GA = geographic atrophy; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effects model for repeated measures; NA = not applicable; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline is defined as the last available, nonmissing observation prior to the first study drug administration. Percentage difference is derived as the difference in LS means between the arms divided by the comparison group LS means. For Studies APL2-304 and APL2-304, the model included treatment + baseline GA lesion area (<7.5 mm2 or ≥7.5 mm2) + analysis visit + presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit.
Sources: Study APL2-304 Month 12 CSR Table 14.2.1.1.2, Study APL2-303 Month 12 CSR Table 14.2.1.1.2.

Reviewer's comment (s):

Study APL2-304 met the primary endpoint and demonstrated a statistically significant difference in change from baseline through Month 12 in total area of GA lesions in the pegcetacoplan monthly (PM), p=0.0004, and pegcetacoplan every other month (PEOM), p=0.0055 versus the sham pooled group. However, the difference between the treatment groups and sham is approximately 0.3 to 0.4 mm^2. This difference is not considered clinically significant because it was less than one fifth the size of the normal blind spot.

Study APL2-303 failed to meet its primary endpoint for both groups (PM and PEOM). The treatment effect of pegcetacoplan for PM had a p value=0.0609, and PEOM, a p value=0.0853. Even if statistically significant, the difference between the treatment groups and sham was approximately 0.2 mm^2, approximately one tenth the size of the normal blind spot.

The Division, during the Type B Pre-NDA meeting on 21 January 2022, and prior to the NDA submission on May 26, 2022, recommended the Applicant submit at least the complete Month 18 efficacy and safety data and preferably longer follow-up in the initial NDA.

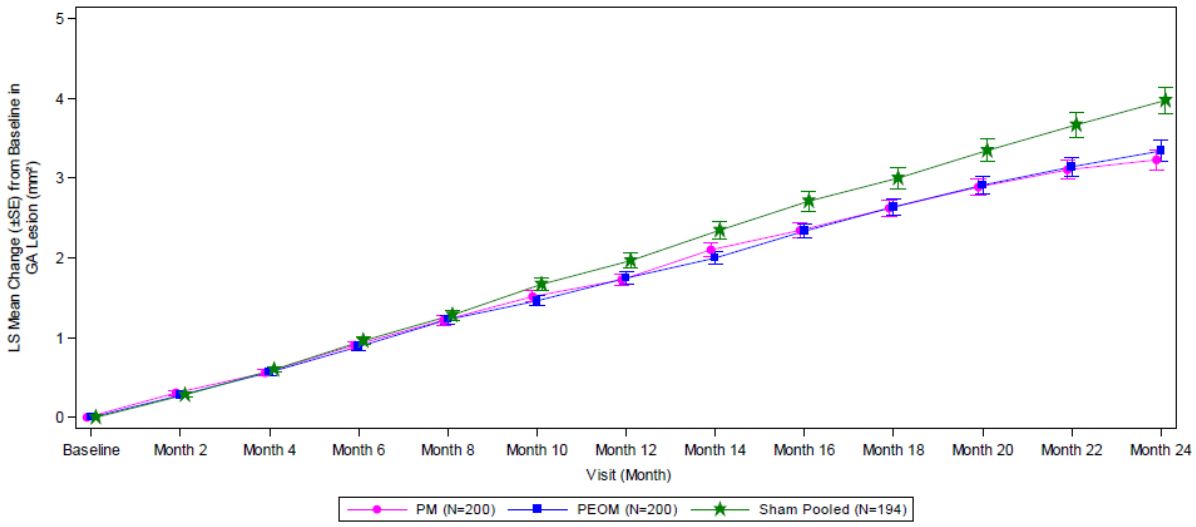
On November 2, 2022, the Agency requested that 24 month follow-up data be submitted for Studies APL2-304 and APL2-303. The Applicant agreed to submit the 24-month data and the PDUFA date was extended to allow time for the Agency to review the additional data. The 24-month data set for Studies APL2-304 and APL2-303 was received at the Agency November 17, 2022.

Mean Rate of GA Growth (Slope; mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
	Study APL-303				
Month 12: Slope (SE) [1]	1.762 (0.0762)	1.749 (0.0737)	1.959 (0.0905)	−0.197 (−0.430, 0.035)	−0.210 (−0.439, 0.019)
Month 18: Slope (SE) [2]	2.644 (0.1013)	2.600 (0.1026)	3.001 (0.1361)	−0.356 (−0.689, −0.023)	− 0.401 (−0.735, −0.067)
Month 24: Slope (SE) [3]	3.363 (0.1254)	3.358 (0.1283)	3.992 (0.1686)	−0.628 (−1.040, −0.216)	−0.633 (−1.049, −0.217)
	Study APL2-304				
Month 12: Mean (SE) [1]	1.560 (0.0802)	1.656 (0.0760)	1.968 (0.0797)	−0.407 (−0.629, −0.185)	−0.311 (−0.529, −0.094)
Month 18: Mean (SE) [2]	2.338 (0.1101)	2.490 (0.1076)	2.970 (0.1144)	−0.632 (−0.943, −0.320)	−0.480 (−0.789, −0.171)
Month 24: Mean (SE) [3]	3.103 (0.1451)	3.283 (0.1359)	3.966 (0.1435)	−0.863 (−1.263,−0.463)	−0.683 (−1.071,−0.295)

