

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA217171
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Applicant:	Apellis Pharmaceuticals, Inc.
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1 EXECUTIVE SUMMARY

This is an addendum to the statistical review of the New Drug Application (NDA) submitted by Apellis Pharmaceuticals, Inc. (Applicant) for the treatment of adult subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The original NDA was submitted on 05/26/2022 with efficacy and safety data up to 18 months of follow up. Based on the review of the originally submitted safety and efficacy data up to Month 18, this reviewer concluded that the results in the two pivotal Phase 3 studies, APL2-303 and APL2-304, support the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD (See DARRTS entry on 10/24/2022 for the original Biometrics Review). In the current submission, the Applicant submitted the complete 24-week safety and efficacy data from the two pivotal studies. The objective of this addendum is to determine whether the 24-month safety and efficacy results in the two studies still support the proposed indication.

The analyses based on the complete 24-week data provided results that are consistent with those observed with efficacy data through Month 18. In both studies, nominally significant treatment differences are observed at Month 24 in favor of the two pegcetacoplan dosing frequencies [every month (PM) and every other month (PEOM)] with respect to both the mean change from baseline GA area as well as the Division's preferred endpoint, the mean rate of GA growth (**Error! Reference source not found.** and **Error! Reference source not found.**) .

Table 1: Summary of Mean Change from Baseline in Total GA Area by Visit (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
Study APL-303					
Month 12: Mean (SE) [1]	1.733 (0.0792)	1.756 (0.0744)	1.964 (0.0959)	-0.2301 (-0.470, 0.010)	-0.2077 (-0.444, 0.029)
Month 18: Mean (SE) [2]	2.621 (0.1007)	2.633 (0.1032)	3.001 (0.1383)	-0.3800 (-0.713, -0.046)	-0.3677 (-0.706, -0.029)
Month 24: Mean (SE) [3]	3.227 (0.1245)	3.339 (0.1303)	3.972 (0.1682)	-0.7451 (-1.153, -0.336)	-0.633 (-1.050, -0.215)
Study APL2-304					
Month 12: Mean (SE) [1]	1.557 (0.0835)	1.650 (0.0815)	1.968 (0.0821)	-0.4113 (-0.639, -0.183)	-0.3181 (-0.542, -0.093)
Month 18: Mean (SE) [2]	2.351 (0.1069)	2.516 (0.1088)	3.009 (0.1153)	-0.657 (-0.965, -0.350)	-0.492 (-0.802, -0.183)
Month 24: Mean (SE) [3]	3.123 (0.1432)	3.282 (0.1323)	4.025 (0.1464)	-0.901 (-1.302, -0.500)	-0.742 (-1.128, -0.357)

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

Source: [2] Table 24 of the Applicant's original study reports

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

Table 2: Summary of Mean Rate of GA Growth (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
Study APL-303					
Month 12: Slope (SE) [1]	1.762 (0.0762)	1.749 (0.0737)	1.959 (0.0905)	-0.197 (-0.430, 0.035)	-0.210 (-0.439, 0.019)
Month 18: Slope (SE) [2]	2.644 (0.1013)	2.600 (0.1026)	3.001 (0.1361)	-0.356 (-0.689, -0.023)	-0.401 (-0.735, -0.067)
Month 24: Slope (SE) [3]	3.363 (0.1254)	3.358 (0.1283)	3.992 (0.1686)	-0.628 (-1.040, -0.216)	-0.633 (-1.049, -0.217)
Study APL2-304					
Month 12: Slope (SE) [1]	1.560 (0.0802)	1.656 (0.0760)	1.968 (0.0797)	-0.407 (-0.629, -0.185)	-0.311 (-0.529, -0.094)
Month 18: Slope (SE) [2]	2.338 (0.1101)	2.490 (0.1076)	2.970 (0.1144)	-0.632 (-0.943, -0.320)	-0.480 (-0.789, -0.171)
Month 24: Slope (SE) [3]	3.103 (0.1451)	3.283 (0.1359)	3.966 (0.1435)	-0.863 (-1.2631, -0.4630)	-0.683 (-1.0719, -0.2958)

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

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

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

Regarding safety, over the 24-week period, a higher percentage of subjects in the two pegcetacoplan arms reported at least one ocular adverse event compared to the sham arms (62% in PM, 55% in PEOM, 46% in SM and 46% in SEOM). The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms (PM, PEOM) were: vitreous floaters (9.8%, 6.9%), Neovascular age-related macular degeneration (9.8%, 5.7%), conjunctival haemorrhage (8.1%, 8.1%), visual acuity reduced (7.9%, 6.4%) and eye pain (7.2%, 5.7%). The incidence rate of these adverse events in the sham arms (SM, SEOM) were vitreous floaters (1.4%, 1.0%), Neovascular age-related macular degeneration (1.9%, 1.9%), conjunctival haemorrhage (2.4%, 4.8%), visual acuity reduced (7.7%, 5.7%) and eye pain (6.3%, 6.7%). In addition, a slightly higher proportion of subjects in the PM pegcetacoplan arm reported at least one serious adverse event compared to the PEOM as well as the sham arms (32.9% in PM, 24.5% in PEOM, 27.5% in SM and 24.3% in SEOM). The proportion of subjects who died during the 24-month study period was 6.7% in PM, 3.6% in PEOM, 5.3% in SM and 2.4% in SEOM. The proportion of subjects who discontinued the study due to adverse events was 9.5% in PM, 6.2% in PEOM, 7.2% in SM and 4.3% in SEOM.

Overall, the results of the efficacy analyses based on the complete 24-month data in the two pivotal studies demonstrated the efficacy of pegcetacoplan for the treatment of GA secondary to AMD. However, issues related to missing data, increased incidence of adverse events with continued use, and treatment compliance are notable. First, the issue of missing efficacy data, which was also raised for the safety and efficacy summary based on data through Month 18, is notable. For example, at the Week 18 visit, around 26% of subjects randomized to the PM arm in both studies had missing efficacy data. At Month 24, this has increased to 30% and 33% in Study APL2-303, and Study APL2-304, respectively. Second, compared to pooled sham, incidence of adverse events, including adverse events of special interest (intraocular inflammations and exudative AMD), were higher in the two peregctogol arms; with more adverse events reported in subjects randomized to the PM arm. Third, based on the drug exposure summary (See Section 3.3.1), less than 20% of the subjects in the PM arm received the total allowed 24 injections during the 24-month period. Consequently, given the observed dose-response of safety, it is likely that the actual incidence of adverse events with a full monthly treatment regimen might be higher. Therefore, the final determination for the approval of this drug, including the selection of the to-be-marketed dosing frequency, should be made based on the totality of evidence, taking the absence of alternative treatment for this indication, and the potential safety and compliance issues into account.

2 INTRODUCTION

This is a statistical review addendum for the original NDA submitted by Apellis Pharmaceuticals, Inc., referred to as the Applicant on May 26, 2022, for intravitreal (IVT) pegcetacoplan therapy (pegcetacoplan). The proposed indication is for the treatment of GA secondary to AMD. The primary evidence of efficacy and safety for this NDA comes from two identically designed pivotal Phase 3 studies (Studies APL2-303 and APL2-304). The two studies were conducted across multiple sites located in the US and elsewhere (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, the Netherlands, New Zealand, Poland, Spain, and the UK). Study APL2-303 enrolled 621 subjects in 122 study sites, of which, 400 (64.4%) subjects were enrolled in sites located within the United States (US). Similarly, Study APL2-304 enrolled 637 subjects, of which, 453 (71.1%) subjects were enrolled in sites located within the US.

The Applicant proposes to include findings from Study APL2-303 and Study APL2-304 into the “Clinical Studies” (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of intravitreal (IVT) pegcetacoplan therapy in the treatment of adult patients with GA secondary to AMD. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology Products (DOP) if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant’s summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

Per the Applicant, a major contributing factor to the pathogenesis of GA appears to be overactivation of the complement cascade (part of the body’s immune system), resulting in chronic inflammation, cell dysregulation, and retinal cell death. The Applicant states that peptide moieties of pegcetacoplan molecule bind to complement C3 and C3b resulting in broad inhibition of complement activation.

