CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217171Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	NDA 217171
Priority or Standard	Priority
Submit Date(s)	May 26, 2022
Received Date(s)	May 26, 2022
PDUFA Goal Date	November 26, 2022 (PDUFA date Amended to February 26, 2023, due to the submission of additional data during the review cycle)
Division/Office	Division of Ophthalmology
Reviewer Name(s)	Martin P. Nevitt M.D., M.P.H.
Review Completion Date	February 16, 2022
Established/Proper Name	pegcetacoplan ophthalmic solution, 150 mg/mL
(Proposed) Trade Name	Syfovre
Applicant	Apellis Pharmaceuticals, Inc.
Dosage Form(s)	intravitreal injection
Applicant Proposed Dosing Regimen(s)	(b) (4) intravitreal injection
Applicant Proposed Indication(s)/Population(s)	geographic atrophy secondary to age-related macular degeneration
Recommendation on Regulatory Action	Approval is recommended for Syfovre 15 mg (0.1 mL of 150 mg/mL solution), intravitreal injection, to each affected eye once every 25 - 60 days
Recommended Indication(s)/Population(s)	Subjects with geographic atrophy secondary to age-related macular degeneration

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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 an inhibition of the complement cascade. Pegcetacoplan is formulated into the drug product for intravitreal injection, each single-use vial contains (b) (4) mg of pegcetacoplan in (b) (4) mL solution. Each vial will permit delivery of a single dose of 0.1 mL solution containing 15 mg of pegcetacoplan.

The Applicant is seeking licensure for Syfovre, 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

In considering the totality of the evidence submitted in Studies APL2-304 and APL2-303, the two adequate and well controlled studies with most subjects and 24-month follow-up, the data set submitted by the Applicant demonstrates that Syfovre (pegcetacoplan ophthalmic solution, 150 mg/mL) intravitreal injection, is recommended for approval. Approval is recommended for Syfovre 15 mg (0.1 mL of 150 mg/mL solution), intravitreal injection, to each affected eye once every 25 - 60 days.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

There is a favorable Risk- Benefit of Syfovre (pegcetacoplan ophthalmic solution,150 mg/mL), intravitreal injection, for treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Efficacy at the Month 24 exam in Studies APL2-303 and APL2-304 has been demonstrated.

Syfovre (pegcetacoplan ophthalmic solution, 150 mg/mL), intravitreal injection, demonstrated in Studies APL2-303 and APL2-304 to be reasonable safe when dosed as frequently as once every 25 - 60 days.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GA secondary to AMD is characterized by progressive and irreversible atrophy of retinal cells and is a leading cause of severe vision loss worldwide • Approximately 1 million people in the US are affected by GA and experience profound decrease in quality of life, including difficulty reading and recognizing faces and loss of independence	The goal of treatment of GA secondary to AMD is the preservation of retina cells (RPE, photoreceptors, and choriocapillaris) and preserving vision in the long term.
Current Treatment Options	• None	N/A
Benefit	• The benefit of Syfovre (pegcetacoplan ophthalmic solution,150 mg/mL), dosed once every 25- 60 days intravitreal injection, for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) has been demonstrated at the Month 24 exam.	Month 24 exam in Studies APL2-303 and APL2-304 data demonstrated Efficacy and Safety of Syfovre (pegcetacoplan ophthalmic solution, 150 mg/mL), intravitreal injection, dosed once every 25 – 60 days.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.	Routine monitoring and reporting of all adverse events are adequate.

1.4. 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
	☒	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	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		[e.g., Sec 2.1 Analysis of Condition]
	☐	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	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant is seeking licensure for Syfovre 15 mg (0.1 mL of 150 mg/mL solution) for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

GA secondary to AMD is a serious medical condition with both health and social impacts for patients. GA is an advanced form of AMD and is characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris that leads to progressive and irreversible loss of visual function. No therapy is currently available for the treatment of GA.

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

2.2. Analysis of Current Treatment Options

None. There are no currently approved drugs for this indication.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

None. There are no currently approved drugs for this indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

During development, prior to initiating Studies APL2-304 and APL2-303, the Applicant obtained feedback from the FDA and the European Medicines Agency on plans to support registration of pegcetacoplan in GA secondary to AMD. Specifically, clinical, nonclinical, and chemistry, manufacturing, and controls development plans were the subject of meetings or interactions

with the FDA and the European Medicines Agency. A series of discussions occurred with the FDA to reach agreement on the development program for IVT pegcetacoplan. These meetings included:

- Type B end-of-Phase 2 meeting on 01 December 2017 (written response) with the objective of the meeting to obtain agreement on the two Phase 3 protocol designs as adequate and well-controlled confirmatory studies to support the indication of pegcetacoplan for the treatment of patients with GA secondary to AMD.
- Type C written response only on 21 October 2019.
  The Division of Ophthalmology agreed that the proposed (b) (4)-mL overfill was acceptable on the basis of dead volume loss and filling machine variability. Applicant was asked to provide supporting data relevant to overfill in the NDA for the Division's review.
- Type C meeting on 01 March 2021. The objective of the meeting was to discuss the statistical analysis strategy and pooling proposals for the Phase 3 studies for pegcetacoplan. In response to feedback on the statistical analysis plans (SAPs), Applicant made several modifications to the plans, and the revised SAPs were submitted to Investigational New Drug Application 124784 on 17 August 2021.
- Type C written response only on 28 September 2021. The Division agreed that the concentration for leachables was acceptable but disagreed with Applicant's proposal to provide 9-month drug product registration stability data. The Division expects 12-month drug product registration stability data at the time of NDA submission.
- Type A preliminary meeting comments on 09 November 2021. The Division advised Applicant that Studies APL2-303, APL2-304, and POT-CP121614 appeared to be adequate and well controlled, although the final determination would be a review issue. The Division recommended analysis of the mean rate of change from baseline (CFB) in total GA lesion area using fundus autofluorescence (FAF) for the primary endpoint.
- Type B Pre-NDA meeting on 21 January 2022. The Division recommended that Applicant submit complete Month 18 efficacy and safety data in the initial NDA and to focus on the post–Month 12 endpoints that are most relevant for informing the benefit-risk profile. The Division agreed to Applicant's plan to include Month 12 clinical study reports (CSRs) in the initial NDA, full data sets through Month 18, brief summaries of key findings at Month 18, and brief summaries of pertinent data beyond Month 18.

In July 2020, both Studies APL2-304 and APL2-303 completed enrollment, and the last subject visit for the Month 24 endpoints is anticipated to be July 2022.

On May 23, 2018, the Applicant submitted a request for Fast Track designation. July 19, 2018, the Agency designated the investigation of APL-2 intravitreal injection for the treatment of geographic atrophy secondary to age-related macular degeneration as a Fast-Track development program.

On May 26, 2022, the Applicant requested a priority review designation for this new drug application (NDA) for pegcetacoplan in the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). This NDA received Priority review designation given there are currently no approved drugs for GA.

At the time of the NDA submission the Applicant requested a full waiver of Pediatric Research Equity Act requirements for intravitreal pegcetacoplan based on studies are impossible or highly impractical per section 505B(a)(4)(A)(i) of the act. On October 18, 2022, a PeRC meeting concurred with a full waiver for pediatric studies.

On November 2, 2022, the Agency had a Telecon with the Applicant requesting 24 month follow up data be submitted for Studies APL2-304 and APL2-303. The Applicant agreed to submit the 24-month data which amended the PDUFA date extending the date 3 months to February 26, 2023.

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

4.1. Office of Scientific Investigations (OSI)

Studies APL2-303 and APL2-304 were conducted at 110 US sites and 122 non-US investigational sites. A routine inspection at two US sites was requested for Studies APL2-303 and APL2-304.

International inspections were not requested because there were no serious issues to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations. No single investigational site included enough subjects to significantly alter the result of the clinical trial. There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

Studies APL2-303 and APL2-304 were considered to have been conducted adequately, and the data generated by the applicant appeared acceptable in support of the application.

4.2. Product Quality

SYFOVRE (pegcetacoplan injection) is a sterile, preservative-free, clear, colorless to light yellow aqueous solution in a single-dose vial. Each vial allows for the delivery of 0.1 mL of solution containing 15 mg pegcetacoplan, trehalose dihydrate (5.95 mg), glacial acetic acid (0.0895 mg), sodium acetate trihydrate (0.0353 mg), and Water for Injection. SYFOVRE may also contain sodium hydroxide and/or additional glacial acetic acid for adjustment to a target pH of 5.0.
SPECIFICATIONS

Compendial excipients used in the formulation of pegcetacoplan, solution for intravitreal injection, 15 mg/0.1 mL are listed in Table 1 with reference to the corresponding pharmacopeia.

Table 1: Compendial References for Excipients Used in Pegcetacoplan Drug Product

Excipient	Function	Specification Reference
Trehalose dihydrate	(b) (4)	NF/Ph.Eur./JP
Glacial acetic acid	(b) (4) pH adjustment	USP/Ph.Eur./JP
Sodium acetate trihydrate	(b) (4)	USP/Ph.Eur./JP
Sodium hydroxide	pH adjustment	NF/Ph.Eur./JP
Water for Injection	Solvent	USP/Ph.Eur.

NF- National Formulary; USP - United States Pharmacopoeia; Ph.Eur. - European Pharmacopoeia; JP – Japanese Pharmacopoeia

4.3. Clinical Microbiology

Not applicable. This is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

Carcinogenesis
Animal carcinogenicity studies of pegcetacoplan have not been conducted.

Mutagenesis
Pegcetacoplan was not mutagenic when tested *in vitro* bacterial reverse mutation (Ames) assays and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Impairment of Fertility
There are no fertility data in humans or animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys indicative of an impact of pegcetacoplan on fertility.

Animal Pharmacology / Toxicology
Repeated once-monthly intravitreal dosing of pegcetacoplan to monkeys for 9 months at 3.3 times the human dose (based on estimated initial vitreous concentrations) was well tolerated with no ocular or systemic adverse effects.

Effects in non-clinical SC repeated dose toxicity studies were observed only at systemic exposures substantially higher than the maximum human exposure after intravitreal administration, indicating little relevance to clinical use.

Repeated daily SC dosing of 28 mg/kg/day pegcetacoplan to monkeys (more than 350 times the human exposure (C_{max} and AUC) resulted in microscopic renal tubular degeneration which was minimal and nonprogressive.

4.5. Clinical Pharmacology

Mechanism 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.

Pharmacodynamics / Pharmacokinetics
SYFOVRE is administered directly into the vitreous to exert local effects in the eye. Following repeat intravitreal administration of pegcetacoplan at a dose of 15 mg/0.1 mL, geometric mean (%CV) serum C_{max} value at steady state was 2.2 µg/mL (28.7%) and 1.5 µg/mL (58.1%) for GA patients dosed monthly and every other month, respectively. The steady state geometric mean (%CV) serum trough concentrations were 1.0 µg/mL (52.3%) and 0.2 µg/mL (89.6%) for patients treated monthly and every other month, respectively.

Absorption
Following intravitreal administration of pegcetacoplan, the systemic median T_{max} of pegcetacoplan is between 7 and 14 days. Following intravitreal treatment, systemic exposure of pegcetacoplan increases approximately proportionally over a dosage range from 4 to 20 mg.

Distribution
The geometric mean (95%CI) volume of distribution of pegcetacoplan is approximately 1.85 L (1.62 - 2.12) in patients with GA following intravitreal administration.

Elimination
The estimated geometric mean (%CV) of clearance (CL) is 0.284 L/day (21.1%) and geometric mean half-life of elimination ($t_{1/2}$) is 4.5 days (21.1%) in patients with GA. Results of a radiolabeled study in monkeys suggest the primary route of elimination is via urinary excretion.

Metabolism
Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways.

Specific Populations
There were no clinically significant differences on the pharmacokinetics of pegcetacoplan intravitreal administration based on age (60 to 97 years old), gender, renal impairment, and hepatic function as evaluated by total bilirubin (0.05-1.7 mg/dL), albumin (2.96-5.38 g/dL), aspartate aminotransferase (8.7-101 IU/L), or alanine aminotransferase (5.9-136 IU/L).

4.6. Devices and Companion Diagnostic Issues

Clinical Trial Medical Devices

For convenience during the clinical trial, the sponsor provided the medical devices required for delivery. The pegcetacoplan DP was aseptically transferred into a luer-lock syringe using a 5-µm filter needle or vial adapter at the time of administration, then delivered via an intravitreal injection by a qualified HCP through an injection needle, and a 1 mL luer-lock syringe.

A variety of devices were chosen and provided for use in the clinical study. Each was separately sourced from the multitude of commercially available medical devices available for use in the USA. They were chosen based on dose capability and compatibility.

Devices Required for Injection

As none of the devices required for injection are to be provided with the drug product, Pegcetacoplan, solution for intravitreal injection, 150 mg/mL is not a Combination Product as defined in 21 CFR Part 3 and is regulated as drug product. The devices that are required for

injection are to be sourced by the HCP from commercially available devices. They must meet the following conditions of use:

1. The transfer needle used to withdraw DP from the drug vial to syringe must have (b) (4) a 5-µm filter.
2. The syringe used to transfer and administer the drug must have a luer-lock hub and a 0.1 mL dose mark.
3. The needle used to inject should be a (b) (4) thin-wall injection needle with a luer-lock hub.
    a. Note: Increased injection forces and/or increased injection time could be experienced if a is used (e.g., 30G).
4. None of the devices should be contraindicated for intravitreal injection.

Reviewer's comment(s):

Pegcetacoplan solution is for intravitreal injection and is not a Combination Product. It is regulated as a drug product.