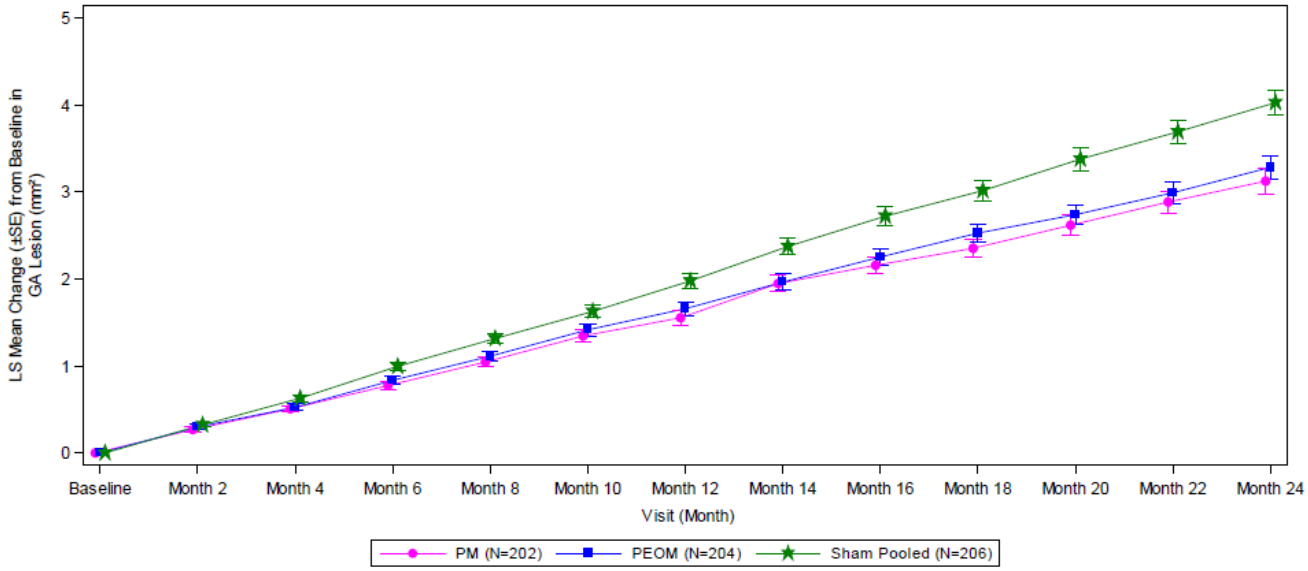
[1] Source: Table 26 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 12 included.
[2] Source: Table 14.2.1.3.8 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 18 included.
[3] Source: Table 35 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 24 included.

Study APL2-303 LS Mean (+/- SE) Plot of Change From Baseline to Month 24 in Total Area of GA Lesion(s) (mm2) (FAF) of the Study Eye by Visit and Treatment Group From MMRM Model - mITT Population



Abbreviations: CNV = choroidal neovascularization; GA = geographic atrophy; FAF = fundus autofluorescence; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Model includes treatment + baseline GA lesion area (<7.5 mm2 or ≥7.5 mm2) + analysis visit + presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit.
Source: Figure 14.2.1.1.3.

Study APL2-304 LS Mean (+/-SE) Plot of Change From Baseline to Month 24 in Total Area of GA Lesion(s) (mm2) (FAF) of the Study Eye by Visit and Treatment Group From MMRM Model - mITT Population



Abbreviations: CNV = choroidal neovascularization; GA = geographic atrophy; FAF = fundus autofluorescence; LS = least-square; mITT = modified intent-to-treat; MMRM = mixed-effect model for repeated measures; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline is defined as the last available, nonmissing observation prior to first study drug administration. Model includes treatment + baseline GA lesion area (<7.5 mm2 or ≥7.5 mm2) + analysis visit + baseline presence of CNV in the fellow eye (yes or no) + analysis visit × treatment + baseline GA lesion area × analysis visit. Source: Figure 14.2.1.1.3.

Efficacy Summary

1) Study APL2-304 (OAKS) demonstrated that for patients starting with geographic atrophy lesions approximately 8 mm^2 in area, dosing administered every 25-60 days leads to numerically greater slowing of geographic atrophy growth than in patients assigned to sham. While geographic atrophy lesions continue to grow in size, the area of growth in patients treated monthly was approximately 22% less than the area of growth demonstrated in the group assigned to a sham. The area of growth in patients treated every other month was approximately 18% less than the area of growth demonstrated in the group assigned to a sham. After 24 months, lesions in the group of patients assigned to sham had grown by approximately 4 mm^2, while lesions treated with Syfovre had grown approximately 3.1-3.3 mm^2.

2) Study APL2-303 (DERBY) demonstrated that for patients starting with geographic atrophy lesions approximately 8 mm^2 in area, dosing administered every 25-60 days leads to numerically greater slowing of geographic atrophy growth than in patients assigned to sham. While geographic atrophy lesions continue to grow in size, the area of continued growth in patients treated either monthly or every other month was approximately 18% less than the area of continued growth demonstrated in the group assigned to a sham. After 24 months, lesions in the group of patients assigned to sham had grown by approximately 4 mm^2, while lesions treated with Syfovre had grown approximately 3.2-3.3 mm^2.