Per the Applicant, although there is treatment for exudative AMD, also known as wet (neovascular) AMD, with anti-vascular endothelial growth factor (VEGF) therapies, no approved therapy exists for GA, which is usually bilateral and relentlessly progressive. The Applicant is therefore developing pegcetacoplan for the treatment of GA secondary to AMD.

2.1.2 History of Drug Development

The protocols (original and amendments) and the statistical analysis plans (SAPs) for Studies APL2-304 and APL2-303 were reviewed under IND124784. The Applicant had a series of discussions with the DOP to reach agreement on the development program for IVT

pegcetacoplan. The summary of the relevant interactions between the Applicant and the DOP is provided below:

- On 12/05/2017, the Applicant had a Type B end-of-Phase 2 meeting with the DOP. The objective of the meeting was to obtain agreement on the design of the two Phase 3 protocols. In response to the Applicant's question regarding the primary efficacy endpoint, the Division agreed that the primary endpoint of the mean rate of growth from baseline to month 12, measured as the total area of the GA lesion is acceptable. The Division also recommended the Applicant to evaluate the data upon completion of the trial to determine the best model to describe the total area growth over time. The Division requested the Applicant to clearly specify the proposed mixed effects model and the missing data method they planned to conduct based on the multiple imputation approach.
- On 03/01/2021, the Applicant had a Type C meeting with the DOP. The objective of the meeting was to discuss the statistical analysis strategy and pooling proposals for the Phase 3 studies for pegcetacoplan. The Division provided feedback on the SAPs. The Applicant incorporated the feedbacks and submitted an updated SAP.
- On 11/09/2021, the Division informed the Applicant that Studies APL2-303 and APL2-304 appeared to be adequate and well controlled, although the final determination will be a review issue. The Division recommended analysis of the mean rate of change from baseline in total GA lesion area using fundus autofluorescence (FAF) for the primary endpoint.
- On 01/21/2022, the Applicant had a Type B Pre-NDA meeting with the DOP. The Division recommended the Applicant to 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 the Applicant's plan to include Month 12 clinical study reports (CSRs) in the initial NDA, full data sets through Month 18, brief summaries of key findings at Month 18, and brief summaries of pertinent data beyond Month 18.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary for the protocol defined primary efficacy endpoint, mean change from baseline in total GA area at Month 12, is presented in Table 3.

Table 3: Efficacy Summaries of APL2-303 and APL2-304

Design	Treatment (Sample size)	Endpoint/Analysis	Applicant's findings ²
APL2-303	▪ PM (N=206) ▪ PEOM (N=208) ▪ SM (N=102) ▪ SEOM (N=105)	Primary Endpoint: Mean change from baseline (CFB) in total area of GA lesion(s) in the study eye at Month 12. The primary efficacy analysis provided the least squares (LS) mean difference between each of the two dosing	The study did not meet its primary objective of demonstrating the statistical superiority of either of the two dosing frequencies against sham at the prespecified significance
¹ MC, RD, DB, PG, SC			

		frequencies of pegcetacoplan (PM and PEOM) and the sham group and its two-sided 95% CI using a MMRM. The primary efficacy analysis was conducted based on modified intent to treat population (mITT). Multiplicity was controlled for the primary endpoint using a fixed sequence approach where the comparison between PM and sham pooled was tested and if statistically significant, the comparison between PEOM and sham pooled was tested.	level (0.0496). The difference in LS mean CFB (95% CI, P-value) between the PM group and the sham pooled group was -0.2301mm^2 $[-0.4708, 0.0105]$; $P=0.0609$. The difference (95% CI; P-value) between the PEOM group and Sham group was -0.2207mm^2 $[-0.4445, 0.0290]$; $P=0.0853$.
APL2-304 ¹ MC, RD, DB, PG, SC	- PM (N=213) - PEOM (N=212) - SM (N=106) - SEOM (N=106)	Primary Endpoint: Mean change from baseline (CFB) in total area of GA lesion(s) in the study eye at Month 12. The primary efficacy analysis provided the least squares (LS) mean difference between each of the two dosing frequencies of pegcetacoplan (PM and PEOM) and the sham group and its two-sided 95% CI using a MMRM. The primary efficacy analysis was conducted based on modified intent to treat population (mITT). Multiplicity was controlled for the primary endpoint using a fixed sequence approach where the comparison between PM and sham pooled was tested and if statistically significant, the comparison between PEOM and sham pooled was tested.	The study met its primary objective of demonstrating the statistical superiority of both dosing frequencies against sham at the prespecified significance level (0.0496). The difference in LS mean CFB (95% CI, P-value) between the PM group and the sham pooled group was -0.4113mm^2 $[-0.6396, -0.1830]$; $P=0.0004$. The difference (95% CI; P-value) between the PEOM group and sham group was -0.3181mm^2 $[-0.5424, -0.0939]$; $P=0.0055$.

Source: Applicant's study reports. ¹ MC: Multi -center, RD: Randomized, DB: Double-blind, PG: Parallel-group, SC: Sham-controlled. ² The studies anticipated four unmasked reviews of safety data by the data safety monitoring committee (DSMC). Because some of the safety outcomes are also related to efficacy, the DOP recommended an alpha adjustment of 0.0001 for each of the 4 independent data monitoring committee unmasked data reviews that occurred before the primary analysis. Therefore, hypothesis testing in each study was performed at a 2-sided $\alpha=0.0496$ (0.05-0004).

2.2 Data Sources

This NDA application was submitted electronically and includes full study reports as well as standardized datasets using SDTM and ADaM formats that are relevant for the analyses of studies APL2-303 and APL2-304 presented in this review. Datasets and corresponding definition files can be found at the following location:

<\\CDSESUB1\evsprod\NDA217171\0019\m5\datasets>

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt contains the demographic and disposition data.
- adga.xpt contains the GA area efficacy data.
- adae.xpt contains the adverse event data.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the NDA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of studies APL2-303 and APL2-304 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Studies APL2-303 and APL2-304 were multicenter, double-masked, randomized, parallel-group, sham-controlled, studies. These studies were designed to evaluate the safety and efficacy of pegcetacoplan compared with sham injection in subjects with GA secondary to AMD. To be eligible for these studies, patients had to meet the following ocular inclusion criteria for the study eye:

- Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
- The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
 - o Total GA area must be ≥ 2.5 and ≤ 17.5 mm² (1 and 7 disk areas respectively).
 - o If GA is multifocal, at least 1 focal lesion must be ≥ 1.25 mm² (0.5 disk areas), with the overall aggregate area of GA as specified above.
 - o The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy.
 - o Presence of any pattern of hyper autofluorescence in the junctional zone of GA.
- Normal luminance best corrected visual acuity of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent).

