CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217171Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY MEMO

NDA Number	217171
Link to EDR	\\CDSESUB1\evsprod\NDA217171\0019
Applicant	Apellis Pharmaceuticals, Inc.
Proposed Brand Name, Drug, Dosage Form and Strength	SYFOVRE, Intravitreal Injection, 15 mg/0.1 mL solution
Submission Type	Priority
Submission Date	05/26/2022
PUDFA Goal Date	2/26/2022
Proposed Indication	Geographic atrophy secondary to age-related macular degeneration
Proposed Dosing Regimen & Instructions	Intravitreal injection of 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4)
Associated IND	124784
OCP Division	Division of Inflammation and Immune Pharmacology (DIIP)
OCP Review Team	Da Zhang, Ph.D. Clinical Pharmacology Reviewer, DIIP Ping Ji, Ph.D. Team Leader, DIIP

Executive Summary

Pegcetacoplan, a complement inhibitor, is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. The Applicant (Apellis) submitted an Original Non-NME New Drug Application (NDA) for the pegcetacoplan solution for intravitreal (IVT) injection for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) on May 26, 2022. In this initial NDA, the Applicant focused on the up to Month 12 endpoints, for which the clinical pharmacology review was completed and placed in DARRTS on October 26, 2022.

On November 15, 2022, the Applicant submitted the 24-month efficacy and safety data from the Phase 3 APL2-303 (DERBY) and APL2-304 (OAKS) studies (eCTD Sequence Number 0019). This memo is focused on reviewing the updated PK, PD and immunogenicity data at Month 24.

The updated PK, PD and immunogenicity data at Month 24 are consistent with those in the initial NDA.

Data

PK/PD were collected at Day 720 (Month 24) at selected sites in APL2-303 only. No PK/PD data were collected in Study APL-2-304. The PD endpoints were assessed based on the change from baseline in serum complement profile for C3, CH50, AH50. Immunogenicity data were collected at Days 420, 540 and 720 for both Study APL2-303 and Study APL2-304 (**Table 1**).

Table 1. ADA and PK/PD Sampling between Month 12 and Month 24

Study	ADA Sampling (Months 13 – 24)	PK/PD Sampling
APL2-303	Days 420 (month 14), 540 (month 18) and 720 (month 24)	Day 720 (at selected sites only)
APL2-304	Days 420 (month 14), 540 (month 18) and 720 (month 24)	NA

PK

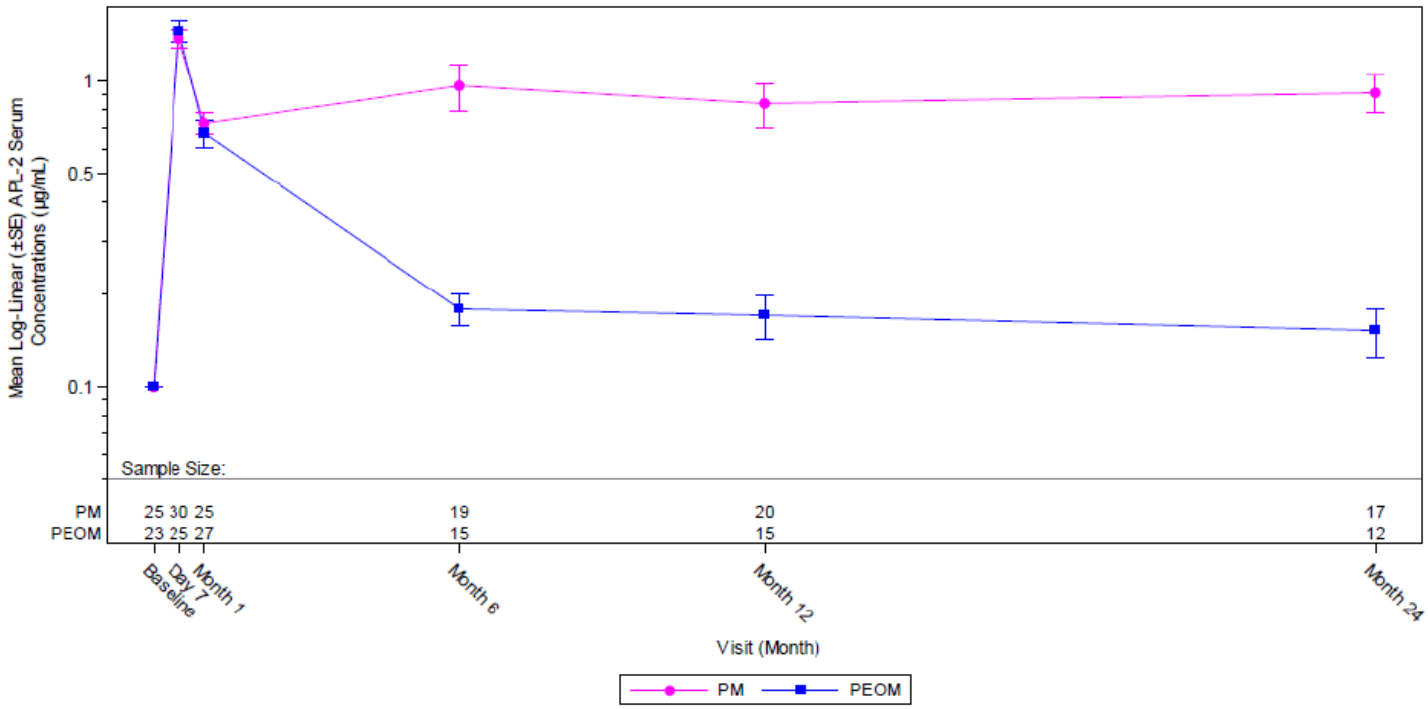
Table 2 summarizes APL-2 pegcetacoplan concentration data by treatment groups for the PK population at Month 24. The steady state mean trough concentrations observed following 24 months of treatment were consistent with the trough concentrations on or before 12 months of treatment (**Figure 1**).

Table 1. Mean Pegcetacoplan Serum Concentration (µg/mL) at Month 24 in Study APL2-303 (DERBY)

	15 mg PM	15 mg PEOM
n	17	12
Mean (SD)	0.9061 (0.53777)	0.0857 (0.13826)
CV, %	59.3526	161.3886

Abbreviations: BLQ = below low quantity; CV = coefficient of variation; N = number of subjects in group; n = number of evaluable subjects; PM = pegcetacoplan monthly; PEOM = pegcetacoplan every other month.
Source: Adapted from Table 61. APL2-303 Month 24 Clinical Study Report

Figure 1. Mean Log-Linear (±SE) of Pegcetacoplan Serum Concentrations (µg/mL) Over Time by Treatment Groups - PK Population (Study APL2-303, DERBY)



Abbreviations: APL-2 = pegcetacoplan; PEOM = pegcetacoplan every other month; PK = pharmacokinetics; PM = pegcetacoplan monthly.
Source: Figure 9. APL2-303 Month 24 Clinical Study Report

PD

The complement biomarkers CH50, C3, and AH50 observed following 24 months of treatment were consistent with the biomarkers measured on or before 12 months of treatment (**Figures 2, 3, 4**).

Figure 2. Mean (±SE) Percentage Change from Baseline of Pharmacodynamic Assessments of C3 Level Over Time - PD Population (Study APL2-303, DERBY)

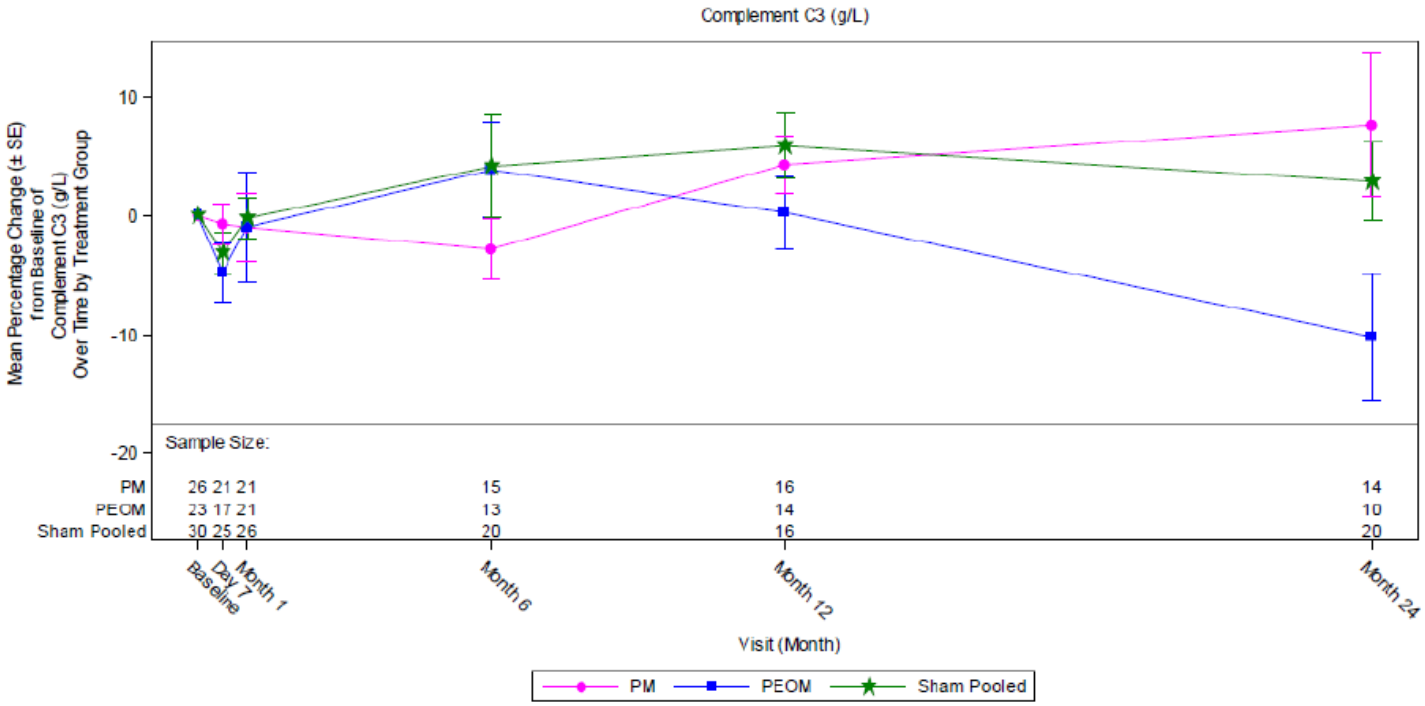


Figure 3. Mean (±SE) Percentage Change from Baseline of Pharmacodynamic Assessments of CH50 Over Time – PD Population (Study APL2-303, DERBY)

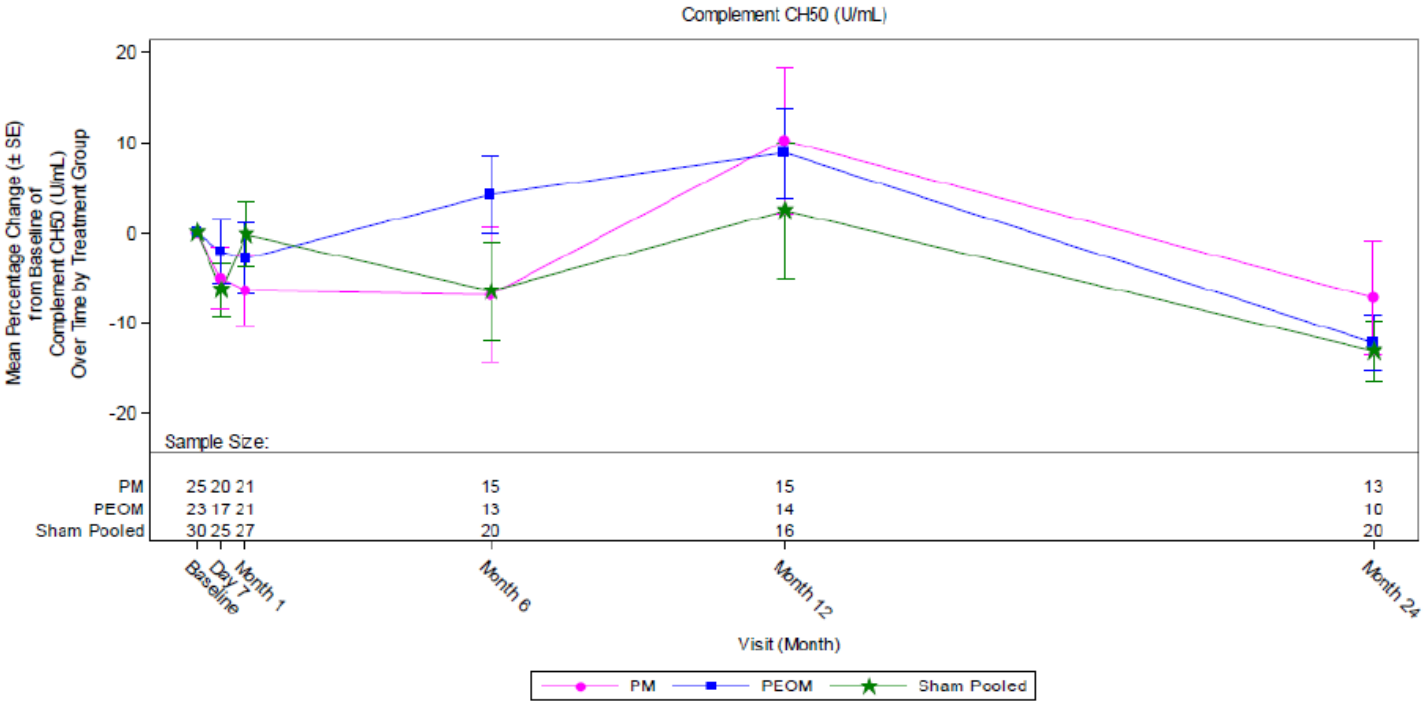
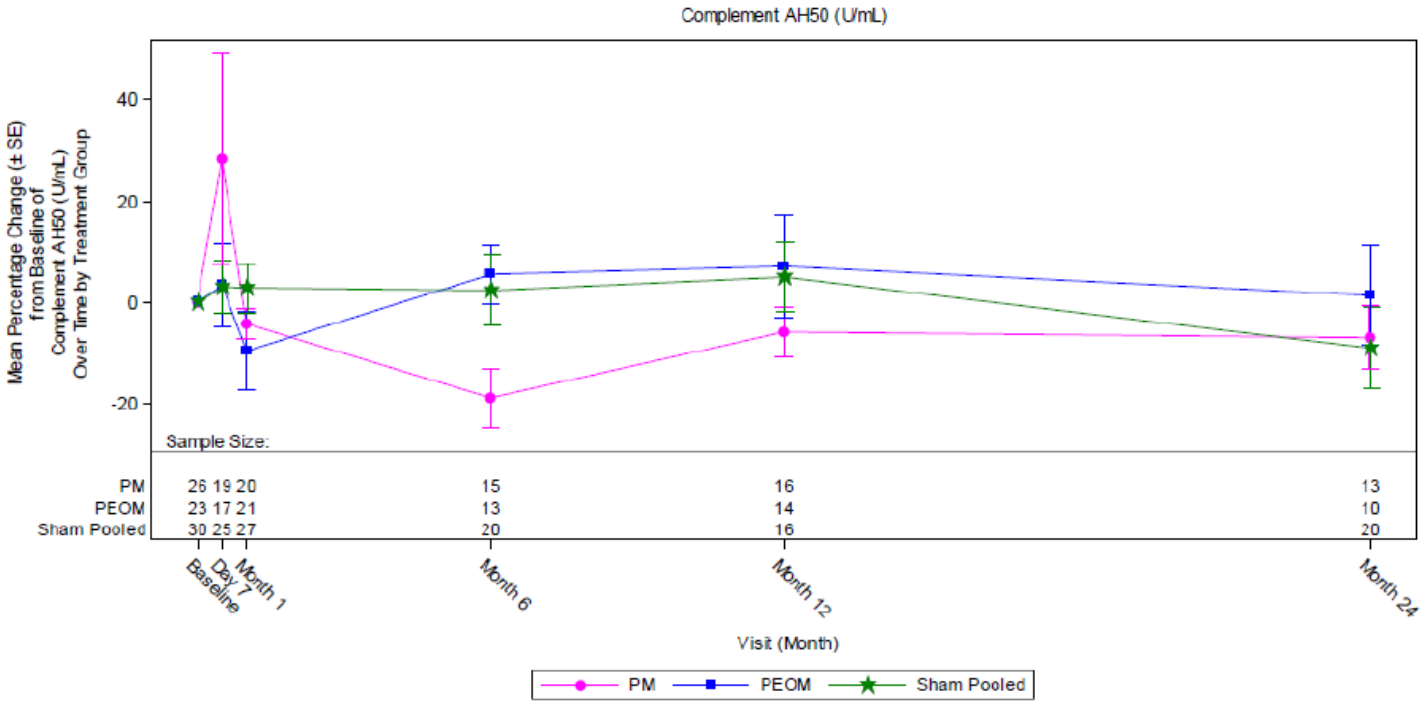


Figure 4. Mean (±SE) Percentage Change from Baseline of PD Assessments of AH50 Over Time - PD Population (Study APL2-303, DERBY)



Abbreviations: AH50 = alternative pathway hemolytic complement activity assay; PD = pharmacodynamic; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Source: Figures 10, 11, 12. APL2-303 Month 24 Clinical Study Report

Immunogenicity

The anti–pegcetacoplan peptide antibody and anti-PEG antibody incidence through Month 24 were 2.5% and 14.1% for study APL2-303 (**Table 3** and **Table 4**), and 4.3% and 10.2% for APL2-304 (**Table 5** and **Table 6**).

Table 3. Summary of Subject-Level Anti–Pegcetacoplan Peptide Antibody Responses Through Month 24 - Safety Population (Study APL2-303, DERBY)

	PM (N = 206) n (%)	PEOM (N = 208) n (%)	Pegcetacoplan pooled N = 414) n (%)	Sham pooled (N = 206) n (%)
Subjects with evaluable baseline sample	201	204	405	201
Subjects positive at baseline[a]	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Subjects evaluable for ADA response[b]	202 (98.1)	202 (97.1)	404 (97.6)	194 (94.2)
Positive ADA response	4 (2.0)	6 (3.0)	10 (2.5)	4 (2.1)
Emergent	4 (2.0)	6 (3.0)	10 (2.5)	4 (2.1)
Transient	4 (2.0)	6 (3.0)	10 (2.5)	3 (1.5)
Persistent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unclassified	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Boosted	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Persistent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unclassified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Negative ADA response	198 (98.0)	196 (97.0)	394 (95.7)	190 (97.9)
Undefined ADA response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ADA = antidrug antibodies; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Source: Table 62. APL2-303 Month 24 Clinical Study Report

Table 4. Summary of Subject-Level Anti–PEG Antibody Responses Through Month 24 - Safety Population (Study APL2-303, DERBY)

	PM (N = 206) n (%)	PEOM (N = 208) n (%)	Pegcetacoplan Pooled (n = 414) n (%)	Sham pooled (n = 206) n (%)
Subjects with evaluable baseline sample	202	204	406	201
Subjects positive at baseline[a]	125 (61.9)	119 (58.3)	244 (60.1)	119 (59.2)
Subjects evaluable for ADA response[b]	202 (98.1)	202 (97.1)	404 (97.6)	194 (94.2)
Positive ADA response	32 (15.8)	25 (12.4)	57 (14.1)	58 (29.9)
Emergent	21 (10.4)	15 (7.4)	36 (8.9)	29 (14.9)
Transient	12 (5.9)	9 (4.5)	21 (5.2)	10 (5.2)
Persistent	4 (2.0)	3 (1.5)	7 (1.7)	12 (6.2)
Unclassified	5 (2.5)	3 (1.5)	8 (2.0)	7 (3.6)
Boosted	11 (5.4)	10 (5.0)	21 (5.2)	29 (14.9)
Transient	5 (2.5)	5 (2.5)	10 (2.5)	8 (4.1)
Persistent	2 (1.0)	0 (0.0)	2 (0.5)	5 (2.6)
Unclassified	4 (2.0)	5 (2.5)	9 (2.2)	16 (8.2)
Negative ADA response	168 (83.2)	175 (86.6)	343 (84.9)	131 (67.5)
Undefined ADA response	2 (1.0)	2 (1.0)	4 (1.0)	5 (2.6)

Abbreviation: ADA = antidrug antibodies; PEG = polyethylene glycol; PEOM = pegcetacoplan every other month. PM = pegcetacoplan monthly.
Source: Table 63. APL2-303 Month 24 Clinical Study Report

Table 5. Summary of Subject-Level Anti–Pegcetacoplan Peptide Antibody Responses Through Month 24 - Safety Population (Study APL2-304, OAKS)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacoplan pooled (N = 425) n (%)	Sham pooled (N = 211) n (%)
Subjects with evaluable baseline sample	200	197	397	192
Subjects positive at baseline[a]	5 (2.5)	2 (1.0)	7 (1.8)	8 (4.2)
Subjects evaluable for ADA response[b]	208 (97.7)	207 (97.6)	415 (97.6)	207 (98.1)
Positive ADA response	10 (4.8)	8 (3.9)	18 (4.3)	9 (4.3)
Emergent	10 (4.8)	8 (3.9)	18 (4.3)	9 (4.3)
Transient	10 (4.8)	6 (2.9)	16 (3.9)	8 (3.9)
Persistent	0	1 (0.5)	1 (0.2)	0
Unclassified	0	1 (0.5)	1 (0.2)	1 (0.5)
Boosted	0	0	0	0
Transient	0	0	0	0
Persistent	0	0	0	0
Unclassified	0	0	0	0
Negative ADA response	196 (94.2)	196 (94.7)	392 (94.5)	196 (94.7)
Undefined ADA response	2 (1.0)	3 (1.4)	5 (1.2)	2 (1.0)

Abbreviations: ADA = antidrug antibodies; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly. a The percentage is based on the number of subjects evaluated for the respective summary. b Evaluable subjects are used as the denominator for all ADA response analyses.
Source: Table 62. APL2-304 Month 24 Clinical Study Report.