Safety

Safety Database

Studies OAKS and DERBY	PM	PEOM	Sham
	(N=419)	(N=420)	(N=417)
	n (%)	n (%)	n (%)
Subjects received at least one dose of IP	419	420	417
Completed Treatment Through Month 24	294 (70.2)	330 (78.6)	321 (77.0)
Discontinued from Treatment Prior to Month 24	125 (29.8)	90 (21.4)	96 (23.0)
Continued in the Study to Month 24 After Treatment Discontinuation	5 (1.2)	5 (1.2)	0
Primary Reason for Discontinuation from Treatment			
Adverse Event	23 (5.5)	17 (4.0)	15 (3.6)
Lost to Follow-up	5 (1.2)	9 (2.1)	8 (1.9)
Non-Compliance with Study Drug	0	0	0
Physician Decision	2 (0.5)	1 (0.2)	3 (0.7)
Protocol Violation	0	0	0
Consent Withdrawal	58 (13.8)	34 (8.1)	38 (9.1)
Death	24 (5.7)	14 (3.3)	13 (3.1)
Due to COVID Impact [a]	13 (3.1)	14 (3.3)	19 (4.6)
Other	0	1 (0.2)	0

Number of Injections/Missed Injections

Studies OAKS and DERBY	PM	PEOM	Sham Pooled
	(N=419)	(N=420)	(N=417)
Total Number of Injections Received	7600	4136	5845
Total Number of Missed Injections	1154	448	790
Summary of Total Number of Injections per Subject n	419	420	417
Mean	18.1	9.8	14.0
SD	6.85	3.21	6.84
Median	21.0	11.0	12.0
Q1, Q3	15.0, 23.0	9.0, 12.0	10.0, 21.0

Min, Max	1, 24	1, 12	0, 24
Total Number of Injections per Subject, n (%)			
0	0	0	1 (0.2)
1	14 (3.3)	16 (3.8)	14 (3.4)
2	5 (1.2)	15 (3.6)	9 (2.2)
3	5 (1.2)	8 (1.9)	7 (1.7)
4	8 (1.9)	10 (2.4)	13 (3.1)
5	6 (1.4)	11 (2.6)	7 (1.7)
6	7 (1.7)	6 (1.4)	7 (1.7)
7	10 (2.4)	7 (1.7)	8 (1.9)
8	6 (1.4)	10 (2.4)	2 (0.5)
9	7 (1.7)	24 (5.7)	12 (2.9)
10	6 (1.4)	36 (8.6)	26 (6.2)
11	3 (0.7)	94 (22.4)	59 (14.1)
12	9 (2.1)	183 (43.6)	87 (20.9)
13	10 (2.4)	0	3 (0.7)
14	8 (1.9)	0	3 (0.7)
15	9 (2.1)	0	6 (1.4)
16	5 (1.2)	0	2 (0.5)
17	6 (1.4)	0	6 (1.4)
18	17 (4.1)	0	8 (1.9)
19	19 (4.5)	0	11 (2.6)
20	17 (4.1)	0	8 (1.9)
21	38 (9.1)	0	15 (3.6)
22	60 (14.3)	0	18 (4.3)
23	65 (15.5)	0	39 (9.4)
24	79 (18.9)	0	46 (11.0)
Number of Missed Injections per Subject, n (%)			
0	99 (23.6)	204 (48.6)	159 (38.1)
1	91 (21.7)	117 (27.9)	114 (27.3)
2	70 (16.7)	43 (10.2)	48 (11.5)
3	51 (12.2)	26 (6.2)	24 (5.8)
4	24 (5.7)	11 (2.6)	16 (3.8)
5	20 (4.8)	7 (1.7)	18 (4.3)
6	21 (5.0)	5 (1.2)	9 (2.2)
7	10 (2.4)	3 (0.7)	6 (1.4)
8	4 (1.0)	2 (0.5)	4 (1.0)
9	8 (1.9)	0	6 (1.4)
10	4 (1.0)	1 (0.2)	2 (0.5)
11	5 (1.2)	1 (0.2)	2 (0.5)
12	3 (0.7)	0	4 (1.0)
13	3 (0.7)	0	2 (0.5)
15	1 (0.2)	0	0
16	2 (0.5)	0	1 (0.2)
17	2 (0.5)	0	0
20	0	0	2 (0.5)
23	1 (0.2)	0	0

Deaths- Non-ocular Treatment Emergent Adverse Events Leading to Death by System Organ Class- Studies OAKS and DERBY