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

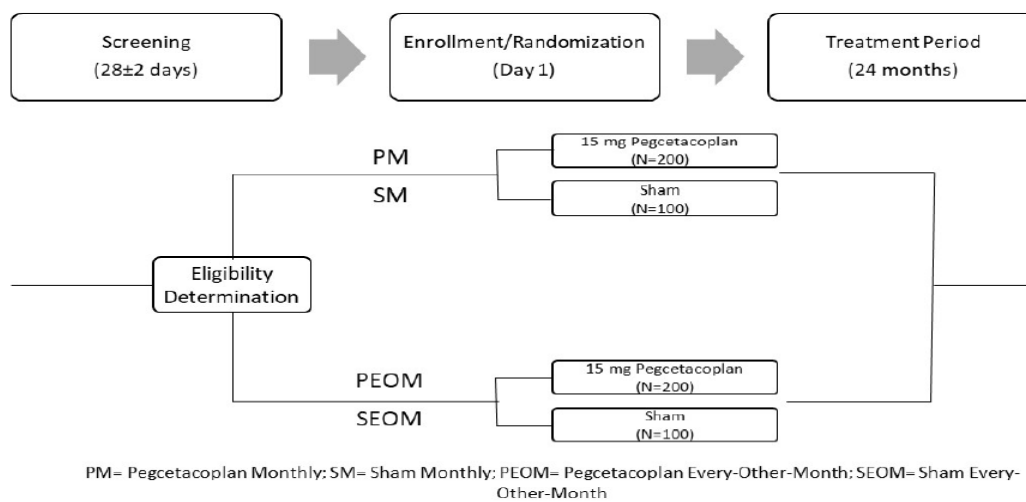
3.2.1.2 Randomization and Treatment

Both studies used a 2:2:1:1 randomization ratio for allocating eligible patients to the four study arms:

- Pegcetacoplan monthly (PM): Pegcetacoplan 15 mg/0.1 mL monthly for 24 months.
- Pegcetacoplan every other month (PEOM): Pegcetacoplan 15 mg/0.1 mL every other month for 24 months.
- Sham monthly (SM): Sham injection monthly for 24 months.
- Sham every other month (SEOM): Sham injection every other month for 24 months.

Per the Applicant, the procedure for sham injection was the same as that used for IVT pegcetacoplan injection but no actual injection occurred. Randomization was stratified according to GA lesion area at screening ($<7.5 \text{ mm}^2$; $\geq 7.5 \text{ mm}^2$), and presence of choroidal neovascularization (CNV) in the fellow eye. Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham. The total duration of both studies was 24 weeks. For the first 12 months, all randomized subjects were to return every month to the clinical site for assessments and additional pegcetacoplan or sham injections according to their randomization scheme. From Month 12 onwards, subjects were to return to the clinical site based on their randomized treatment schedule (monthly or every other month) and will follow the treatment regimen and assessments outlined in the visit schedule until Month 24 (See Study design schema in Figure 1).

Figure 1: Study Design Schema



3.2.1.3 Efficacy Endpoints

The protocol defined primary efficacy endpoint of these studies was the mean change from baseline in total GA area at Month 12. However, the DOP recommended the Applicant to use the mean rate of growth (Slope) as the primary efficacy endpoint.

Reviewer's remark: The requirement to use the mean rate of GA growth (Slope) as a primary efficacy endpoint was communicated to the Applicant on multiple occasions during the review process. For example, at the end of Phase 2 meeting (12/05/2017), the Division recommended the primary efficacy endpoint to be the mean rate of GA growth evaluated based on the best linear fit. In addition, at the Type-C meeting (3/1/2021), the Division had stated that the magnitude of change observed at Month 12 will not be clinically relevant for this indication and recommended the endpoint to be based on a rate of change. Furthermore, at the Type-A meeting held on 11/18/2021, the DOP stated the following: "Analysis of the mean rate change of growth from baseline through all available measurements, measured as the total area of the GA lesion using fundus autofluorescence is recommended for the primary endpoint."

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, the primary estimand and methods to deal with missing data and intercurrent events, and statistical analyses presented in this review that are performed by the Applicant, as described in the SAPs for studies APL2-303 and APL2-304, as well as independent analyses performed by the statistical reviewer.

3.2.2.1 Statistical Hypotheses and Sample size

□ Hypothesis Testing

The primary null and alternative hypotheses related to the protocol defined primary efficacy endpoint for the comparison of each dosing frequency against the pooled sham can be mathematically stated as follows:

$$H_{01}: \mu_{pm} = \mu_{sham}$$

$$H_{a1}: \mu_{pm} \neq \mu_{sham}$$

And

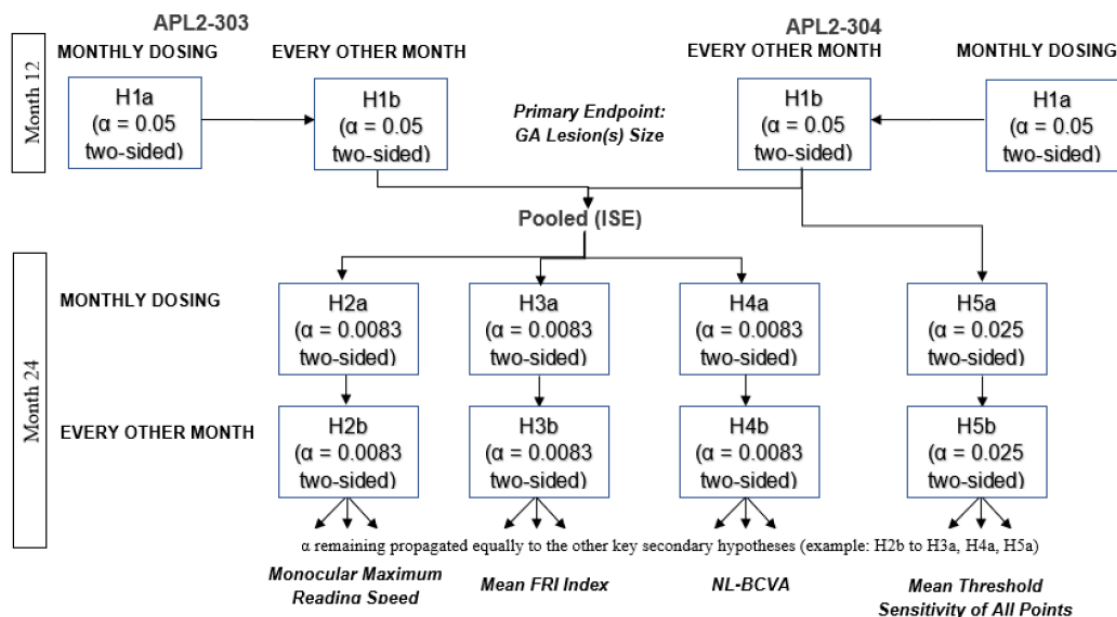
$$H_{02}: \mu_{peom} = \mu_{sham}$$

$$H_{a2}: \mu_{peom} \neq \mu_{sham}$$

where μ_{pm} , μ_{peom} , and μ_{sham} are the mean change from baseline in total GA area at Month 12 in the PM, PEOM and the pooled sham arms, respectively. To adjust for multiplicity due to the test of the two pegcetacoplan arms, a sequential testing procedure was used. In this procedure, the superiority of PM against pooled sham was tested first, followed by the comparison of PEOM against pooled sham. The study will be considered positive if the first hypothesis (H_{01}) is rejected. If the two hypotheses are rejected within each study, the Applicant planned to

compare each dosing frequency against the pooled sham arm using the combined data from the two studies followed by the comparison of the two dosing frequencies against the pooled sham with respect to the key secondary efficacy endpoints. The Type I error control for the planned tests is summarized in Figure 2.

Figure 2: Hypothesis Testing and Type I Error Control



Reviewer's remark: The hypotheses formulated above could also be used for the DOP's recommended endpoint, the mean rate of growth (slope), with μ_{pm} , μ_{peom} , and μ_{sham} now representing the rate of growth (slopes) in total GA area in the PM, PEOM and the pooled sham arms, respectively.

Reviewer's remark: The studies anticipated four unmasked reviews of safety data by the data safety monitoring committee (DSMC). Because some of the safety outcomes are also related to efficacy, the DOP recommended an alpha adjustment of 0.0001 for each of the 4 independent data monitoring committee unmasked data reviews that occurred before the primary analysis. Therefore, hypothesis testing in each study was performed at a 2-sided $\alpha=0.0496$ (0.05-0004). The studies planned to use the testing procedure provided in Figure 2.

❑ Sample Size

In both studies, a total of approximately 600 subjects were to be randomized in a 2:2:1:1 ratio to receive treatment with PM, PEOM, SM, or SEOM, respectively. This sample size assumed an annual growth rate in GA lesion area of 1.47, 1.70 and 2.13 mm²/year for PM, PEOM and Sham-Pooled groups, respectively. These values were estimated from the results of a Phase 2 trial of pegcetacoplan. Based on the same Phase 2 trial data, a standard deviation (common for all arms) of the lesion growth was assumed to be 1.50 mm².