Source: Table 62. APL2-304 Month 24 Clinical Study Report.

Table 6. Summary of Subject-Level Anti-PEG Antibody Responses Through Month 24 - Safety Population (Study APL2-304, OAKS)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacoplan pooled (N = 425) n (%)	Sham pooled (N = 211) n (%)
Subjects with evaluable baseline sample	191	178	369	180
Subjects positive at baseline[a]	99 (51.8)	107 (60.1)	206 (55.8)	96 (53.3)
Subjects evaluable for ADA response[b]	206 (96.7)	206 (97.2)	412 (96.9)	206 (97.6)
Positive ADA response	18 (8.7)	24 (11.7)	42 (10.2)	41 (19.9)
Emergent	10 (4.9)	17 (8.3)	27 (6.6)	27 (13.1)
Transient	4 (1.9)	11 (5.3)	15 (3.6)	5 (2.4)
Persistent	4 (1.9)	2 (1.0)	6 (1.5)	12 (5.8)
Unclassified	2 (1.0)	4 (1.9)	6 (1.5)	10 (4.9)
Boosted	8 (3.9)	7 (3.4)	15 (3.6)	14 (6.8)
Transient	5 (2.4)	2 (1.0)	7 (1.7)	2 (1.0)
Persistent	0	0	0	2 (1.0)
Unclassified	3 (1.5)	5 (2.4)	8 (1.9)	10 (4.9)
Negative ADA response	183 (88.8)	173 (84.0)	356 (86.4)	149 (72.3)
Undefined ADA response	5 (2.4)	9 (4.4)	14 (3.4)	16 (7.8)

Abbreviations: ADA = antidrug antibodies; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly. a The percentage is based on the number of subjects evaluated for the respective summary. b Evaluable subjects are used as the denominator for all ADA response analyses.
Source: Table 63. APL2-304 Month 24 Clinical Study Report.

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Office of Clinical Pharmacology Review

NDA Number	217171
Link to EDR	\\CDSESUB1\evsprod\NDA217171\0001
Applicant	Apellis Pharmaceuticals, Inc.
Proposed Brand Name, Drug, Dosage Form and Strength	SYFOVRE, Intravitreal Injection, 15 mg/0.1 mL solution
Submission Type	Priority
Submission Date	5/26/2022
PUDFA Goal Date	11/26/2022
Proposed Indication	Geographic atrophy secondary to age-related macular degeneration
Proposed Dosing Regimen & Instructions	Intravitreal injection of 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4)
Associated IND	124784
OCP Division	Division of Inflammation and Immune Pharmacology (DIIP)
OCP Review Team	Da Zhang, Ph.D. Clinical Pharmacology/Pharmacometric Reviewer, DIIP Youwei Bi, Ph.D. Team Leader, DPM Ping Ji, Ph.D. Team Leader, DIIP
OCP Final Signatory	Suresh Doddapaneni, Ph.D.

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1. EXECUTIVE SUMMARY

Pegcetacoplan, a complement inhibitor, is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol (PEG) molecule. Pegcetacoplan for subcutaneous (SC) administration was approved in the US (New Drug Application [NDA] 215014; 14 May 2020) for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). In this original non-NME NDA, the Applicant (Apellis) submitted pegcetacoplan solution for intravitreal (IVT) injection for the treatment of adult patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The proposed dosage of IVT pegcetacoplan is 15 mg (15 mg/0.1 mL solution) to each affected eye once every (b) (4)

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

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen for the treatment of adult patients with GA secondary to AMD.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the relevant Clinical Pharmacology information provided by the Applicant in NDA 217171 for GA secondary to AMD and recommends approval of this NDA from a clinical pharmacology perspective. The key review issues with specific clinical pharmacology recommendations and comments are summarized in **Table 1** .

Table 1. Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of IVT pegcetacoplan, administered either monthly or EOM, in patients with GA secondary to AMD was established in three randomized and sham-controlled studies based on change from baseline to Month 12 in total area of GA lesion(s) in the study eye (Study APL2-303 and Study APL2-304) or the change from baseline to Month 12 in square root of total area of GA lesion in the study eye (Study POT-CP121614).
General dosing instructions	Pegcetacoplan is recommended to be administered by intravitreal injection at 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4) .

Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment in any patient subgroups (e.g., age, sex or baseline C3 concentration) is needed.
Labeling	Refer to Section 2.4.
Bridge between the to-be- marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical studies.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

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.

Pharmacokinetics

Following repeat intravitreal administration of pegcetacoplan of 15 mg, 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.

Following intravitreal administration of pegcetacoplan, the systemic median Tmax 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. 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. 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. There were no clinically significant differences on the pharmacokinetics of pegcetacoplan intravitreal administration based on age (60 to 97 years old), sex, 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).

Pharmacodynamics

No systemic PD effects (CH50, C3, and AH50) were observed in subjects with GA secondary to AMD; this is consistent with the low systemic exposure of pegcetacoplan observed following IVT administration of 15 mg doses either monthly or EOM.

Immunogenicity

The incidence of anti–pegcetacoplan peptide antibodies was low across all studies, and there was no apparent relationship between incidence of ADAs and dose group. Additionally, low incidences of treatment-emergent and treatment-boosted anti-PEG antibody responses were observed, and many of those responses were transient. Given the low incidence of anti-pegcetacoplan peptide antibodies and treatment-emergent/boosted anti-PEG antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosage of IVT pegcetacoplan is administered by intravitreal injection at 15 mg

(0.1 mL of 150 mg/mL solution) to each affected eye once every [redacted] (b) (4)

2.2.2 Therapeutic individualization

No dose adjustment is necessary for any specific populations.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following recommendations on the labeling:

12.3 Pharmacokinetics

[redacted] (b) (4)

12.6 Immunogenicity

Because of the low [redacted] (b) (4) incidence of anti-pegcetacoplan peptide antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Pegcetacoplan is a symmetrical molecule composed of two identical pentadecapeptides covalently bound to the ends of a linear 40 kiloDalton (kDa) polyethylene glycol (PEG) molecule. The peptide portions of pegcetacoplan contain 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino (ethoxyethoxy) acetic acid (AEEA) in position 14. Pegcetacoplan intravitreal injection is a sterile, preservative-free, clear, colorless to light yellow aqueous solution in a single-dose vial.

A summary of key regulatory interactions with the Applicant is listed in **Table 2**:

Table 2. Summary of Key Regulatory Interactions

NDA 215014 Approval (May 14, 2021)	FDA approved the EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Type B EOP2 Meeting (Dec 05, 2017)	Discussed 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 WRO (Oct 21, 2019)	Discussed the acceptability of the proposed (b) (4)-mL overfill on the basis of dead volume loss and filling machine variability
Type C Meeting (Mar 01, 2021)	Discussed the statistical analysis strategy and pooling proposals for the Phase 3 studies for pegcetacoplan
Type C WRO (Sep 28, 2021)	Discussed the concentration for leachables and the Division required 12-month drug product registration stability data at the time of NDA submission.
Type A Meeting (Scheduled on Nov 18, 2021)	Discussed the adequacy of Studies APL2-303, APL2-304, and POT-CP121614 to support the indication and the appropriateness of the mean rate of change from baseline (CFB) in total GA lesion area using fundus autofluorescence (FAF) as the primary endpoint.
Type B Pre-NDA Meeting (Jan 21, 2022)	The Division recommended that Apellis 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 Apellis'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.

3.2 General Pharmacology and Pharmacokinetic Characteristics

The PK of IVT pegcetacoplan was evaluated in subjects with nAMD (Studies POT-CP043014 and APL2-203), and 3 clinical studies in subjects with GA secondary to AMD (Studies POT-CP121614, APL2-303, and APL2-304). All but one clinical study (Study APL2-304) evaluated the PK of pegcetacoplan. Population PK (PopPK) analysis of pegcetacoplan was conducted using pooled PK data from 4 clinical studies following IVT administration. Based on the PopPK analysis, none of the investigated covariate effects were anticipated to be clinically meaningful given the low absolute maximum serum concentrations achieved (<5 µg/mL). General pharmacology and pharmacokinetic characteristics of pegcetacoplan is shown in **Table 3**.

Table 3. General Pharmacology and Pharmacokinetic Characteristics of Pegcetacoplan

Characteristic	Drug Information
Pharmacologic Activity	

Characteristic	Drug Information
Established pharmacologic class (EPC)	Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kiloDalton (kDa) PEG molecule.
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. Overactivation of the complement system is strongly associated with the progression of GA. Increased levels of complement activity have been found in patients with GA, specifically in lesions and surrounding areas. Pegcetacoplan acts centrally by regulating C3 in the complement cascade, thereby exerting broad control of complement activation, and of the complement effectors that are involved in the pathogenesis of GA.
Active moieties	Pegcetacoplan
General Information	
Bioanalysis	Pegcetacoplan concentrations in human serum were quantified using validated LC-MS/MS. These assays along with its related validation reports were found to be acceptable. (*Reference: Appendix 4.1*)
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in pivotal clinical studies.
Absorption	
Cmax	Median (5th, 95th) steady-state serum Cmax among GA patients is predicted to be 1.70 (0.60, 2.30) µg/mL and 2.20 (1.40, 3.00) µg/mL at doses of 15 mg IVT EOM and 15 mg IVT every month, respectively. (*Reference: Appendix 4.3.1*)
Serum pegcetacoplan exposure at steady state	Steady-state serum pegcetacoplan exposure is predicted to be below the level required for systemic PD effects on the basis of systemic C3 inhibition (655-706 µg/mL in paroxysmal nocturnal hemoglobinuria [PNH] patients, reference to NDA 215014 Integrated Review in DARRTS dated May 14, 2021). Steady-state vitreous pegcetacoplan

Characteristic	Drug Information
	exposure is predicted to be approximately 1300-fold higher than serum exposure. (*Reference: Appendix 4.3.1*)
Dosage proportionality	Serum PK of pegcetacoplan increased in a dose-proportional manner as assessed by AUC and Cmax across the dose range evaluated (4, 10, and 20 mg IVT/0.1 mL injection). (*Reference: Appendix 4.2.2)*
Accumulation	There is almost no systemic accumulation from first dose to steady state with EOM dosing (median accumulation ratio [AR] = 1.10) and only a small amount of accumulation with monthly dosing (median AR = 1.50). (*Reference: Appendix 4.3.1*)
Distribution	
Volume of 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. (*Reference: Appendix 4.3.1*)
Elimination	
Clearance	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 secondary to AMD. (*Reference: Appendix 4.3.1*)
Half-life	Pegcetacoplan disposition following IVT administration is absorption limited with median individual predicted absorption and elimination half-lives of 13.0 days (T½, abs) and 4.49 days (T½, elim), respectively. (*Reference: Appendix 4.3.1*)
Metabolic pathway(s)	Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways.
Intrinsic Factors and Specific Populations	
Body weight	Based on the PopPK model, body weight-based dosage adjustment is not needed. (*Reference: Appendix 4.3.1*)
Age	Based on the PopPK model, age-based dosage adjustment is not needed. (*Reference: Appendix 4.3.1*)

Characteristic	Drug Information
Renal and hepatic impairment	Based on the PopPK model, there were no clinically significant differences on the pharmacokinetics of pegcetacoplan intravitreal administration based on 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). (*Reference: Appendix 4.3.1*)
Pharmacodynamics	
Pharmacodynamics	In studies where systemic complement biomarkers CH50, C3, and AH50 were collected (Studies POT-CP121614 [CH50 and C3 only] and APL-303), no systemic PD effects were observed in subjects with GA secondary to AMD; This is consistent with the low systemic exposure of pegcetacoplan observed following IVT administration of 15 mg doses either monthly or EOM.
Immunogenicity	
Bioanalysis	Serum anti-pegcetacoplan peptide Ab and pegcetacoplan Nab were assessed using electro-chemiluminescent. Anti-PEG Ab was assessed via ELISA. (*Reference: Appendix 4.1*)
Incidence and clinical impact	Overall, the incidence of anti–pegcetacoplan peptide antibodies was low across all studies (in Phase 2 and 3 studies, 67 of 1466 evaluated subjects [4.6%] or 131 of 7303 evaluated samples [1.8%]), and rare incidences of NAb responses have been detected in pegcetacoplan-treated subjects across all clinical studies. Low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response were observed, and many of those responses were transient. There was no apparent relationship between incidence of ADAs and dose group. Given the low incidence of anti-pegcetacoplan peptide antibodies and treatment-emergent/boosted anti-PEG antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Pegcetacoplan is administered via IVT route, and the site of action is the eye; therefore, the systematic exposure is not expected to affect treatment effect, and thus does not provide pivotal or supportive evidence for the effectiveness of IVT pegcetacoplan.

The Applicant conducted the exploratory population vitreous exposure-response analysis to characterize the impact of pegcetacoplan vitreous exposure following IVT administration on disease progression in patients with GA secondary to AMD. The maximal reduction in the rate of lesion growth was estimated to be 14.0%; a vitreous concentration of 272 µg/mL was predicted to achieve 50% of this maximal effect (EC50) (**Figure 15**). While the model estimation appeared to support the effectiveness of IVT pegcetacoplan, the analysis is considered exploratory given the unavailability of observed subject-level vitreous pegcetacoplan concentration data in the well-controlled studies.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed IVT pegcetacoplan dosing regimen of 15 mg (0.1 mL of 150 mg/mL solution) to each affected eye once every (b) (4) is appropriate for the adult patient population for which the indication is being sought.

Dose Selection

In the Phase 1 Study POT-CP043014, 3 escalating single doses (4, 10, or 20 mg IVT pegcetacoplan IVT 0.1 mL injection) were studied in 13 subjects with neovascular AMD across 3 cohorts. A dose-dependent increase in pegcetacoplan serum exposure metrics and area under the curve was observed across the doses investigated (**Figure 1**) and no dose-limiting toxicity was observed.

The dose of 15 mg/0.1 mL was considered the highest practical concentration because the viscosity of pegcetacoplan solution increases exponentially and becomes significant at doses ≥15 mg/0.1 mL; therefore, 15 mg/0.1 mL was selected for the subsequent phase 2 clinical trial in subjects with GA secondary to AMD (Study POT-CP121614). Following monthly or EOM 15 mg/0.1 mL pegcetacoplan dosing in Study POT-CP121614, mean pegcetacoplan trough concentrations were approximately 5 times higher in the PM group than in the PEOM group, which supports a dose response (**Figure 3**). Because the 15 mg/0.1 mL dose was observed to be efficacious when given monthly or EOM, these dosages were also used in Phase 3 Studies APL2-304 and APL2-303.

Efficacy in Phase 2 and Phase 3 Studies

Results across 3 studies of IVT pegcetacoplan, administered either monthly or EOM, demonstrated substantial evidence of a clinically meaningful reduction in GA lesion growth at Month 12 compared with sham. A persistent treatment effect was observed

for PM and PEOM groups through Month 18 and is likely to persist through Month 24 in Studies APL2-304 and APL2-303 as assessed with the reduction of GA growth in the study eye compared with the fellow eye in bilateral GA subjects treated with pegcetacoplan. In addition, the results of Studies APL2-304 and APL2-303 at Month 18 support persistence of the efficacy of pegcetacoplan compared with sham. The treatment effect observed in the Study APL2-304 PM group was numerically greater than in that study's PEOM group. The observed effect sizes in Study APL2-303 were similar in the PM and PEOM groups. Refer to Clinical Review for additional details regarding evidence of effectiveness for the proposed product.

Safety Considerations

Population PK modeling demonstrated that systemic serum pegcetacoplan concentrations at steady state following monthly or EOM IVT pegcetacoplan administration are predicted to be well below any thresholds anticipated to result in meaningful inhibition of systemic C3 at clinically relevant doses (655-706 μg/mL in paroxysmal nocturnal hemoglobinuria [PNH] patients, reference to NDA 215014 Integrated Review in DARRTS dated May 14, 2021). Median (5th, 95th) steady-state serum Cmax among GA patients is predicted to be 1.70 (0.60, 2.30) μg/mL and 2.20 (1.40, 3.00) μg/mL at doses of 15 mg IVT EOM and 15 mg IVT every month, respectively (*Reference to Appendix 4.3.1*).

In studies where systemic complement biomarkers CH50, C3, and AH50 were collected (Studies POT-CP121614 [CH50 and C3 only] and APL-303), no systemic PD effects were observed in subjects with GA secondary to AMD; this is consistent with the low systemic exposure of pegcetacoplan observed following IVT administration of 15 mg doses either monthly or EOM, providing supportive systemic safety evidence of IVT pegcetacoplan for GA secondary to AMD treatment **(Figures 4, 5, 7, 8, 9).**

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternative dosing regimen and/or management strategy is not required for subpopulations based on intrinsic factors. For the proposed drug product, the intended site of drug delivery and action is the eye; therefore, the systemic exposure is not considered to affect the effectiveness of pegcetacoplan. The low systemic exposure of pegcetacoplan after intravitreal dosing is considered to have no effect on systemic safety. Further, based on the population PK analyses, the Applicant did not identify any covariate with a clinically meaningful impact on the plasma or ocular exposure of pegcetacoplan (*Reference to Appendix 4.3.1*). There were no clinically significant differences on the PK of pegcetacoplan via intravitreal administration based on age (60 to 97 years old), sex, 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).