5. Sources of Clinical Data and Review Strategy

Type of study	Study identifier	Study design and type of control	Test product(s); dosage regimen; route of administration	Number of subjects	Duration of treatment	Study status; type of report
Safety/PK Phase 1	POT-CP043014 (ASAP II) (Study POT-CP043014)	Open-label, prospective, nonrandomized, single-dose escalation	Cohort 1: Single dose of 4 mg pegcetacoplan (100 µL of 40 mg/mL) IVT Cohort 2: Single dose of 10 mg pegcetacoplan (100 µL of 100 mg/mL) IVT Cohort 3: Single dose of 20 mg pegcetacoplan (100 µL of 200 mg/mL) IVT	13 subjects	Approximately 123 days	Completed Full CSR
Safety Phase 1b	APL2-103 (Study 103)	Multicenter, open-label study	Cohort 1: Pegcetacoplan 15 mg/0.1 mL monthly Cohort 2a: Pegcetacoplan 15 mg/0.1 mL monthly Cohort 2b: Pegcetacoplan 15 mg/0.1 mL EOM	19 subjects Cohort 1: 16 subjects Cohort 2a: 2 subjects Cohort 2b: 1 subject	Duration of participation: Cohort 1 approximately 61 months Cohort 2 approximately 37 months	Completed Full CSR
Safety Phase 1b/2	APL2-203 (Furlong) (Study 203)	Open-label, multicenter, nonrandomized	Pegcetacoplan 15 mg/100 µL IVT	17 subjects	Screening: 4 weeks Treatment period: 48 weeks Follow-up period: 24 weeks Duration of participation: Approximately 76 weeks	Completed Abbreviated CSR
Safety Phase 2	POT-CP121614 (Filly) (Study CP121614)	Prospective, multicenter, randomized, single-masked, Sham-controlled study	Pegcetacoplan 15 mg/100 µL monthly IVT Pegcetacoplan 15 mg/100 µL EOM IVT Sham injection monthly Sham injection EOM	246 subjects	18.5 months	Completed Full CSR
Efficacy/safety Phase 3	APL2-303 (DERBY) (Study 303)	Multicenter, randomized, double-masked, sham-controlled study	Pegcetacoplan 15 mg/0.1 mL IVT monthly Pegcetacoplan 15 mg/0.1 mL IVT EOM Sham IVT monthly Sham IVT EOM	Month 12: 621 subjects randomized, broken down as follows: PM = 206 subjects PEOM = 208 subjects SM = 102 subjects SEOM = 105 subjects	Treatment duration: 24 months Duration of participation: Approximately 27 months	Ongoing (Month 12 CSR and Post-Month 12 Addendum available)

Efficacy/safety Phase 3	APL2-304 (OAKS) (Study 304)	Multicenter, randomized, double-masked, sham-controlled study	Pegcetacoplan 15 mg/0.1 mL IVT monthly Pegcetacoplan 15 mg/0.1 mL IVT EOM Sham IVT monthly Sham IVT EOM	Month 12: 637 subjects randomized, broken down as follows: PM = 213 subjects PEOM = 212 subjects SM = 106 subjects SEOM = 106 subjects	Treatment duration: 24 months Duration of participation: Approximately 27 months	Ongoing (Month 12 CSR and Post-Month 12 Addendum available)
Safety and efficacy Phase 3	APL2-GA-305 (Gale)	Open-label, multicenter long-term extension study	Pegcetacoplan IVT 15 mg/0.1 mL monthly PEOM: Pegcetacoplan 15 mg/0.1 mL EOM	Planned: ~1200 subjects	Up to 36 months	Ongoing
Population PK Model	GA PK APL-EX21- CP-012	Population PK modeling using subjects treated with IVT pegcetacoplan in 4 studies: Phase 1, Phase 1b/2, Phase 2, and Phase 3	All studies: Pegcetacoplan, IVT: Study POT-CP043014 = SAD: 4, 10, 20 mg Study APL2-203 = 15 mg monthly Study POT-CP121614 = Cohort 1: 15 mg monthly; Cohort 2: 15 mg EOM APL2-303 = Cohort 1: 15 mg monthly; Cohort 2: 15 mg EOM	261 subjects	Not applicable, used previously collected data following the first dose of study medication	Completed Full report
Population Exposure Response Model	GA ER APL-EX21- CP-013	Disease progression modeling using subjects treated with either pegcetacoplan (monthly or EOM) or sham (monthly or EOM)	Sham treatment, 2 treatment groups: 15 mg monthly and 15 mg every other month:	Approximately 500 subjects	Not applicable, used previously collected data	Completed Full report

Abbreviations: AMD = age-related macular degeneration; CSR = clinical study report; EOM = every other month; ER = exposure response; FAF = fundus autofluorescence; GA = geographic atrophy; HV = healthy volunteer; IV = intravenous; IVT = intravenous therapy; NA = not applicable; nAMD=neurovascular age-related macular degeneration; PEOM = pegcetacoplan every other month; PK = pharmacokinetics; PM = pegcetacoplan monthly; SAD = single ascending dose; SEOM = sham every other month; SM = sham monthly; VEGF = vascular endothelial growth factor

Reviewer's comment(s):

APL2-303 and APL2-304 were two adequate and well controlled, randomized clinicals with up to 24-month follow-up submitted and are the basis for this NDA review.

Studies APL2-303 and APL2-304 were conducted at 122 and 304 clinical sites, respectively. The list of Investigators is provided for those sites where ten (10) or more subjects were enrolled.

Table 2: Sites and Subjects Enrolled

Study APL2-303 List of Investigators Enrolling 10 or more Subjects			
Institution	Principal Investigator	Site Number	Number of Subjects Enrolled
Cumberland Valley Retina Consultants (CVRC) 1150 Opal Court Hagerstown, MD 21740-5940, USA	Allen Y. Hu, MD	01-007	16
Ophthalmic Consultants of Boston, Inc. 50 Staniford St., Suite 600 Boston, MA 02114 USA	Jeffrey Heier, MD	01-013	20
Black Hills Regional Eye Institute 2800 Third Street, Rapid City, SD 57701-7374 USA	Prema Abraham, MD	01-016	12
The Retina Partners - Encino 16500 Ventura Blvd Ste 250 Encino, CA 91436-2018 USA	Amir Guerami, MD	01-018	12
Charlotte Eye, Ear, Nose & Throat Associates, PA – SouthPark Location Charlotte Eye Ear Nose and Throat Associates, PS 6035 Fairview Rd., Charlotte, NC 28210 USA	Andrew Antoszyk, MD	01-029	13
Retina Associates of Cleveland, Inc - Beachwood 3401 Enterprise Parkway, Suite 300 Cleveland, OH 44122-7344 USA	Lawrence J. Singerman FACS, MD	01-036	17
Asheville Eye Associates (AEA) - Asheville Western Carolina Retinal Associates 21 Medical Park Dr. Asheville, NC. 28803- 2493 USA	William Z. Bridges, MD	01-040	16
Bay Area Retina Associates - Walnut Creek Bay Area Retina 365 Lennon Ln., Suite 250 Walnut Creek, CA. 94598 USA	Roger A. Goldberg, MD	01-041	10
Bascom Palmer Eye Institute - University of Miami Health 7101 Fairway Drive Palm Beach Gardens, FL. 33136-1119 USA	Zohar Yehoshua, MD	01-044	10
Retina Associates of Cleveland, Inc - Youngstown 5390 Belmont Ave. Youngstown, OH. 44505-1025 USA	Joseph Coney, MD	01-055	10
Retina Consultants of Texas - The Woodlands 17350 St. Luke's Way, Ste 120	Charles Wykoff, MD, PhD	01-057	25

The Woodlands, TX. 77384-4167 USA			
Mid Atlantic Retina - Huntingdon Valley Mid Atlantic Retina 727 Welsh Road Suite 206 Huntingdon Valley, PA 19006-6398 USA	Mitchell Fineman, MD	01-058	23
Retina Associates of Cleveland, Inc – Beachwood 15299 Bagley Rd., Ste 200 Middleburg Heights, OH 44130 USA	Llewelyn J. Rao, MD	01-071	11
Centre Monticelli Paradis d'Ophtalmologie Centre Paradis- Monticelli 433 rue Paradis Marseille, 13 13008 FRA	Francois Devin, MD	06-003	12
Centrum Medyczne UNO-MED – Tarnowie - ul. Gumniska 11 Centrum Medyczne UNO-MED Gumniska 11 Tarnów, MA 33-100 POL	Piotr Oleksy, MD	31-004	10
Centro Oftalmologico Dr. Charles S.A Riobamba 841 Recoleta Ciudad Autónoma Buenos Aires, C C1116ABA ARG	Anibal Andres Francone, MD	33-007	21
Buenos Aires Macula Arenales 981 Piso 4 Caba, C ARG	Mario J. Saravia, MD	33-009	11
Hospital Medicina dos Olhos -Unidade Retina Rua Estados Unidos 1881 Sao Paulo, SP 01427-002 BRA	Andre Correa Maia de Carvalho, MD	34-005	11
Clínica Ocular Oftalmologia LTDA Rua Fortunato Ramos 411, Praia Do Canto Vitória, ES 29055-290 BRA	Laurentino Biccas Neto, MD	34-008	11

Study APL2-304 List of Investigators Enrolling 10 or more Subjects			
Institution	Principal Investigator	Site Number	Number of Subjects Enrolled
West Texas Retina Consultants (WTRC) - Abilene Location Retina Research Institute of Texas 5441 Health Center Dr. Abilene, TX 79606-1224 USA	Sunil S. Patel MD, PhD	01-502	11
Cumberland Valley Retina Consultants (CVRC) 1150 Opal Court Hagerstown, MD 21740-5940 USA	Allen Y. Hu MD	01-506	31
Retina Consultants of Texas – Houston 6560 Fannin Street Suite 750	David Warren Brown MD	01-512	14

Houston, TX 77030-2727 USA			
Retinal Consultants Medical Group, Inc. – Sacramento – Parkcenter Drive Retinal Consultants Medical Group, Inc. 3939 J. Street Suite 106 Sacramento, CA 95819-3631 USA	Joel Pearlman, MD	01-518	10
Wills Eye Hospital Mid Atlantic Retina 840 Walnut St., Suite 1020 Philadelphia, PA 19107-5109 USA	Sunir Garg, MD Former PI: Allen Ho, MD	01-527	16
Retina Research Institute at New England Retina Consultants, PC 3640 Main Street Suite 201 + 202 A Springfield, MA 01107-1139 USA	David R. Lally MD	01-530	29
Retina Specialty Institute - Pensacola 5150 N Davis Hwy, Pensacola, FL 32503-2030 USA	Sunil Gupta MD	01-531	12
Orange County Retina Medical Group 1200 N Tustin Avenue, Suite 140 Santa Ana, CA 92705-3592 USA	Timothy T. You MD	01-536	10
Mid Atlantic Retina - Bethlehem 5325 Northgate Drive Suite 103 Bethlehem, PA 18017-9411 USA Mid Atlantic Retina – Bethlehem 727 Welsh Rd Ste 206 Huntingdon Valley, PA 19006-6398 USA	Allen Chiang, MD Former PI: Carl Regillo, MD	01-546	18
Colorado Retina Associates (CRA) - Red Rocks Medical Center Location Colorado Retina Associates 400 Indiana Street, Suite 310 Golden, CO 80401-5033 USA	Nancy J. Christmas MD	01-547	15
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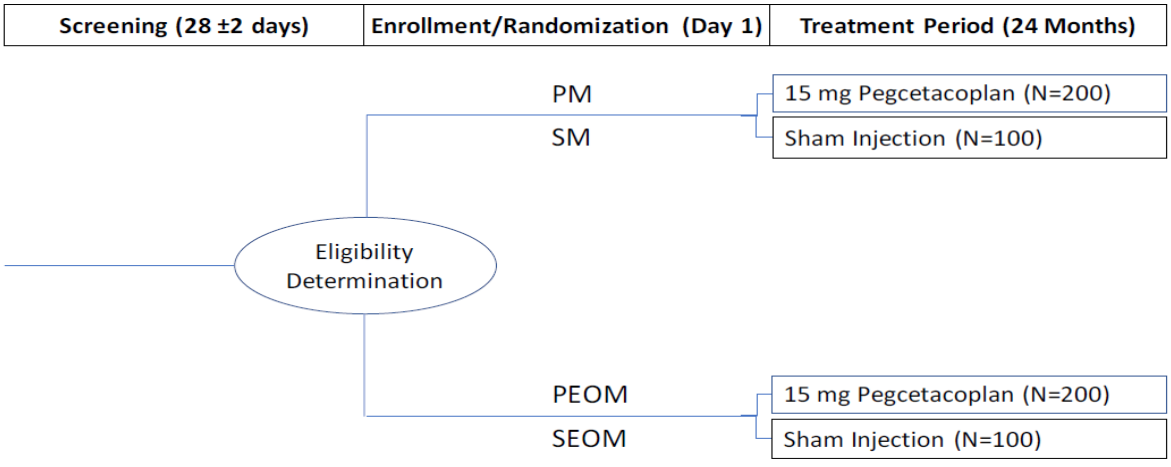
5.1. Review Strategy

Data from Studies APL2-303 and APL2-304 in subjects with GA secondary to AMD form the basis of the pegcetacoplan effectiveness and safety claims. Studies APL2-303 and APL2-304 were Phase 3, multicenter, randomized, double-masked, sham-controlled studies. The primary endpoint of these studies was to evaluate the efficacy of pegcetacoplan compared with sham injection as assessed by change in the total area of GA lesions from baseline to Month 12 measured by Fundus autofluorescence (FAF). Subjects who met all inclusion criteria and no exclusion criteria were randomly assigned to treatment in a 2:2:1:1 manner to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly (SM), or sham every other month (SEOM), respectively. Randomization was stratified according to GA lesion area at screening (<7.5 mm^2; ≥7.5 mm^2) and presence/absence of choroidal neovascularization (CNV) in the fellow eye.

Figure 1: Study APL2-303 and APL-304 Study Design



Abbreviations: PM = pegcetacoplan monthly; SM = sham monthly; PEOM = pegcetacoplan every other month; SEOM = sham every other month.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Studies to Support Efficacy

A Phase 3, multicenter, randomized, double-masked, sham-controlled study to compare the efficacy and safety of intravitreal pegcetacoplan therapy with sham injections in subjects with geographic atrophy secondary to age-related macular degeneration (APL2-303, Derby)

A Phase 3, multicenter, randomized, double-masked, sham-controlled study to compare the efficacy and safety of intravitreal pegcetacoplan therapy with sham injections in subjects with geographic atrophy secondary to age-related macular degeneration (APL2-304, Oaks)

6.1.1. Study Design

Studies APL2- 303 and APL2-304 were of similar design and characteristics.