3.2.2.2 Analysis Populations

The studies defined the following analysis populations:

- The intent-to-treat (ITT): The ITT set includes all randomized subjects. Subjects were to be analyzed in the treatment arm assigned at randomization with the 2 sham treatment arms being combined into a single ‘control’ group.
- The modified ITT (mITT): The mITT set includes all randomized subjects who receive at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline value of GA lesion in the study eye as assessed by FAF. The primary efficacy analysis is conducted based on the mITT population.
- The per-protocol (PP): The PP set includes all ITT subjects who follow the protocol without any major deviation(s) that could impact the integrity of the data.

Reviewer’s remark: The analysis based on the mITT population excluded randomized and treated subjects from each arm. Upon request by the statistical reviewer, the Applicant conducted a sensitivity analysis incorporating the subjects excluded from the mITT population. The result of this analysis provided numerically favorable results for the active treatment.

3.2.2.3 Analysis Methods

A. Primary Analyses

☐ Analysis of the Protocol Defined Primary Efficacy Endpoint

Per the Applicant, the primary scientific research question of interest in the two studies was to assess the effect of pegcetacoplan compared with that of sham at Month 12 regarding the impact on GA lesion progression under real-life conditions following the ITT principle. The Applicant provided the following attributes of the primary estimand:

- Population: GA subjects defined through inclusion and exclusion criteria in the mITT population.
- Treatment conditions: The treatment regimen of interest in this study is PM, PEOM, and Sham.
- Variable (or endpoint): Change in total area of GA lesions in the study eye from baseline measured by FAF to Month 12.
- The intercurrent events listed below were to be handled with a treatment policy strategy whereby any measured value would be used as is.

○ Treatment discontinuation

- Lost to follow up
- Withdrawal from the study
- Missing data resulting from these intercurrent events were handled implicitly within a mixed effects model for repeated measures (MMRM) analysis that assumes missing at random (MAR).

The proposed MMRM model included treatment (PM, PEOM, sham), presence of CNV in the fellow eye at baseline (Yes, No) and baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) as fixed effects, time (study month, categorical) as a factor, the time $\times$ treatment interaction term, and the baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) $\times$ time interaction term. A common unstructured covariance matrix was used to model the within-subject errors. From the model, the least square (LS) mean change from baseline to Month 12 was estimated for each of 3 groups as well as the comparisons of each treatment group against each other.

☐ Analysis of the DOP's Preferred Primary Efficacy Endpoint (Slope)

The analysis of mean rate of GA growth (slope) was conducted using a linear mixed effects model assuming time as continuous and linear ("slope model"). The response variable is the GA lesion area. The model included treatment (PM, PEOM, sham), presence of choroidal neovascularization in the fellow eye at baseline (Yes, No), baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) as fixed effects, time (study month, continuous assuming linearity), the time $\times$ treatment interaction term as well as the baseline GA lesion area $\times$ time interaction term.

A common unstructured covariance matrix was used to model the within-subject errors, the sandwich estimator was used to estimate the standard errors of the fixed effects parameters, and the degrees of freedom was partitioned into between-subject and within-subject portions. From the model, the mean rate of change (slope), standard error, and the estimated difference in slopes among the treatment groups along with the 2-sided 95.1% CIs are reported.

To allow for slope of lesion growth to differ between the different periods for each of the treatment groups, a second analysis using a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model") was used. This analysis was conducted similar to the "slope model" except that a knot (s) was added at 6-month intervals. For example, for the analysis with all data up to Month 24, knots were added at Month 6, 12, and 18.

B. Sensitivity and Supplemental Analyses

☐ Sensitivity Analysis for Missing Data

The Applicant conducted a control-based multiple imputation, and a tipping point analyses of the protocol defined primary as well as the DOP's primary efficacy endpoints. For both analyses, intermittent missing data were first imputed using Markov chain Monte Carlo (MCMC) approach to create a monotone missing data pattern. Multiple imputation was then carried out on the resultant monotone missing data as described below:

- Control-Based Imputation

In this analysis, for the active treatment arms, missing data due to reasons that are potentially related to study drug or lack of efficacy were imputed based on observed data from the pooled sham arm. Subjects who discontinued treatment or study due to reasons that are potentially related to study drug or lack of efficacy include:

- Subjects who discontinued due to ocular adverse event, adverse event related to treatment, or adverse event related to injection procedure.
- Subjects who withdrew consent due to lack of efficacy (specify field includes 'Lack of efficacy') or not otherwise specified as not related to efficacy (specified field includes "Not specified").

For the active treatment arms, missing data due to reasons that are not related to study drug or lack of efficacy were imputed based on the observed data from their respective arm. All missing data in the pooled sham arm were imputed based on the observed values in the pooled sham arm.

- Tipping Point Analysis (Delta-adjusted Approach)

In this approach, missing data after the last assessment were explicitly imputed by multiple imputation assuming missing not at random (MNAR). For this analysis, first missing data in each arm was multiply imputed using observed data from each respective randomized arm. Then, for the active treatments, a shift parameter was added to the imputed values. The shift parameters were allocated to the missing data point(s) proportionally across timepoints. For example, for a shift parameter of 0.48 mm² at Month 12, incremental shifts of 0.08 mm² would apply to Month 2, Month 4, ... and Month 12, respectively [0.08 mm² x 6 visits = 0.48 mm²]. The range of the shift parameters will be from 0.06 mm² to 0.72 mm² by increments of 0.06 mm² for Month 12 and 0.09 mm² to 1.08 mm² by increments of 0.09 for Month 18.

- Supplemental Analysis

- Post-hoc Analysis Adjusting for Baseline Characteristic

Per the Applicant, although randomization is intended to balance risk factors among treatment groups on average, chance imbalances may sometimes occur for any study, introducing random biases to the treatment effect estimate. To account for any major chance imbalances observed across treatment groups within each study, and to evaluate the impact of these imbalances on the treatment effect, the Applicant conducted post-hoc analyses adjusting for selected baseline characteristics. In this analysis, the Applicant first selected geographic region and 7 baseline disease characteristics for which they state is evidence of association with GA progression:

- study eye focality (multifocal/unifocal)

- study eye lesion location (subfoveal/nonsubfoveal)
- study eye lesion size (continuous)
- study eye pseudodrusen (present/absent)
- study eye low-luminance deficit (continuous)
- GA laterality (bilateral/study eye only)
- study eye number of intermediate/large drusen (>20/≤20)
- region (US/Latin America/ex-ROW)

To determine if there is imbalance across the three treatment arms with respect to these baseline characteristics, the three treatment arms within each study were compared using a chi-square test. Imbalance is assumed to have happened if the p-value associated with the treatment comparison with respect to a given characteristics is <0.2. With this approach, GA lesion focality (multifocal or unifocal) and number of intermediate/large drusen (>20/≤20 category) were identified to have major imbalances in study APL2-303. Similarly, in Study APL2-304, GA lesion location (with subfoveal involvement or without subfoveal involvement) was identified to have major imbalances between treatment groups. For the Phase 2 study (see Appendix for summary of this study), low-luminance deficit and intermediate/large drusen (>20/≤20 category) were identified to have major imbalances.

To estimate the treatment effects adjusted for the selected baseline characteristics with major imbalance, all identified baseline characteristics with major imbalance across the 3 studies [Studies APL2-304, APL2-303, and POT-CP121614 (See Appendix)] as well as the interaction terms between each baseline characteristic with major imbalance and the analysis visit were added to the primary analysis model (MMRM) for each study.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

The studies had three database locks. The first one, referred to as primary database lock, occurred after all subjects completed the Month 12 evaluation or exited the study early. The second database lock occurred after all subjects completed the 18 Month evaluation or exited the study early. The final database lock occurred after all subjects have completed the Month 24 evaluation or exited the study early. The patient disposition at the Month 12 and 18 database locks are included in the original biometric review. The patient dispositions following the final database lock at Month 24 are summarized in this section.