3.3.4 What is the impact of immunogenicity on exposure, safety and efficacy of IVT pegcetacoplan?

Assessment:

In studies APL2-203, OT-CP121614, APL2-303 and APL2-304, ADAs and NAbs against the peptide moiety of pegcetacoplan (i.e., anti–pegcetacoplan peptide) and against the PEG component of pegcetacoplan (i.e., anti-PEG) were assessed (**Table 4**). Two specific ADA assays were developed for assessing immunogenicity potential of pegcetacoplan following IVT administration, one specific for ADAs against the peptide moiety of pegcetacoplan (ie, anti–pegcetacoplan peptide) and one specific for ADAs against the PEG component of pegcetacoplan (ie, anti-PEG). Both assays were validated. (Refer to Appendix 4.1 for details)

Table 4. ADA and PK Sampling

Study	ADA Sampling Points	PK sampling Points
APL2-203	Days 30, 180, and 360	Days 30, 180, and 360
POT-CP121614	Days 0, 7, 60, 120, 180, 240, 300, 360, 450 and 540	Days 0, 7, 60, 120, 180, 240, 300, 360, 450 and 540
APL2-303	Days 1, 30, 60, 180, 360	Days 1, 7, 30, 180, 360
APL2-304	Days 1, 30, 60, 180, 360	NA

Source: Reviewer's summary per individual study CSRs

Incidence:

Overall, the incidence of anti–pegcetacoplan peptide antibodies was low across all studies (in phase 2 and 3 studies, 67 of 1466 evaluated subjects [4.6%] or 131 of 7303 evaluated samples [1.8%]), and no apparent relationship between dose groups was identified (**Table 5**). Low incidences of treatment-emergent or treatment-boosted anti-PEG antibody response were observed, and many of those responses were transient (**Table 6**). Additionally, no impact of formulations on the immunogenicity responses was observed across the investigated studies.

In summary, infrequent and generally transient anti–pegcetacoplan peptide antibody responses and rare incidences of NAb responses have been detected in pegcetacoplan-treated subjects across all clinical pharmacology studies. There was no apparent relationship between incidence of ADAs and dose group.

Table 5. Summary of Anti–Pegcetacoplan Peptide Antibody Results

Clinical study	Study APL2-203	Study POT-CP121614				Study APL2-303				Study APL2-304			
ROA	IVT	IVT				IVT				IVT			
Subjects	nAMD	GA secondary to AMD				GA secondary to AMD				GA secondary to AMD			
Cohort	NA	PM	PEOM	SM	SEOM	PM	PEOM	SM	SEOM	PM	PEOM	SM	SEOM
Dose, mg	15	15	15	Sham	Sham	15	15	Sham	Sham	15	15	Sham	Sham
Dosing frequency	Monthly	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM
Number of subjects	17	246				598				622			
By cohort	17	86	79	41	40	202	202	96	98	208	207	104	103
Total number of samples screened	35	515				3394				3394			
Number (%) of samples confirmed positive	0 (0)	21 (4.1)				18 (0.5)				92 (2.7)			
Titer values	NA	≤1:80				≤1:10				≤1:80			
Number (%) of subjects with a confirmed positive[a]	0 (0)	2 (2.3)	3 (3.8)	0 (0)	0 (0)	4 (2.0)	7 (3.5)	0 (0)	3 (3.1)	17 (8.2)	14 (6.8)	9 (8.7)	8 (7.8)

Abbreviations: AMD = age-related macular degeneration; EOM = every other month; GA = geographic atrophy; IVT = intravitreal; NA = not applicable; nAMD = neovascular age-related macular degeneration; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; ROA = route of administration; SEOM = sham every other month; SM = sham monthly.

[a] Inclusive of predose and postdose positive subjects except in Studies APL2-303 and APL2-304, which include only postdose positive subjects

Source: 2.7.2 Summary of Clinical Pharmacology, Table A1.

Table 6. Summary of Anti-PEG Antibody Results

Clinical study	Study APL2-203	Study POT-CP121614				Study APL2-303				Study APL2-304			
ROA	IVT	IVT				IVT				IVT			
Subjects	nAMD	GA secondary to AMD				GA secondary to AMD				GA secondary to AMD			
Cohort	NA	PM	PEOM	SM	SEOM	PM	PEOM	SM	SEOM	PM	PEOM	SM	SEOM
Dose, mg	15	15	15	Sham	Sham	15	15	Sham	Sham	15	15	Sham	Sham
Dosing frequency	Monthly	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM	Monthly	EOM
Number of subjects	17	246				598				615			
By cohort	17	86	79	41	40	202	202	96	98	204	205	103	103
Total number of samples screened	35	543				3395				3369			
Number (%) of samples confirmed positive	11 (31.4)	257 (47.3)				1626 (47.9)				1385 (41.1)			
Titer values	≤1:640	≤1:40,960				≤1:20,500				≤ 1:10,342.4			
Number (%) of subjects with a confirmed positive[a]	8 (47.1)	49 (57.0)	59 (74.7)	30 (73.2)	27 (67.5)	129 (63.9)	119 (58.9)	71 (74.0)	69 (70.4)	109 (53.4)	121 (59.0)	67 (65.0)	63 (61.2)
Number (%) of subjects with a positive response at baseline	NA	46 (53.5)	57 (72.2)	24 (58.5)	23 (57.5)	125 (61.9)	119 (58.3)	61 (61.6)	58 (56.9)	99 (52.1)	105 (60.3)	54 (58.1)	42 (48.8)
Clinical study	**Study APL2-203**	**Study POT-CP121614**				**Study APL2-303**				**Study APL2-304**			
Number (%) of subjects with a treatment-emergent response	NA	3 (3.5)	1 (1.3)	5 (12.2)	3 (7.5)	17 (8.4)	13 (6.4)	12 (12.5)	13 (13.3)	9 (4.4)	15 (7.3)	9 (8.7)	10 (9.7)
Number (%) of subjects with a treatment-boosted response	NA	0 (0)	0 (0)	3 (7.3)	2 (5.0)	9 (4.5)	9 (4.5)	17 (17.7)	9 (9.2)	7 (3.4)	6 (2.9)	4 (3.9)	7 (6.8)

Source: 2.7.2 Summary of Clinical Pharmacology, Table A2

Impact of ADAs on Exposure, Efficacy and Safety:

Anti-PEG ADA appeared to have no impact pegcetacoplan serum exposure. (**Figure 14**).

Following monthly or EOM IVT pegcetacoplan treatment, there is no evidence of risk of adverse effects (AEs), e.g., hypersensitivity, anaphylaxis, etc. caused by antidrug antibodies. However, because of the low incidence of anti-pegcetacoplan peptide and treatment emergent/boosted anti-PEG antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of pegcetacoplan is unknown.

3.3.5 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No, there are no clinically relevant food-drug or drug-drug interactions for pegcetacoplan.

Pegcetacoplan is given via IVT route; therefore, the issue of a food-drug interaction is not relevant.

Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways, hence it has a low potential for mediating a DDI with co-administered agents via CYP or drug transporter pathways.

3.3.6 Was there PK bridging between to-be-marketed product and clinical trial product?

The to-be-marketed product was used in the pivotal clinical trials.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods for determining serum pegcetacoplan concentration and immunogenicity were developed and validated for the quantitative determination of pegcetacoplan concentrations in human serum in the completed clinical studies (**Table 7**).

Table 7. Summary of Bioanalytical Methods for PK, PD, and Immunogenicity

	Matrix/anticoagulant	Method
Serum concentration (PK)		
Pegcetacoplan	Serum	LC-MS/MS
Immunogenicity		
Anti–pegcetacoplan peptide Ab	Serum	Electrochemiluminescent
Anti-PEG Ab	Serum	ELISA
Pegcetacoplan NAb	Serum	Electrochemiluminescent
PD complement biomarkers		
AH50	Serum	Hemolytic assay
CH50	Serum	Hemolytic assay, EIA
C3	Serum	Nephelometry, immunoturbidimetric

Abbreviations: Ab = antibody; AH50 = functional assay measuring activity of the complement alternative pathway; CH50 = functional assay measuring activity of the complement classical pathway; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; LC-MS/MS = liquid chromatography with tandem mass spectrometry; NAb = neutralizing antibody; PD = pharmacodynamics; PEG = polyethylene glycol; PK = pharmacokinetics.

Source: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2.

Details of the methods and validation parameters are listed in **Table 8**. Standard curve linearity, selectivity/specificity, assay accuracy and precision, extraction efficiency, and dilution fulfilled the standard acceptance criteria. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period.

Table 8. Summary of Bioanalytical Methods for the Measurement of Serum Pegcetacoplan

Parameter	Information (Studies POT-CP043014 and APL2-203)
Methodology	The analyte (pegcetacoplan) and internal standard (d22-pegcetacoplan) were extracted from 100 µL of human serum by protein precipitation using acetonitrile. The

<table>
<tr><td></td><td>supernatant was filtered, evaporated to dryness, reconstituted, and then analyzed by LC-MS/MS.</td></tr>
<tr><td>Calibration curve range</td><td>0.100-10.0 µg/mL</td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td><table>
<tr><td>No. of standard calibrators from LLOQ to ULOQ</td><td>8</td></tr>
<tr><td>Cumulative accuracy (%bias) from LLOQ to ULOQ</td><td>−2.94% to 2.17%</td></tr>
<tr><td>Cumulative precision (CV) from LLOQ to ULOQ</td><td>≤7.05%</td></tr>
</table></td></tr>
<tr><td>Performance of QCs during accuracy and precision runs</td><td><table>
<tr><td>Cumulative accuracy (%bias) in 4 QCs</td><td>−4.85% to 3.86%</td></tr>
<tr><td>Interbatch CV</td><td>≤8.67%</td></tr>
</table></td></tr>
<tr><td>Bench-top/ process stability</td><td>21 hours</td></tr>
<tr><td>Long term stability</td><td>Long-Term Freezer Storage Stability (−20 °C): 339 days
Long-Term Freezer Storage Stability (−70 °C): 2114 days</td></tr>
<tr><td>Freeze-thaw stability</td><td>−20 °C: 3 cycles
−70 °C: 3 cycles</td></tr>
<tr><td>Method reproducibility</td><td>Incurred sample reanalysis was performed in ⩾10% of study samples, and 20 of 23 (87.0%) of the samples met the prespecified criteria.</td></tr>
<tr><td>Study sample analysis/ stability</td><td>Duration of matrix stability required: 350 days
Duration of matrix stability established: 2114 days</td></tr>
<tr><td>Parameter</td><td>Information (POT-CP121614)</td></tr>
<tr><td>Validated assay range</td><td>0.100-10.0 µg/mL</td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td><table>
<tr><td>No. of standard calibrators from LLOQ to ULOQ</td><td>8</td></tr>
<tr><td>Cumulative accuracy (%bias) from LLOQ to ULOQ</td><td>−2.7% to 4.0%</td></tr>
<tr><td>Cumulative precision (CV) from LLOQ to ULOQ</td><td>≤8.0%</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Performance of QCs during accuracy and precision runs</td><td><table><tr><td><u>Cumulative accuracy (%bias) in 4 QCs</u></td><td>−1.7% to 2.0%</td></tr><tr><td><u>Interbatch CV</u></td><td>≤10.9%</td></tr></table></td></tr>
<tr><td>Bench-top/ process stability</td><td>Bench top stability at room temperature: 21 hours
Processed sample stability at room temperature: 66 hours</td></tr>
<tr><td>Long term stability</td><td>Long-Term Freezer Storage Stability (−20 °C): 94 days
Long-Term Freezer Storage Stability (−70 °C): 776 days</td></tr>
<tr><td>Freeze-thaw stability</td><td>3 cycles</td></tr>
<tr><td>Method reproducibility</td><td>ISR was supposed to be conducted by reanalyzing 10% of the total samples originally analyzed for the first 1000 samples and 5% of any further samples. There were 2247 samples originally analyzed, so the number of samples reanalyzed for ISR should have been 162 instead of 161. Given that 91.9% (148 of 161) of ISR samples met the acceptance criteria, the 1 sample not analyzed would have no impact on the results.</td></tr>
<tr><td>Study sample analysis/ stability</td><td>Duration of matrix stability required: 372 days
Duration of matrix stability established: 776 days</td></tr>
<tr><td>Parameter</td><td>Information (APL2-303)</td></tr>
<tr><td>Validated assay range</td><td>0.100-10.0 µg/mL</td></tr>
<tr><td>Standard calibration curve performance during accuracy and precision runs</td><td><table><tr><td>No. of standard calibrators from LLOQ to ULOQ</td><td>8</td></tr><tr><td>Cumulative accuracy (%bias) from LLOQ to ULOQ</td><td>−2.5% to 2.0%</td></tr><tr><td>Cumulative precision (CV) from LLOQ to ULOQ</td><td>≤8.2%</td></tr></table></td></tr>
<tr><td>Performance of QCs during accuracy and precision runs</td><td><table><tr><td><u>Cumulative accuracy (%bias) in 5 QCs</u></td><td>−2.7% to 8.0%</td></tr><tr><td><u>Interbatch CV</u></td><td>≤9.1%</td></tr></table></td></tr>
<tr><td>Bench-top/ process stability</td><td>Bench-top stability at room temperature: 6.8 hours</td></tr>
<tr><td>Long term stability</td><td>Long-term stability for PEGCETACOPLAN in human serum at −70 °C: 37 days (40 days for samples >ULOQ)</td></tr>
<tr><td>Freeze-thaw stability</td><td>At least 4 cycles at −70 °C</td></tr>
<tr><td>Method reproducibility</td><td>Incurred sample reanalysis was performed in >10% of study samples, and 38 of 42 (90.5%) of the samples met the prespecified criteria.</td></tr>
</table>

Study sample analysis/ stability	Duration of matrix stability required: 959 days Duration of matrix stability established: 37 days. This will be amended once adequate long-term stability time is established. In the other validation reports included in this filing, serum matrix stability has been established at 2114 days at −70 °C and 776 days at −80 °C.

Source: 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Appendix 2A.

Bioanalytical Methods for Monitoring Immunogenicity:

Two ADA assays were developed and validated: one specific for antibodies against the peptide domain of pegcetacoplan (the anti–pegcetacoplan peptide antibody assay) and one specific for antibodies against the PEG domain of pegcetacoplan (the anti-PEG antibody assay). A competitive ligand-binding NAb assay was also developed and validated to detect pegcetacoplan NAbs.

To assess the immunogenicity risk for pegcetacoplan, Applicant developed anti-drug antibody (ADA) assays to detect antibodies against the functional peptide or the PEG portion of pegcetacoplan. Patient samples were screened for the presence of ADA using the screening assay. The screened positive samples were then tested in the confirmatory assay and those confirmed positive were characterized for the ADA titer. The Applicant also developed a neutralizing anti-drug antibody (NAb) assay to assess the neutralizing activity of detected ADA. Refer to the review conducted by in the Office of Biotechnology Products (OBP) for details regarding the methods and validation of the immunogenicity assay.

Reviewer's Comments:

The reviewer deemed the bioanalytical method validation and sample analysis acceptable.

4.2. Clinical Pharmacology Studies

4.2.1 Study POT-CP043014

Title: Assessment of Safety, Tolerability and Pharmacokinetics of Intravitreal Pegcetacoplan Therapy for Patients with Neovascular Age-Related Macular Degeneration (AMD) – ASAP II

Objectives:

The objective of this study was to provide initial safety, tolerability, and pharmacokinetics information of intravitreal (IVT) administration of *pegcetacoplan* in order to support further development into larger Phase 2 studies for treatment of patients with AMD.

Trial Design:

This Phase 1, prospective, open-label, uncontrolled, nonrandomized, single-dose escalation study assessed the safety, tolerability, and pharmacokinetics of IVT pegcetacoplan in subjects with exudative AMD currently receiving anti-vascular endothelial growth factor (VEGF) therapy. Subjects were sequentially enrolled into 3 cohorts (4, 10, and 20 mg of pegcetacoplan in a 100 µL IVT injection). Initially, 3 subjects were enrolled in each cohort. Cohort 3 was expanded to 12

subjects once the initial 3 subjects had reached their Day 7 Visit (only 7 were recruited).

Subjects who met all entry criteria received IVT pegcetacoplan on Day 1. Subjects returned to the clinical site on Days 3, 8, and 15 during the 14-day acute safety observation period. After the acute safety period, subjects returned to the clinical site for additional follow-up visits on Days 29, 57, 85, and the Termination Visit on Day 113. Safety was assessed throughout the study; blood samples and urine samples were collected for safety laboratory determinations.

Blood samples were also collected for the pharmacokinetic assessment of pegcetacoplan. No PD samples were collected.

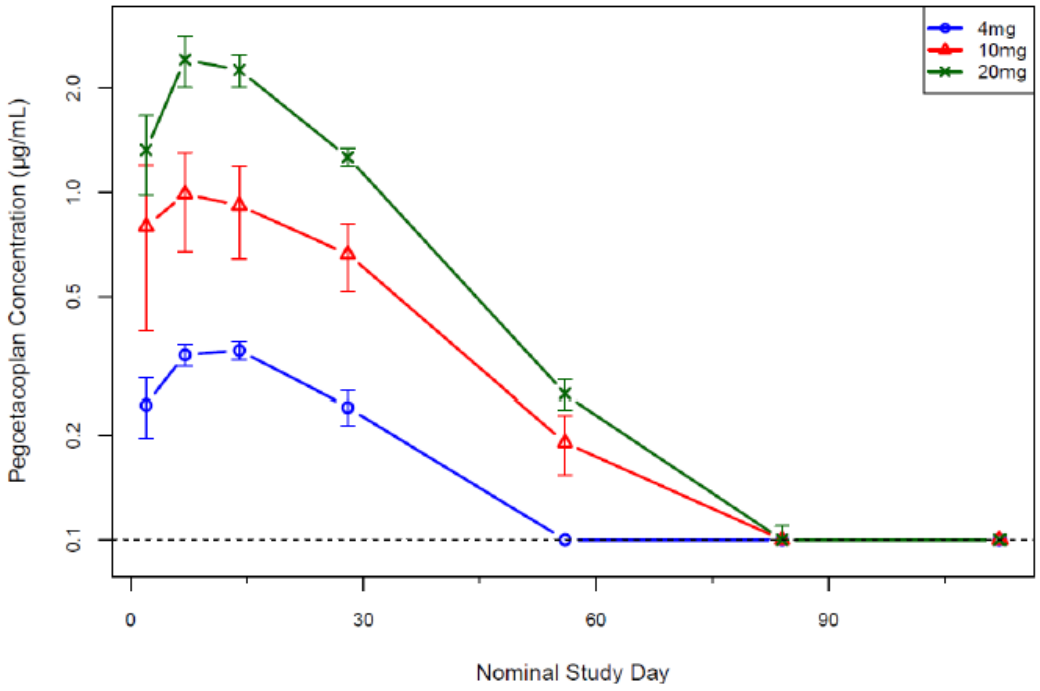
Results:

A total of 13 subjects were enrolled in the study, 3 received 4 mg pegcetacoplan, 3 received 10 mg pegcetacoplan, and 7 received 20 mg pegcetacoplan. All 13 subjects were included in the Safety Set, the Efficacy Set, and the Pharmacokinetic set.

Pharmacokinetic Results:

Pegcetacoplan was slowly absorbed into the systemic circulation, with Tmax values between 7 and 16 days across all subjects. Pegcetacoplan serum concentrations declined in a steady mono-exponential manner. There was a dose-dependent increase in exposure (Cmax and AUC0-t), broadly consistent with the pegcetacoplan serum pharmacokinetics being dose-proportional across the doses investigated (**Figure 1** and **Table 9**).

Figure 1. Study POT-CP043014: Mean (SE) Pegcetacoplan Serum Concentrations Following IVT Administration



Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.
Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL, dashed line). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 1.

Table 9. Study POT-CP043014: Summary of Pegcetacoplan Serum PK Parameters

Dose	n	Median (range)				
		t_{max}, day	C_{max}, µg/mL	Dose-normalized C_{max}, µg/mL	AUC_{0-t}, µg·day/mL	Dose-normalized AUC_{0-t}, µg·day/mL
4 mg	3	14.0 (8.9-14.9)	0.38 (0.32-0.39)	0.096 (0.079-0.097)	11.9 (11.5-13.8)	2.97 (2.87-3.46)
10 mg	3	7.9 (7.0-14.9)	0.76 (0.60-1.61)	0.076 (0.060-0.161)	29.8 (24.3-53.6)	2.98 (2.43-5.36)
20 mg	7	15.0 (6.9-16.0)	2.14 (1.44-3.97)	0.107 (0.072-0.199)	69.53 (55.0-86.9)	3.42 (2.75-4.35)

Abbreviations: AUC_{0-t} = area under the curve from time 0 to the last measurable concentration; C_{max} = maximum observed concentration occurring at t_{max}; n = number of evaluable subjects; PK = pharmacokinetic; t_{max} = time of maximum observed concentration sampled during a dosing interval.

Source: 2.7.2 Summary of Clinical Pharmacology, Table 5.