Studies OAKS and DERBY	PM	PEOM	Sham
System Organ Class/Preferred Term	(N=419)	(N=420)	(N=417)
	n (%) M	n (%) M	n (%) M
Number of Subjects with at Least One Non-ocular TEAE Leading to Death	28 (6.7) 29	15 (3.6) 22	16 (3.8) 17
Cardiac disorders	6 (1.4) 6	5 (1.2) 5	3 (0.7) 3
Cardiac failure congestive	2 (0.5) 2	1 (0.2) 1	1 (0.2) 1
Cardiac arrest	2 (0.5) 2	1 (0.2) 1	0
Myocardial infarction	2 (0.5) 2	0	0
Cardiac failure	0	2 (0.5) 2	1 (0.2) 1
Arrhythmia	0	1 (0.2) 1	0
Coronary artery occlusion	0	0	1 (0.2) 1
Gastrointestinal disorders	0	1 (0.2) 1	0
Intestinal perforation	0	1 (0.2) 1	0
General disorders and administration site conditions	3 (0.7) 3	1 (0.2) 1	4 (1.0) 4
Death	2 (0.5) 2	1 (0.2) 1	2 (0.5) 2
Disease complication	1 (0.2) 1	0	0
Sudden death	0	0	1 (0.2) 1
Ill-defined disorder	0	0	1 (0.2) 1
Hepatobiliary disorders	0	1 (0.2) 1	0
Hepatic failure	0	1 (0.2) 1	0
Infections and infestations	9 (2.1) 9	3 (0.7) 4	4 (1.0) 4
COVID-19	6 (1.4) 6	0	2 (0.5) 2
Pneumonia	2 (0.5) 2	0	1 (0.2) 1
Septic shock	0	2 (0.5) 2	0
Sepsis	1 (0.2) 1	0	0
Infective exacerbation of chronic obstructive airways disease	0	1 (0.2) 1	0
Pyelonephritis acute	0	1 (0.2) 1	0
COVID-19 pneumonia	0	0	1 (0.2) 1
Injury, poisoning and procedural complications	2 (0.5) 2	0	0
Subdural haematoma	1 (0.2) 1	0	0
Subdural haemorrhage	1 (0.2) 1	0	0
Metabolism and nutrition disorders	0	2 (0.5) 3	0
Dehydration	0	1 (0.2) 1	0
Hypernatraemia	0	1 (0.2) 1	0
Malnutrition	0	1 (0.2) 1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.0) 4	5 (1.2) 5	3 (0.7) 3
Endometrial cancer	1 (0.2) 1	0	0
Lung neoplasm malignant	1 (0.2) 1	0	0
Ovarian cancer	1 (0.2) 1	0	0
Pancreatic carcinoma metastatic	1 (0.2) 1	0	0
Chronic myeloid leukaemia	0	1 (0.2) 1	0
Lung adenocarcinoma stage III	0	1 (0.2) 1	0
Plasma cell myeloma	0	1 (0.2) 1	0
Squamous cell carcinoma of the oral cavity	0	1 (0.2) 1	0
Urethral cancer	0	1 (0.2) 1	0
Brain cancer metastatic	0	0	1 (0.2) 1
Prostate cancer	0	0	1 (0.2) 1
Neoplasm malignant	0	0	1 (0.2) 1
Nervous system disorders	4 (1.0) 4	1 (0.2) 1	0
Cerebrovascular accident	2 (0.5) 2	0	0
Cerebellar stroke	1 (0.2) 1	0	0
Haemorrhagic stroke	1 (0.2) 1	0	0
Subarachnoid haemorrhage	0	1 (0.2) 1	0
Respiratory, thoracic and mediastinal disorders	1 (0.2) 1	1 (0.2) 1	2 (0.5) 3
Respiratory failure	1 (0.2) 1	0	1 (0.2) 1
Acute respiratory failure	0	1 (0.2) 1	0
Pneumonia aspiration	0	0	1 (0.2) 1
Pulmonary embolism	0	0	1 (0.2) 1

No specific patterns were identified. The deaths are consistent with an elderly population.

Adverse Events

Adverse Events	PM	PEOM	Sham
System Organ Class/	(N=419)	(N=420)	(N=417)
Preferred Term	n (%) M	n (%) M	n (%) M
Number of Subjects with at Least One Ocular TEAE in Study Eye	258 (61.6) 753	231 (55.0) 571	193 (46.3) 420
Congenital, familial and genetic disorders	3 (0.7) 3	2 (0.5) 3	3 (0.7) 3
Corneal dystrophy	2 (0.5) 2	2 (0.5) 3	3 (0.7) 3
Tilted disc syndrome	1 (0.2) 1	0	0
Eye disorders	250 (59.7) 691	220 (52.4) 513	183 (43.9) 391
Vitreous floaters	41 (9.8) 49	29 (6.9) 37	5 (1.2) 5
Conjunctival haemorrhage	34 (8.1) 55	34 (8.1) 46	15 (3.6) 16
Neovascular age-related macular degeneration	41 (9.8) 43	24 (5.7) 25	8 (1.9) 9
Visual acuity reduced	33 (7.9) 37	27 (6.4) 30	28 (6.7) 40
Eye pain	30 (7.2) 37	24 (5.7) 27	27 (6.5) 33
Dry eye	23 (5.5) 25	20 (4.8) 21	17 (4.1) 17
Vitreous detachment	15 (3.6) 15	25 (6.0) 26	14 (3.4) 14
Retinal haemorrhage	18 (4.3) 19	21 (5.0) 22	12 (2.9) 14
Punctate keratitis	23 (5.5) 24	8 (1.9) 8	3 (0.7) 3
Posterior capsule opacification	15 (3.6) 15	15 (3.6) 15	11 (2.6) 12
Cataract	16 (3.8) 16	13 (3.1) 14	16 (3.8) 17
Eye irritation	18 (4.3) 23	10 (2.4) 11	20 (4.8) 23
Low luminance best-corrected visual acuity decreased	15 (3.6) 17	13 (3.1) 14	15 (3.6) 16
Visual impairment	13 (3.1) 15	13 (3.1) 21	12 (2.9) 12
Blepharitis	9 (2.1) 10	17 (4.0) 17	9 (2.2) 10
Vision blurred	13 (3.1) 18	10 (2.4) 10	16 (3.8) 19
Foreign body sensation in eyes	13 (3.1) 15	10 (2.4) 11	7 (1.7) 7
Choroidal neovascularization	12 (2.9) 12	4 (1.0) 4	5 (1.2) 6
Ocular hyperaemia	9 (2.1) 13	5 (1.2) 8	7 (1.7) 13
Photopsia	7 (1.7) 8	6 (1.4) 6	3 (0.7) 3
Ocular discomfort	8 (1.9) 9	4 (1.0) 4	3 (0.7) 4
Lacrimation increased	6 (1.4) 7	6 (1.4) 6	8 (1.9) 9
Dry age-related macular degeneration	6 (1.4) 6	6 (1.4) 6	6 (1.4) 6
Eye pruritus	6 (1.4) 7	6 (1.4) 6	6 (1.4) 7
Vitreous haemorrhage	8 (1.9) 9	3 (0.7) 3	0
Ocular hypertension	5 (1.2) 10	6 (1.4) 6	0
Lenticular opacities	5 (1.2) 6	4 (1.0) 4	0
Vitritis	8 (1.9) 9	0	0
Optic ischaemic neuropathy	7 (1.7) 7	1 (0.2) 1	0
Glaucoma	4 (1.0) 4	3 (0.7) 4	3 (0.7) 3
Chorioretinal atrophy	4 (1.0) 4	3 (0.7) 3	1 (0.2) 1
Photophobia	4 (1.0) 4	3 (0.7) 3	1 (0.2) 1
Foreign body in eye	5 (1.2) 5	1 (0.2) 1	0
Chalazion	3 (0.7) 4	3 (0.7) 5	0
Vitreal cells	3 (0.7) 3	3 (0.7) 3	0
Vitreous opacities	3 (0.7) 3	3 (0.7) 3	0
Retinal drusen	5 (1.2) 5	0	0
Retinal degeneration	4 (1.0) 4	1 (0.2) 1	0
Macular oedema	3 (0.7) 3	2 (0.5) 2	0
Retinal oedema	3 (0.7) 4	2 (0.5) 2	0
Iridocyclitis	2 (0.5) 2	3 (0.7) 5	0
Corneal erosion	4 (1.0) 5	0	0
Macular cyst	4 (1.0) 5	0	0
Diplopia	3 (0.7) 5	1 (0.2) 1	2 (0.5) 2
Macular fibrosis	3 (0.7) 3	1 (0.2) 1	1 (0.2) 1
Lacrimation decreased	3 (0.7) 3	1 (0.2) 1	0
Conjunctivitis allergic	2 (0.5) 2	2 (0.5) 2	4 (1.0) 4
Hordeolum	2 (0.5) 2	2 (0.5) 2	2 (0.5) 2
Cystoid macular oedema	2 (0.5) 2	2 (0.5) 2	1 (0.2) 1
Cataract cortical	2 (0.5) 2	2 (0.5) 2	0
Open angle glaucoma	2 (0.5) 2	2 (0.5) 2	0
Conjunctival oedema	1 (0.2) 1	3 (0.7) 3	1 (0.2) 1