As can be seen from Table 4 and Table 5, in both studies, the proportion of subjects who discontinued the study and/or treatment is slightly higher in the two dosing frequencies of pegcetacoplan compared to the sham arm. The main reason for study discontinuation was withdrawal by the patient followed by adverse event. Subjects withdrew consent mainly due to reasons such as subjects' poor general health, study burden, and personal reasons. In both studies, a numerically higher number of subjects in the two pegcetacoplan arms died. In addition, overall, more subjects in the two pegcetacoplan arms discontinued the study due to adverse events.

Table 4: Patient Disposition (Month 24: APL2-303: ITT)

	PM (N=206)	PEOM (N=208)	SM (N=102)	SEOM (N=105)	Sham pooled (N = 207)
Randomized, n	206	208	102	105	207
Completed treatment through month 24, n (%)	146 (70.9)	163 (78.4)	79 (77.5)	84 (80.0)	163 (78.7)
Continued in the study to month 24 after treatment discontinuation, n (%)	3 (1.5)	1 (0.5)	0	0	0
Completed study through month 24, n (%)	147 (71.4)	161 (77.4)	78 (76.5)	83 (79.0)	161 (77.8)
Discontinued from treatment through month 24, n (%)	60 (29.1)	45 (21.6)	23 (22.5)	20 (19.0)	43 (20.8)
Adverse event	11 (5.3)	7 (3.4)	6 (5.9)	2 (1.9)	8 (3.9)
Lost to follow-up	2 (1.0)	4 (1.9)	3 (2.9)	0	3 (1.4)
Noncompliance with study drug	0	0	0	0	0
Physician's decision	2 (1.0)	0	2 (2.0)	0	2 (1.0)
Protocol violation	0	0	0	0	0
Consent withdrawal	34 (16.5)	18 (8.7)	6 (5.9)	12 (11.4)	18 (8.7)
Pregnancy	0	0	0	0	0
Death	7 (3.4)	5 (2.4)	3 (2.9)	3 (2.9)	6 (2.9)
Because of COVID-19 impact ²	4 (1.9)	10 (4.8)	3 (2.9)	3 (2.9)	6 (2.9)
Other	0	1 (0.5)	0	0	0
Discontinued from study through month 24, n (%)	59 (28.6)	47 (22.6)	24 (23.5)	22 (21.0)	46 (22.2)
Adverse event	9 (4.4)	6 (2.9)	5 (4.9)	3 (2.9)	8 (3.9)
Lost to follow-up	2 (1.0)	4 (1.9)	4 (3.9)	0	4 (1.9)
Noncompliance with study drug	0	0	0	0	0
Physician's decision	1 (0.5)	0	2 (2.0)	0	2 (1.0)
Protocol violation	0	0	0	0	0
Consent withdrawal	36 (17.5)	20 (9.6)	6 (5.9)	13 (12.4)	19 (9.2)
Pregnancy	0	0	0	0	0
Death	7 (3.4)	6 (2.9)	4 (3.9)	4 (2.9)	7 (3.4)
Due to COVID-19 impact ²	4 (1.9)	10 (4.8)	3 (2.9)	3 (2.9)	6 (2.9)
Other	0	1 (0.5)	0	0	0

Source: Table 14 of the Applicant's study report for Month 24. ¹Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study before Month 12. ²Any discontinuation due to COVID impact except for Adverse Event of COVID. Instances of Adverse Event of COVID are captured under the Adverse Event category.

Table 5: Patient Disposition (Month 24: APL2-304: ITT)

	PM (N=213)	PEOM (N=212)	SM (N=106)	SEOM (N=106)	Sham pooled (N = 212)
Randomized, n	213	212	106	106	212
Completed treatment through month 24, n (%)	147 (69.0)	167 (78.8)	76 (71.7)	83 (78.3)	159 (75.0)
Discontinued from treatment prior to month 24, n (%)	65 (30.5)	45 (21.2)	30 (28.3)	23 (21.7)	53 (25.0)
Continued in the study to month 24 after treatment discontinuation ^a , n (%)	2 (0.9)	4 (1.9)	0	0	0
Not treated, n (%)	1 (0.5)	0	0	0	0
Adverse event	12 (5.6)	10 (4.7)	4 (3.8)	3 (2.8)	7 (3.3)
Lost to follow-up	3 (1.4)	5 (2.4)	3 (2.8)	2 (1.9)	5 (2.4)
Noncompliance with study drug	0	0	0	0	0
Physician's decision	0	1 (0.5)	0	1 (0.9)	1 (0.5)
Protocol violation	0	0	0	0	0
Consent withdrawal	24 (11.3)	16 (7.5)	12 (11.3)	8 (7.5)	20 (9.4)
Pregnancy	0	0	0	0	0

Death	17 (8.0)	9 (4.2)	6 (5.7)	1 (0.9)	7 (3.3)
Because of COVID impact ^b	9 (4.2)	4 (1.9)	5 (4.7)	8 (7.5)	13 (6.1)
Other	0	0	0	0	0
Completed study through month 24, n (%)	144 (67.6)	169 (79.7)	76 (71.7)	82 (77.4)	158 (74.5)
Discontinued from study prior to month 24, n (%)	69 (32.4)	43 (20.3)	30 (28.3)	24 (22.6)	54 (25.5)
Adverse event	11 (5.2)	8 (3.8)	3 (2.8)	3 (2.8)	6 (2.8)
Lost to follow-up	4 (1.9)	5 (2.4)	3 (2.8)	2 (1.9)	5 (2.4)
Noncompliance with study drug	0	0	0	0	0
Physician's decision	0	1 (0.5)	0	1 (0.9)	1 (0.5)
Protocol violation	0	0	0	0	0
Consent withdrawal	25 (11.7)	16 (7.5)	12 (11.3)	9 (8.5)	21 (9.9)
Pregnancy	0	0	0	0	0
Death	20 (9.4)	9 (4.2)	7 (6.6)	1 (0.9)	8 (3.8)
Because of COVID impact ^b	9 (4.2)	4 (1.9)	5 (4.7)	8 (7.5)	13 (6.1)
Other	0	0	0	0	0

Source: Table 14 of the Applicant's study report for Month 24. ¹Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study before Month 12. ²Any discontinuation due to COVID impact except for Adverse Event of COVID. Instances of Adverse Event of COVID are captured under the Adverse Event category.

Also note, in both studies, in addition to subject dropout, the extent of intermittent missing GA data (subjects with missing efficacy data without completely discontinuing the study) is notable (Table 6 and Table 7). The Applicant stated that the main reason for the missed intermittent GA data was due to subjects missing study visits because of the disruption caused by the COVID-19 pandemic.

- In Study APL2-303, over 22% of subjects randomized to the two pegcetacoplan arms (25.4% in the PM arm and 18.9% in the PEOM arm) had missing GA data at Month 12. This figure increased to 24% at Month 18 (26.4% in the PM arm and 22.4% in PEOM arm) and to 27% (30.8% in the PM arm and 23.4% in PEOM arm) at Month 24. A slightly different pattern is observed in the sham arm. At Month 12, 24.1% of subjects in two sham arms (32.0% in SM arm and 16.3% in the SEOM) had missing GA data; and this has decreased to 22% by Month 18 (24.7% in SM and 19.4% in SEOM). At Month 24, 23.7% subjects in the SM arm and 18.4% in the SEOM arm had missing GA data.
- In Study APL2-304, over 20% of subjects randomized to the two pegcetacoplan arms (21.5% in the PM arm and 19.5% in the PEOM arm) compared to 17% of subjects in two sham arms (21.9% in SM arm and 12.7% in the SEOM) had missing GA data at Month 12. At Month 18, missing data has increased to 24% in the two pegcetacoplan arms [PM (26.7%) and PEOM (21.5%)] and to 25% in the two sham arms [SM (29.5%) and SEOM (20.6%)]. At Month 24, 33.7%, 21.0%, 27.6% and 24.2% subjects in the PM, PEOM, SM and SEOM arms, respectively, had missing GA data.