Safety Results: The maximum tolerated dose was not determined in the study as no DLTs were reported. Study drug was considered safe and well tolerated for all cohorts with a similar incidence of

TEAEs across the 3 cohorts. No clinically meaningful changes in laboratory (chemistry, hematology, urinalysis, and complement) or vital sign values were observed during the study.

Reviewer's Comments:

1. No maximum tolerated dose was determined with the investigated dose range.

2. PK of pegcetacoplan was estimated in this study. No PD samples were collected.

3. In the pegcetacoplan IVT dose range of 4 mg – 20 mg, there was a dose-dependent increase in PEGCETACOPLAN exposure, with serum concentrations declining in a steady mono-exponential manner.

4. Two formulations, namely 1). a liquid drug product composed of pegcetacoplan dissolved in (b) (4) solution of 5% w/v dextrose and, 2). a (b) (4) drug substance (with no excipients) to be reconstituted in 5% w/v dextrose, were evaluated in Study POT-CP043014.

4.2.2 Study ALP2-203

Title: An 18-Month Phase 1b/2 Multicenter, Open-Label Study to Evaluate the Safety of Intravitreal Pegcetacoplan Therapy in Patients with Neovascular Age-Related Macular Degeneration (AMD)

Objectives:

The objective of this study was to establish the safety of intravitreally injected pegcetacoplan inpatients with neovascular AMD.

Trial Design:

This was an 18-month, Phase 1b/2, multicenter, open-label study to assess the safety and tolerability of monthly intravitreal (IVT) injections of pegcetacoplan in subjects with neovascular AMD. One cohort of 17 subjects with neovascular AMD in the study eye, who were receiving anti-vascular endothelial growth factor (anti-VEGF) IVT injections and who met all selection criteria, were enrolled at 3 sites in the United States. It was planned that subjects, starting at the baseline visit (Day 1; Visit 3) would receive monthly 15 mg pegcetacoplan IVT injections through Visit 15 (Day 360).

Serial blood and urine samples for assessment of safety were planned to be collected at prespecified time points throughout the study. Blood samples were also planned to be collected for pharmacokinetic (PK) and immunogenicity assessments:

Immunogenicity: Blood samples for assessment of anti-pegcetacoplan antibodies were planned to be collected at Visits 4, 9, and 15 (Days 30, 180, and 360).

Pharmacokinetics: Predose blood samples for PK assessment of pegcetacoplan were planned to be collected at Visits 4, 9, and 15.

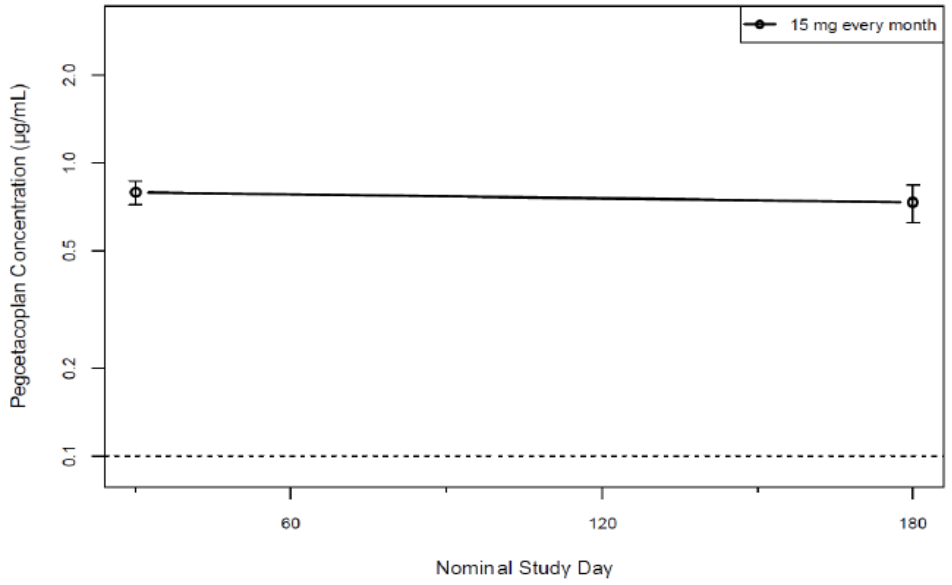
Results:

No subjects completed the treatment phase because of study termination by the Applicant for reasons not related to safety. At the time of study termination, 3 subjects withdrew consent, and 14 subjects completed the early termination visit.

Pharmacokinetic Results:

Pharmacokinetic analyses were not performed as planned because the study was terminated, and subjects were not exposed to the predetermined number of pegcetacoplan injections necessary for meaningful PK analysis. PK data were collected at Month 1 and Month 6 (**Figure 2** and **Table 10**). No PD samples were collected.

Figure 2. Study Pegcetacoplan-203: Mean (SE) Pegcetacoplan Serum Concentration Following IVT Administration



Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.
Notes: Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot. The horizontal dashed line indicates the LLOQ of 0.10 µg/mL.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 2.

Table 10. Study Pegcetacoplan-203: Mean Pegcetacoplan Serum Concentration

	Month 1	Month 6
15 mg monthly		
n	17	15
Mean (SE), µg/mL	0.792 (0.074)	0.732 (0.109)
SD, µg/mL	0.307	0.420

Abbreviations: BLQ = below the limit of quantification; LLOQ = lower limit of quantification; n = number of evaluable subjects.
Note: Values that were BLQ were set to one-half of the LLOQ (LLOQ = 0.10 µg/mL).
Source: 2.7.2 Summary of Clinical Pharmacology, Table 6.

Safety Results:

The duration of exposure was shorter than expected since dosing in the study was paused after 4 subjects experienced events of uveitis in the study eye. The likely root cause of the uveitis events was identified as low-level impurity present in the active pharmaceutical ingredient that was introduced during the scale up of the manufacturing process. No subject was dosed with pegcetacoplan after the study was paused. The study was subsequently terminated for reasons not due to safety.

Overall, the data from this study support the conclusion that multiple-dose IVT administration of pegcetacoplan (15 mg/month) has an acceptable safety profile and is generally well tolerated in subjects who are receiving concomitant anti-VEGF treatment.

Reviewer's Comments:

1. The study was early terminated by the Applicant for reasons not related to safety.

2. PK data were collected and summarized at Month 1 and Month 6. No PD samples were collected.

3. The formulation of (b) (4) *drug substance (with no excipients) to be reconstituted in 5% w/v dextrose was investigated in Study APL2-203.*

4.2.3 Study CP121614

Title: 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 (Filly)

Objectives:

The primary objective was to assess the safety, tolerability, and evidence of activity of multiple intravitreal (IVT) injections of pegcetacoplan in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Trial Design:
This was a Phase 2, prospective, multicenter, randomized, single-masked, sham-injection controlled study to assess the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD.

Subjects were randomly assigned in a 2:2:1:1 manner to receive treatment with pegcetacoplan, 15 mg pegcetacoplan/100 µL administered IVT, monthly (PM), every other month (PEOM), sham monthly (SM), or sham every other month (SEOM), respectively. Subjects in the PM and SM groups received monthly pegcetacoplan injections or sham injections, respectively, for up to 12 months, resulting in a total of 13 IP administrations. Subjects in the PEOM and SEOM groups received EOM pegcetacoplan injections or sham injections, respectively, for up to 12 months, resulting in a total of 7 IP administrations.

Sparse PK samples were collected before dosing, on Day 7, and at trough during the 12-month treatment period. Serum samples from Months 15 and 18 after discontinuing drug treatment were also collected for PK analysis. Complement biomarkers CH50 and C3 were measured for PD serum samples collected at baseline and at Months 2, 6, 12 (during treatment), and 18 (post treatment).

Results:

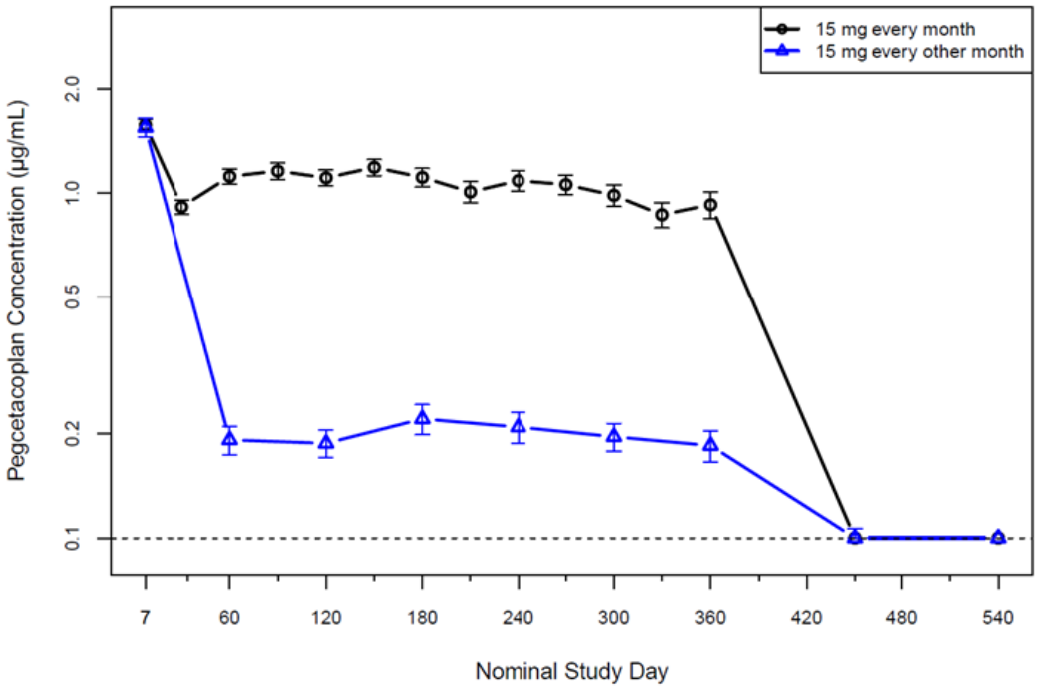
The demographic and baseline characteristics of the study population were balanced among treatment groups across all assessed ophthalmic and nonophthalmic categories. Compliance with the treatment regimen was acceptable; approximately 80% of subjects in the monthly groups and over 90% of subjects in the EOM groups received all scheduled IP administrations.

The primary efficacy endpoint of the trial was met. After 12 months of monthly or EOM pegcetacoplan treatment, the GA lesion growth in the study eye was significantly reduced in pegcetacoplan-treated subjects versus sham-treated controls.

Pharmacokinetic Results:

Serum concentration data from 62 of 86 subjects in the PM group and 60 of 79 subjects in the PEOM group were available for analysis. During the treatment period (until Month 12), the observed median maximum serum concentration of pegcetacoplan was approximately 1.5 μg/mL (at Day 7) for both the PM and PEOM groups. The PM group displayed median trough concentrations ranging from 0.91 to 1.24 μg/mL following multiple dosing during the treatment period, and the PEOM group showed measurable median trough concentrations ranging from 0.14 to 0.17 μg/mL (**Figure 3** and **Table 11**). Median trough pegcetacoplan concentrations observed after the treatment period was completed (ie, at Month 15 and Month 18) were below the limit of quantification (ie, <0.10 μg/mL). The results indicate that there are no apparent systemic drug accumulations following IVT administration of 15 mg pegcetacoplan doses in GA patients either monthly or EOM.

Figure 3. Study POT-CP121614: Mean (SE) Pegcetacoplan Serum Concentrations Following IVT Administration



Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.
Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot. The horizontal dashed line indicates the LLOQ of 0.10 µg/mL.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 3.

Table 11. Study POT-CP121614: Mean Pegcetacoplan Serum Concentration

	Day 7	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Month 15	Month 18
15 mg monthly (N = 86)									
n	84	83	79	75	72	69	65	62	65
Mean, µg/mL (SD)	1.58 (0.58)	1.12 (0.52)	1.11 (0.53)	1.11 (0.59)	1.08 (0.62)	0.98 (0.60)	0.92 (0.67)	0.02 (0.07)	0
CV, %	36.7	46.9	48.1	53.3	56.8	61.0	72.8	291.2	—
15 mg EOM (N = 79)									
n	75	77	71	71	69	69	64	60	62
Mean, µg/mL (SD)	1.57 (0.83)	0.18 (0.17)	0.17 (0.16)	0.21 (0.20)	0.20 (0.20)	0.19 (0.17)	0.18 (0.17)	0.02 (0.06)	0
CV, %	52.9	99.1	93.6	95.4	98.1	90.1	98.7	355.2	—

Abbreviations: CV = coefficient of variation; EOM = every other month; N = number of subjects in the treatment group; n = number of evaluable subjects.

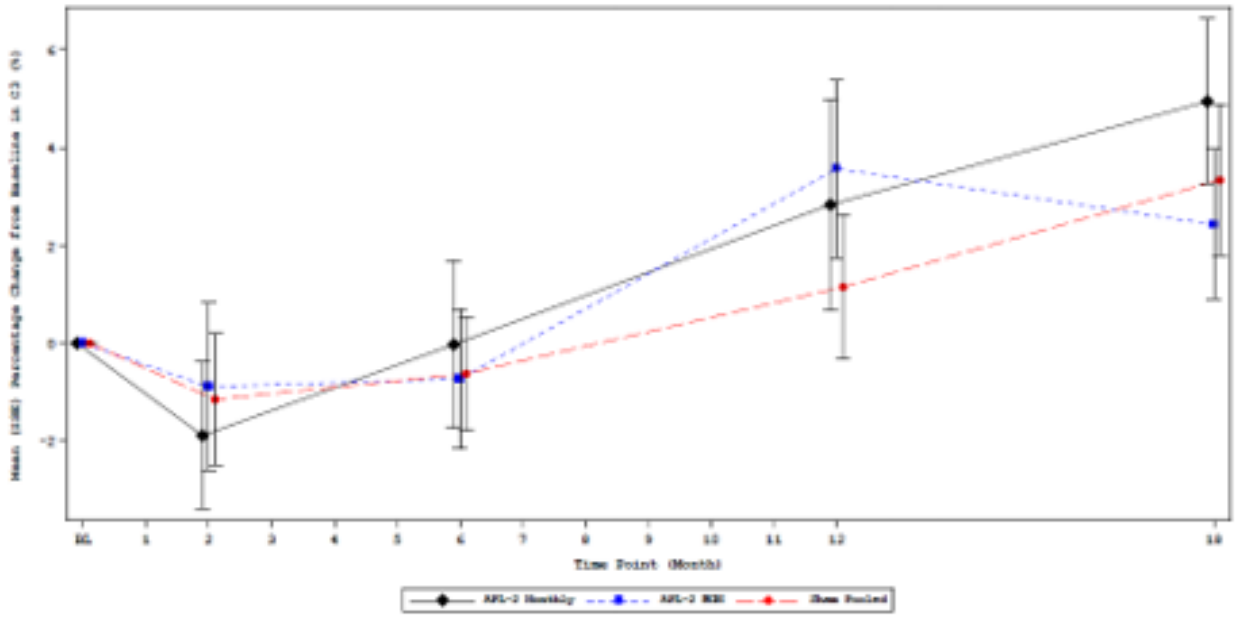
Source: 2.7.2 Summary of Clinical Pharmacology, Table 7.

Pharmacodynamic Results:

During the treatment period (until Month 12) and at Month 18, mean percentage change from baseline (CFB) in CH50 remained within ±13% of the baseline value for the PM, PEOM, and sham pooled groups. Mean percentage CFB in C3 level for the PM, PEOM, and sham pooled groups

followed similar upward trends beginning at Month 2 and remained within ±4% of the baseline value during the treatment period or within ±5% of the baseline value at Month 18 (**Figure 4** and **Figure 5**). Because of the low systemic exposure of pegcetacoplan, the observed lack of systemic PD effects is expected following IVT administration of 15 mg pegcetacoplan doses in GA patients either monthly or EOM.

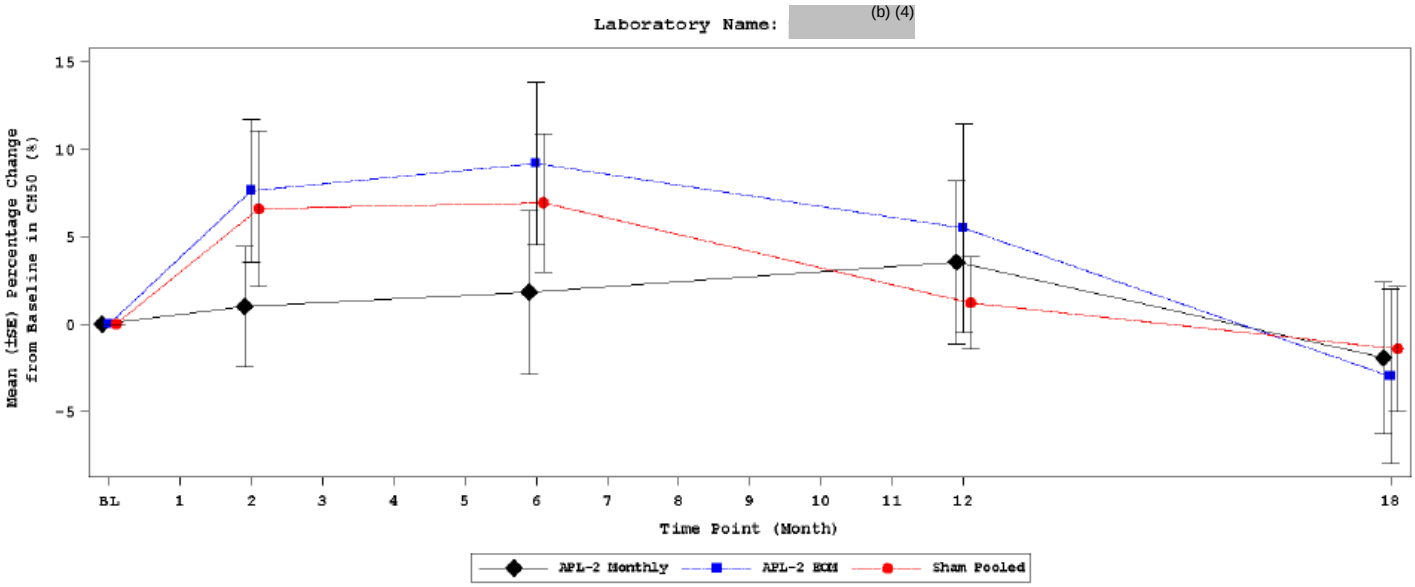
Figure 4. Study POT-CP121614: Mean (SE) Percentage Change from Baseline in C3 Level by Treatment Group through Month 18



Abbreviations: APL-2 = pegcetacoplan; BL = baseline; EOM = every other month.
Note: Baseline was defined as the last available nonmissing observation prior to first study drug administration. For baseline values of 0, the percentage change from baseline was not calculated.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 4.

Figure 5. Study POT-CP121614: Mean (SE) Percentage Change from Baseline in CH50 through Month 18— (b) (4)



Abbreviations: PEGCETACOPLAN = pegcetacoplan; BL = baseline; CH50 = total hemolytic complement activity assay; EOM = every other month.
Notes: Baseline was defined as the last available non-missing observation prior to first study drug administration.
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 5.

Safety Results:

The administration of IVT pegcetacoplan was well tolerated. There did not appear to be a meaningful difference in the percentage of pegcetacoplan-treated subjects (92.1%; 152 of 165 subjects) and sham-treated subjects (87.7%; 71 of 81 subjects) with AEs.

Reviewer's Comments:

1. Overall, the results of this study support the monthly and EOM IVT pegcetacoplan (15 mg pegcetacoplan/100 µL) as a well-tolerated and effective potential treatment for GA secondary to AMD in confirmatory phase 3 studies.

2. PK and PD of pegcetacoplan were estimated following both the PM and PEOM pegcetacoplan (15 mg pegcetacoplan/100 µL) administration.

3. These results indicate that there was no inhibitory effect of pegcetacoplan on PD parameters (C3 and CH50) following repeated IVT administration of 15 mg pegcetacoplan in subjects with GA either PM or EOM in Study POT-CP121614.