Adverse Events	PM	PEOM	Sham
Keratitis	1 (0.2) 1	3 (0.7) 3	0
Meibomian gland dysfunction	1 (0.2) 1	3 (0.7) 3	0
Eye discharge	3 (0.7) 4	0	5 (1.2) 5
Blindness transient	3 (0.7) 3	0	1 (0.2) 1
Cataract nuclear	3 (0.7) 3	0	1 (0.2) 1
Retinal tear	3 (0.7) 3	0	1 (0.2) 1
Corneal opacity	2 (0.5) 2	1 (0.2) 1	0
Papilloedema	2 (0.5) 2	1 (0.2) 2	0
Uveitis	1 (0.2) 1	2 (0.5) 2	0
Vitreous degeneration	1 (0.2) 1	2 (0.5) 2	0
Retinal vein occlusion	0	3 (0.7) 3	2 (0.5) 2
Retinal pigment epitheliopathy	0	3 (0.7) 3	1 (0.2) 1
Borderline glaucoma	2 (0.5) 2	0	0
Detachment of retinal pigment epithelium	2 (0.5) 2	0	0
Iritis	2 (0.5) 2	0	0
Periorbital pain	2 (0.5) 2	0	0
Conjunctival hyperaemia	1 (0.2) 1	1 (0.2) 1	3 (0.7) 3
Optic disc haemorrhage	1 (0.2) 1	1 (0.2) 1	2 (0.5) 2
Cataract subcapsular	1 (0.2) 1	1 (0.2) 1	1 (0.2) 1
Swelling of eyelid	1 (0.2) 1	1 (0.2) 1	1 (0.2) 1
Trichiasis	1 (0.2) 1	1 (0.2) 2	2 (0.5) 4
Conjunctival irritation	1 (0.2) 1	1 (0.2) 1	1 (0.2) 1
Retinal cyst	1 (0.2) 1	1 (0.2) 1	1 (0.2) 1
Retinal detachment	1 (0.2) 1	1 (0.2) 1	1 (0.2) 1
Ectropion	1 (0.2) 1	1 (0.2) 1	0
Subretinal fluid	1 (0.2) 1	1 (0.2) 1	0
Optic atrophy	0	2 (0.5) 2	1 (0.2) 1
Retinopathy hypertensive	0	2 (0.5) 2	1 (0.2) 1
Abnormal sensation in eye	0	2 (0.5) 2	0
Corneal pigmentation	0	2 (0.5) 2	0
Eyelid ptosis	1 (0.2) 1	0	3 (0.7) 3
Retinal artery embolism	1 (0.2) 1	0	2 (0.5) 2
Corneal disorder	1 (0.2) 1	0	1 (0.2) 1
Arcus lipoides	0	0	1 (0.2) 1
Eyelid cyst	0	0	1 (0.2) 1
Lens dislocation	0	0	1 (0.2) 1
Optic nerve sheath haemorrhage	0	0	1 (0.2) 1
Strabismus	0	0	1 (0.2) 1
General disorders and administration site conditions	1 (0.2) 1	1 (0.2) 2	0
Injection site irritation	1 (0.2) 1	0	0
Injection site erythema	0	1 (0.2) 1	0
Injection site pain	0	1 (0.2) 1	0
Immune system disorders	1 (0.2) 1	0	2 (0.5) 2
Sjogren's syndrome	1 (0.2) 1	0	2 (0.5) 2
Infections and infestations	8 (1.9) 8	13 (3.1) 13	7 (1.7) 7
Conjunctivitis	3 (0.7) 3	6 (1.4) 6	4 (1.0) 4
Endophthalmitis	2 (0.5) 2	3 (0.7) 3	0
Hordeolum	1 (0.2) 1	2 (0.5) 2	3 (0.7) 3
Conjunctivitis bacterial	1 (0.2) 1	0	0
Conjunctivitis viral	1 (0.2) 1	0	0
Dacryocystitis	0	1 (0.2) 1	0
Viral uveitis	0	1 (0.2) 1	0
Injury, poisoning and procedural complications	13 (3.1) 21	7 (1.7) 7	7 (1.7) 7
Corneal abrasion	5 (1.2) 8	4 (1.0) 4	5 (1.2) 5
Foreign body in eye	3 (0.7) 3	0	1 (0.2) 1
Intra-ocular injection complication	2 (0.5) 5	1 (0.2) 1	1 (0.2) 1
Periorbital haematoma	1 (0.2) 1	1 (0.2) 1	0
Eye injury	1 (0.2) 1	0	0
Hyphaema	1 (0.2) 1	0	0
Periorbital haemorrhage	1 (0.2) 1	0	0
Post procedural complication	1 (0.2) 1	0	0