Trial Design

Refer to Figure 1 above for Diagram of Trial Design.

The study eye must have met all inclusion criteria. If both eyes met the inclusion criteria, the eye with the worst normal luminance visual acuity at the screening visit was designated as the study eye. If both eyes had the same visual acuity, the right eye was selected as the study eye. Ocular-specific inclusion criteria applied to the study eye only, unless otherwise specified.

Subjects were aged ≥ 60 years, with normal luminance best-corrected visual acuity (NL-BCVA) of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent), a clinical diagnosis of GA secondary to AMD as determined by the investigator and confirmed by the reading center, as meeting the following criteria on FAF imaging at screening as follows:

- Total GA area was ≥2.5 and ≤17.5 mm^2 (1 and 7 disk areas respectively).
- If GA was multifocal, at least 1 focal lesion was ≥1.25 mm^2 (0.5 disk areas), with the overall aggregate area of GA as specified above for total GA area.
- The entire GA lesion had to be completely visualized on the macula centered image and had to be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy.
- Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e., pattern = none) was exclusionary.

There had to be adequate clarity of ocular media, adequate pupillary dilation, and fixation to permit the collection of good quality images as determined by the investigator.

Statistical Analysis Plan

Primary efficacy analyses were performed using the mITT population, with subjects grouped according to the treatment assigned at randomization. The SM group and the SEOM group were pooled into a single group for analyses. The primary endpoint was the Change From Baseline (CFB) to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF images assessed by the central reading center.

A mixed effect model for repeated measure (MMRM) was used to analyze the primary endpoint. The analysis model included treatment (PM, PEOM, sham), presence of CNV in the fellow eye at baseline (yes, no) and baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) as fixed effects, time (study month, categorical) as a factor, the time × treatment interaction term, and the baseline GA lesion area (<7.5 mm^2 or ≥7.5 mm^2) × time interaction term. The least square (LS) mean CFB to Month 12 was estimated from the model for each of 3 groups as well as the comparisons of each of the 3 groups to each other. A common unstructured covariance matrix was used to model the within- subject errors.

Hypothesis testing in each study was performed at a 2-sided $\alpha = 0.0496$ to account for a 0.0001 penalty for each of 4 independent data monitoring committee unmasked data reviews occurring before the primary analysis. Multiplicity was controlled for the primary endpoint using a fixed sequencing approach where the comparison between PM and sham pooled was tested and if statistically significant, the comparison between PEOM and sham pooled was tested.

Sensitivity analyses were performed to evaluate the robustness of the primary analysis results. Analyses were performed in the mITT population. The primary endpoint was also analyzed without pooling the 2 sham arms (SM and SEOM), and also excluding GA total area assessments with an indeterminate boundary. Analyses of endpoints closely related to the primary efficacy endpoint were performed for the mITT population to provide supplemental information. These included change in square root of GA area and percent change in GA area/square root of GA area. Supplemental analyses of the primary efficacy endpoint included a coronavirus disease 19 (COVID-19) adjusted Month 12 threshold estimand, analysis of the PP population, rate of change in GA area analysis, and subgroup analyses.

For the COVID-19 adjusted analyses, the hypothetical strategy was used whereby assessments after the intercurrent event (relevant undertreatment) occurred were set to missing/censored in the analysis. The threshold for missed/not received injections due to the COVID-19 pandemic was missing 2 or more injections (monthly group) and missing 1 or more injections (every other month group) prior to the Month 12 visit attributable due to the COVID-19 pandemic.

For the rate of change analysis, the mean rate of change in GA area (i.e., slope) was compared between each pegcetacoplan group and the sham pooled group by use of linear mixed effects model assuming time as continuous and linear ("slope model"). A second rate of change analysis used a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model"). This analysis added a knot at the Month 6 Visit that allowed for the slope of lesion growth to differ between the 2 periods for each of the treatment groups.

Analyses of endpoints closely related to the primary efficacy endpoint were performed for the mITT population to provide supplemental information. These included change in square root of GA area and percent change in GA area/square root of GA area.

Reviewer's comment(s):
During the Type B Pre-NDA meeting on 21 January 2022, the Division recommended the Applicant submit complete Month 18 efficacy and safety data in the initial NDA. For Studies APL2-303 and APL2-304 the Applicant had submitted the analysis through the 18-month follow-up exam.

On November 2, 2022, the Agency had a Telecon with the Applicant requesting 24 month follow up data be submitted for Studies APL2-304 and APL2-303. The Applicant agreed and subsequently submitted the 24-month data to the NDA.

Protocol Amendments

Protocol Amendments for Study APL2-303 – Brief Summary of Changes Made

Protocol amendment	Effective date	Main changes made
Original Protocol Version 1.0	09 December 2017	N/A
Protocol Amendment 1	31 May 2018	• Study objectives were expanded to describe the endpoints that will be utilized to meet them. • It was noted that exploratory objectives utilizing digital applications will be conducted in select sites/countries only as these applications will be utilized according to local regulation. • It was clarified that to participate in the study, subjects must be diagnosed with GA of the macula secondary to AMD in the study eye. • It was noted that if both eyes have the same visual acuity score, the right eye will be selected as the study eye. • "Endothelial cell count" was removed as an assessment that will be provided to the reading center for objective assessment of subject eligibility. "Optical Coherence Tomography Angiography (OCT-A, selected sites only)" was added as an assessment that will be provided to the reading center for objective assessment of subject eligibility. • OCT-A was added as a monitoring assessment for select sites to confirm the diagnosis of new active CNV. • "Country" was removed as a stratification factor. • Blood volume for genetic biorepository was updated. • Clarified that all SAEs will be reported to the safety monitor by the investigator via fax or email within one calendar day of becoming aware of the event, whether or not the serious events are deemed drug related. • Text was modified to clarify that the study staff performing visual acuity should be masked to the treatment assignment only; the protocol previously stated that staff should also be blinded to the study eye.

Protocol Amendment 2	08 August 2018	• Exclusion criteria #4 and #10 were modified for clarity and to exclude subjects with history of IVT injection in either eye. • The following exclusion criteria was implemented as Exclusion Criteria #13 (EC criteria following this were renumbered):13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo. • Clarified that the following endpoint will not be limited to select sites only: CFB at each planned assessment in the total area of GA lesion(s) in the study eye (in mm^2) as assessed by FAF. • Noted that the NEI VFQ-25 distance activity and near activity subscale score endpoints will be conducted in select countries as these subscales are not available in all languages. • Masking language was modified to indicate that the PI is required to remain masked to subjects' treatment assignments, while the treating investigator and any associated support staff involved in IP administration will be unmasked. • Guidance on the treatment of new exudation related to active choroidal neovascularization in the study eye and/or fellow eye was modified to clarify that the reading center will provide a report to indicate whether or not there is evidence of active, exudative AMD, and the investigator will then determine if anti-VEGF treatment should be initiated. The investigator should wait for the reading center report before making a decision regarding treatment, except in cases where there is clear evidence of disease activity that may have a detrimental visual impact if not treated immediately. It was also clarified that either ranibizumab or aflibercept should be selected as the anti-VEGF therapy, and that the unmasked investigator should administer anti-VEGF treatment if the treatment is administered on the same day as APL-2. It was also noted that any treatments of therapies administered to the fellow eye within 5 years of screening should be recorded as a concomitant medication. • Clarified that in the event that a subject is suspected to have new active CNV in the study eye and/or the fellow eye, an SD-OCT and FA using the protocol specified procedures should be performed and sent to the Reading Center to confirm the diagnosis. In addition, in selected sites, OCT-A should also be captured according to the study imaging protocol and sent to the Reading Center.

Protocol Amendment 3	14 February 2019	• PK and complement profile assessments have been removed from this study. • Updated to include the following statement: In recent studies conducted with APL-2 IVT from a single manufacturer, events of transient moderate and severe intraocular inflammation have been observed. • Treatment administration section was revised to allow study treatment administration to occur on a day separate from the assessment visit. • The procedure for sham injection was further described. The procedure for sham injection will be the same as that used for IVT injection until the actual injection but no actual injection will occur. The injecting investigator will only touch the study eye with the blunt end of the syringe. No needle or medication will be injected inside the eye. Detailed instructions on sham injection procedures and postinjection procedures will be provided in the Manual of Procedures. • Throughout the Study Procedures section, it has also been noted that endothelial cell count assessment is for "select sites only." This was previously noted in the schedule of events but not consistently in the body of the protocol. In addition, FAF and NAR are no longer "study eye only." • The following assessments were removed as they will no longer be conducted at the screening Visit 1: - Low-luminance BCVA - Endothelial cell count - OCT-A • The following assessments were added at Day 1 (Visit 2): - Endothelial cell count - OCT-A (select sites)

Protocol Amendment 4	27 April 2020	Following information related to COVID-19–related changes was added: • Rescreening procedure If a subject was deemed a screen failure for not being able to meet the original screening window (Day −28 to Day −1 [+/- 2 days]) because of COVID-19 related restrictions, a rescreening visit was allowed. • Extended IP administration window as follows: - Monthly treatment group:-8 days to + 15 days. Note, interval for consecutive injections was at least 14 days. - EOM treatment group: −8 days to + 30 days for the first study year and −16 days to +30 days for the second study year. • Temporary changes to masking rules were implemented Every masked individual that performed IP administration and/or postinjection assessment (all unmasked assessment) as a temporary measure, was permanently considered an unmasked individual and was not able to perform masked assessments once these exemptions were lifted.
Protocol Amendment 5	12 August 2020	• Added the descriptor "maximum" when referencing reading speed • Removed the 6-month follow-up period and updated the study length from 30 months to 24 months and made it a 30-or 60-day follow-up period on the basis of treatment group because that length of time is deemed sufficient to evaluate the safety of pegcetacoplan on the basis of its half-life in the vitreous. Additionally, there is an option for subjects to enroll in a separate extension study (StudyAPL2-GA-305) during which longer-term safety and efficacy will be collected.

Abbreviations: AMD = age-related macular degeneration; anti-VEGF = anti–vascular endothelial growth factor; APL-2 = pegcetacoplan; CFB = change from baseline; CNV = choroidal neovascularization; COVID-19 = coronavirus disease 2019; FAF = fundus autofluorescence; GA = geographic atrophy; IP = investigational product; IVT = intravenous; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire 25-Item Version; OCT-A = optical coherence tomography angiography; SD-OCT = spectral domain optical coherence tomography.

Protocol Amendments for Study APL2-304 – Brief Summary of Changes Made

Protocol amendment	Effective date	Main changes made
Original Protocol Version 1.0	18 April 2018	NA
Protocol Amendment 1	31 May 2018	• Study objectives were expanded to describe the endpoints that would be utilized to meet them. • It was noted that exploratory objectives utilizing digital applications would be conducted in select sites/countries only as these applications would be utilized according to local regulation. • It was clarified that to participate in the study, subjects must be diagnosed with GA of the macula secondary to AMD in the study eye. • It was noted that if both eyes had the same visual acuity score, the right eye would be selected as the study eye. • The inclusion criterion for microperimetry was incorporated to the main list of inclusion criteria (as No. 6) as all patients in this study would now be participating in this portion. • "Endothelial cell count" was removed as an assessment that was provided to the reading center for objective assessment of subject eligibility. • OCT-A (selected sites only) was added as an assessment that was provided to the reading center for objective assessment of subject eligibility. • OCT-A was added as a monitoring assessment for select sites to confirm the diagnosis of new active CNV. • Protocol updated to specify that microperimetry should be conducted on both eyes. • Text was modified to clarify that the study staff performing visual acuity should be masked to the treatment assignment only; the protocol had previously stated that staff should also be blinded to the study eye.

Protocol amendment	Effective date	Main changes made
Protocol Amendment 2	08 August 2018	• Exclusion criteria 4 and 10 were modified for clarity and to exclude subjects with history of IVT injection in either eye. • The following exclusion criterion was implemented as exclusion criterion 13 (exclusion criteria following this were renumbered): 13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo. • Noted that the NEI VFQ-25 distance activity and near activity subscale score endpoints would be conducted in select countries as these subscales were not available in all languages. • Masking language was modified to indicate that the PI was required to remain masked to subjects' treatment assignments, while the treating physician and any associated support staff involved in IP administration would be unmasked. • Guidance on the treatment of new exudation related to active CNV in the study eye and/or fellow eye was modified to clarify that the reading center would provide a report to indicate whether or not there was evidence of active, exudative AMD, and the investigator would then determine if anti-VEGF treatment should be initiated. The investigator should wait for the reading center report before making a decision regarding treatment, except in cases where there was clear evidence of disease activity that may have had a detrimental visual impact if not treated immediately. It was also clarified that either ranibizumab or aflibercept should be selected as the anti-VEGF therapy, and that the unmasked physician should administer anti-VEGF treatment if the treatment was administered on the same day as pegcetacoplan. It was also noted that any treatments of therapies administered to the fellow eye within 5 years of screening should be recorded as a concomitant medication. • Clarified that: In the event that a subject was suspected to have new active CNV in the study eye and/or the fellow eye, an SD-OCT and FA using the protocol specified procedures should be performed and sent to the reading center to confirm the diagnosis. In addition, in selected sites, OCT-A should also be captured according to the study imaging protocol and sent to the reading center.