4. The formulation of (b) (4) *drug substance (with no excipients) to be reconstituted in 5% w/v dextrose was investigated in Study POT-CP121614.*

4.2.4 Study APL2-303

Title: 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)

Objectives:

Primary Objective was to evaluate the efficacy of pegcetacoplan compared to sham injection in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) assessed by change from baseline (CFB) in the total area of GA lesions at Month 12 in the study eye as measured on fundus autofluorescence (FAF) images by a central reading center.

Safety Objective was to evaluate the safety and tolerability of pegcetacoplan compared to sham injection in subjects with GA secondary to AMD after up to 12 months of monthly or every other month (EOM) intravitreal (IVT) administration.

Trial Design:

This was a Phase 3, multicenter, randomized, double-masked, sham injection-controlled study to assess the efficacy and safety of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD. Subjects were randomized 2:2:1:1 to receive IVT pegcetacoplan, 15 mg pegcetacoplan/100 µL, monthly (PM), every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively, for up to 12 months.

The procedure for sham injection was the same as that used for IVT pegcetacoplan injection but no actual injection occurred. The injecting physician only touched the study eye with the blunt end of the syringe. No needle or medication was injected inside the eye.

Sparse blood samples in a total of 101 subjects were collected predose and on Days 1, 7, 30, 180 and 360 for PK and PD assessments. Immunogenicity was summarized at the sample level and the subject level for anti-APL2 peptide antibody assay and the anti-PEG antibody response.

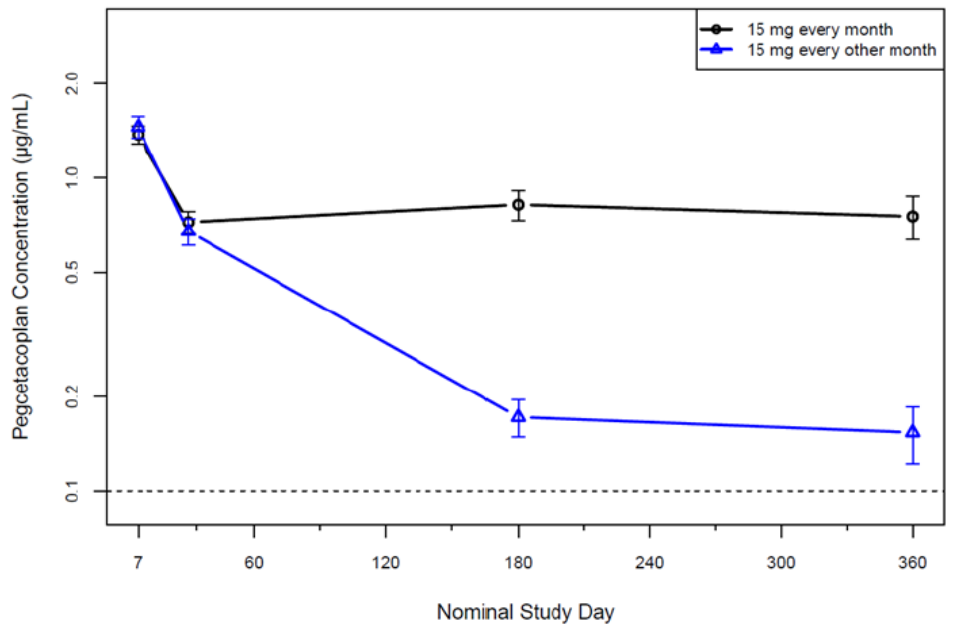
Results:

The intent-to-treat (ITT) population included 206 subjects in the PM group, 208 subjects in the PEOM group, and 207 subjects in the sham pooled group. The modified intent-to-treat (mITT) population included 201 subjects in the PM group, 200 subjects in the PEOM group, and 194 subjects in the sham pooled group. The safety population included 206 subjects in the PM group, 208 subjects in the PEOM group and 206 subjects in the sham pooled groups, respectively.

Pharmacokinetic Results:

The observed mean Cmax of pegcetacoplan was 1.37 and 1.46 µg/mL at Day 7 for the PM and PEOM groups, respectively. The steady state mean trough concentrations were observed at the range of 0.83 to 0.96 µg/mL and 0.14 to 0.17 µg/mL for the PM and PEOM groups, respectively, following more than 6 months of treatment (**Figure 6** and **Table 12**).

Figure 6. Study APL2-303: Mean (SE) Pegcetacoplan Serum Concentrations Following IVT Administration



Abbreviations: BLQ = below the limit of quantification; IVT = intravitreal; LLOQ = lower limit of quantification.
Notes: Values that were BLQ were set to the one-half the LLOQ (LLOQ = 0.10 µg/mL). Mean (points) and SE (error bars) pegcetacoplan concentrations are presented in semilogarithmic scale with values BLQ censored at the LLOQ in the plot. The horizontal dashed line indicates the LLOQ of 0.10 µg/mL.

Source: 2.7.2 Summary of Clinical Pharmacology, Figure 7.

Table 12. Study APL2-303: Mean Pegcetacoplan Serum Concentration

	Day 7	Month 1	Month 6	Month 12
15 mg monthly (N = 35)				
n	30	25	19	20
Mean (SD), µg/mL	1.3747 (0.50487)	0.7220 (0.29895)	0.9621 (0.71331)	0.8324 (0.62643)
CV, %	36.7258	41.4063	74.1404	75.2565
15 mg EOM (N = 32)				
n	25	27	15	15
Mean (SD), µg/mL	1.4551 (0.59359)	0.6750 (0.34566)	0.1657 (0.10150)	0.1375 (0.13715)
CV, %	40.7933	51.2123	61.2701	99.7689

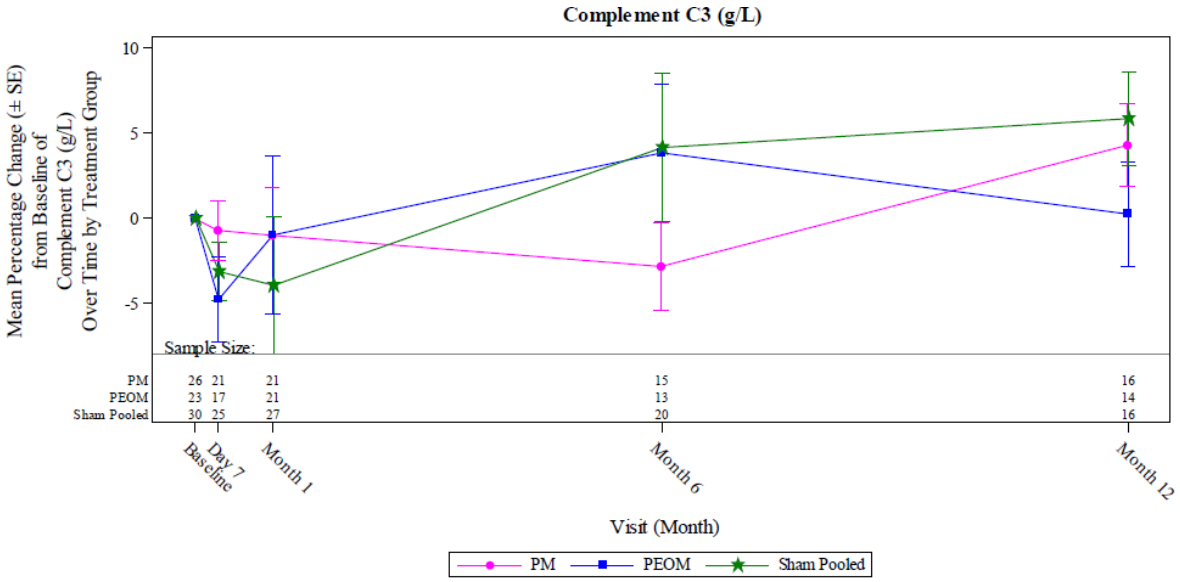
Abbreviations: CV = coefficient of variation; EOM = every other month; N = number of subjects in group; n = number of evaluable subjects.

Source: 2.7.2 Summary of Clinical Pharmacology, Table 8.

Pharmacodynamic Results:

Mean percentage CFB in C3 level for the PM, PEOM, and sham pooled groups were all between -4.8% and 5.8% during the 12-month treatment period (**Figure 7**). Mean percentage CFB in CH50 level for the PM, PEOM, and sham pooled groups were all between −6.9% and 10.3% during the 12-month treatment period (**Figure 8)**. Mean percentage CFB in AH50 level for the PM, PEOM, and sham pooled groups were all between −18.9% and 28.3% during the 12-month treatment period (**Figure 9)**. No clinically meaningful changes of mean CFB in any of the biomarkers were observed for any of the PM, PEOM, or sham groups during the treatment period.

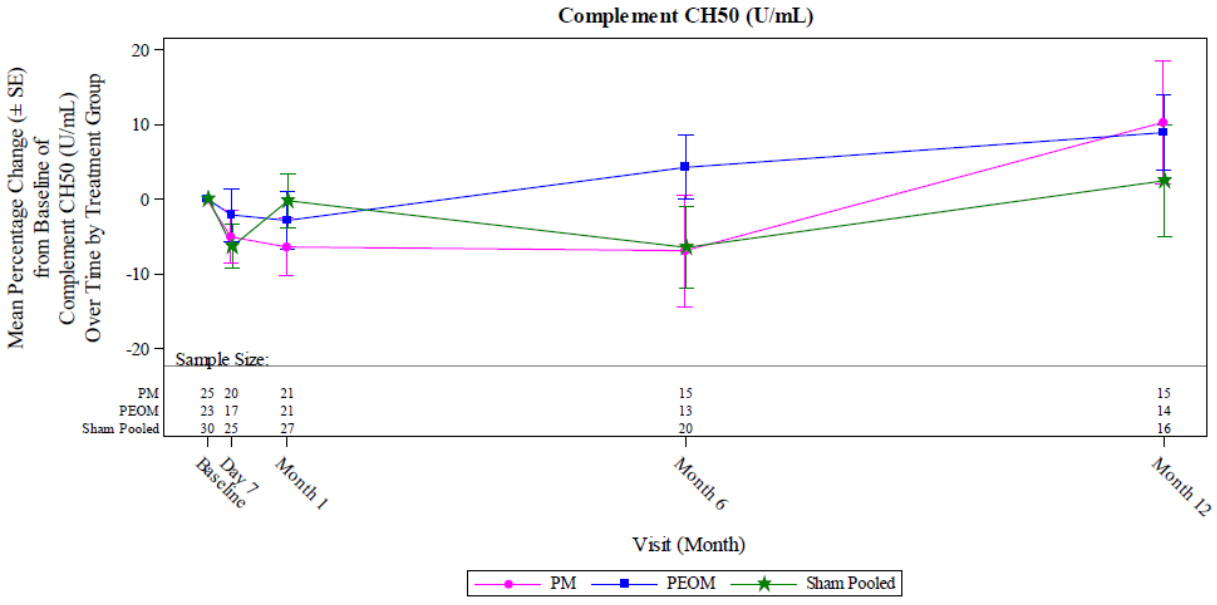
Figure 7. Study APL2-303: Mean (SE) Percentage Change from Baseline in C3 Level



Abbreviation: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.
Note: Baseline was defined as the last available nonmissing observation prior to first study drug administration.

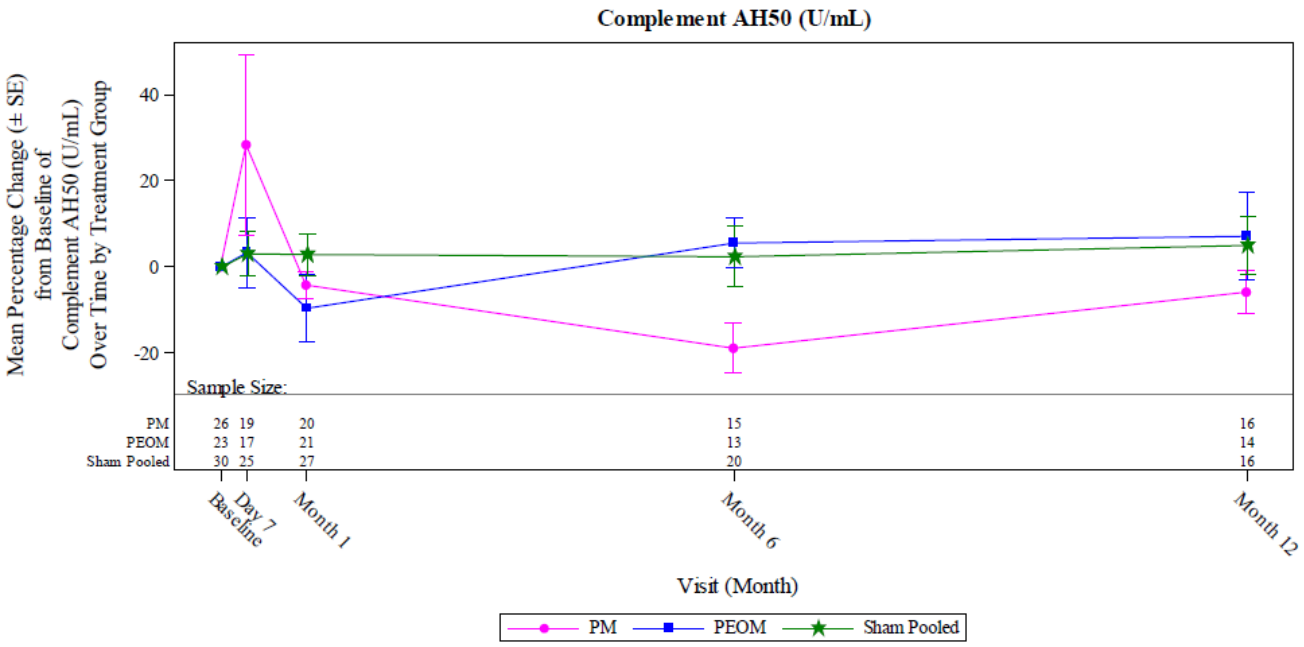
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 8.

Figure 8. Study APL2-303: Mean (SE) Percentage Change from Baseline in CH50



Abbreviation: CH50 = total hemolytic complement activity assay; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly. Note: Baseline is defined as the last available non-missing observation prior to first study drug administration.
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 9.

Figure 9. Study APL2-303: Mean (SE) Percentage Change from Baseline in AH50



Abbreviation: AH50 = alternative pathway hemolytic complement activity assay; PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly.

Note: Baseline is defined as the last available non-missing observation prior to first study drug administration.
Source: 2.7.2 Summary of Clinical Pharmacology, Figure 10.

Safety Results:

IVT pegcetacoplan injections, administered either monthly or EOM, were well tolerated and demonstrated an acceptable safety profile in subjects with GA secondary to AMD.

Immunogenecity Results:

A low incidence of anti–pegcetacoplan peptide antibody responses were observed in the study.

Reviewer's Comments:

1. IVT pegcetacoplan, administered either monthly or EOM, demonstrated a positive benefit-risk profile in treating patients with GA secondary to AMD.

2. PK and PD of pegcetacoplan were estimated following both the PM and PEOM administration.

3. These results indicate that there was no clinically meaningful impact of pegcetacoplan on PD parameters (i.e., C3, CH50, and AH50) following repeated IVT administration of 15 mg pegcetacoplan in subjects with GA either PM or EOM.

4. The intended commercial formulation, drug product in (b) (4) *, pH 5.0, containing* (b) (4) *, was used in the Phase 3 study APL2-303.*

4.2.5 Study APL2-304

Title:

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).

Objectives:

The primary objective was to investigate the efficacy of pegcetacoplan compared to sham injection in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) assessed by change in the total area of GA lesions at Month 12 in the study eye as measured on fundus autofluorescence (FAF) images by a central reading center.

A secondary objective was to investigate the safety and tolerability of pegcetacoplan compared to sham injection in subjects with GA secondary to AMD after up to 12 months of monthly or every other month intravitreal (IVT) administration.

Trial Design:

This was a Phase 3, multicenter, randomized, double-masked, sham injection-controlled study to assess the efficacy and safety of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD. Subjects were randomized 2:2:1:1 to receive IVT pegcetacoplan, 15 mg

pegcetacoplan/100 μL, monthly (PM), every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively, for up to 12 months.

The procedure for sham injection was the same as that used for IVT injection but no actual injection occurred. The injecting investigator only touched the study eye with the blunt end of the syringe, and nothing was injected inside the eye.

PK and PD of pegcetacoplan assessments were not planned for this study.

Results:

The ITT population included 213 subjects in the PM group, 212 subjects in the PEOM group, and 212 subjects in the sham pooled group. The mITT population included 202 subjects in the PM group, 205 subjects in the PEOM group, and 206 subjects in the sham pooled group. The safety population included 213, 212, and 211 subjects in the PM, PEOM, and sham pooled groups, respectively.

The percentage of subjects who completed treatment through Month 12 was similar in subjects receiving pegcetacoplan (85.9% for the PM group and 88.7% for the PEOM group) and in subjects receiving sham (90.1%). A similar percentage of subjects completed the study through Month 12 (86.4% for the PM group, 89.6% for the PEOM group, and 90.1% in the sham pooled group).

Mean age was 78.5 years for all treatment groups for the mITT population. More subjects were enrolled from the US compared with the rest of the world (ROW) in all treatment groups. The majority of subjects were White (91.5%) and female (61.2%). The sex, age, country of origin, race, and ethnicity of the PM, PEOM, and sham pooled groups were similar. Demographic characteristics were similar between the ITT and mITT population.

Safety Results:

IVT pegcetacoplan injections, administered either monthly or EOM, were well tolerated and demonstrated an acceptable safety profile in subjects with GA secondary to AMD.

Immunogenecity Results:

A low incidence of anti–pegcetacoplan peptide antibody responses were observed in the study.

Reviewer's Comments:

1. IVT pegcetacoplan, administered either monthly or EOM, demonstrated a clinically meaningful and statistically significant reduction in GA lesion growth at Month 12 compared with sham, and a well-tolerated safety profile in study subjects.

2. PK and PD of pegcetacoplan assessments were not conducted for this study.

3. The intended commercial formulation, drug product in [redacted] (b) (4) *, pH 5.0, containing* [redacted] (b) (4) *, was used in the Phase 3 study APL2-304.*

4.3 Pharmacometrics Analyses

4.3.1 Population Pharmacokinetic Analysis

Title: Development of a population pharmacokinetic model for pegcetacoplan (ALP-2) in phase 1, 2, and 3 studies in patients with neovascular age-related macular degeneration and geographic atrophy secondary to age-related macular degeneration

Objectives:

The primary objectives were to develop a population pharmacokinetic (PK) model to characterize the serum concentration-time profile of pegcetacoplan following intravitreal (IVT) administration to patients with neovascular age-related macular degeneration (nAMD) or geographic atrophy (GA), including the assessment of intrinsic and extrinsic factors as covariates.

Data:

The population PK analysis includes pegcetacoplan serum concentration-time data from 4 studies following IVT administration, including one phase 1 study in patients with nAMD, one phase 1b/2 study in patients with nAMD, one phase 2 study in patients with GA, and one phase 3 study in patients with GA. The analysis included a total of 261 unique subjects and 2033 PK samples collected after the first dose of study medication, 1561 (76.8%) of which were detectable and 472 (23.2%) of which were BLQ (**Table 13**). The assay LLOQ was 0.1 µg/mL for all studies.

Table 13. Summary of Subjects and PK Samples by Study

Study	Study Population	No. of Subjects	All Samples	Quantifiable	BLQ
Study POT-CP043014	nAMD	13	91	63	28 (30.8%)
Study APL2-203		17	38	31	7 (18.4%)
Study POT-CP121614	GA	164	1725	1301	424 (24.6%)
Study APL2-303		67	179	166	13 (7.30%)
Total		261	2033	1561	472 (23.2%)

BLQ = below the limit of quantification; nAMD = neovascular age-related macular degeneration; GA = geographic atrophy

Source: PPK_APL-ex2-cp-012, Figure S4., Table 5.