Adverse Events	PM	PEOM	Sham
Cataract operation complication	0	1 (0.2) 1	0
Investigations	9 (2.1) 24	13 (3.1) 26	3 (0.7) 3
Intraocular pressure increased	8 (1.9) 23	12 (2.9) 24	3 (0.7) 3
Optic nerve cup/disc ratio increased	1 (0.2) 1	0	0
Intraocular pressure test abnormal	0	1 (0.2) 1	0
Vital dye staining cornea present	0	1 (0.2) 1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2) 2	3 (0.7) 3	3 (0.7) 3
Eye naevus	1 (0.2) 1	1 (0.2) 1	2 (0.5) 2
Blepharal papilloma	0	2 (0.5) 2	0
Eyelid haemangioma	1 (0.2) 1	0	0
Malignant neoplasm of eyelid	0	0	1 (0.2) 1
Nervous system disorders	0	1 (0.2) 1	1 (0.2) 1
Visual field defect	0	1 (0.2) 1	1 (0.2) 1
Product issues	0	1 (0.2) 1	0
Device dislocation	0	1 (0.2) 1	0
Skin and subcutaneous tissue disorders	2 (0.5) 2	1 (0.2) 2	1 (0.2) 1
Ecchymosis	2 (0.5) 2	1 (0.2) 2	0

Adverse events highlighted in yellow occurred more frequently in the patients treated with Syfovre than in the patients assigned to Sham. (b) (4)

Advisory Committee Meeting

The drug product is not a new molecular entity, and the application did not raise issues that required input from an external review panel.

Pediatrics

This NDA triggered PREA because SYFOVRE is a new dosage form and new route of administration of pegcetacoplan. The applicant requested a product specific waiver for all pediatric age groups (i.e., birth to <18 years) for geographic atrophy secondary to age-related macular degeneration on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients. The Agency agreed that the condition does not exist or exists very rarely in pediatric patients.

BIOSTATISTICS

The statistical review team completed a primary review and an addendum to the primary review. Based on the review of the originally submitted safety and efficacy data up to Month 18, this reviewer concluded that the results in the two pivotal Phase 3 studies, APL2-303 and APL2-304, support the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD. In the current submission, the Applicant submitted the complete 24-month safety and efficacy data from the two pivotal studies.

The analyses based on the complete 24-month data provided results that were consistent with those observed with efficacy data through Month 18. In both studies, nominally significant treatment differences are observed at Month 24 in favor of the two pegcetacoplan dosing frequencies [every month (PM) and every other month (PEOM)] with respect to both the mean change from baseline GA area as well as the Division's preferred endpoint, the mean rate of GA growth.

Mean Change from Baseline in Total GA Area (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
	Study APL-303				
Month 12: Mean (SE) [1]	1.733 (0.079)	1.756 (0.074)	1.964 (0.0959)	−0.230 (−0.470, 0.010)	−0.208 (−0.444, 0.029)
Month 18: Mean (SE) [2]	2.621 (0.101)	2.633 (0.103)	3.001 (0.1383)	−0.380 (−0.713, –0.046)	−0.368 (−0.706, –0.029)
Month 24: Mean (SE) [3]	3.227 (0.125)	3.339 (0.130)	3.972 (0.1682)	−0.745 (−1.153, −0.336)	−0.633 (−1.050, −0.215)
	Study APL2-304				
Month 12: Mean (SE) [1]	1.557 (0.083)	1.650 (0.081)	1.968 (0.0822)	−0.411 (−0.639, −0.183)	−0.318 (−0.542, −0.093)
Month 18: Mean (SE) [2]	2.351 (0.107)	2.516 (0.109)	3.009 (0.1153)	−0.657 (−0.965, −0.350)	−0.492 (−0.802, −0.183)
Month 24: Mean (SE) [3]	3.123 (0.143)	3.282 (0.132)	4.025 (0.1464)	−0.901 (−1.302, −0.500)	−0.742 (−1.128, −0.357)

Source: [1] Table 24 of the Applicant's original study reports.
Source: [2] Table 24 of the Applicant's original study reports
Source: [3] Table 33 of the Applicant's Month 24 study reports.