Protocol amendment	Effective date	Main changes made
Protocol Amendment 3	14 February 2019	• PK and complement profile assessments were removed from this study. • Updated to include the following statement: In recent studies conducted with APL-2 IVT from a single manufacturer, events of transient moderate and severe intraocular inflammation have been observed. • The treatment administration section was revised to allow study treatment administration to occur on a day separate from the assessment visit. • The procedure for sham injection was further described: The procedure for sham injection was to be the same as that used for IVT injection until the actual injection but no actual injection would occur. The injecting physician only touched the study eye with the blunt end of the syringe. No needle or medication was to be injected inside the eye. Detailed instructions on sham injection procedures and postinjection procedures were provided in the manual of procedures. • Through the study procedures section it had also been noted that endothelial cell count assessment was for "select sites only". This had been previously noted in the schedule of events but not consistently in the body of the protocol. In addition, FAF and NIR were no longer "study eye only". • The following assessments were removed as they would no longer be conducted at the screening Visit 1: – Low-luminance BCVA – Endothelial cell count – OCT-A • The following assessments were added at Day 1 (Visit 2): – Endothelial cell count – OCT-A (select sites)

Protocol amendment	Effective date	Main changes made
Protocol Amendment 4	27 April 2020	An appendix was added to include information related to COVID-19–related changes to the study: • Rescreening procedure: If a subject was deemed a screen failure for not being able to meet the original screening window (Day −28 to Day −1 [+/− 2 days]) due to COVID-19 related restrictions, a rescreening visit was allowed. • Extended IP administration windows: - Monthly treatment group: −8 days to + 15 days. Note, interval for consecutive injections was at least 14 days. - EOM treatment group: −8 days to + 30 days for the first study year and −16 days to +30 days for the second study year • Temporary changes to masking rules: Every masked individual who performed IP administration and/or postinjection assessment (all unmasked assessment) as a temporary measure, was permanently considered an unmasked individual and was not able to perform masked assessments once these exemptions were lifted. • Minimum schedules of assessments: Minimum assessment tables were temporarily implemented to reduce the time required for each study visit and eliminate non-IP administration visits.
Protocol Amendment 5	12 August 2020	• Added the descriptor "maximum" when referencing reading speed • Removed the 6-month follow-up period and updated the study length from 30 months to 24 months and made it a 30- or 60-day follow-up period based on treatment group because that length of time is deemed sufficient to evaluate the safety of pegcetacoplan based on its half-life in the vitreous. Additionally, there was an option for subjects to enroll in a separate extension study (StudyAPL2-GA-305) during which longer-term safety and efficacy will be collected. • Inclusion criterion 6c was updated from "Reliability test ratio must be ≤20%"to "Fixation losses must be ≤20%"on the basis of regulatory feedback provided to the microperimetry device manufacturer

APL-2 = pegcetacoplan; BCVA = best-corrected visual acuity; CFB = change from baseline; CNV = choroidal neovascularization; COVID-19 = coronavirus disease 2019; EOM = every other month; FA = fluorescein angiography; FAF = fundus autofluorescence; GA = geographic atrophy; IP = investigational product; IVT = intravenous; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire 25-Item Version; NIR = near-infrared reflectance; OCT-A = optical coherence tomography angiography; PI = principal investigator; PK = pharmacokinetic; SD-OCT = spectral domain optical coherence tomography.

Reviewer's comment(s):
The protocol amendments for APL2-303 and APL2-304 were acceptable.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with Good Clinical Practice (GCP). The reviewer found the quality of the submitted data and analysis acceptable. There are no concerns regarding the data quality and integrity for this clinical study.

Financial Disclosure

Refer to Financial Disclosure Section 13.2.

Patient Disposition

Month 12 Data

Table 3: Subject Disposition of PM, PEOM, and Sham Pooled Groups of the Study Populations at Month 12 for Studies PPL2-304, APL2-303, and POT-CP121614-ITT Population

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 213)	PEOM (N = 212)	Sham pooled (N = 212)	PM (N = 206)	PEOM (N = 208)	Sham pooled (N = 207)	PM (N = 86)	PEOM (N = 79)	Sham pooled (N = 81)
Randomized	213	212	212	206	208	207	86	79	81
Completed treatment	183 (85.9)	188 (88.7)	191 (90.1)	182 (88.3)	188 (90.4)	179 (86.5)	52 (60.5)	60 (75.9)	69 (85.2)
Completed study	184 (86.4)	190 (89.6)	191 (90.1)	183 (88.8)	188 (90.4)	179 (86.5)	71 (82.6)	69 (87.3)	72 (88.9)
Withdrawn from treatment	29 (13.6)	24 (11.3)	21 (9.9)	24 (11.7)	20 (9.6)	27 (13.0)	34 (39.5)	19 (24.1)	12 (14.8)
Withdrawn from study	29 (13.6)	22 (10.4)	21 (9.9)	23 (11.2)	20 (9.6)	28 (13.5)	15 (17.4)	10 (12.7)	9 (11.1)
Primary reason for withdrawal from treatment									
AE	3 (1.4)	7 (3.3)	2 (0.9)	1 (0.5)	4 (1.9)	6 (2.9)	17 (19.8)	5 (6.3)	4 (4.9)
Lost to follow-up	2 (0.9)	1 (0.5)	1 (0.5)	1 (0.5)	0	0	NA	NA	NA
Physician's decision	0	0	0	1 (0.5)	0	0	5 (5.8)	1 (1.3)	0
Sponsor's decision	NA	NA	NA	NA	NA	NA	1 (1.2)	0	1 (1.2)
Consent withdrawal	13 (6.1)	11 (5.2)	9 (4.2)	15 (7.3)	9 (4.3)	14 (6.8)	6 (7.0)	5 (6.3)	3 (3.7)
Death	7 (3.3)	3 (1.4)	4 (1.9)	5 (2.4)	0	2 (1.0)	0	2 (2.5)	2 (2.5)
Because of COVID impact[a]	4 (1.9)	2 (0.9)	5 (2.4)	1 (0.5)	6 (2.9)	5 (2.4)	NA	NA	NA
Other	0	0	0	0	1 (0.5)	0	5 (5.8)	6 (7.6)	2 (2.5)
Primary reason for withdrawal from study									
AE	3 (1.4)	5 (2.4)	2 (0.9)	1 (0.5)	4 (1.9)	5 (2.4)	5 (5.8)	2 (2.5)	3 (3.7
Lost to follow-up	2 (0.9)	1 (0.5)	1 (0.5)	1 (0.5)	0	0	1 (1.2)	1 (1.3)	0
Consent withdrawal	14 (6.6)	11 (5.2)	9 (4.2)	15 (7.3)	10 (4.8)	15 (7.2)	7 (8.1)	5 (6.3)	3 (3.7)
Physician's decision	0	0	0	0	0	0	2 (2.3)	0	0
Death	7 (3.3)	3 (1.4)	4 (1.9)	5 (2.4)	0	3 (1.4)	0	2 (2.5)	2 (2.5)
Because of COVID impact[b]	3 (1.4)	2 (0.9)	5 (2.4)	1 (0.5)	6 (2.9)	5 (2.4)	NA	NA	NA
Other	0	0	0	0	0	0	0	0	1 (1.2)

Abbreviations: AE = adverse event; NA = not applicable

Notes: Disposition data for Studies APL2-304 and APL2-303 are based on the Month 12 analysis. Two subjects in the PEOM group (Subject (b) (6) and Subject (b) (6)) were incorrectly reported as having discontinued because of an AE. These have been corrected in the APL2-303 CSR erratum to death as the reason for discontinuation. Discontinuations due to COVID-19 impact include any discontinuation except for AE of COVID-19. Instances of AE of COVID-19 were captured under the AE category.

Sources: Study APL2-304 Month 12 CSR Table 14.1.2.2, Study APL2-303 Month 12 CSR Table 14.1.2.2, Study POT-CP121614 Post Hoc Table 14.5.1.

Across APL2-304 and APL2-303, similar percentages of subjects discontinued from the study or from treatment across the PM, PEOM, and sham pooled groups.

In POT-CP121614, a lower percentage of subjects completed the treatment in the PM and PEOM groups than in the sham pooled group. This difference was primarily attributable to the percentage of subjects who discontinued from treatment because of an AE. In POT-CP121614, subjects who had AEs of exudative AMD were discontinued from treatment.

Table 4: Drug Exposure for PM, PEOM, and Sham Pooled Groups of the Study Populations at Month 12 for Studies APL2-304, APL2-303, and POT-CP121614-mITT Population

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Number of injections									
Mean (SD)	10.2 (2.31)	5.4 (1.12)	7.8 (3.08)	10.2 (2.24)	5.3 (1.05)	7.7 (3.02)	10.1 (2.89)	5.5 (1.14)	8.4 (3.07)
Median	11.0	6.0	6.0	11.0	6.0	6.0	12.0	6.0	6.0
Min, max	2, 12	1, 7	1, 12	1, 12	1, 7	1, 12	2, 12	1, 6	1, 12
Duration of treatment (days)									
Mean (SD)	332.7 (65.16)	334.3 (67.62)	330.4 (63.97)	333.7 (60.63)	335.1 (58.63)	333.5 (61.88)	312.8 (88.11)	335.0 (67.58)	339.5 (63.35)
Median	358.0	358.0	357.0	358.0	358.0	357.0	360.0	360.0	360.0
Min, max	91, 368	1, 369	31, 372	31, 367	61, 385	30, 376	57, 369	57, 374	57, 380
Number of subjects with ≥75% of planned injections									
n (%)	170 (84.2)	182 (88.8)	170 (82.5)	164 (81.6)	169 (84.5)	162 (83.5)	67 (79.8)	69 (88.5)	73 (91.3)
Number of subjects with <75% of planned injections									
n (%)	32 (15.8)	23 (11.2)	36 (17.5)	37 (18.4)	31 (15.5)	32 (16.5)	17 (20.2)	9 (11.5)	7 (8.8)

Abbreviations: GA = geographic atrophy; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: 75% means patients received at least 9 of 12 injections for monthly group, 5 of 6 injections for EOM group.
Sources: Study APL2-304 Month 12 CSR Table 14.1.8.1.1 and Table 14.1.8.1.2; Study APL2-303 Month 12 CSR Table 14.1.8.1.1 and Table 14.1.8.1.2, Study POT-CP121614 CSR Post Hoc Table 14.5.4.

Study drug exposure was balanced across studies within the respective treatment groups. In Studies APL2-304 and APL2-303, compliance with the treatment regimen was acceptable with approximately 80% and 85% of subjects receiving ≥75% of planned injections across all groups, respectively.

Reviewer's comment(s):
APL2-303 and APL2-304 are the Applicant's two pivotal trials. The POT-CP121614 had been submitted as supportive information but does not have follow up after 12 months as recommended by the Agency.

Month 18 Data

Table 5: Subject Disposition at Month 18 in Studies APL2-304 and APL2-303 - mITT Population

	Study APL2-304			Study APL2-303		
	PM (N = 213)	PEOM (N = 212)	Sham pooled (N = 212)	PM (N = 206)	PEOM (N = 208)	Sham pooled (N = 207)
Completed treatment through Month 18	161 (75.6)	175 (82.5)	172 (81.1)	163 (79.1)	175 (84.1)	172 (83.1)
Discontinued treatment prior to Month 18	51 (23.9)	37 (17.5)	40 (18.9)	43 (20.9)	33 (15.9)	34 (16.4)
Completed study through Month 18	165 (77.5)	179 (84.4)	172 (81.1)	167 (81.1)	176 (84.6)	172 (83.1)
Discontinued study prior to Month 18	48 (22.5)	33 (15.6)	40 (18.9)	39 (18.9)	32 (15.1)	35 (16.9)
Primary reason for treatment discontinuation prior to Month 18						
AE	9 (4.2)	8 (3.8)	4 (1.9)	6 (2.9)	4 (1.9)	6 (2.9)
Lost to follow-up	3 (1.4)	4 (1.9)	4 (1.9)	1 (0.5)	2 (1.0)	0
Physician decision	0	1 (0.5)	1 (0.5)	3 (1.5)	0	0
Consent withdrawal	21 (9.9)	14 (6.6)	14 (6.6)	24 (11.7)	14 (6.7)	17 (8.2)
Death	12 (5.6)	7 (3.3)	6 (2.8)	6 (2.9)	4 (1.9)	5 (2.4)
Due to COVID impact	6 (2.8)	3 (1.4)	11 (5.2)	3 (1.5)	9 (4.3)	6 (2.9)
	Study APL2-304			Study APL2-303		
Primary reason for study discontinuation prior to Month 18						
AE	6 (2.8)	4 (1.9)	3 (1.4)	3 (1.5)	4 (1.9)	5 (2.4)
Lost to follow-up	3 (1.4)	4 (1.9)	4 (1.9)	1 (0.5)	2 (1.0)	0
Physician's decision	0	1 (0.5)	1 (0.5)	2 (1.0)	0	0
Consent withdrawal	22 (10.3)	14 (6.6)	14 (6.6)	24 (11.7)	13 (6.3)	18 (8.7)
Death	12 (5.6)	7 (3.3)	7 (3.3)	6 (2.9)	4 (1.9)	6 (2.9)
Due to COVID impact	5 (2.3)	3 (1.4)	11 (5.2)	3 (1.5)	9 (4.3)	6 (2.9)

Abbreviations: AE = adverse event; COVID = corona virus 2019; ITT = intent-to-treat; n = number of subjects; N = number of subjects in the treatment group; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study. Discontinuation due to COVID impact includes any discontinuation except for AE of COVID. Instances of AE of COVID are captured under the AE category.
Source: Study APL2-304 Post–Month 12 Report, Table 14.1.2.2; Study APL2-303 Post–Month 12 Report, Table 14.1.2.2.

The subject disposition Table through Month 18 summarizes the intent-to-treat population. Across both studies, overall, the percentage of subjects who completed treatment and study through Month 18 was similar across all treatment groups. In both studies, similar percentages of subjects discontinued from treatment across all treatment groups. Most subjects discontinuing treatment also discontinued from the study without further follow-up.

Through Month 18, the most frequent reasons for study or treatment discontinuation by subject percentage in the PM, PEOM, and sham pooled groups were consent withdrawal, COVID-19 impact, AEs, and death.