A pre-commercial solution formulation was used for 6 patients in Study POT-CP 043014 and the planned commercial solution was used for 67 patients in Study APL2-303. A (b) (4) formulation was used for all other dose administrations. Patients were relatively well balanced between female (56.7%) and male (43.3%) and were almost exclusively of White race (97.3%) and non-Hispanic ethnicity (95.4%). The median age was 80 years (range, 60-97 years), which is consistent with the natural history of nAMD and GA. The median baseline C3-concentration was 1.20 g/L (range, 0.616-1.91 g/L). Measures of body size (height, weight, body surface-area) were not available from studies POT-CP043014 or POT-CP121614, which represents over 50% of subjects included in the analysis dataset.

Concomitant anti-VEGF medications were used for all nAMD patients and approximately 12% of GA patients. Anti-PEG antibodies were detectable in 109 of 165 (66.1%) GA patients in POT-CP121614 and 41 of 67 (61.2%) of GA patients in APL2-303, primarily to preexisting antibodies present at baseline. Anti-pegcetacoplan peptide antibodies were detected infrequently among GA

patients with positive anti-pegcetacoplan peptide antibody results among only 5 of 165 (3.0%) GA patients in POT-CP121614 and 1 of 67 (1.5%) GA patients in APL2-303.

Methods:

Prior to model development, exploratory data analysis was performed to characterize the observed data and inform model selection. A preliminary structural model, including the assessment of the random effects structure, was then identified using data from nAMD patients in Phase 1 study POT-CP043014 and GA patients in Phase 2 study POT-CP121614.The predictive performance of the preliminary structural model was evaluated using a visual predictive check (VPC).

A model update was performed to incorporate data from nAMD patients in Phase 1b/2 Study APL2-203 and GA patients in Phase 3 Study APL2-303 into the preliminary structural model developed for IVT administration. Prior to updating the model, the ability of the preliminary structural model to predict the new study data was evaluated using an external VPC. Following external predictive assessment, the previous preliminary structural model was updated using pooled data from all four clinical studies. A working full covariate model was developed using a forward selection procedure followed by backward elimination to identify a preliminary parsimonious final model.

The preliminary final model was evaluated using an internal VPC procedure to ensure adequate predictive ability across the full combined data set prior to applying the model to generate exposure predictions. The dependent variable in this analysis was log-transformed serum concentration of pegcetacoplan following IVT administration. All post-dose concentration measurements, both quantifiable and below the lower limit of quantification (BLQ), were included in the analysis using the M3 approach.

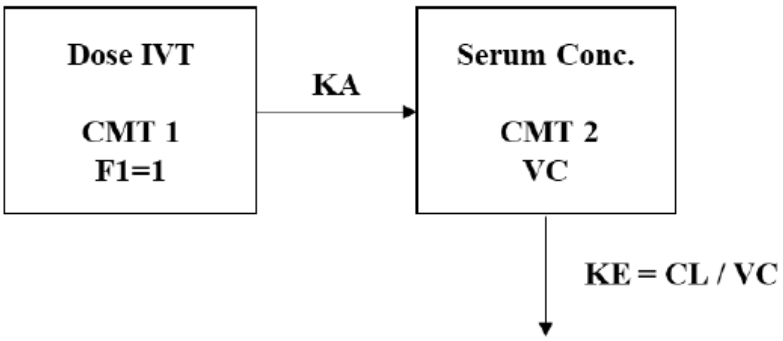
Results:

Basic Structure Model:

A preliminary structural population PK model trained on data from nAMD and GA patients from studies POT-CP043014 and POT-CP121614 was developed and verified through external predictive check on the other two nAMD and GA patient studies, APL2-203 and APL2-303.

The basic structure model built upon all 4 studies was established with an IVT dose administration compartment (CMT =1), representing the vitreous space, and one systemic disposition compartment (CMT = 2), representing serum, with first-order absorption following IVT administration from the vitreous compartment to the serum compartment and subsequent first-order elimination from the serum compartment (**Figure 10**). Because all pegcetacoplan administered via IVT injection was anticipated to be eliminated via absorption into systemic circulation, bioavailability (F1) was assumed to be one such that serum parameters of clearance (CL) and central volume of distribution (VC) were interpreted as apparent values (i.e., CL/F, VC/F). Random effects included inter-individual variability (IIV) on CL/F and vitreous-to-serum absorption rate (KA) with log-additive residual error.

Figure 10. Basic Structure Model



Source: PPK_APL-ex2-cp-012, Figure S4.

The distribution of IIV on CL/F was found to deviate from log-normal and the Manly transformation was used to meet the NONMEM assumption of normality in the distribution of $\eta 1^{CL/F}$ as follows:

$$ET1 = \frac{(\exp(\eta_{1i}{}^{CL/F} \cdot \lambda) - 1)}{\lambda}$$

$$CL/F = TVCL \cdot \exp(ET1)$$

Where $\eta 1^{CL/F}$ is a random effect describing the ith individual's deviation from the population CL/F described using the Manly transform including distribution shape parameter λ. Structural parameters were subsequently log transformed to facilitate estimation of covariate models in subsequent steps.

Covariate Model:

Covariate-parameter relationships were evaluated using a forward selection procedure starting with the updated structural model trained on the pooled analysis dataset including all four clinical studies. In this procedure, the covariate-parameter relationship which had the largest change in OFV and met the inclusion criteria (ΔOFV <-3.84 [p>0.05]) was retained and the stepwise procedure repeated until no additional covariate-parameter relationships met the inclusion criteria. A stepwise backward elimination procedure was then used to identify a preliminary final model containing similar 'information' content as the working full model, but with fewer covariates. At each step in backward elimination, the covariate-parameter relationship which had the lowest change in OFV and did not meet the inclusion criteria (ΔOFV >10.83 [p>0.001]) was eliminated and the stepwise backward elimination procedure was repeated until all covariate-parameter relationships met the inclusion criteria.

Covariates evaluated included: patient type (GA vs nAMD [reference]), sex (female vs male[reference]), age, baseline C3, total bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and estimated glomerular filtration rate (eGFR). Body weight was not evaluated as a covariate due to missing values in >50% of subjects. Race and ethnicity were not evaluated due to the homogeneity of the analysis population. The following seven covariate-parameter relationships were added to the updated structural model in the working full model: female sex, age, and C3 on CL/F; female sex on KA; and nAMD, C3, and albumin on VC/F. Four of these covariates were subsequently removed in the backward elimination

procedure resulting in three covariate effects in the final model: female sex, age, and C3 on CL/F.

Final Model:

PK parameter estimates for the final model are provided in **Table 14**. Parameters in the final model were well estimated (RSE ≤37%). PK parameters for the typical patient with nAMD or GA in the final model (male, 80 years of age, baseline C3 1.2 g/L) were as follows: CL/F of 0.325 L/day, VC/F of 1.85 L, and KA of 0.0523 day-1. Residual unexplained variability was modest at 30.0%.

Pegcetacoplan disposition is absorption-limited following IVT administration, displaying a "flipflop"kinetic profile (typical T1/2,abs = 13.3 days; typical T1/2, elim = 3.95 days). Even in the setting of absorption-limited disposition, the parameter estimate for the typical systemic clearance (0.325 L/day) was intermediate to the typical systemic clearance estimates for healthy subjects (0.298 L/day) and PNH patients (0.353 L/day) following systemic administration routes of administration.

Table 14. Pharmacokinetic Parameter Estimates for the Final Model

Theta / Parameter (Units)	Estimate	%RSE	95% CI	Transformed Estimate[a]	Transformed 95% CI
1 CL/F (L/day)	-1.12	3.13	(-1.19; -1.05)	0.325	(0.304; 0.350)
2 VC/F (L)	0.617	10.9	(0.485; 0.750)	1.85	(1.62; 2.12)
3 KA (day^{-1})	-2.95	1.30	(-3.03; -2.88)	0.0523	(0.0483; 0.0561)
5 Lambda	2.38	30.3	(0.965; 3.80)	--	--
6 Age on CL/F	-0.569	28.4	(-0.886; -0.253)	--	--
7 C3 on CL/F	-0.332	37.0	(-0.573; -0.0912)	--	--
8 Female sex on CL/F	-0.286	11.6	(-0.351; -0.222)	0.751	(0.704; 0.801)
Residual Variability (%)					
4 Log additive	0.300	2.34	(0.287; 0.314)	30.0%	(28.7%; 31.4%)
Inter-individual Variability (ω^2)					
CL/F	0.0541		(0.0195; 0.0886)	--	--
KA	0.136		(0.0806; 0.192)	38.2% CV	(29.0% CV; 46.0% CV)
Condition Number	70				

RSE = percent relative standard error; 95% CI = 95 percent confidence interval; CV = coefficient of variation; CL/F = apparent systemic clearance from serum; VC/F = apparent volume of the central serum compartment; KA = first-order absorption rate constant from the vitreous to serum compartments; Lambda = shape parameter in the Manly transformation of $\eta_{1i}^{CL/F}$

[a]For categorical covariates, transformed estimates represent the multiplicative difference in the parameter value from the reference category

η-shrinkage: 15.2% ($\eta_{1i}^{CL/F}$), 19.5% (η_{3i}^{KA})

The following equations describe the covariate-parameter relationships in the final model:

$$COVCL = \vartheta_6 \cdot \left(Log(AGE) - Log(80)\right) + \vartheta_7 \cdot \left(Log(BC3) - Log(1.2)\right) + \vartheta_8 \cdot SEXF$$

$$ET1 = \frac{\left(\exp\left(\eta_{1i}^{CL/F} \cdot \lambda\right) - 1\right)}{\lambda}$$

$$CL/F_i = \exp(TVCL + COVCL + ET1)$$
$$VC/F_i = \exp(TVVC)$$
$$KA_i = \exp(TVKA + \eta_{3i}^{KA})$$
$$F1 = 1$$

where parameters are defined as follows:

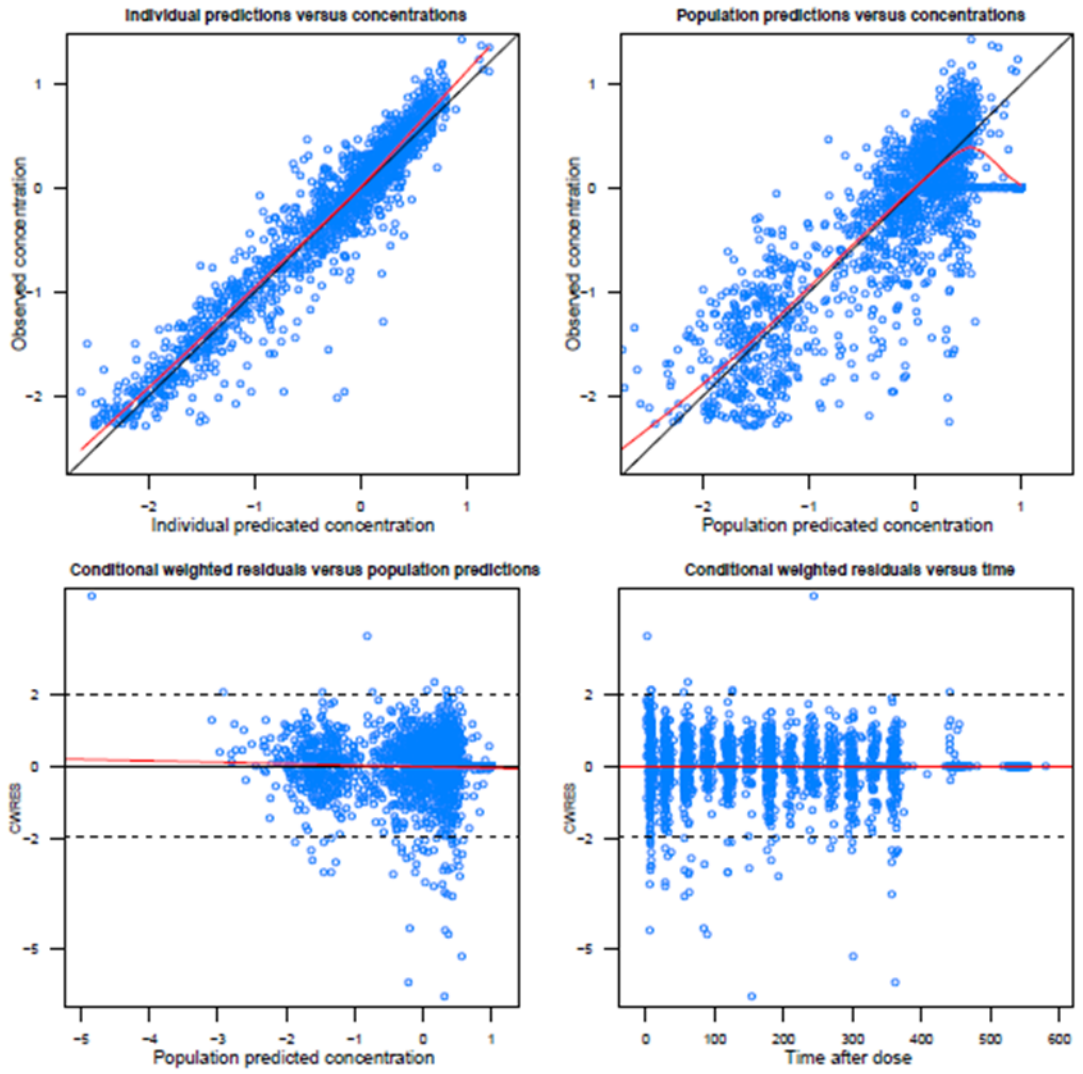
- CL/F_i is the systemic clearance from serum for the i[th] subject; $TVCL$ is the log-transformed typical value of CL/F (θ_1)
- ϑ_6 is the change in the log CL/F per unit deviation in log age from the approximate median reference age of 80 years
- ϑ_7 is the change in the log CL/F per unit deviation in log baseline C3 from the approximate median reference baseline C3 of 1.2 g/L
- ϑ_8 is the change in the log CL/F for females compared to males
- η_{1i}^{CL} is a random effect describing the i[th] individual's deviation from the population CL described using the Manly transform including distribution shape parameter λ (θ_5)
- VC/F_i is the central serum volume of distribution (VC/F) for the i[th] subject; $TVVC$ is the log-transformed typical value of VC (θ_2)
- KA_i is the first-order absorption rate constant for transfer from the vitreal to serum compartments for the i[th] subject; $TVKA$ is the log-transformed typical value of KA (θ_3); η_i^{KA} is a random effect describing the i[th] individual's deviation from the population KA
- $F1$ is the intravitreal bioavailability, which is assumed to be 1

Source: PPK_APL-ex2-cp-012, Figure S4., Table S1

Final Model Evaluation:

Overall, the goodness-of-fit plots plots demonstrated appropriate description of the observed data (**Figure 11)**. In addition, the predictive performance of the final model was evaluated with internal pcVPCs as demonstrated in **Figure 12**. These plots indicate that the final model can simulate pegcetacoplan concentration data that are consistent with the observed data included in the pooled analysis.

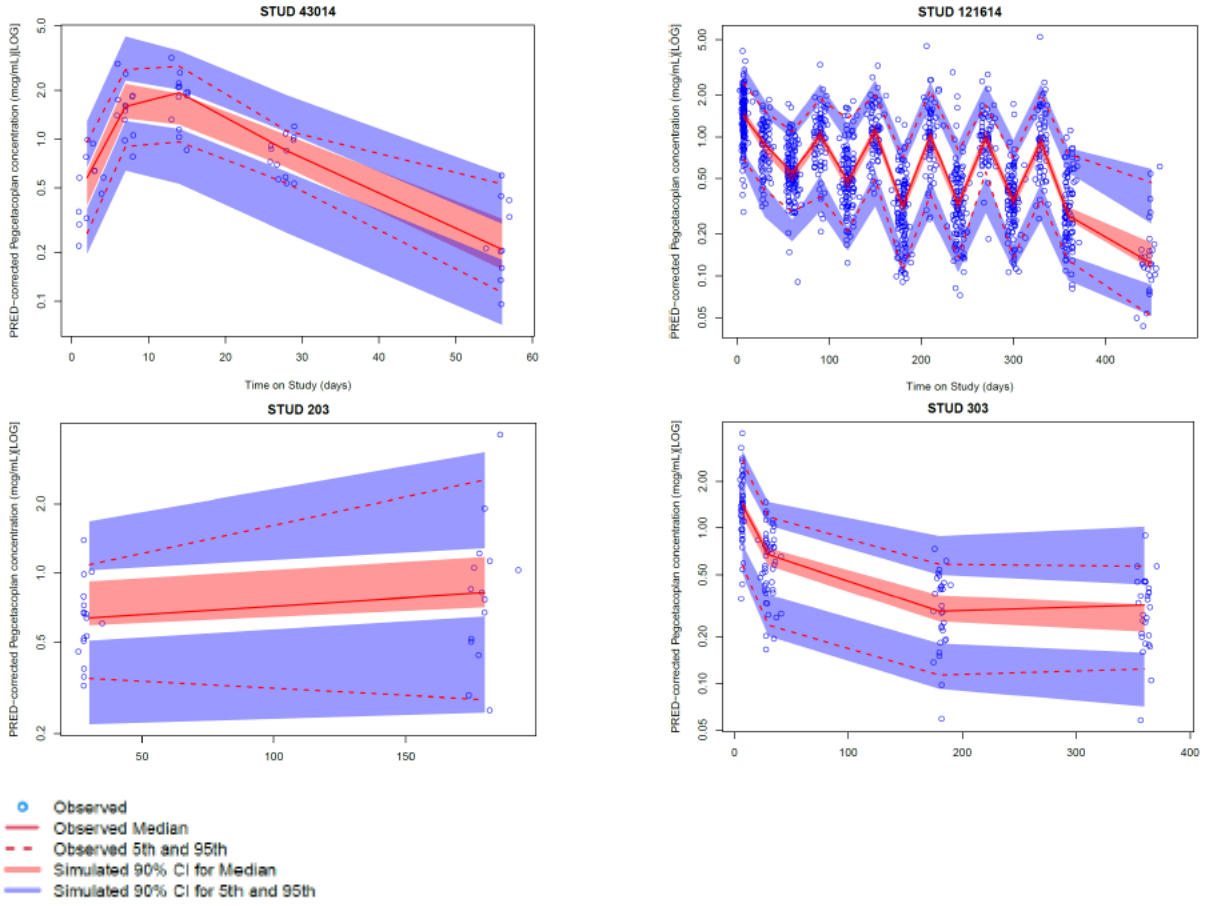
Figure 11. Goodness of fit plot of the final model



Top left: Correlation between the dependent variable (log (pegcetacoplan serum concentration)) and the individual predictions. Top right: Correlation between the dependent variable (log (pegcetacoplan serum concentration)) and the population predictions. Bottom left: Correlation between the conditional weighted residuals and the population predictions. Bottom right: Correlation between the conditional weighted residuals and time. The black circles represent the individual observations/predictions/conditional weighted residual and the red line is the trend line (LOESS).