Analysis of Agency's Preferred Primary Endpoint

The results of the analysis of this endpoint based on data collected through Month 12 mirrored the results observed for the protocol defined primary efficacy endpoint such that differences between each of the two dosing frequencies of pegcetacoplan against pooled sham in annual growth rates were nominally significant in Study APL2-304 but not in Study APL2-303. However, when a similar analysis is conducted based on data collected through Month 18, and through Month 24, the treatment differences in slope between each dosing frequency of pegcetacoplan and the pooled sham are nominally significant in favor of the two dosing frequencies in both studies. The results of the piecewise regression provided similar conclusions as the linear model.

Mean Rate of GA Growth (Slope; mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
	Study APL-303				
Month 12: Slope (SE) [1]	1.762 (0.0762)	1.749 (0.0737)	1.959 (0.0905)	−0.197 (−0.430, 0.035)	−0.210 (−0.439, 0.019)
Month 18: Slope (SE) [2]	2.644 (0.1013)	2.600 (0.1026)	3.001 (0.1361)	−0.356 (−0.689, −0.023)	− 0.401 (−0.735, −0.067)
Month 24: Slope (SE) [3]	3.363 (0.1254)	3.358 (0.1283)	3.992 (0.1686)	−0.628 (−1.040, −0.216)	−0.633 (−1.049, −0.217)
	Study APL2-304				
Month 12: Mean (SE) [1]	1.560 (0.0802)	1.656 (0.0760)	1.968 (0.0797)	−0.407 (−0.629, −0.185)	−0.311 (−0.529, −0.094)
Month 18: Mean (SE) [2]	2.338 (0.1101)	2.490 (0.1076)	2.970 (0.1144)	−0.632 (−0.943, −0.320)	−0.480 (−0.789, −0.171)
Month 24: Mean (SE) [3]	3.103 (0.1451)	3.283 (0.1359)	3.966 (0.1435)	−0.863 (−1.263,−0.463)	−0.683 (−1.071,−0.295)

[1] Source: Table 26 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 12 included.
[2] Source: Table 14.2.1.3.8 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 18 included.
[3] Source: Table 35 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 24 included.

Statistical Reviewer's Remark: For the Division of Ophthalmology's primary efficacy endpoint, the efficacy results for the two doing frequencies are mixed. In Study APL2-303, the PEOM arm appears to have slightly slower GA progression compared to the PM arm. Conversely, in Study APL2-304, the PM arm performed better than PEOM. These findings should be taken into consideration when the to-be-marketed dose is determined.

Figure 1: Mean Rate of Change from Baseline in Study Eye GA Lesion Area Measured by FAF in OAKS

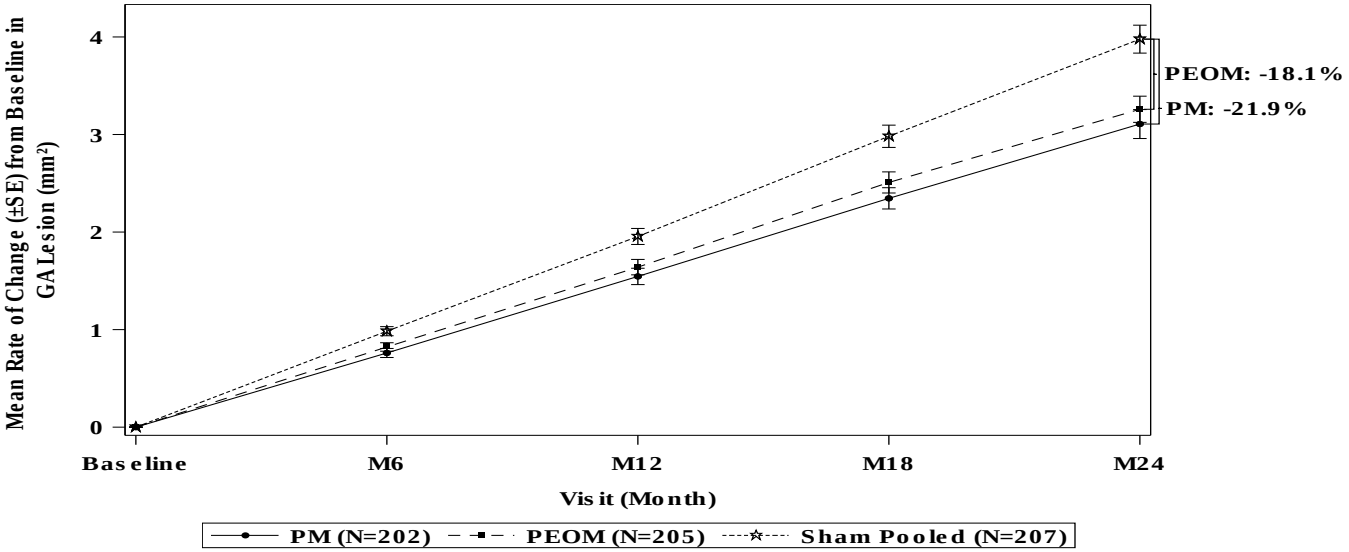
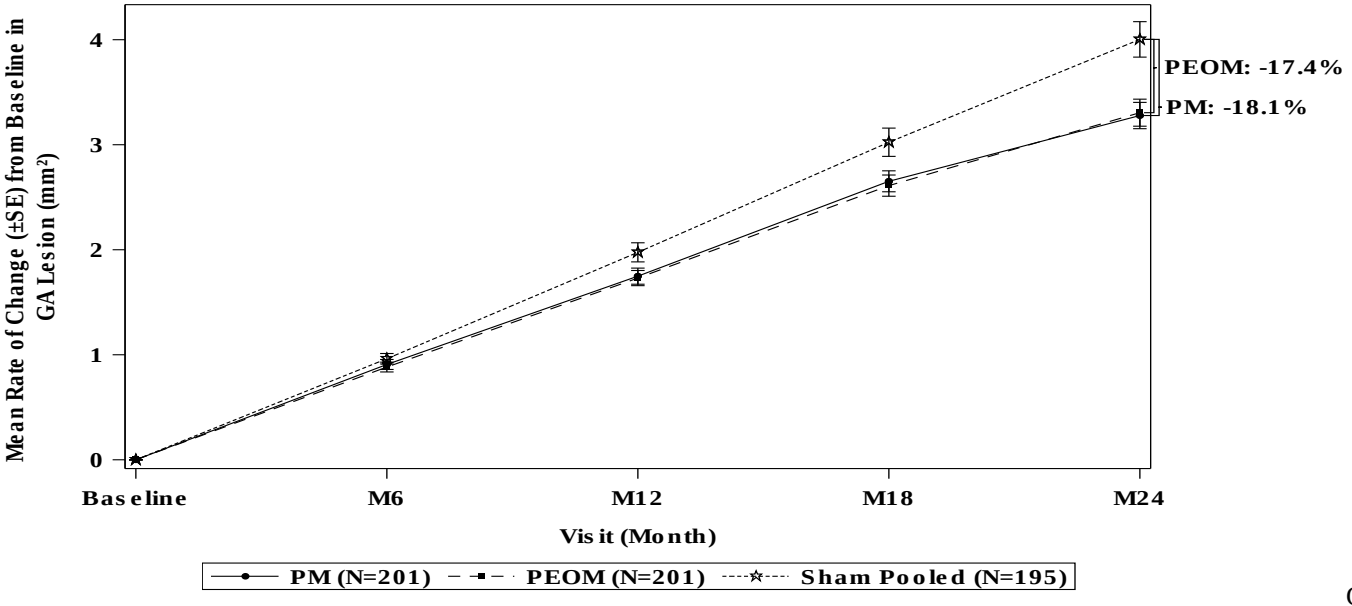