Reviewer's remark: Per the Applicant, during the COVID-19 pandemic, although sites were encouraged to follow the full schedule of assessments (based on their treatment group assignment), a minimized schedule of assessment was implemented to reduce the pandemic exposure risk of subjects enrolled in the studies. This might partly explain the high rate of intermittent missing data. Note, in Study APL2-303, the first subject was enrolled (dosed) on

09/20/2018 and the last subject completed the Month 18 visit on 12/12/2021. Similarly, in Study APL2-304, the first subject was enrolled on 09/10/2018 and the last subject completed the Month 18 visit on 02/07/2022. These timeframes, especially for Study APL2-303, appear to coincide with the height of the COVID pandemic.

Table 6: Summary of GA Outcome Observed and Missing: APL2-303

Visit	GA Data in the Study Eye	Pegcetacoplan		Sham		
		PM (N=201)	PEOM (N=201)	SM (N=97)	SEOM (N=98)	Pooled Sham (N=195)
		N (%)	N (%)	N (%)	N (%)	N (%)
Baseline	Available	201 (100.0)	201 (100.0)	97 (100.0)	98 (100.0)	195 (100.0)
	Missing	0	0	0	0	0
Month 2	Available	151 (75.1)	166 (82.6)	76 (78.4)	81 (82.7)	157 (80.5)
	Missing	50 (24.9)	35 (17.4)	21 (21.6)	17 (17.3)	38 (19.5)
Month 4	Available	167 (83.1)	159 (79.1)	78 (80.4)	75 (76.5)	153 (78.5)
	Missing	34 (16.9)	42 (20.9)	19 (19.6)	23 (23.5)	42 (21.5)
Month 6	Available	165 (82.1)	180 (89.6)	80 (82.5)	83 (84.7)	163 (83.6)
	Missing	36 (17.9)	21 (10.4)	17 (17.5)	15 (15.3)	32 (16.4)
Month 8	Available	155 (77.1)	155 (77.1)	70 (72.2)	81 (82.7)	151 (77.4)
	Missing	46 (22.9)	46 (22.9)	27 (27.8)	17 (17.3)	44 (22.6)
Month 10	Available	149 (74.1)	153 (76.1)	65 (67.0)	73 (74.5)	138 (70.8)
	Missing	52 (25.9)	48 (23.9)	32 (33.0)	25 (25.5)	57 (29.2)
Month 12	Available	150 (74.6)	163 (81.1)	66 (68.0)	82 (83.7)	148 (75.9)
	Missing	51 (25.4)	38 (18.9)	31 (32.0)	16 (16.3)	47 (24.1)
Month 14	Available	140 (69.7)	145 (72.1)	64 (66.0)	72 (73.5)	136 (69.7)
	Missing	61 (30.3)	56 (27.9)	33 (34.0)	26 (26.5)	59 (30.3)
Month 16	Available	142 (70.6)	149 (74.1)	66 (68.0)	78 (79.6)	144 (73.8)
	Missing	59 (29.4)	52 (25.9)	31 (32.0)	20 (20.4)	51 (26.2)
Month 18	Available	148 (73.6)	156 (77.6)	73 (75.3)	79 (80.6)	152 (77.9)
	Missing	53 (26.4)	45 (22.4)	24 (24.7)	19 (19.4)	43 (22.1)
Month 20	Available	133 (66.2)	147 (73.1)	71 (73.2)	81 (82.6)	152 (77.9)
	Missing	68 (33.8)	54 (26.9)	26 (26.8)	17 (17.4)	43 (22.1)
Month 22	Available	129 (64.2)	150 (74.6)	70 (72.2)	77 (78.6)	147 (75.4)
	Missing	72 (35.8)	51 (25.4)	27 (27.8)	21 (21.4)	48 (24.6)
Month 24	Available	139 (69.1)	154 (76.6)	74 (76.3)	80 (81.6)	154 (79.0)
	Missing	62 (30.8)	47 (23.4)	23 (23.7)	18 (18.4)	41 (21.0)

Source: Table 14.2.1.1.1.2 of the Applicant's response to information request (IR) submitted on July 21, 2022. Summaries for Months 20, 22 and 24 are provided by the reviewer.

Table 7: Summary of GA Outcome Observed and Missing: APL2-304

Visit	GA Data in the Study Eye	Pegcetacoplan		Sham		
		PM (N=202)	PEOM (N=205)	SM (N=105)	SEOM (N=102)	Pooled Sham (N=207)
		N (%)	N (%)	N (%)	N (%)	N (%)
Baseline	Available	202 (100.0)	205 (100.0)	105 (100.0)	102 (100.0)	207 (100.0)
	Missing	0	0	0	0	0
Month 2	Available	173 (85.6)	176 (85.9)	83 (79.0)	91 (89.2)	174 (84.1)
	Missing	29 (14.4)	29 (14.1)	22 (21.0)	11 (10.8)	33 (15.9)
Month 4	Available	166 (82.2)	171 (83.4)	83 (79.0)	89 (87.3)	172 (83.1)
	Missing	36 (17.8)	34 (16.6)	22 (21.0)	13 (12.7)	35 (16.9)
Month 6	Available	166 (82.2)	176 (85.9)	88 (83.8)	89 (87.3)	177 (85.5)
	Missing	36 (17.8)	29 (14.1)	17 (16.2)	13 (12.7)	30 (14.5)
Month 8	Available	149 (73.8)	170 (82.9)	75 (71.4)	82 (80.4)	157 (75.8)
	Missing	53 (26.2)	35 (17.1)	30 (28.6)	20 (19.6)	50 (24.2)
Month 10	Available	135 (66.8)	160 (78.0)	66 (62.9)	70 (68.6)	136 (65.7)
	Missing	67 (33.2)	45 (22.0)	39 (37.1)	32 (31.4)	71 (34.3)
Month 12	Available	159 (78.7)	165 (80.5)	82 (78.1)	89 (87.3)	171 (82.6)

Month 14	Missing	43 (21.3)	40 (19.5)	23 (21.9)	13 (12.7)	36 (17.4)
	Available	132 (65.3)	156 (76.1)	70 (66.7)	82 (80.4)	152 (73.4)
Month 16	Missing	70 (34.7)	49 (23.9)	35 (33.3)	20 (19.6)	55 (26.6)
	Available	133 (65.8)	157 (76.6)	70 (66.7)	81 (79.4)	151 (72.9)
Month 18	Missing	69 (34.2)	48 (23.4)	35 (33.3)	21 (20.6)	56 (27.1)
	Available	148 (73.3)	161 (78.5)	74 (70.5)	81 (79.4)	155 (74.9)
Month 20	Missing	54 (26.7)	44 (21.5)	31 (29.5)	21 (20.6)	52 (25.1)
	Available	125 (61.9)	158 (77.1)	69 (65.7)	80 (78.4)	149 (71.9)
Month 22	Missing	77 (38.1)	47 (22.9)	36 (34.3)	22 (21.6)	58 (28.1)
	Available	124 (61.4)	154 (75.1)	64 (61.0)	73 (71.6)	137 (66.2)
Month 24	Missing	78 (38.6)	51 (24.9)	41 (39.0)	29 (28.4)	70 (33.8)
	Available	134 (66.3)	162 (79.0)	76 (72.4)	81 (79.4)	157 (75.8)
	Missing	68 (33.7)	43 (21.0)	29 (27.6)	21 (20.6)	50 (24.2)

Source: Table 14.2.1.1.1.2 of the Applicant's response to information request (IR) submitted on July 21, 2022. Summaries for Months 20, 22 and 24 are provided by the reviewer.

3.2.3.2 Demographic and Baseline Characteristics

Within each study, there were no significant baseline imbalances between the three arms in the demographics of age, gender, or race (Table 8). In all arms, there were more female participants than male participants, and most of the study participants were White and over 65 years of age (over 20% of subjects in both studies were over the age of 85 years). Black and Asian subjects appear to be severely under-represented, comprising of $\leq 1.5\%$ of the ITT subjects in both studies.