Source: This reviewer's analysis results

Figure 12. Prediction-Corrected Visual Predictive Check Plots - Stratified by Study



Source: PPK_APL-ex2-cp-012, Figure 11

Model Application:

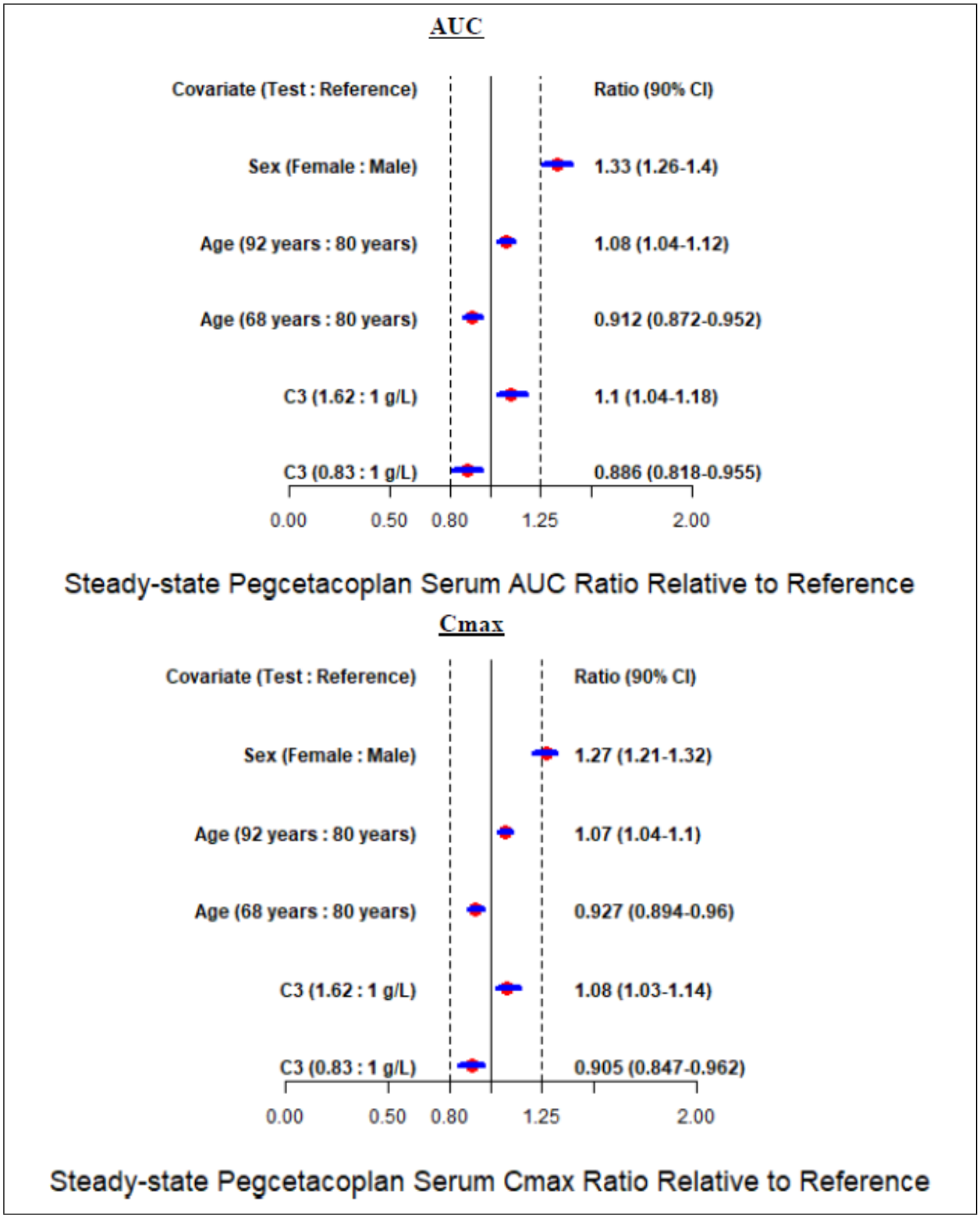
The impact of covariates of interest on steady state pegcetacoplan exposure was evaluated using the final model and dedicated post-hoc models fit (**Table15, Figure 13, Figure 14)**.

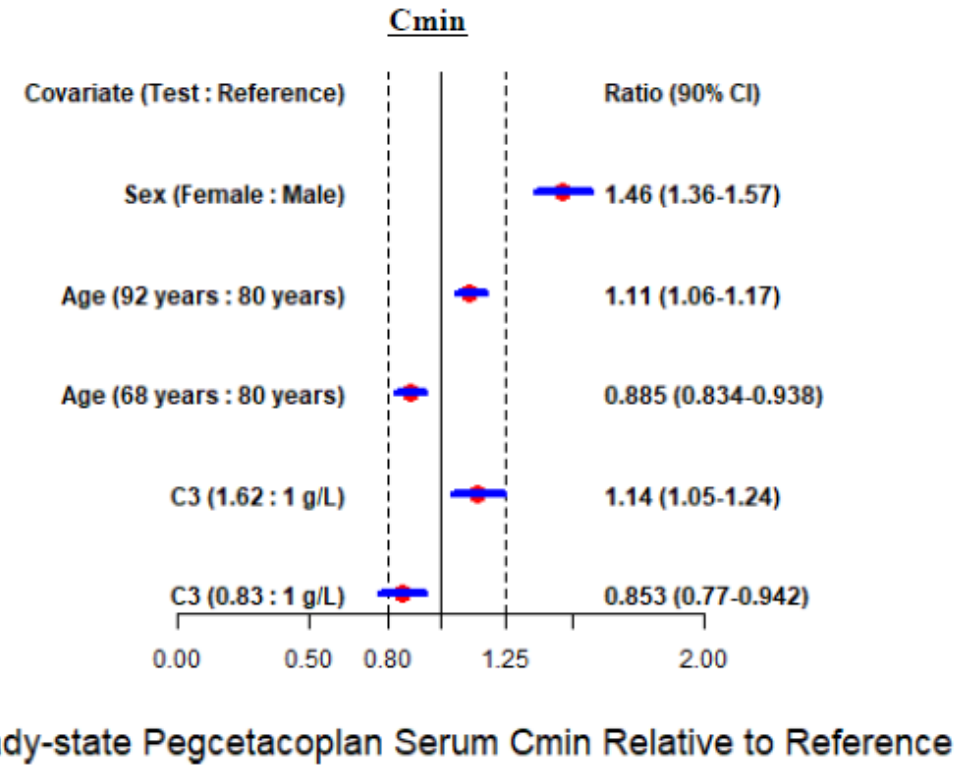
Table 15. Predicted Pegcetacoplan Steady-state Serum Exposure – Final Model

		Value (90% CI)		
Covariate	**Test Condition**	**AUC_τ (mg·day/L)**	**Cmax (µg/mL)**	**Cmin (µg/mL)**
Reference[a]	--	46.2 (43.6-49.0)	2.01 (1.91-2.11)	0.889 (0.821-0.961)
Sex	Female sex	61.4 (58.4-64.6)	2.54 (2.43-2.66)	1.30 (1.21-1.39)
Age	92 years	49.8 (46.2-54.1)	2.14 (2.01-2.29)	0.984 (0.885-1.10)
	68 years	42.1 (39.4-44.7)	1.86 (1.76-1.97)	0.786 (0.722-0.854)
C3	1.62 g/L	51.0 (46.4-56.3)	2.18 (2.01-2.37)	1.01 (0.894-1.16)
	0.83 g/L	40.8 (37.6-44.3)	1.82 (1.70-1.94)	0.757 (0.678-0.847)

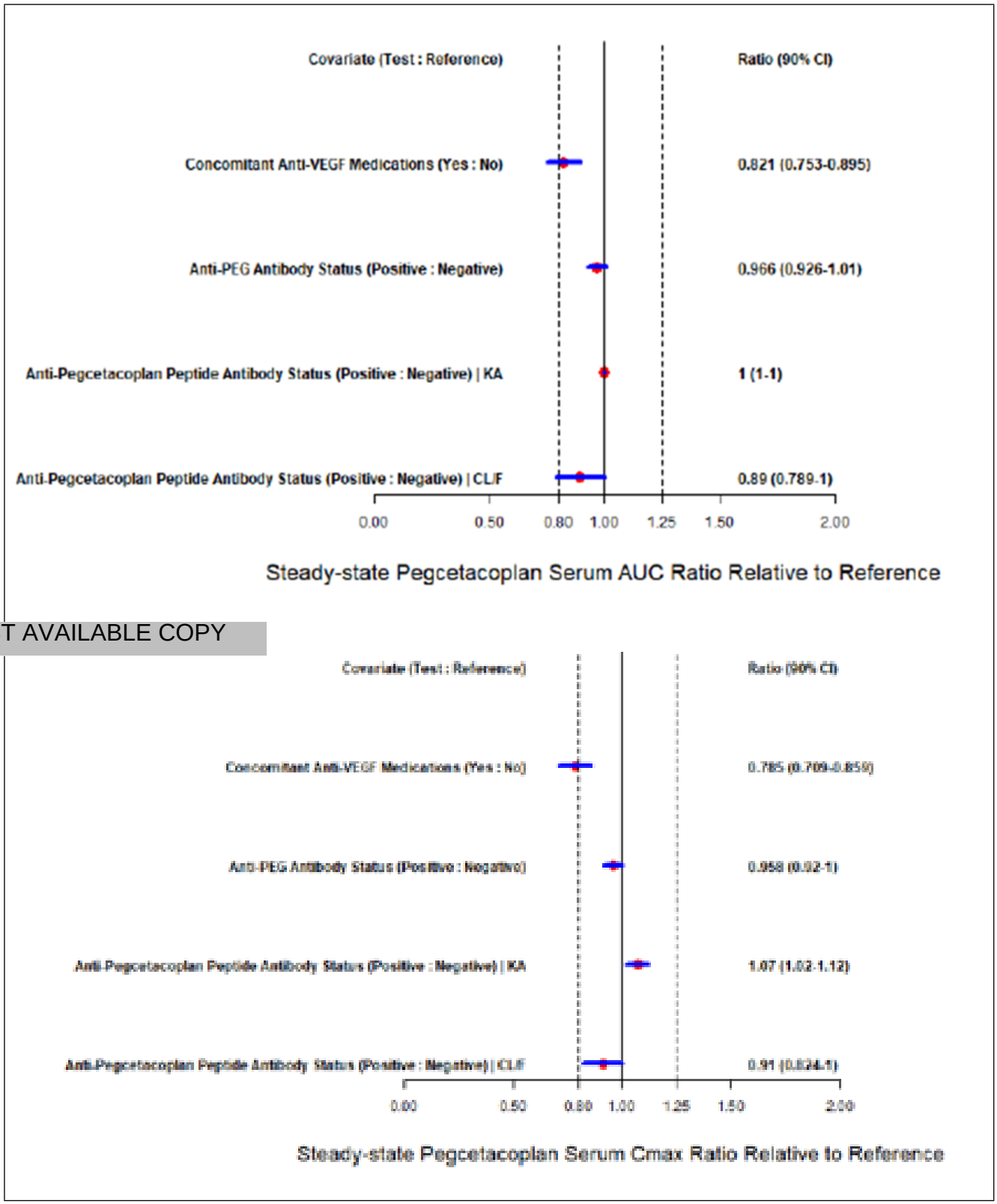
Source: PPK_APL-ex2-cp-012, Table 26.

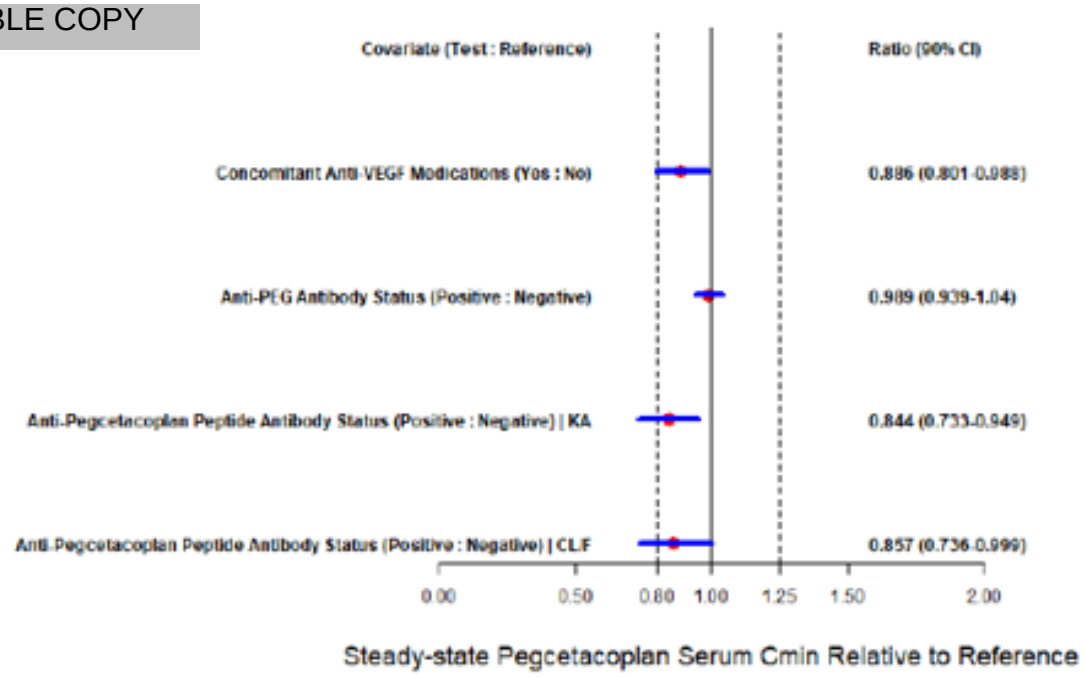
Figure 13. Covariate Impacts on Predicted Pegcetacoplan Steady-state Serum Exposure – Final Model





Source: Source: This reviewer's analysis to duplicate Figure 13 in PPK_APL-ex2-cp-012





Source: APL-EX21-CP-013, Figure 15.

The final model identified covariates, namely sex, age and baseline C3, are not predicted to have any clinically meaningful impact due to the low absolute serum pegcetacoplan concentrations predicted under all conditions of interest (<5 µg/mL) and lack of a predicted impact on vitreous pegcetacoplan exposure. Similar simulation investigations were conducted for patient type, formulation types, time varying anti-VEGF and ADA, which also suggested no clinical meaningful impact from patient type (nAMD vs GA), formulation (solution vs (b) (4)), concomitant anti-VEGF and ADA identified on predicted steady state serum pegcetacoplan exposure.

Conclusions:

Pegcetacoplan PK was adequately described by 1-compartment serum disposition, first-order absorption from the vitreous to serum compartments, and first-order elimination from the serum compartment adequately described the serum concentration-time profile of pegcetacoplan following IVT administration to adults with nAMD or GA. Pegcetacoplan disposition was absorption-limited following IVT administration with median individual predicted absorption ($T_{1/2,abs}$) and elimination ($T_{1/2,elim}$) half-lives of 13.0 days and 4.49 days, respectively (**Table 16**).

Table 16. Simulated Pegcetacoplan PK Parameters Following IVT Monthly Administration

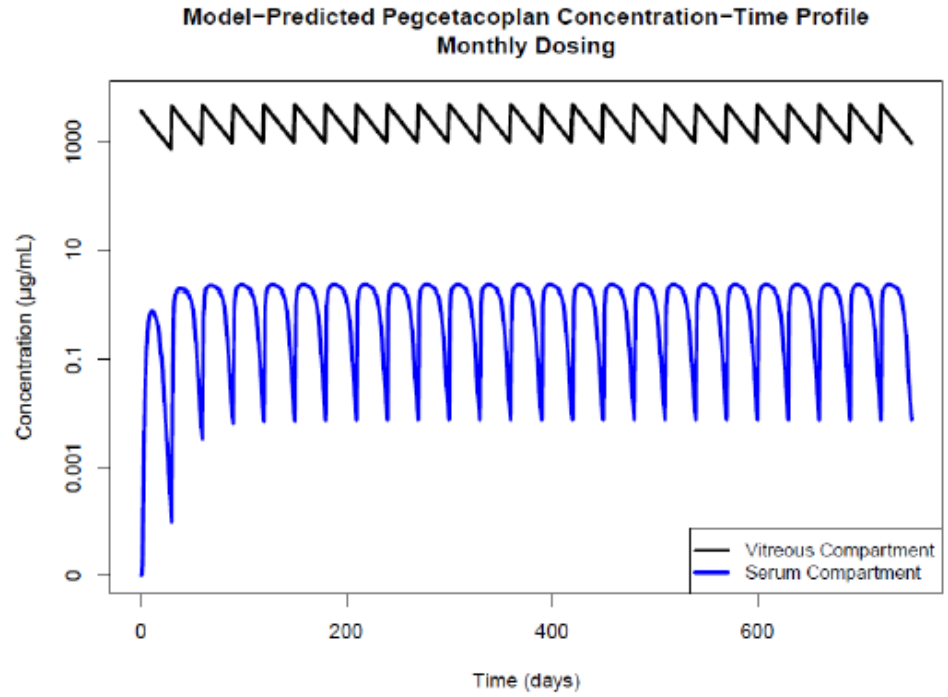
	KA, $days^{-1}$	VC/F, L	CL/F, L/day	$t_{½,abs}$, days	$t_{½,elim}$, days
Median	0.0520	1.85	0.277	13.3	4.65
5th, 95th percentile	0.0292, 0.0949	–	0.215, 0.398	7.31, 23.7	3.23, 5.97
Geometric mean	0.0519	1.85	0.284	13.4	4.53
	KA, %	**VC/F, %**	**CL/F, %**	**$t_{½,abs}$, %**	**$t_{½,elim}$, %**
Geometric CV	44.5	–	21.1	44.5	21.1

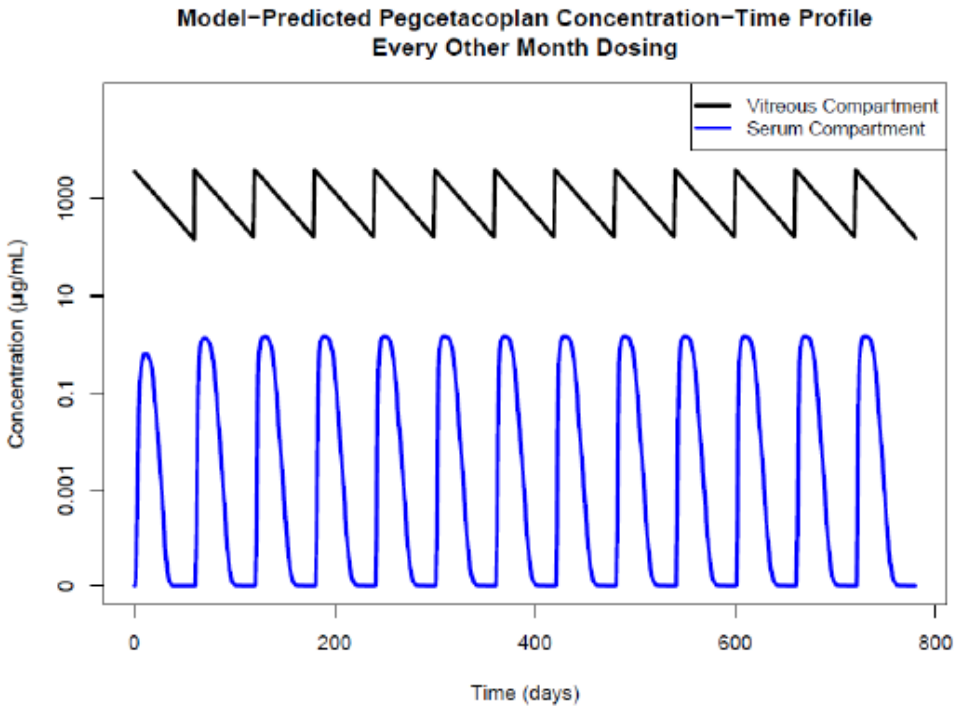
Abbreviations: CL/F = apparent systemic clearance from serum; CV = coefficient of variation; IVT = intravitreal; KA = absorption rate constant; PK = pharmacokinetic; $t_{½,abs}$ = vitreous-to-serum absorption half-life; $t_{½,elim}$ = serum elimination half-life; VC/F = apparent volume of the central serum compartment.

Source: PPK_APL-ex2-cp-012, Table 29.

Steady-state serum pegcetacoplan exposure was predicted to be below the level required for systemic pharmacodynamic effects (i.e., serum concentration needed to achieve 1% of the maximum LDH response [EC1] in PNH patients is 49 µg/mL). Median (5^{th}, 95^{th} percentile) steady-state serum Cmax among GA patients was predicted to be 1.70 (0.60, 2.30) µg/mL and 2.20 (1.40, 3.00) µg/mL, and geometric mean (% CV) was predicted to be 1.50 µg/mL (58.1% CV) and 2.20 µg/mL (28.7% CV) at doses of 15 mg IVT every other month and 15 mg IVT every month, respectively. Steady-state vitreous exposure was predicted to be approximately 1300-fold higher than serum exposure. No intrinsic or extrinsic patient factors were anticipated to influence vitreous exposure (**Figure 14**).