Figure 2: Mean Rate of Change from Baseline in Study Eye GA Lesion Area Measured by FAF in DERBY



GA: Geographic atrophy; FAF: fundus autofluorescence; PM: SYFOVRE monthly; PEOM: SYFOVRE every other month; SE: standard error. 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.

Treatment effects in evaluable subgroups (e.g., age, gender, GA lesion location, GA lesion focality) in each study were generally consistent with the results in the overall population. There are only a small number of non-white subjects in the clinical trials because age related macular degeneration does not occur equally in white and non-white population.

The key secondary efficacy endpoints of the two studies are changes from baseline at Month 24 in monocular maximum reading speed, FRI index score, and NL-BCVA score. For each endpoint, the analysis was conducted using a similar MMRM that was used for the protocol defined primary efficacy endpoint based on all observed data on the mITT population. From each model, the least squares mean change from baseline for

each treatment arm, the differences between treatment arms and the associated 2-sided 95.1% confidence intervals are provided. Per the study results summarized below, none of the differences observed between each dosing frequency of pegcetacoplan and the pooled sham with respect to these secondary efficacy endpoints are statistically significant.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators in the original NDA submission.

Covered Clinical Study (Name and/or Number): APL2 – 303 and APL2 -304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 232 (Prinicipal Investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
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: 5 Significant payments of other sorts: ____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Stock: 2 (of 5 listed 2 also had Stock > $50,000) 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)

Study Integrity

From the OSI Clinical Inspections Summary dated October 14, 2022:
Four clinical investigators, Drs. Fineman, Wykoff, Lally, and Chiang were inspected in support of this NDA. The primary efficacy data were requested from the sites of Drs. Fineman, Wykoff, and Chiang and provided by the sponsor. These data were compared with the line listings and no discrepancies were noted. In assessing the reliability of safety data, the inspections of Drs. Lally and Chiang revealed a number of adverse events (AEs) that appear to have been reported by these CIs but not by the sponsor. We recommended that the review division include any unreported AEs in its evaluation of the safety data. We also recommended that the review division forward an information request to the sponsor asking that the sponsor audit the safety data and report all AEs that were not included in this NDA (see Addendum). Otherwise, based on the results of these inspections, Protocols APL-303 and 304 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the proposed indication.

From the OSI Clinical Inspections Summary Addendum dated November 6, 2022: Some of the clinical site inspections noted what appeared to be unreported AEs. FDA sent an IR requesting that the sponsor address any unreported AEs by clinical site, severity, dates of occurrence, actions taken with the study treatment, outcome, causality, reason(s) why the unreported AE was not reported, and relevant data cutoff dates. Review of the sponsor's response to the IR concludes that perceived inconsistencies in AE reporting appeared attributable to the sequential reporting of AEs in multiple reports and the result of timing as to when subjects reported their AEs to the site and/or the timing of the sites in entering the AEs into the EDC system. Overall, AE reporting for this application appears adequate.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) dated 1/12/23 stated that their evaluation of the proposed Syfovre Prescribing information (PI) did not identify areas of vulnerability that may lead to medication errors. They did have recommendations for the container labels and carton labeling received on November 15, 2022, which were incorporated into the Division's comments.

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

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Regulatory Action

NDA 217171 for Syfovre 15 mg (0.1 mL of 150 mg/mL solution), intravitreal injection, will be approved for the treatment of geographic atrophy secondary to age-related macular degeneration when administered every 25-60 days.

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
02/17/2023 12:09:41 PM

WILEY A CHAMBERS
02/17/2023 12:12:09 PM