Table 8: Baseline and Demographic Characteristics (mITT)

	Study APL2-303			Study APL2-304		
	PM N=201	PEOM N= 200	Sham pooled N=194	PM N=202	PEOM N=205	Sham pooled N=206
Age, years						
n	201	200	194	202	205	206
Mean (SD)	78.7 (6.91)	79.2 (7.07)	78.6 (7.29)	78.8 (7.24)	78.1 (7.74)	78.6 (7.26)
Min, Max	60, 93	61, 93	61, 96	61, 95	60, 100	60, 93
Age group, n (%)						
<65 years	5 (2.5)	6 (3.0)	8 (4.1)	5 (2.5)	9 (4.4)	9 (4.4)
≥65-<75 years	46 (22.9)	51 (25.5)	49 (25.3)	52 (25.7)	50 (24.4)	45 (21.8)
≥75- <86 years	110 (54.7)	95 (47.5)	90 (46.4)	97 (48.0)	99 (48.3)	109 (52.9)
≥85 years	40 (19.9)	48 (24.0)	47 (24.2)	48 (23.8)	47 (22.9)	43 (20.9)
Sex						
Female, n (%)	118 (58.7)	120 (60.0)	122 (62.9)	125 (61.9)	117 (57.1)	133 (64.6)
Male, n (%)	83 (41.3)	80 (40.0)	72 (37.1)	77 (38.1)	88 (42.9)	73 (35.4)
Country						
US, n (%)	142 (70.6)	122 (61.0)	122 (62.9)	147 (72.8)	142 (69.3)	147 (71.4)
Rest of world, n (%)	59 (29.4)	78 (39.0)	72 (37.1)	55 (27.2)	63 (30.7)	59 (28.6)
Race						
White	187	185	187	185	189	187

	(93.0)	(92.5)	(96.4)	(91.6)	(92.2)	(90.8)
Not reported	12 (6.0)	10 (5.0)	6 (3.1)	12 (5.9)	12 (5.9)	14 (6.8)
Asian	0	1 (0.5)	0	3 (1.5)	1 (0.5)	2 (1.0)
Unknown	0	1 (0.5)	0	0	1 (0.5)	3 (1.5)
Black or African American	1 (0.5)	1 (0.5)	0	2 (1.0)	0	0
Missing	1 (0.5)	1 (0.5)	1 (0.5)	0	2 (1.0)	0
American Indian or Alaska Native	0	0	0	0	0	0
Multiple	0	1 (0.5)	0	0	2 (1.0)	0
Study eye lesion size, mm ²						
n	201	200	194	202	205	206
Mean (SD)	8.3666 (4.184)	8.2198 (3.8779)	8.2617 (4.2600)	8.1779 (3.895)	8.2962 (3.904)	8.2048 (3.721)
Minimum, maximum	2.264, 17.832	2.439, 17.151	2.599, 17.490	2.489, 18.111	2.652, 17.706	2.587, 17.771
Study eye GA lesion location						
Subfoveal involvement, n (%)	129 (64.2)	119 (59.5)	121 (62.4)	116 (57.4)	131 (63.9)	146 (70.9)
Without subfoveal involvement, n (%)	72 (35.8)	81 (40.5)	73 (37.6)	86 (42.6)	74 (36.1)	60 (29.1)
Study eye GA focality (FAF)						
Unifocal, n (%)	54 (26.9)	53 (26.5)	66 (34.0)	59 (29.2)	62 (30.2)	68 (33.0)
Multifocal, n (%)	147 (73.1)	147 (73.5)	128 (66.0)	143 (70.8)	143 (69.8)	138 (67.0)
Study eye NL-BCVA score, ETDRS letters						
n	201	200	194	202	205	206
Mean (SD)	59.5 (17.40)	58.9 (15.97)	59.1 (16.85)	61.0 (15.30)	58.2 (17.03)	57.5 (16.57)
Minimum, maximum	24, 94	24, 93	23, 89	25, 86	24, 89	24, 87
Study eye LL-BCVA score, ETDRS letters						
n	200	199	191	202	205	206
Mean (SD)	32.1 (17.73)	33.0 (16.03)	33.7 (16.75)	34.0 (17.43)	32.3 (16.43)	32.7 (16.19)
Minimum, maximum	0, 73	0, 78	0, 73	0, 76	0, 72	0, 72
Study eye LLD, ETDRS letters						
n	200	199	191	202	205	206
Mean (SD)	27.5 (17.79)	25.9 (16.56)	25.6 (16.52)	26.9 (16.92)	25.9 (17.80)	24.9 (17.43)
Min, Max	-7, 77	-4, 73	-4, 71	-4, 66	-10, 76	-12, 71
Study eye number of intermediate or large drusen						
≤20, n (%)	123 (61.2)	122 (61.0)	96 (49.5)	108 (53.5)	101 (49.3)	102 (49.5)
>20, n (%)	78 (38.8)	78 (39.0)	98 (50.5)	93 (46.0)	104 (50.7)	103 (50.0)
GA laterality, n (%)						
Bilateral GA	164 (81.6)	160 (80.0)	149 (76.8)	167 (82.7)	174 (84.9)	165 (80.1)
Study eye GA only	37 (18.4)	40 (20.0)	45 (23.2)	35 (17.3)	31 (15.1)	41 (19.9)
Fellow eye lesion size, mm ²						
n	164	160	149	167	174	165
Mean (SD)	8.3053 (5.8533)	8.7382 (5.8234)	8.1401 (6.2022)	7.9042 (5.4671)	8.3894 (5.5955)	8.5792 (5.4305)
Minimum, maximum	0.213, 26.416	0.195, 35.857	0.172, 28.487	0.121, 25.227	0.040, 28.057	0.138, 26.026
NV in the fellow eye						
Present, n (%)	39	41	36	43	37	43

	(19.4)	(20.5)	(18.6)	(21.3)	(18.0)	(20.9)
Absent, n (%)	162 (80.6)	159 (79.5)	158 (81.4)	159 (78.7)	168 (82.0)	163 (79.1)

Source: Adapted from Table 14 and 15 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Australia, Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

A. Primary Efficacy Analysis

- Analysis of Protocol Defined Primary Endpoint

Recall, that the protocol defined primary efficacy endpoint was the mean change from baseline in total GA area at Month 12; and evaluated in the mITT population for the primary analysis. The results are shown in Table 9. The treatment differences for this endpoint between each pegcetacoplan arm and the pooled sham are statistically significant in Study APL2-304 but not in Study APL2-303. Note, in both studies, the treatment differences for the mean change from baseline in total GA area at Month 18 and Month 24 between each pegcetacoplan arm and the pooled sham are nominally significant (Table 9).

Table 9: Mean Change from Baseline in Total GA Area (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
Study APL2-303					
Month 12: Mean (SE) [1]	1.733 (0.0792)	1.756 (0.0744)	1.964 (0.0959)	-0.2301 (-0.470, 0.010)	-0.2077 (-0.444, 0.029)
Month 18: Mean (SE) [2]	2.621 (0.1007)	2.633 (0.1032)	3.001 (0.1383)	-0.3800 (-0.713, -0.046)	-0.3677 (-0.706, -0.029)
Month 24: Mean (SE) [3]	3.227 (0.1245)	3.339 (0.1303)	3.972 (0.1682)	-0.7451 (-1.153, -0.336)	-0.633 (-1.050, -0.215)
Study APL2-304					
Month 12: Mean (SE) [1]	1.557 (0.0834)	1.650 (0.0811)	1.968 (0.0822)	-0.4113 (-0.639, -0.183)	-0.3181 (-0.542, -0.093)
Month 18: Mean (SE) [2]	2.351 (0.1069)	2.516 (0.1088)	3.009 (0.1153)	-0.657 (-0.965, -0.350)	-0.492 (-0.802, -0.183)
Month 24: Mean (SE) [3]	3.123 (0.1432)	3.282 (0.1323)	4.025 (0.1464)	-0.901 (-1.302, -0.500)	-0.742 (-1.128, -0.357)

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

Source: [2] Table 24 of the Applicant's original study reports

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

- ❑ Analysis of DOP's Preferred Primary Endpoint

The results of the analysis of this endpoint based on data collected through Month 12 mirrored the results observed for the protocol defined primary efficacy endpoint such that differences between each of the two dosing frequencies of pegcetacoplan against pooled sham in annual growth rates were nominally significant in Study APL2-304 but not in Study APL2-303 (Table 10). However, when a similar analysis is conducted based on data collected through Month 18, and through Month 24, the treatment differences in slope between each dosing frequency of pegcetacoplan and the pooled sham are nominally significant in favor of the two dosing frequencies in both studies (Table 10). The results of the piecewise regression provided similar conclusions as the linear model (Table 50--Table 53).