Table 6: Drug Exposure at Month 18 for Studies APL2-304 and APL2-303 - mITT Population

	Study APL2-304			Study APL2-303		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)
Total number of injections per subject, n						
Mean (SD)	14.8 (4.08)	7.9 (1.97)	11.2 (4.74)	14.7 (4.03)	7.7 (1.87)	11.2 (4.70)
Median	16.0	9.0	9.0	16.0	8.0	9.0
Min, Max	2, 18	1, 9	0, 18	1, 18	1, 10	1, 18
Duration of treatment, days						
Mean (SD)	485.5 (120.49)	491.1 (120.20)	489.7 (113.78)	482.5 (117.63)	496.1 (105.89)	492.2 (115.21)
Median	538.0	537.0	537.0	537.0	536.0	537.0
Min, max	91, 547	1, 568	59, 552	31, 548	61, 559	30, 549
Compliance, %						
Mean (SD)	88.5 (13.65)	92.4 (13.72)	88.6 (15.99)	87.0 (16.29)	89.5 (15.48)	88.8 (15.65)
Median	94.4	100.0	94.4	94.4	100.0	94.4
	Study APL2-304			Study APL2-303		
Min, max	29, 100	22, 113	0, 100	17, 100	22,111	22,100
Number of subjects with ≥75% of planned injections, n (%)	155 (76.7)	175 (85.4)	168 (81.2)	146 (72.6)	168 (83.6)	156 (80.0)
Number of subjects with <75% of planned injections, n (%)	47 (23.3)	30 (14.6)	39 (18.8)	55 (27.4)	33 (16.4)	39 (2.0)

Abbreviations: AE = adverse event; COVID = corona virus 2019; ITT = intent-to-treat; n = number of subjects; N = number of subjects in the treatment group; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Number of injections means number of injections in accordance with the schedule and treatment arm allocation. Duration of Treatment (days): Monthly group as (date of last injection + 30 days) -date of first injection + 1; EOM group as (date of last injection + 60 days) -date of first injection + 1. Duration of treatment will be truncated to a subject's early termination date, month 18 cutoff date, or study completion date, as appropriate. Compliance (%) is the number of injections administered divided by the number of scheduled injections up to completion or discontinuation of study treatment × 100. 75% means patients received at least 14 of 18 injections for monthly group, 7 of 9 injections for EOM group
Source: Study APL2-304 Post–Month 12 Report, Table 14.1.8.1.2; Study APL2-303 Post–Month 12 Report, Table 14.1.8.1.2.

Study drug exposure was balanced across studies within the respective treatment groups in the mITT population.

Reviewer's comment(s):
APL2-303 and APL2-304 are the Applicant's two pivotal trials with 24 month follow up data to compare with the studies' 18 month follow up data as recommended by the Agency.

Table of Demographic Characteristics

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Race									
White	185 (91.6)	189 (92.2)	187 (90.8)	187 (93.0)	185 (92.5)	187 (96.4)	82 (97.6)	75 (96.2)	80 (100)
Not reported	12 (5.9)	12 (5.9)	14 (6.8)	12 (6.0)	10 (5.0)	6 (3.1)	NA	NA	NA
Asian	3 (1.5)	1 (0.5)	2 (1.0)	0	1 (0.5)	0	1 (1.2)	0	0
Unknown	0	1 (0.5)	3 (1.5)	0	1 (0.5)	0	NA	NA	NA
Black or African American	2 (1.0)	0	0	1 (0.5)	1 (0.5)	0	1 (1.2)	1 (1.3)	0
Missing	0	2 (1.0)	0	1 (0.5)	1 (0.5)	1 (0.5)	NA	NA	NA
American Indian or Alaska Native	0	0	0	0	0	0	0	2 (2.6)	0
Multiple	0	2 (1.0)	0	0	1 (0.5)	0	NA	NA	NA
Study eye lesion size, mm^2									
n	202	205	206	201	200	194	84	78	80
Mean (SD)	8.1779 (3.8950)	8.2962 (3.9044)	8.2048 (3.7212)	8.3666 (4.1814)	8.2198 (3.8779)	8.2617 (4.2600)	7.969 (3.8477)	8.975 (4.4694)	8.197 (4.0720)
Minimum, maximum	2.489, 18.111	2.652, 17.706	2.587, 17.771	2.264, 17.832	2.439, 17.151	2.599, 17.490	2.53, 17.28	2.54, 16.96	2.56, 16.55
Study eye GA lesion location									
Subfoveal involvement, n (%)	116 (57.4)	131 (63.9)	146 (70.9)	129 (64.2)	119 (59.5)	121 (62.4)	47 (56.0)	52 (66.7)	46 (57.5)
Without subfoveal involvement, n (%)	86 (42.6)	74 (36.1)	60 (29.1)	72 (35.8)	81 (40.5)	73 (37.6)	37 (44.0)	26 (33.3)	34 (42.5)
Study eye GA focality (FAF)									
Unifocal, n (%)	59 (29.2)	62 (30.2)	68 (33.0)	54 (26.9)	53 (26.5)	66 (34.0)	21 (25.0)	29 (37.2)	27 (33.8)
Multifocal, n (%)	143 (70.8)	143 (69.8)	138 (67.0)	147 (73.1)	147 (73.5)	128 (66.0)	63 (75.0)	49 (62.8)	52 (65.0)
Study eye NL-BCVA score, ETDRS letters									
n	202	205	206	201	200	194	84	78	80
Mean (SD)	61.0 (15.30)	58.2 (17.03)	57.5 (16.57)	59.5 (17.40)	58.9 (15.97)	59.1 (16.85)	59.5 (15.71)	58.2 (15.95)	59.5 (17.08)
Minimum, maximum	25, 86	24, 89	24, 87	24, 94	24, 93	23, 89	27, 86	23, 88	25, 87

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Study eye LL-BCVA score, ETDRS letters									
n	202	205	206	200	199	191	84	78	80
Mean (SD)	34.0 (17.43)	32.3 (16.43)	32.7 (16.19)	32.1 (17.73)	33.0 (16.03)	33.7 (16.75)	36.5 (16.71)	30.9 (16.67)	33.0 (17.08)
Minimum, maximum	0, 76	0, 72	0, 72	0, 73	0, 78	0, 73	0, 80	1, 69	0, 73
Study eye LLD, ETDRS letters									
n	202	205	206	200	199	191	84	78	80
Mean (SD)	26.9 (16.92)	25.9 (17.80)	24.9 (17.43)	27.5 (17.79)	25.9 (16.56)	25.6 (16.52)	23.0 (14.33)	27.3 (15.63)	26.5 (17.08)
Minimum, maximum	−4, 66	−10, 76	−12, 71	−7, 77	−4, 73	−4, 71	−3, 58	−3, 64	1, 69
Study eye number of intermediate or large drusen									
≤20, n (%)	108 (53.5)	101 (49.3)	102 (49.5)	123 (61.2)	122 (61.0)	96 (49.5)	40 (47.7)	47 (60.3)	48 (60.1)
>20, n (%)	93 (46.0)	104 (50.7)	103 (50.0)	78 (38.8)	78 (39.0)	98 (50.5)	43 (51.2)	31 (39.7)	31 (38.8)
GA laterality, n (%)									
Bilateral GA	167 (82.7)	174 (84.9)	165 (80.1)	164 (81.6)	160 (80.0)	149 (76.8)	69 (85.2)	62 (80.5)	71 (89.9)
Study eye GA only	35 (17.3)	31 (15.1)	41 (19.9)	37 (18.4)	40 (20.0)	45 (23.2)	3 (3.7)	8 (10.4)	2 (2.5)
Can't determine	NA	NA	NA	NA	NA	NA	9 (11.1)	7 (9.1)	6 (7.6)
Fellow eye lesion size, mm^2									
n	167	174	165	164	160	149	69	69	72
Mean (SD)	7.9042 (5.4671)	8.3894 (5.5955)	8.5792 (5.4305)	8.3053 (5.8533)	8.7382 (5.8234)	8.1401 (6.2022)	8.305 (5.8417)	8.582 (6.6769)	8.014 (5.9558)
Minimum, maximum	0.121, 25.227	0.040, 28.057	0.138, 26.026	0.213, 26.416	0.195, 35.857	0.172, 28.487	0, 20.51	0, 28.23	0, 21.95
CNV in the fellow eye									
Present, n (%)	43 (21.3)	37 (18.0)	43 (20.9)	39 (19.4)	41 (20.5)	36 (18.6)	35 (41.7)	28 (35.9)	29 (36.3)

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Absent, n (%)	159 (78.7)	168 (82.0)	163 (79.1)	162 (80.6)	159 (79.5)	158 (81.4)	49 (58.3)	50 (64.1)	51 (63.8)

Abbreviations: CNV = choroidal neovascularization; CRF = case report form; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; GA = geographic atrophy; LL-BCVA = low-luminance best-corrected visual acuity; LL-VA = low-luminance visual acuity; mITT = modified intent-to-treat; NL-BCVA = normal-luminance best-corrected visual acuity; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Baseline was defined as the last available, nonmissing observation prior to first study drug administration.
For Studies APL2-303 and APL2-304, age (years) collected on the CRF was used. For Study POT-CP121614, age (years) = integer value ([informed consent date – date of birth + 1] / 365.25]. For Study APL2-304, rest of world included Australia, Brazil, Czech Republic, France, Germany, Israel, Italy, the Netherlands, New Zealand, Poland, Spain, and UK.
For Study APL2-303, rest of world included Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, New Zealand, Poland, Spain, and UK. For Study POT-CP121614, rest of world included Australia and New Zealand.
Fellow Eye category percentages are based on the number of subjects with presence of GA lesion in fellow eye at baseline.
Sources: Study APL2-304 Month 12 CSR Table 14.1.4.2 and Table 14.1.5.2, Study APL2-303 Month 12 CSR Table 14.1.4.2 and Table 14.1.5.2, Study POT-CP121614 CSR Table 14.1.3.1.2, Table 14.2.1.1.1, Table 14.2.1.13.1, Table 14.1.3.2.2, Table 14.2.2.1.1, Table 14.2.4.1, Post Hoc Table 14.5.2

Reviewer's comment(s):

Most demographics and baseline characteristics of the study populations were similar both across treatment groups and across these 3 studies. Studies APL2-303 and APL2-304 are the two pivotal trials with follow up submitted through Month 24. Study POT-CP121614 had follow up only through Month 12.

Efficacy Results – Primary Endpoint

The Applicant's Primary Endpoint was the 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 injections.

Month 12 Data

Table 7: Analyses of CFB in Total Area of GA Lesion(s) (mm2) (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 the model	202	204	205	200	199	193
LS mean (SE) CFB in GA lesion area, mm^2	1.5575 (0.08349)	1.6506 (0.08118)	1.9688 (0.08226)	1.7339 (0.07921)	1.7563 (0.07446)	1.9641 (0.09592)
95% CI of LS mean CFB in GA lesion area, mm^2	1.3935-1.7215	1.4912-1.8101	1.8072-2.1303	1.5784-1.8895	1.6101-1.9025	1.7757-2.1524
Difference in LS mean (95% CI) CFB in GA lesion area vs sham pooled group, mm^2	−0.4113 (−0.6396 to −0.1830)	−0.3181 (−0.5424 to −0.0939)	NA	−0.2301 (−0.4708 to 0.0105)	−0.2077 (−0.4445 to 0.0290)	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):

Based on p values (recommended p value ≤ 0.05), 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 = .0004, and pegcetacoplan every other month (PEOM), P = .0055 versus the sham pooled group, but the difference is not clinically significant.

Study APL2-303 failed its primary endpoint for both groups (PM and PEOM). The treatment effect of pegcetacoplan for PM had a p value = .0609, and PEOM, a p value = .0853.

The agency recommends two adequate and well controlled trials with consistent results which support a clinically significant difference due to treatment.

The Applicant submitted their Phase 2 trial, Study POT-CP121614 in supportive evidence for approval of their NDA. Study POT-CP121614 was "A Phase 2, Multicenter, Randomized, Single-Masked, Sham-Controlled Study of Safety, Tolerability and Evidence of Activity of Intravitreal Pegcetacoplan Therapy in Patients With Geographic Atrophy."

Table 8: Analyses of CFB in Total of GA Lesion(s) (mm2) (FAF) of the Study Eye With MMRM Model at Month 12 in POT-CP121614 - mITT Population

	Study POT - CP121614		
	PM (N=84)	**PEOM (N=78)**	**Sham pooled (N=80)**
Number of subjects included in model	84	78	80
LS mean (SE) CFB in GA lesion area, mm^2	1.47 (0.162	1.70 (0.169)	2.13 (0.162)
95% CI of LS mean CFB in GA lesion area, mm^2	1.15 - 1.79	1.36 – 2.03	1.81 – 2.45
Difference in LS mean (95% CI) CFB in GA lesion area vs sham pooled group, mm^2	-0.66 (-1.11 to -0.21)	-0.44 (-0.90 to 0.03)	NA
Percentage difference in LS mean CFB in GA lesion area vs sham pooled group	-30.9%	-20.5%	NA
P value vs sham pooled group	.004	.064	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 Study POT-CP121614, the model included treatment + baseline value + visit + treatment × visit + visit × baseline.
Sources: Study POT-CP121614 CSR Table 14.2.1.13.2.

Reviewer's comment (s):

Study POT-CP121614 had some protocol differences from Studies APL2- 303 and APL2-304. The POT-CP121614 Study was designed as only a 12-month study and there was no randomization / stratification based on GA lesion size at screening. Studies APL2- 303 and APL2-304 were designed for up to 24 months follow-up and randomization was stratified according to GA lesion area at screening (< 7.5 mm ^{2}; ≥ 7.5 mm^2).

Study POT-CP121614 showed a reduction in lesion growth from baseline through Month 12 in total GA lesion area in the PM group, p value = .004, but the PEOM group, p value = .064 vs the sham pooled group, failed its endpoint. Study POT-CP121614 did not demonstrate a clinically significant difference and the study had no additional follow-up after Month 12.

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 complete Month 18 efficacy and safety data in the initial NDA. The Division requested 18-month data to confirm the 12-month results for the companies' pivotal trials, Studies APL2- 303 and APL2-304.

Given Study APL2-303 failed both doses (PM and PEOM), the additional Month 18 data could only confirm the results of Study APL2-304. If at Month 18 Study APL2-303 results trended in a positive direction, then this trend would need to be further confirmed with Month 24 data.

Month 18 Data

The Division requested the mean rate of GA growth (slope) at Month 18 using the piecewise linear regression approaches. The analysis was expected to determine whether the growth rates were diverging with time.