Figure 14. Model-Predicted Geometric Mean Pegcetacoplan Concentration-Time Profiles in the Vitreous and Serum Compartments – Stratified by Dose Group





Source: This reviewer's analysis to duplicate Figure 16 in PPK_APL-ex2-cp-012

Age, sex, and baseline C3 level were identified as significant ($p < 0.001$) predictors of apparent serum pegcetacoplan clearance following IVT administration. Females are predicted to have a 1.27-fold increase (90% CI, 1.21-1.32) in steady-state serum Cmax compared to males. Age and baseline C3 were not predicted to result in exposure outside of 0.8- to 1.25-fold of reference

over the range of values representing 90% of individuals in the analysis. In addition, concomitant use of intravitreal anti-VEGF medications was predicted to result in 0.821- fold (90% CI, 0.753-0.895) and 0.785-fold (90% CI, 0.709-0.859) decreases in serum AUC and Cmax, respectively. Overall, none of these covariate effects were anticipated to be clinically meaningful given the low absolute maximum serum concentrations achieved (<5 µg/mL).

Reviewer's Comments:

1. The Applicant's final PopPK model is repeatable and considered adequate. It provided an adequate description of the observed serum concentration–time profiles of pegcetacoplan in adults with GA secondary to AMD following IVT administration.

2. None of the investigated covariate effects were anticipated to be clinically meaningful given the low absolute maximum serum concentrations achieved (<5 µg/mL). The effect of body weight on pegcetacoplan exposure is unknown as the information is missing in >50% of subjects

3. *Steady-state vitreous exposure was predicted to be approximately 1300-fold higher than serum exposure. No intrinsic or extrinsic patient factors were anticipated to influence vitreous exposure. However, because of lack of observed vitreous concentrations from all dosages of IVT pegcetacoplan, the reliability of the predicted vitreous concentrations in human subjects cannot be assessed.*

4.3.2 Exposure-Response Analysis

Title: Development of a Population Exposure Response Model for Lesion Area in Patients with Geographic Atrophy Secondary to Age Related Macular Degeneration Treated with Pegcetacoplan (APLl-2) or Sham in Phase 2 and 3 Studies

Objectives:

- Develop a disease progression model to characterize the natural history of lesion area in patients with GA
- Develop a population ER model to characterize the impact of pegcetacoplan exposure following IVT administration on disease progression in patients with GA
- Predict disease progression at landmark timepoints following sham treatment compared to clinically relevant doses administered via IVT injection

Data:

The population ER analysis included GA lesion area measurements from 3 clinical studies (one Phase 2 study and two Phase 3 studies) following sham treatment or IVT administration of pegcetacoplan to patients with GA secondary to AMD.

Methods:

Prior to model development, exploratory data analysis was performed to help inform model selection. First, a disease progression model, including the assessment of the random effects

structure, was identified using study eye data from sham treatment only. Fellow eye data from all patients irrespective of treatment assignment were assessed for inclusion in the disease progression model at this stage. The analysis planned a priori to include data from both study and fellow eyes, if supported by the observed data, in order to leverage all available information at the time of the 12-month analysis. It was hypothesized that fellow eye data may serve as an intra-subject control for disease progression, which may aid in separation of treatment effect from inter-subject variation in disease progression. Once a suitable disease progression model was identified, a base ER model was developed by evaluating the impact of pegcetacoplan exposure on disease progression. Following identification of the base ER model, a full ER model was evaluated by including prespecified covariates simultaneously in a single model. A covariate reduction procedure was performed to identify a parsimonious preliminary final ER model. The predictive performance of the preliminary final ER model was evaluated using a visual predictive check (VPC). The preliminary final ER model was accepted as the final ER model if the predictive performance was adequate; otherwise, the preliminary final ER model would undergo model refinement until the predictive performance was adequate.

Results:

There were approximately 500 subjects with study eye data for each dosing level of sham, 15 mg monthly, and 15 mg every other month (**Table 17**).

Table 17. Summary of Subjects

Treatment Arm	Eye	No. of Subjects			
		Study POT-CP121614	Study APL2-303	Study APL2-304	Total
Pegcetacoplan 15 mg Monthly	Study	86	206	213	505
	Fellow	74	170	178	422
Pegcetacoplan 15 mg Every Other Month	Study	78	208	212	498
	Fellow	70	170	181	421
Sham Pooled	Study	81	206	211	498
	Fellow	76	155	172	403
Total	Study	245	620	636	1501
	Fellow	220	495	531	1246

Note: The sham pooled treatment arm is a combination of the sham monthly and sham every other month treatment arms.

Source: APL-EX21-CP-013, Table 5.

Growth in lesion area in the untreated condition was adequately characterized using a disease progression model that was linear with respect to time. A common set of population parameter estimates was able to characterize disease progression in study eyes undergoing sham treatment and untreated fellow eyes, although separate random effects were needed to describe interindividual and residual variability.

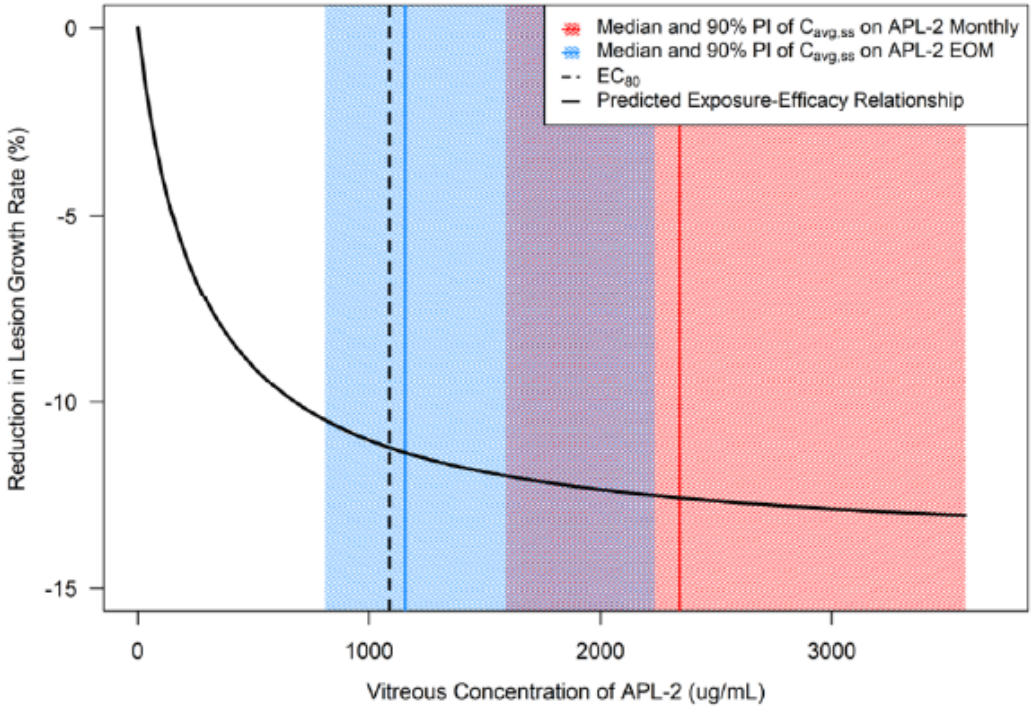
The initial lesion area estimate was 7.17 mm2 with a constant 0.00455 mm2/day (1.66 mm2/year) rate of lesion growth in the absence of treatment. There was a moderately strong correlation ($\rho = 0.733$) between individual variation in the rate of disease progression in the study and fellow eyes in the absence of treatment, suggesting that incorporation of fellow eye data may be useful to inform intrasubject disease progression in ER modeling.

Table 18 summarizes parameters for the final ER model. The covariates included were no subfoveal involvement and more (>20) intermediate/large drusen groups on initial lesion area; no subfoveal involvement, unifocal GA, more (>20) intermediate/large drusen groups, and LLD on time slope. To account for the differential effect of subfoveal involvement on disease progression in study and fellow eyes, 2 covariate-parameter relationships were added to the preliminary final model to differentiate the effect of subfoveal involvement on fellow and study eyes: no subfoveal involvement on initial lesion area (fellow eye difference) and no subfoveal involvement on time slope (fellow eye difference). Parameters in the final model were well estimated with RSE values <50%.

In the final ER model, the maximal reduction in the rate of disease progression is estimated to be 14.0%, and 50% of this maximal reduction is achieved at a vitreous concentration of 272 µg/mL (95% CI, 4.57-16,200 µg/mL). The large CI for EC_{50} may be influenced by the limited observed subject-level PK data in Phase 3 studies available, which narrows the distribution of predicted concentration data in these patients. Derived values for the vitreous concentrations associated with 80% (EC_{80}) and 90% (EC_{90} [concentration required to achieve 90% of the maximal response]) of maximal effect are 1088 µg/mL and 2448 µg/mL, respectively.

Per the exploratory ER analysis conducted to characterize the natural disease progression of GA and the impact of IVT pegcetacoplan treatment on the progression of GA lesion area, IVT pegcetacoplan drug effect is described as percentage reduction in the rate of lesion growth with increasing vitreous concentration of pegcetacoplan (**Figure 15**).

Figure 15. Exposure-Response Relationship Final Model



Abbreviations: APL-2 = pegcetacoplan; $C_{avg,ss}$ = average concentration at steady state; EC_{80} = concentration producing 80% of the maximal effect; E_{MAX} = maximal effect; PI = prediction interval;

Notes: Drug effect is described as percentage reduction in the rate of lesion growth with increasing vitreous concentration of pegcetacoplan (solid black); the EC_{80} is denoted using a vertical dashed line.
Source: APL-EX21-CP-013, Figure 23.

Steady-state vitreous average concentrations with pegcetacoplan 15 mg IVT monthly represent the plateau of the quantified ER relationship, indicating that more frequent dosing or larger absolute doses is unlikely to result in greater response. Furthermore, steady-state vitreous average concentrations with pegcetacoplan 15 mg IVT EOM are centered approximately around the EC_{80}, indicating that this dosing regimen is likely the minimally effective dosage; any further reduction in dosing intensity would likely result in a substantial proportion of subjects with exposure below the EC_{80} threshold.

Of note, even though IVT pegcetacoplan is administered via IVT route into the eye, the vitreous pegcetacoplan concentrations were predicted based the established PopPK model without actual measurement. Because of the lack of robust assessment of the predicted versus observed vitreous pegcetacoplan concentrations from all dosages of IVT pegcetacoplan in this submission, the ER analysis is considered exploratory.

Conclusion:

An exploratory population exposure-response model of disease progression was developed to characterize the natural time course of GA and the impact of IVT pegcetacoplan treatment on the progression of GA lesion area. Growth in lesion area in the untreated condition (study eyes on sham treatment and fellow eyes only) was characterized using a disease progression model that was linear with respect to time.

The maximal reduction in the rate of lesion growth was estimated to be 14.0%; a vitreous concentration of 272 μg/mL was predicted to achieve 50% of this maximal effect (EC_{50}). GA patients receiving pegcetacoplan 15 mg IVT EOM achieved median predicted average vitreous concentrations approximating the concentration required to achieve 80% of the maximal response (EC_{80}) (1088 μg/mL) for reduction in the rate of lesion growth. GA patients receiving pegcetacoplan 15 mg IVT monthly achieved exposures above the EC_{80} in over 95% of patients (**Figure 15**).

Reviewer's Comments:

1. The ER analysis of disease progression was conducted to characterize the natural time course of GA and the impact of IVT pegcetacoplan treatment on the progression of GA lesion area.

2. It is notable that the ER relationship is largely limited by the by the unavailability of observed subject-level PK (serum pegcetacoplan) data in Phase 3 studies (e.g., APL2-304), which likely narrows the distribution of predicted concentration data in these patients.

3. Furthermore, the vitreous pegcetacoplan concentrations were predicted based the established PopPK model without actual measurement. Because of the lack of robust assessment

of the predicted versus observed vitreous pegcetacoplan concentrations from all dosages of IVT pegcetacoplan in this submission, the ER analysis is considered exploratory.

Table 18. Parameter Estimates for the Final ER Model

	Estimate	ASE	RSE, %	95% CI	Transformed estimate[a]	Transformed 95% CI[a]
Theta/parameter, unit						
1 Initial lesion area, mm^2	7.76	0.145	1.87	7.47-8.04	–	–
3 Time slope, mm^2/day	0.00487	0.000121	2.48	0.00464-0.00511	–	–
7 Fellow eye initial shape parameter, λ	−0.552	0.0256	4.63	−0.602 to −0.502	–	–
10 E_{max}, proportion	−0.140	0.0596	42.6	−0.257 to −0.0231	−14.0%	−25.7% to −2.31%
11 Log EC_{50} (vitreous concentration, µg/mL)	5.61	2.08	37.2	1.52 to 9.69	272	4.57-16,200
15 No subfoveal involvement on initial lesion area	−0.0689	0.0209	30.4	−0.110 to −0.0279	–	–
17 More (>20) intermediate/large drusen groups on initial lesion area	−0.0959	0.0205	21.4	−0.136 to −0.0556	–	–
23 No subfoveal involvement on time slope	0.134	0.0337	25.2	0.0675 to 0.199	–	–
24 Unifocal GA on time slope	−0.176	0.0206	11.7	−0.217 to −0.136	–	–
25 More (>20) intermediate/large drusen groups on time slope	−0.195	0.0212	10.8	−0.237 to −0.154	–	–
27 Low-luminance deficit on time slope [reference: 20]	0.00541	0.000721	13.3	0.00400 to 0.00682	–	–
28 No subfoveal involvement on initial lesion area (fellow eye difference)	−0.165	0.0267	16.2	−0.218 to −0.113	–	–
29 No subfoveal involvement on time slope (fellow eye difference)	−0.0774	0.0368	47.5	−0.150 to −0.0053	–	–
Residual variability, unit						
5 Study eye proportional, proportion	0.0277	0.000966	3.49	0.0258-0.0295	2.77%	2.58%-2.95%
6 Study eye additive, mm^2	0.139	0.0110	7.90	0.117-0.160	–	–
8 Fellow eye proportional, proportion	0.0284	0.00181	6.39	0.0248-0.0319	2.84%	2.48%-3.19%
9 Fellow eye additive, mm^2	0.201	0.0192	9.56	0.163-0.238	–	–

Interindividual variability						
$\omega_{1,1}^2$ Study eye initial lesion area	0.263	–	–	0.249-0.277	54.9% CV	53.2% CV-56.5% CV
$\omega_{2,1}$ Fellow eye initial lesion area: Study eye initial lesion area	0.304	–	–	–	$\rho = 0.648$	–
$\omega_{2,2}^2$ Fellow eye initial lesion area	0.835	–	–	0.752-0.918	–	–
$\omega_{3,1}$ Study eye time slope: Study eye initial lesion area	0.106	–	–	–	$\rho = 0.359$	–
$\omega_{3,2}$ Study eye time slope: Fellow eye initial lesion area	0.163	–	–	–	$\rho = 0.311$	–
$\omega_{3,3}^2$ Study eye time slope	0.328	–	–	0.297-0.359	62.3% CV	58.8% CV-65.7% CV
$\omega_{4,1}$ Fellow eye time slope: Study eye initial lesion area	0.138	–	–	–	$\rho = 0.427$	–
$\omega_{4,2}$ Fellow eye time slope: Fellow eye initial lesion area	0.288	–	–	–	$\rho = 0.501$	–
$\omega_{4,3}$ Fellow eye time slope: Study eye time slope	0.243	–	–	–	$\rho = 0.675$	–
$\omega_{4,4}^2$ Fellow eye time slope	0.396	–	–	0.345-0.446	69.7% CV	64.2% CV-75.0% CV
Condition number	89					

Abbreviations: ASE = asymptotic standard error; CV = coefficient of variation; EC_{50} = the vitreous concentration producing 50% of the maximal response; E_{max} = maximum proportional reduction in the rate of disease progression with drug exposure; GA = geographic atrophy; LLD = low-luminance deficit; RSE = relative standard error.

[a] Transformations are calculated as the exponentiation of the estimate for log-transformed parameters, the product of the estimate and 100% for proportional parameters, $\left(\sqrt{\exp(\omega^2) - 1}\right) \cdot 100\%$ for log-normal interindividual random effect parameters, and the correlation coefficient for off-diagonal interindividual random effect parameters.

[b] η-shrinkage: 0.0562% ($\eta_1^{init,study}$), 1.75% ($\eta_2^{init,fellow}$), 9.86% ($\eta_3^{slope,study}$), 10.2% ($\eta_4^{slope,fellow}$)

The following equations describe the final model:

$$A_{i,study}(t) = INIT_{i,study} + SLOPE_{i,study} \cdot t$$

$$INIT_{i,study} = \theta_1 \cdot (1 + \theta_{15} \cdot NOSUBFI) \cdot (1 + \theta_{17} \cdot MILDR) \cdot \exp(\eta_i^{init,study})$$

$$SLOPE_{i,study} = [\theta_3 \cdot (1 + \theta_{23} \cdot NOSUBFI) \cdot (1 + \theta_{24} \cdot UNIF) \cdot (1 + \theta_{25} \cdot MILDR) \cdot \exp(\theta_{27} \cdot (LLD - 20)) \cdot \exp(\eta_i^{slope,study})] \cdot (1 + EDRUG)$$

$$EDRUG = \frac{\theta_{10} \cdot C_v}{\exp(\theta_{11}) + C_v}$$

$$A_{i,fellow}(t) = INIT_{i,fellow} + SLOPE_{i,fellow} \cdot t$$

$$INIT_{i,fellow} = \theta_1 \cdot (1 + [\theta_{15} + \theta_{28}] \cdot NOSUBFI) \cdot (1 + \theta_{17} \cdot MILDR) \cdot \exp(ETIF_i), \text{ where } ETIF_i = \frac{\exp(\eta_i^{init,fellow})^{\theta_7} - 1}{\theta_7}$$

$$SLOPE_{i,fellow} = \theta_3 \cdot (1 + [\theta_{23} + \theta_{29}] \cdot NOSUBFI) \cdot (1 + \theta_{24} \cdot UNIF) \cdot (1 + \theta_{25} \cdot MILDR) \cdot \exp(\theta_{27} \cdot (LLD - 20)) \cdot \exp(\eta_i^{slope,fellow})$$

Parameters are defined as follows:

- $A_{i,eye}(t)$ is the lesion area (mm^2) in the designated *eye* (fellow or study) for the *i*th subject at time *t*.
- $INIT_{i,eye}$ is the initial lesion area for the *i*th subject in the designated *eye* (fellow or study); θ_1 is the typical value of initial lesion area and $\eta_i^{init,eye}$ is a random effect describing the *i*th individual's deviation from the population initial lesion area in the designated *eye* (study or fellow) and θ_7 is a shape parameter (λ) in the Box-Cox transformation for the fellow eye.
- θ_{15} is the proportional change in initial lesion area in the study eye for subjects without subfoveal involvement (NOSUBFI=1) and (θ_{15}+θ_{28}) is the corresponding proportional change in initial lesion area in the fellow eye.
- θ_{17} is the proportional change in initial lesion area in the designated *eye* (fellow or study) for subjects without more (>20) intermediate or large drusen (MILDR=1)
- $SLOPE_{i,eye}$ is the disease progression slope describing the rate of change in lesion area (mm^2/day) for the *i*th subject in the designated *eye* (fellow or study); θ_{slope} is the typical value of the disease progression slope and $\eta_i^{slope,eye}$ is a random effect describing the *i*th individual's deviation from the population disease progression slope in the designated *eye* (fellow or study)
- θ_{23} is the proportional change in disease progression slope in the study eye for subjects without subfoveal involvement (NOSUBFI=1) and (θ_{23}+θ_{29}) is the corresponding proportional change in disease progression slope in the fellow eye.
- θ_{24} is the proportional change in disease progression slope in the designated *eye* (fellow or study) for subjects without more (>20) intermediate or large drusen (MILDR=1).
- θ_{25} is the proportional change in disease progression slope in the designated *eye* (fellow or study) for subjects with unifocal GA (UNIF=1).
- θ_{27} is the log-linear change in disease progression slope in the designated *eye* (fellow or study) with LLD centered on 20.
- EDRUG is the drug effect on disease progression slope; θ_{10} is the maximum proportional reduction in disease progression with vitreous concentration (Cv); θ_{11} is the log vitreous concentration at which 50% of maximal reduction in disease progression occurs.

Source: APL-EX21-CP-013, Table 19.

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