Table 9: Month 18 - Efficacy Results APL2-304 Piecewise Linear Trend

Table 14.2.1.3.11
Analysis of Change from Baseline in Total Area of GA Lesion(s) (mm^2) (FAF) of the Study Eye with MMRM Model
Assuming a Piecewise Linear Trend in Time with Knots at Month 6 and Month 12
mITT Set
Baseline through Month 18

	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Estimates for Baseline to Month 18			
Slope (SE)	2.3510 (0.10991)	2.4988 (0.10878)	2.9806 (0.11508)
95% CI of Slope	(2.1356, 2.5665)	(2.2855, 2.7121)	(2.7550, 3.2062)
Difference (95% CI) in Slope (vs Sham Pooled)	-0.6296 (-0.9414, -0.3177)	-0.4818 (-0.7928, -0.1708)	
Percentage Difference (vs Sham Pooled)	-21.1	-16.2	
p-value (vs Sham Pooled)	<0.0001	0.0024	
Difference (95% CI) in Slope (vs PEOM)	-0.1478 (-0.4517, 0.1562)		
Percentage Difference (vs PEOM)	-5.9		
p-value (vs PEOM)	0.3406		

SE = Standard Error.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Annual Growth Rate is calculated as the Slope for time period multiplied by 2.
Note: Model includes Treatment + Baseline GA lesion area (< 7.5 mm2 or ≥ 7.5 mm2) + Time (continuous) + Time Spline at Month 6 (continuous) + Time Spline at Month 12 (continuous) + Presence of CNV in the fellow eye (Yes or No) + Time (continuous) x Treatment + Time Spline at Month 6 (continuous) x Treatment + Time Spline at Month 12 (continuous) x Treatment + Baseline GA lesion area x Time (continuous) + Baseline GA lesion area x Time Spline at Month 6 (continuous) + Baseline GA lesion area x Time Spline at Month 12 (continuous).
Note: A heterogeneous autoregressive (1) covariance matrix is used to model the within-subject errors.

Reviewer's comment(s):

Study APL2-304 for Piecewise Linear Trend analysis at Month 18 demonstrated a statistically significant p-value (vs Sham pooled) for PM and PEOM doses at < 0.0001 and 0.0024, respectively. The PM dose trend was more beneficial than the PEOM dose but did reach statistical significance (p-value vs. PEOM was 0.3406). (Table 14.2.1.3.11)

Study APL2-303 Piecewise Linear Trend

Table 14.2.1.3.11
Analysis of Change from Baseline in Total Area of GA Lesion(s) (mm^2) (FAF) of the Study Eye with MMRM Model
Assuming a Piecewise Linear Trend in Time with Knots at Month 6 and Month 12
mITT Set
Baseline through Month 18

	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Estimates for Baseline to Month 18			
Slope (SE)	2.6398 (0.09993)	2.5957 (0.10283)	3.0259 (0.13892)
95% CI of Slope	(2.4439, 2.8358)	(2.3941, 2.7973)	(2.7536, 3.2983)
Difference (95% CI) in Slope (vs Sham Pooled)	-0.3861 (-0.7217, -0.0505)	-0.4302 (-0.7691, -0.0912)	
Percentage Difference (vs Sham Pooled)	-12.8	-14.2	
p-value (vs Sham Pooled)	0.0242	0.0129	
Difference (95% CI) in Slope (vs PEOM)	0.0441 (-0.2373, 0.3255)		
Percentage Difference (vs PEOM)	1.7		
p-value (vs PEOM)	0.7587		

SE = Standard Error.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Annual Growth Rate is calculated as the Slope for time period multiplied by 2.
Note: Model includes Treatment + Baseline GA lesion area (< 7.5 mm2 or ≥ 7.5 mm2) + Time (continuous) + Time Spline at Month 6 (continuous) + Time Spline at Month 12 (continuous) + Presence of CNV in the fellow eye (Yes or No) + Time (continuous) x Treatment + Time Spline at Month 6 (continuous) x Treatment + Time Spline at Month 12 (continuous) x Treatment + Baseline GA lesion area x Time (continuous) + Baseline GA lesion area x Time Spline at Month 6 (continuous) + Baseline GA lesion area x Time Spline at Month 12 (continuous).
Note: A heterogeneous autoregressive (1) covariance matrix is used to model the within-subject errors.

Reviewer's comment(s):
Study APL2-303 for Piecewise Linear Trend analysis at Month 18 demonstrated a statistically significant p-value (vs Sham pooled) for PM and PEOM doses at 0.0242 and 0.0129, respectively. The PM dose trend was less beneficial than the PEOM dose (p-value vs. PEOM was 0.7587). (Table 14.2.1.3.11)

Reviewer's comment(s) / Summary for Studies APL2-304 and APL2-303:

1) *Study APL2-304 at Month 18 continues to demonstrate a statistically significant result as initially demonstrated at Month 12 with PM dosing trending to be more beneficial than PEOM dosing.*
2) *Study APL2-303, which had failed both dosing regimens (PM and PEOM) at Month 12, demonstrated a statistically significant result at Month 18 with both dosing regimens, though PM dosing was trending to be less beneficial than PEOM dosing.*
3) *It was recommended the Applicant amend the application with 24-month data for both trials. Month 24 data will be able to confirm the Month 18 results for Study APL2-303 and would further confirm the benefit demonstrated at Months 12 and 18 in Study APL2-304. Additionally, the benefit of PM versus PEOM dosing may be able to be determined.*

On November 2, 2022, the Agency had a Telecon with the Applicant requesting 24 month follow up data be submitted for Studies APL2-304 and APL2-303. The Applicant agreed to submit the 24-month data which amended the PDUFA date extending it 3 months.

The 24-month data set for Studies APL2-304 and APL2-303 was received at the Agency November 17, 2022, and follows:

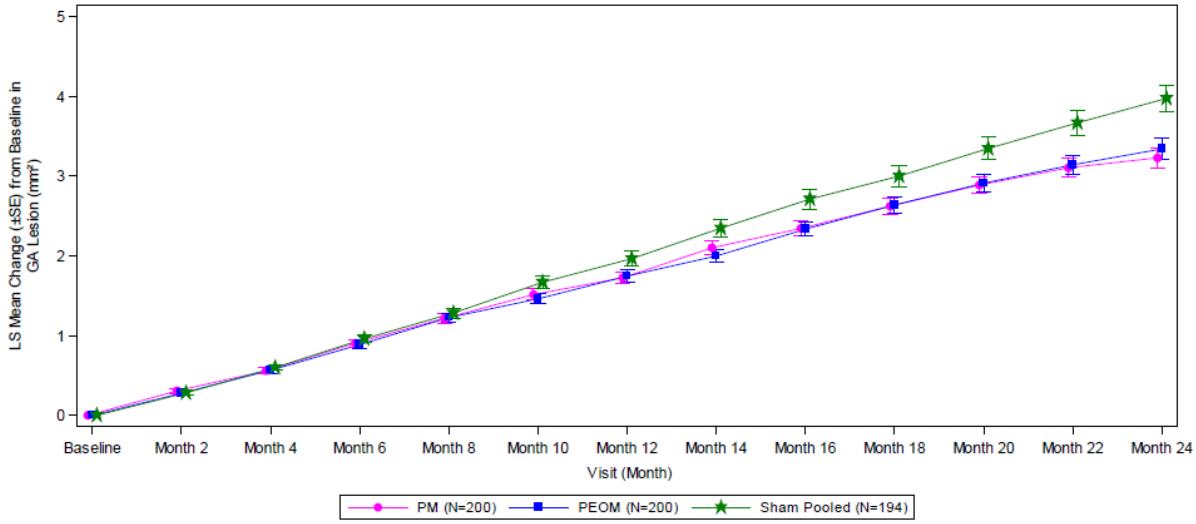
Table 10: Month 24 - Primary Efficacy Results APL2-303 Piecewise Linear Trend

Post-Hoc Table 14.5.8.2.1
Analysis of Change from Baseline in Total Area of GA Lesion(s) (mm ²) (FAF) of the Study Eye with MMRM Model
Assuming a Piecewise Linear Trend in Time with Knots at Month 6, Month 12 and Month 18
mITT set Baseline through Month 24

	PM (N=201)	PEOM (N=201)	Sham Pooled (N=195)
Estimates for Baseline to Month 24			
Slope (SE)	3.2780 (0.12525)	3.3051 (0.12871)	4.0031 (0.16880)
95% CI of Slope	(3.0324, 3.5235)	(3.0528, 3.5574)	(3.6722, 4.3340)
Difference (95% CI) in Slope (vs Sham Pooled)	-0.7251 (-1.1373, -0.3129)	-0.6980 (-1.1142, -0.2817)	
Percentage Difference (vs Sham Pooled)	-18.1	-17.4	
p-value (vs Sham Pooled)	0.0006	0.0010	
Difference (95% CI) in Slope (vs PEOM)	-0.0272 (-0.3794, 0.3251)		
Percentage Difference (vs PEOM)	-0.8		
p-value (vs PEOM)	0.8799		

SE = Standard Error.
Note: Model includes Treatment + Baseline GA lesion area (< 7.5 mm2 or >= 7.5 mm2) + Time (continuous) + Time Spline at Month 6 (continuous) + Time Spline at Month 12 (continuous) + Time Spline at
Month 18 (continuous) + Presence of CNV in the fellow eye (Yes or No) + Time (continuous) x Treatment + Time Spline at Month 6 (continuous) x Treatment + Time Spline at Month 12 (continuous) x
Treatment + Time Spline at Month 18 (continuous) x Treatment + Baseline GA lesion area x Time (continuous) + Baseline GA lesion area x Time Spline at Month 6 (continuous) + Baseline GA lesion area x
Time Spline at Month 12 (continuous) + Baseline GA lesion area x Time Spline at Month 18 (continuous).
Note: Annual Growth Rate is calculated as the Slope for time period multiplied by 2.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.

Figure 2: 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.

Reviewer's comment(s):
Study APL2-303 for Piecewise Linear Trend analysis at Month 24 demonstrated a statistically significant p-value (vs Sham pooled) for PM and PEOM doses at 0.0006 and 0.0010, respectively, with the PM dose trend slightly more beneficial than the PEOM dose. (Table 14.5.8.2.1)

The successful outcome for Study APL2-303 based on Piecewise Linear Trend analysis at Month 24 confirmed the studies successful outcome at Month 18. The Agency had requested confirmation of a successful outcome at Month 18 with the additional successful outcome at Month 24; these Month 18 and Month 24 results satisfied this request.

Figure 3: Study APL2-303 LS Mean (+/- SE) Plot of Change From Baseline to Month 24 demonstrates the separation of the PM dose being slightly more beneficial than the PEOM dose.

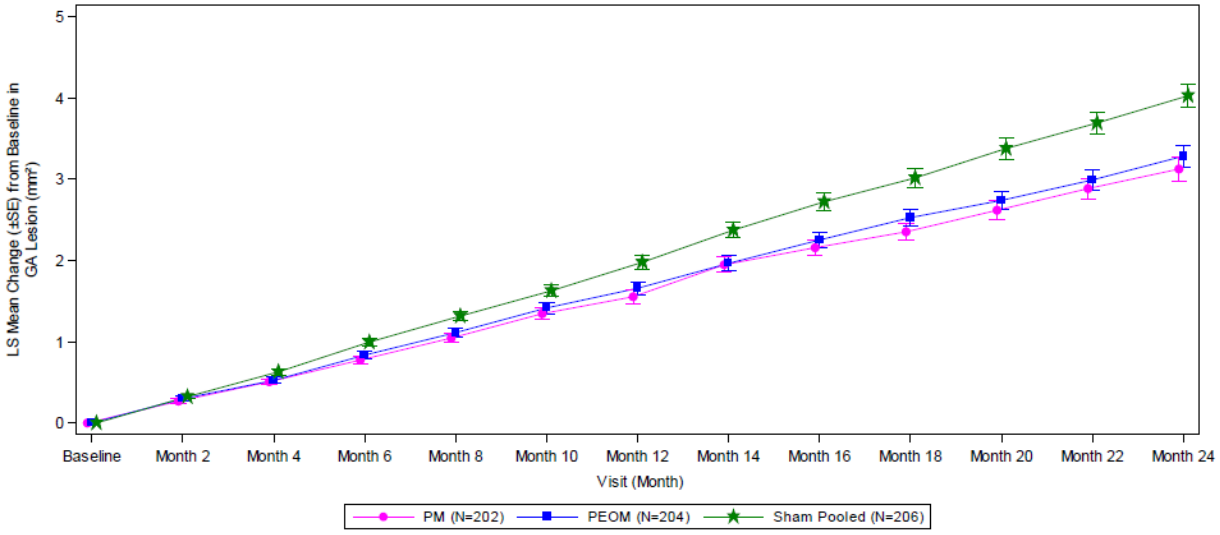
Table 11: Month 24 - Primary Efficacy Results APL2-304 Piecewise Linear Trend

Post-Hoc Table 14.5.8.2.1
Analysis of Change from Baseline in Total Area of GA Lesion(s) (mm^2) (FAF) of the Study Eye with MMRM Model
Assuming a Piecewise Linear Trend in Time with Knots at Month 6, Month 12 and Month 18
mITT set Baseline through Month 24

	PM (N=202)	PEOM (N=205)	Sham Pooled (N=207)
Estimates for Baseline to Month 24			
Slope (SE)	3.1073 (0.14841)	3.2586 (0.13420)	3.9775 (0.14310)
95% CI of Slope	(2.8164, 3.3982)	(2.9955, 3.5217)	(3.6970, 4.2580)
Difference (95% CI) in Slope (vs Sham Pooled)	-0.8702 (-1.2740, -0.4664)	-0.7189 (-1.1039, -0.3339)	
Percentage Difference (vs Sham Pooled)	-21.9	-18.1	
p-value (vs Sham Pooled)	<0.0001	0.0003	
Difference (95% CI) in Slope (vs PEOM)	-0.1513 (-0.5445, 0.2420)		
Percentage Difference (vs PEOM)	-4.6		
p-value (vs PEOM)	0.4508		

Note: Annual Growth Rate is calculated as the Slope for time period multiplied by 2.
Note: Baseline is defined as the last available, non-missing observation prior to first study drug administration.
Note: Model includes Treatment + Baseline GA lesion area (< 7.5 mm_2 or >= 7.5 mm_2) + Time (continuous) + Time Spline at Month 6 (continuous) + Time Spline at Month 12 (continuous) + Time Spline at
Month 18 (continuous) + Presence of CNV in the fellow eye (Yes or No) + Time (continuous) x Treatment + Time Spline at Month 6 (continuous) x Treatment + Time Spline at Month 12 (continuous) x
Treatment + Time Spline at Month 18 (continuous) x Treatment + Baseline GA lesion area x Time (continuous) + Baseline GA lesion area x Time Spline at Month 6 (continuous) + Baseline GA lesion area x
Time Spline at Month 12 (continuous) + Baseline GA lesion area x Time Spline at Month 18 (continuous).
Note: A heterogeneous autoregressive (1) covariance matrix is used to model the within-subject errors.
SE = Standard Error

Figure 4: Study APL2-404 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.

Reviewer's comment(s):

Study APL2-304 for Piecewise Linear Trend analysis at Month 24 demonstrated a statistically significant p-value (vs Sham pooled) for PM and PEOM doses at < 0.0001 and 0.0003, respectively, with The PM dose trend slightly more beneficial than the PEOM dose. (Table 14.5.8.2.1)

The successful outcome for Study APL2-304 based on Linear and Piecewise Linear Trend analysis at Month 24 confirmed the studies successful outcome at Month 18 (and Month 12). The Agency had requested confirmation of successful outcome at Month 18 with the additional successful outcome at Month 24; these Month 18 and Month 24 results satisfied this request.

Figure 4: Study APL2-304 LS Mean (+/- SE) Plot of Change From Baseline to Month 24 demonstrates the separation of the PM dose being more beneficial than the PEOM dose.

Data Quality and Integrity

The primary analysis population had been amended from the intent to treat (ITT: randomized subjects) to the modified intent to treat (mITT) population because the subjects either had no postbaseline GA measurements at Month 12 or no injection of pegcetacoplan or sham.

Table 12: Study APL2-304 - Summary of Specific Reasons for Exclusion From mITT Population at Month 12

	PM	**PEOM**	**Sham pooled**
Intent-to-treat set	**N = 213**	**N = 212**	**N = 212**
Exclusion from mITT set, n (%)	11 (5.2)	7 (3.3)	6 (2.8)
Reason for no postbaseline GA area assessment	**10**	**7**	**6**
Withdrew consent	4	2	2
Lost to follow-up	2	1	1
COVID impact leading to missed visits or discontinuation	2	1	2
Death	1	2	0
AE leading to discontinuation	1	1	0
GA area could not be measured	0	0	1
Reason for no injection of pegcetacoplan or sham	**1**	**0**	**0**
Withdrew consent	1	0	0

Abbreviations: COVID = coronavirus disease 2019; FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Sources: SDTM DS.DSTERM and Study APL2-304 Month 12 Clinical Study Report, Table 14.1.2.1.

Table 13: Study APL2-303 - Summary of Specific Reasons for Exclusions From mITT Population at Month 12

	PM	**PEOM**	**Sham pooled**
Intent-to-treat set	**N = 206**	**N = 208**	**N = 207**
Exclusion from the mITT set, n (%)	5 (2.4)	8 (3.8)	13 (6.3)
Reason for no postbaseline GA area assessment	**5**	**8**	**12**
Withdrew consent	3	2	6
COVID impact leading to missed visits or discontinuation	1	3	4

AE leading to discontinuation	0	2	2
Death	1	0	0
GA area could not be measured	0	1	0
Reason for no injection of pegcetacoplan or sham	**0**	**0**	**1**
Withdrew consent	0	0	1

Abbreviations: FAF = fundus autofluorescence; GA = geographic atrophy; mITT = modified intent-to-treat; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Source: SDTM DS.DSTERM and Study APL2-303 Month 12 CSR, Table 14.1.2.1.

Reviewer's comment (s):
Using the mITT population instead of the ITT population is acceptable given no one group had a disproportionately high percentage of subjects without a GA assessment.

6.1.3. Dose and Dose-Response

Refer to "Efficacy Results – Primary Endpoint." At Month 12 and Month 18 the treatment effect in the PM group was larger than in the PEOM group in Studies APL2-304 and POT-CP121614, while in Study APL2-303 the treatment effect in the PEOM group was slightly better than in the PE group.

7. Review of Safety

7.1. Safety Review Approach

The safety review is based on Month 24 data for the two pivotal trials APL2-303 and APL2-304.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Safety Database

Studies OAKS APL-2-303 and DERBY APL2-304	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

Reviewer's comment(s):
Study APL2-303 had adequate number of injections and exposure with the percentage of subjects who received ≥75% of planned injections, 70.9% in the PM group, 81.3% in the PEOM group, and 75.7% in the sham pooled group, respectively. For Study APL2-304, Table 14.1.8.3 summarizes study drug exposure from baseline through Month 18 for the safety population. Six hundred thirty-six enrolled subjects received at least one pegcetacoplan or sham injection during the study. Subject (b) (6)*, who was assigned to the PM group, did not receive pegcetacoplan administration and was not included in the safety population. Overall, study drug exposure was balanced across the respective treatment groups in the safety population.*

Subjects in the PM and SM groups were scheduled to have received 18 pegcetacoplan or sham injections. Subjects in the PEOM and SEOM groups were scheduled to have received 9 pegcetacoplan or sham injections over 18 months, respectively. The mean number of injections in the treatment groups was 14.1 for the PM group, 7.6 for the PEOM group, 14.3 for the SM group, and 7.7 for the SEOM group.

Mean duration of treatment for the PM and SM groups was 462.1 and 464.7 days, respectively. For the PEOM and SEOM groups, duration of treatment was a mean of 476.9 and 492.9 days, respectively.

Reviewer's comment(s):
At Month 18 Study APL2-304 had adequate number of injections and exposure with the percentage of subjects who received ≥75% of planned injections, 72.8% in the PM group, 82.5% in the PEOM group, and 79.1% in the sham pooled group, respectively.

Pooled Safety Population Studies APL2-303 and APL2 -304

	PM (N = 419) n (%)	PEOM (N = 420) n (%)	Pegcetacoplan pooled (N = 839) n (%)	SM (N = 207) n (%)	SEOM (N = 210) n (%)	Sham pooled (N = 417) n (%)	Total (N = 1256) n (%)
Subjects received at least one dose of IP	419	420	839	207	210	417	1256
Completed treatment through Month 18	325 (77.6)	350 (83.3)	675 (80.5)	166 (80.2)	177 (84.3)	343 (82.3)	1018 (81.1)
Discontinued from treatment prior to Month 18	94 (22.4)	70 (16.7)	164 (19.5)	41 (19.8)	33 (15.7)	74 (17.7)	238 (18.9)
Continued in the study to Month 18 after treatment discontinuation	8 (1.9)	5 (1.2)	13 (1.5)	0	0	0	13 (1.0)
Primary reason for discontinuation from treatment							
AE	15 (3.6)	12 (2.9)	27 (3.2)	8 (3.9)	2 (1.0)	10 (2.4)	37 (2.9)
Lost to follow-up	4 (1.0)	6 (1.4)	10 (1.2)	3 (1.4)	1 (0.5)	4 (1.0)	14 (1.1)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician decision	3 (0.7)	1 (0.2)	4 (0.5)	0	1 (0.5)	1 (0.2)	5 (0.4)
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	45 (10.7)	28 (6.7)	73 (8.7)	14 (6.8)	17 (8.1)	31 (7.4)	104 (8.3)
Pregnancy	0	0	0	0	0	0	0
Death	18 (4.3)	11 (2.6)	29 (3.5)	8 (3.9)	3 (1.4)	11 (2.6)	40 (3.2)
Due to COVID-19 impact[a]	9 (2.1)	12 (2.9)	21 (2.5)	8 (3.9)	9 (4.3)	17 (4.1)	38 (3.0)
Other	0	0	0	0	0	0	0

	PM (N = 419) n (%)	PEOM (N = 420) n (%)	Pegcetacoplan pooled (N = 839) n (%)	SM (N = 207) n (%)	SEOM (N = 210) n (%)	Sham pooled (N = 417) n (%)	Total (N = 1256) n (%)
Completed study through Month 18	333 (79.5)	355 (84.5)	688 (82.0)	166 (80.2)	177 (84.3)	343 (82.3)	1031 (82.1)
Withdrawn from study prior to Month 18	86 (20.5)	65 (15.5)	151 (18.0)	41 (19.8)	33 (15.7)	74 (17.7)	225 (17.9)
Primary reason for discontinuation from study							
AE	9 (2.1)	8 (1.9)	17 (2.0)	6 (2.9)	2 (1.0)	8 (1.9)	25 (2.0)
Lost to follow-up	4 (1.0)	6 (1.4)	10 (1.2)	3 (1.4)	1 (0.5)	4 (1.0)	14 (1.1)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician decision	2 (0.5)	1 (0.2)	3 (0.4)	0	1 (0.5)	1 (0.2)	4 (0.3)
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	45 (10.7)	27 (6.4)	72 (8.6)	14 (6.8)	17 (8.1)	31 (7.4)	103 (8.2)
Pregnancy	0	0	0	0	0	0	0
Death	18 (4.3)	11 (2.6)	29 (3.5)	10 (4.8)	3 (1.4)	13 (3.1)	42 (3.3)
Due to COVID-19 impact[a]	8 (1.9)	12 (2.9)	20 (2.4)	8 (3.9)	9 (4.3)	17 (4.1)	37 (2.9)
Other	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; N = number of subjects in the group; n = number of subjects; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.
[a] Discontinuation due to COVID-19 diagnosis or symptoms was categorized as discontinuation due to an AE.
Note: Pooled consisted of Studies APL2-304 and APL2-303 and included data up to Month 18.

Source: Month 18 Integrated Summary of Safety Table 14.1.2.2a.

Table 14: Pooled Demographic Characteristics - Safety Population

	PM (N = 419)	PEOM (N = 420)	Pegcetacoplan pooled (N = 839)	SM (N = 207)	SEOM (N = 210)	Sham pooled (N = 417)	Total (N = 1256)
Sex, n (%)							
Female	255 (60.9)	248 (59.0)	503 (60.0)	129 (62.3)	138 (65.7)	267 (64.0)	770 (61.3)
Male	164 (39.1)	172 (41.0)	336 (40.0)	78 (37.7)	72 (34.3)	150 (36.0)	486 (38.7)
Age, years							
Mean (SD)	78.9 (7.04)	78.7 (7.46)	78.8 (7.25)	78.7 (7.33)	78.5 (7.11)	78.6 (7.21)	78.7 (7.23)
Minimum, maximum	60, 95	60, 100	60, 100	60, 94	61, 96	60, 96	60, 100
Age group, n (%)							
<65 years	10 (2.4)	16 (3.8)	26 (3.1)	9 (4.3)	8 (3.8)	17 (4.1)	43 (3.4)
≥65-<75 years	101 (24.1)	105 (25.0)	206 (24.6)	50 (24.2)	47 (22.4)	97 (23.3)	303 (24.1)
≥75-<85 years	213 (50.8)	198 (47.1)	411 (49.0)	98 (47.3)	112 (53.3)	210 (50.4)	621 (49.4)
≥85 years	95 (22.7)	101 (24.0)	196 (23.4)	50 (24.2)	43 (20.5)	93 (22.3)	289 (23.0)
Geographic region, n (%)							
US	298 (71.1)	274 (65.2)	572 (68.2)	139 (67.1)	141 (67.1)	280 (67.1)	852 (67.8)
Rest of world	121 (28.9)	146 (34.8)	267 (31.8)	68 (32.9)	69 (32.9)	137 (32.9)	404 (32.2)
Race, n (%)							
Asian	3 (0.7)	2 (0.5)	5 (0.6)	0	2 (1.0)	2 (0.5)	7 (0.6)
Black or African American	3 (0.7)	1 (0.2)	4 (0.5)	0	0	0	4 (0.3)
White	385 (91.9)	388 (92.4)	773 (92.1)	196 (94.7)	195 (92.9)	391 (93.8)	1164 (92.7)
Multiple	0	1 (0.2)	1 (0.1)	0	0	0	1 (0.1)
NR/unknown/missing	28 (6.7)	28 (6.7)	56 (6.7)	11 (5.3)	13 (6.2)	24 (5.8)	80 (6.4)
Ethnicity, n (%)							
Hispanic or Latino	37 (8.8)	44 (10.5)	81 (9.7)	17 (8.2)	16 (7.6)	33 (7.9)	114 (9.1)
Not Hispanic or Latino	355 (84.7)	348 (82.9)	703 (83.8)	181 (87.4)	182 (86.7)	363 (87.1)	1066 (84.9)
NR/unknown/missing	27 (6.4)	28 (6.7)	55 (6.6)	9 (4.3)	12 (5.7)	21 (5.0)	76 (6.1)

Abbreviations: N = number of subjects in the group; n = number of subjects; NR = not reported; PEOM =pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM =sham monthly.
Notes: Pooled consisted of Studies APL2-304 and APL2-303 and included data up to Month 18. Rest of world included Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.
Source: Month 18 Integrated Summary of Safety Table 14.1.4.1a.

Reviewer's comment(s):

Mean age across treatment groups was 78.7 years with the largest percentage of subjects in the age group of ≥75 to <85 years (49.4%). A higher percentage of subjects were enrolled from the US (67.8%) than from rest of world (ROW) (32.2%). Majorities of subjects were White (92.7%), not Hispanic or Latino (84.9%), and female (61.3%). GA occurs in an older population which is reflected by the data set. Inclusion criteria required subjects to be ≥ 60 years.

7.2.2. Adequacy of the safety database:

The safety database is adequate with respect to number of subjects enrolled, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

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

7.3.2. Categorization of Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 and summarized for those occurring in the study eye.

7.3.3. Routine Clinical Tests

The routine clinical testing to evaluate safety concerns was adequately addressed in the design and conduct of the clinical trials.

7.4. Safety Results

7.4.1. 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

Reviewer's comment(s):

No specific patterns were identified. The deaths listed would be expected with the mean age across treatment groups at 78.7 years.

7.4.2. Serious Adverse Events

Table 15: APL2-303 Serious AEs in the Study Eye In Any Treatment Group - Baseline Through Month 18 - Safety Population

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Table 14.3.1.6.1
Ocular Treatment Emergent Serious Adverse Events in Study Eye by System Organ Class and Preferred Term
Safety Set
Baseline through Month 18

System Organ Class/ Preferred Term	PM (N=206) n (%) M	PEOM (N=208) n (%) M	Pegcetacoplan Pooled (N=414) n (%) M	SM (N=102) n (%) M	SEOM (N=104) n (%) M	Sham Pooled (N=206) n (%) M	Total (N=620) n (%) M
Number of Subjects with at Least One Ocular Serious TEAE in the Study Eye	4 (1.9) 4	0	4 (1.0) 4	1 (1.0) 1	1 (1.0) 1	2 (1.0) 2	6 (1.0) 6
Eye disorders	4 (1.9) 4	0	4 (1.0) 4	1 (1.0) 1	1 (1.0) 1	2 (1.0) 2	6 (1.0) 6
Vitritis	2 (1.0) 2	0	2 (0.5) 2	0	0	0	2 (0.3) 2
Optic ischaemic neuropathy	1 (0.5) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Retinal tear	1 (0.5) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Dry age-related macular degeneration	0	0	0	1 (1.0) 1	0	1 (0.5) 1	1 (0.2) 1
Macular hole	0	0	0	0	1 (1.0) 1	1 (0.5) 1	1 (0.2) 1

Source: Listing 16.2.7.2.2

Table 16: APL2-304 Seriuos AEs in the Study Eye In Any Treatment Group - Baseline Through Month 18 - Safety Population

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Table 14.3.1.6.1
Ocular Treatment Emergent Serious Adverse Events in Study Eye by System Organ Class and Preferred Term
Safety Set
Baseline through Month 18

System Organ Class/ Preferred Term	PM (N=213) n (%) M	PEOM (N=212) n (%) M	Pegcetacoplan Pooled (N=425) n (%) M	SM (N=105) n (%) M	SEOM (N=106) n (%) M	Sham Pooled (N=211) n (%) M	Total (N=636) n (%) M
Number of Subjects with at Least One Ocular Serious TEAE in the Study Eye	5 (2.3) 5	4 (1.9) 4	9 (2.1) 9	0	0	0	9 (1.4) 9
Eye disorders	3 (1.4) 3	1 (0.5) 1	4 (0.9) 4	0	0	0	4 (0.6) 4
Optic ischaemic neuropathy	2 (0.9) 2	0	2 (0.5) 2	0	0	0	2 (0.3) 2
Papilloedema	1 (0.5) 1	0	1 (0.2) 1	0	0	0	1 (0.2) 1
Retinal detachment	0	1 (0.5) 1	1 (0.2) 1	0	0	0	1 (0.2) 1
Infections and infestations	2 (0.9) 2	3 (1.4) 3	5 (1.2) 5	0	0	0	5 (0.8) 5
Endophthalmitis	2 (0.9) 2	3 (1.4) 3	5 (1.2) 5	0	0	0	5 (0.8) 5

Source: Listing 16.2.7.2.2
Note: An AE will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product but increases in severity on or after the date of the first dose of investigational product.
Note: If a subject has multiple occurrences of a TEAE, the subject is presented only once in the subject count (n) column and all TEAEs are counted in total events (M) for a given System Organ Class and Preferred Term.
Note: Adverse events were coded to system organ class and preferred term using MedDRA Version 23.1.

Reviewer's comment(s):
Study APL2-303 had no cases of endophthalmitis. For Studies APL2-303 and APL2-304 all Serious Adverse Events occurred at a rate of ≤ 1%.

7.4.3. Dropouts and/or Discontinuations Due to Adverse

Effects

Table 17: Summary of Discontinuations APL2-303 and APL2-304 - Pooled Safety Data Set

	PM (N = 419)	PEOM (N = 420)	Pegcetacoplan pooled (N = 839)	SM (N = 207)	SEOM (N = 210)	Sham pooled (N = 417)	Total (N = 1256)
AEs leading to study discontinuation							
n (%)	30 (7.2)	20 (4.8)	50 (6.0)	17 (8.2)	5 (2.4)	22 (5.3)	72 (5.7)
Total events	34	26	60	18	5	23	83
AEs leading to death							
n (%)	20 (4.8)	11 (2.6)	31 (3.7)	10 (4.8)	3 (1.4)	13 (3.1)	44 (3.5)
Total events	21	17	38	11	3	14	52

Abbreviations: AE = adverse event; IP = investigational product; N = number of subjects in the group; n = number of subjects; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly.
Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data from these studies through Month 18. All tabulated AEs had a start date on or after the first dose of IP or, if the AE had a start date before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. AEs related to treatment had a relationship to study drug of definitely related, possibly related, or not reported. Any AE with a missing or unknown severity was considered as severe.
Source: Month 18 Integrated Summary of Safety Table 14.3.1.1.1a.

Reviewer's comment(s):

No meaningful differences were observed in the percentages of subjects across treatment groups who had AEs leading to treatment (6.9% vs 5.3%) or study discontinuation (6.0% vs 5.3%) or AEs leading to death (3.7% vs 3.1%).

7.4.4. 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

Adverse Events	PM	PEOM	Sham
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
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

Adverse Events	PM	PEOM	Sham
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
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

Reviewer's comment(s):

Overall, 328 subjects (51.6%) had 794 study eye AEs. The most frequent study eye AEs by subject percentage in the pegcetacoplan pooled group were conjunctival hemorrhage (8.7%), vitreous floaters (7.1%), eye pain (6.8%), and neovascular AMD (6.8%).

7.4.5. Laboratory Findings

No meaningful differences in hematology values were observed across treatment groups. No clinically meaningful differences were observed in hematology, clinical chemistry, and urinalysis values across treatment groups.

7.4.6. Vital Signs

Vital signs values demonstrated no meaningful differences between the treatment groups.

7.4.7. Electrocardiograms (ECGs)

Cardiac Electrophysiology

Subcutaneous (SC) dosing of pegcetacoplan did not result in QT prolongation. Systemic exposures following IVT administration are much lower than with SC administration, therefore QT prolongation following IVT pegcetacoplan is not expected.

7.4.8. Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Difference in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies. During the 18-month treatment period in Studies APL2-304 and APL2-303 there was no identified clinically significant effect of anti-PEG antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan.

In studies APL2-304 and APL2-303 anti-PEG antibodies were observed in 478/813 (58.8%) of pegcetacoplan treated patients. Anti-PEG antibodies were also observed in 663/1150 (57.7%) of enrolled patients prior to treatment.

In the 18-month period in Studies APL2-304 and APL2-303, anti-pegcetacoplan peptide antibody formation was observed in 5.1% (42 of 819 total pegcetacoplan treated patients). Because of the low occurrence of anti-pegcetacoplan peptide antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

7.5. Analysis of Submission-Specific Safety Issues

Corneal endothelial cells were assessed using specular microscopy for the CFB in cell density (cells/mm^2) for safety.

7.5.1. Endothelial Cell Count

APL2 -303 and APL2 -304 Pooled Endothelial Cell Counts

Table 18: Observed Values and CFB in Corneal Endothelial Cell Density (cells/mm^2) in the Study Eye Through Month 18 - Safety Population

	PM (N = 419)	**PEOM (N = 420)**	**Sham pooled (N = 417)**
Baseline			
N	139	147	157
Mean (SD), cells/mm^2	2070.9 (494.29)	2189.8 (498.15)	2043.6 (568.91)
Month 6 CFB			
N	99	112	111
Mean (SD), cells/mm^2	–35.0 (199.21)	15.0 (179.59)	–4.3 (163.24)
Month 12 CFB			
N	81	93	98
Mean (SD), cells/mm^2	11.5 (171.71)	9.5 (239.83)	12.1 (149.54)
LOV CFB			
N	115	127	131
Mean (SD), cells/mm^2	4.2 (181.82)	22.4 (248.24)	14.5 (144.36)

Abbreviations: CFB = change from baseline; LOV = last valid assessment obtained after baseline; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Notes: Pool 1 consisted of Studies APL2-304 and APL2-303 and included data up to Month 18. Baseline was defined as the last-available, nonmissing observation prior to first study drug administration. Endothelial cell density was collected only in select sites.
Source: Month 18 Integrated Summary of Safety Table 14.3.13.1.1a.

Reviewer's comment(s):
Changes over time in corneal endothelial cells were similar between treatment groups. This data suggests that pegcetacoplan has no safety impact on corneal endothelial cell density and cell size.

7.6. Safety Analyses by Demographic Subgroups

In the clinical studies 97.1% (975/1004) of patients randomized to treatment were ≥ 65 years and approximately 73.1% (734/1004) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is required in patients 65 years and above.

7.6.1. Human Reproduction and Pregnancy

Pregnancy is unlikely in this population as enrollment criteria were for subjects aged ≥ 60 years.

7.6.2. Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of SYFOVRE in pediatric patients has not been established. GA is not expected in pediatric subjects.

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

Overdose and drug potential are unlikely as the drug is administered intravitreally by a physician in a clinic. There are no reports of pegcetacoplan overdosage in clinical studies. There is unlikely to be a misuse problem with pegcetacoplan because it does not affect the central nervous system.

7.6.4 Human Carcinogenicity or Tumor Development

There is no data to suggest that of pegcetacoplan ophthalmic solution, 150 mg/mL, intravitreal injection (b) (4) has any tumorigenic potential.

7.7. Integrated Assessment of Safety

The safety database contained in this submission establishes the safety of pegcetacoplan ophthalmic solution, 150 mg/mL, intravitreal injection (b) (4). The 120-day safety report was submitted on September 23, 2022. Table 30 provides the pooled cumulative month 24 integrated safety analyses of AEs from Studies APL2-304 and APL2-303 (pool 1).

Table 19: Overall Summary of AEs in Pool 1 - Safety Population- 120 Day Update Report

	PM (N = 419)	PEOM (N = 420)	Pegcetacoplan pooled (N = 839)	SM (N = 207)	SEOM (N = 210)	Sham pooled (N = 417)	Total (N = 1256)
All AEs							
n (%)	370 (88.3)	367 (87.4)	737 (87.8)	166 (80.2)	178 (84.8)	344 (82.5)	1081 (86.1)
Total events	2583	2220	4803	1080	1004	2084	6887
Maximum severity of AEs							
Mild, n (%)	90 (21.5)	116 (27.6)	206 (24.6)	49 (23.7)	63 (30.0)	112 (26.9)	318 (25.3)
Moderate, n (%)	156 (37.2)	151 (36.0)	307 (36.6)	68 (32.9)	74 (35.2)	142 (34.1)	449 (35.7)
Mild or moderate, n (%)	246 (58.7)	267 (63.6)	513 (61.1)	117 (56.5)	137 (65.2)	254 (60.9)	767 (61.1)
Severe, n (%)	124 (29.6)	100 (23.8)	224 (26.7)	49 (23.7)	41 (19.5)	90 (21.6)	314 (25.0)
AEs related to treatment							
n (%)	54 (12.9)	40 (9.5)	94 (11.2)	10 (4.8)	9 (4.3)	19 (4.6)	113 (9.0)
Total events	87	69	156	15	19	34	190
AEs related to the injection procedure							
n (%)	110 (26.3)	94 (22.4)	204 (24.3)	46 (22.2)	27 (12.9)	73 (17.5)	277 (22.1)
Total events	240	168	408	91	54	145	553
SAEs							
n (%)	146 (34.8)	107 (25.5)	253 (30.2)	60 (29.0)	52 (24.8)	112 (26.9)	365 (29.1)
Total events	257	212	469	112	80	192	661
AEs leading to treatment discontinuation							
n (%)	47 (11.2)	32 (7.6)	79 (9.4)	19 (9.2)	9 (4.3)	28 (6.7)	107 (8.5)
Total events	58	41	99	21	9	30	129

	PM (N = 419)	PEOM (N = 420)	Pegcetacoplan pooled (N = 839)	SM (N = 207)	SEOM (N = 210)	Sham pooled (N = 417)	Total (N = 1256)
AEs leading to study discontinuation							
n (%)	47 (11.2)	29 (6.9)	76 (9.1)	19 (9.2)	10 (4.8)	29 (7.0)	105 (8.4)
Total events	52	41	93	20	10	30	123
AEs leading to death							
n (%)	28 (6.7)	15 (3.6)	43 (5.1)	11 (5.3)	5 (2.4)	16 (3.8)	59 (4.7)
Total events	29	22	51	12	5	17	68

Abbreviations: AE = adverse event; IP = investigational product; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SAE = serious adverse event; SEOM = sham every other month; SM = sham monthly.
Notes: Pool 1 consists of Studies APL2-303 and APL2-304 and includes data from these studies through month 24. All tabulated AEs had a start date on or after the first dose of IP or, if the AE had a start date before the date of the first dose of IP, increased in severity on or after the date of the first dose of IP. AEs related to treatment had a relationship to study drug of definitely related, possibly related, or not reported. Any AE with a missing or unknown severity was considered as severe.

Reviewer's comment(s):
The AE findings reported in this 120-day safety update were generally consistent with those previously reported in the original submission, and no new safety signals were identified. The 120-day safety report provided the pooled cumulative month 24 integrated safety analyses of AEs from Studies APL2-304 and APL2-303.

8. Advisory Committee Meeting and Other External Consultations

None.

9. Labeling Recommendations

NDA 217171 is recommended for approval with the revised draft labeling found the CDTL memorandum.

10. Risk Evaluation and Mitigation Strategies (REMS)

None.

11. Postmarketing Requirements and Commitments

None
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12. Appendices

12.1. References

None.

12.2. Financial Disclosure

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: _____		
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)

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/

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