Table 10: Mean Rate of GA Growth (Slope; mITT)

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

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

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

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

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

B. Sensitivity and Supplemental Analyses

□ Sensitivity Analysis for Missing Data

Recall, the analyses of the protocol defined as well as the DOP's preferred primary efficacy endpoints were conducted assuming missing data due to any reason were missing at random (MAR). To evaluate the impact of deviation from this assumption, the Applicant conducted sensitivity analyses using a control-based imputation and a tipping point analysis. In addition, this reviewer conducted the analysis of the DOP's preferred primary efficacy endpoint employing a combination of multiple imputation and trimmed mean approaches. The results from these analyses are generally consistent with the results of the primary analyses (Table 11--Table 16).

Table 11: Sensitivity Analyses of Mean Change from Baseline in GA Area at Month 12 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL-303				
Control-based [1]	1.7342 (0.0810)	1.7526 (0.0757)	1.9689 (0.0971)	−0.2347 (−0.4795, 0.0101)	−0.2163 (−0.4560, 0.0234)
Control-based [2]	1.7440 (0.0816)	1.7600 (0.0769)	1.9690 (0.0970)	−0.2250 (−0.4690, 0.0200)	−0.2090 (−0.4490, 0.0300)
	Study APL2-304				
Control-based [1]	1.5592 (0.0835)	1.6536 (0.0812)	1.9673 (0.0826)	−0.4081 (−0.6365, −0.1797)	−0.3137 (−0.5379, −0.0895)
Control-based [2]	1.5790 (0.0831)	1.6660 (0.0814)	1.9660 (0.0824)	−0.3870 (−0.6140, −0.1600)	−0.3010 (−0.5250, −0.0770)

[1] Source: Table 14.2.1.2.1 of the study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.5.9 of the Applicant's study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

Table 12: Sensitivity Analyses of Mean Change from Baseline in GA Area at Month 24 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Control-based [1]	3.3450 (0.1322)	3.4020 (0.1346)	3.9770 (0.1676)	-0.6330 (-1.0470, -0.2180)	-0.5760 (-0.9960, -0.1550)
Control-based [2]	3.3520 (0.1320)	3.4060 (0.1362)	3.9760 (0.1677)	-0.6240 (-1.0380, -0.2100)	-0.5690 (-0.9900, -0.1490)
Study APL2-304					
Control-based [1]	3.2180 (0.1470)	3.3470 (0.1369)	4.0120 (0.1474)	-0.7940 (-1.1980, -0.3890)	-0.6650 (-1.0560, -0.2740)
Control-based [2]	3.2310 (0.1475)	3.3490 (0.1370)	4.0130 (0.1480)	-0.7820 (-1.1870, -0.3760)	-0.6640 (-1.0550, -0.2720)

[1] Source: Table 14.5.9.1.1 of the Applicant's Month 24 study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.5.9.1.2 of the Applicant's Month 24 study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

Table 13: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 12 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Control-based [1]	1.7597 (0.0775)	1.7457 (0.0761)	1.9658 (0.0925)	-0.2060 (-0.4420, 0.0300)	-0.2201 (-0.4551, 0.0149)
Control-based [2]	1.7684 (0.0771)	1.7540 (0.0753)	1.9736 (0.0923)	-0.2052 (-0.4391, 0.0287)	-0.2196 (-0.4530, 0.0138)
Control-based [3]	1.7841 (0.0802)	1.7689 (0.0771)	1.9654 (0.0916)	-0.1813 (-0.4191, 0.0565)	-0.1965 (-0.4304, 0.0375)
Trimmed Mean +MI [4-1]	1.7579 (0.0770)	1.7487 (0.0744)	1.9831 (0.0908)	-0.2251 (-0.4592, 0.0088)	-0.2344 (-0.4649, -0.00397)
Trimmed Mean +MI [4-2]	1.7547 (0.0768)	1.7482 (0.0742)	1.9720 (0.0905)	-0.2173 (-0.4506, 0.0159)	-0.2237 (-0.4536, 0.00601)
Study APL2-304					
Control-based [1]	1.5665 (0.0813)	1.6542 (0.0765)	1.9622 (0.0798)	-0.3956 (-0.6185, -0.1727)	-0.3079 (-0.5254, -0.0905)
Control-based [2]	1.5833 (0.0805)	1.6684 (0.0772)	1.9668 (0.0797)	-0.3835 (-0.6056, -0.1614)	-0.2984 (-0.5153, -0.0816)
Control-based [3]	1.5948 (0.08054)	1.6776 (0.0773)	1.9601 (0.0797)	-0.3653 (-0.5863, -0.1443)	-0.2825 (-0.5020, -0.0630)
Trimmed Mean +MI [4-1]	1.5550 (0.0807)	1.6398 (0.0770)	1.9649 (0.0798)	-0.4098 (-0.6328, -0.1870)	-0.3251 (-0.5434, -0.1068)
Trimmed Mean +MI [4-2]	1.5654 (0.0807)	1.6522 (0.0768)	1.9668 (0.0794)	-0.4013 (-0.6238, -0.1790)	-0.3145 (-0.5322, -0.0968)

[1] Source: Table 14.2.1.2.5 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Missing data due to other reasons is

imputed using observed data within the patient's treatment arm. In both cases, intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.2.1.2.6 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Table 14.2.1.2.7 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-1] Source: Reviewer's analysis: Subjects with missing data due to adverse event and lack of efficacy are excluded (trimmed). Missing data due to reasons other than lack of efficacy and adverse event in all arms was imputed using a multiple imputation approach.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, adverse event or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

Table 14: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 18 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL-303				
Control-based [1]	2.6252 (0.1005)	2.5895 (0.1051)	2.9805 (0.1354)	-0.3552 (-0.6867, -0.0238)	-0.3910 (-0.7287, -0.0532)
Control-based [2]	2.6593 (0.1056)	2.6193 (0.1065)	2.9823 (0.1350)	-0.3230 (-0.6569, 0.0108)	-0.3630 (-0.6993, -0.0267)
Control-based [3]	2.6505 (0.1048)	2.6167 (0.1075)	2.9607 (0.1331)	-0.3102 (-0.6412, 0.0209)	-0.3440 (-0.6780, -0.0100)
Trimmed Mean +MI [4-1]	2.6383 (0.1015)	2.5774 (0.1046)	3.0116 (0.1343)	-0.3733 (-0.7043, -0.0424)	-0.4342 (-0.7666, -0.1018)
Trimmed Mean +MI [4-2]	2.6371 (0.1047)	2.5765 (0.1045)	3.0021 (0.1342)	-0.3650 (-0.7004, -0.0296)	-0.4255 (-0.7597, -0.0914)
Study APL2-304					
Control-based [1]	2.3336 (0.1100)	2.5101 (0.1075)	3.0232 (0.1147)	-0.6895 (-1.0037, -0.3753)	-0.5131 (-0.8209, -0.2053)
Control-based [2]	2.3966 (0.1079)	2.5418 (0.1069)	3.0399 (0.1138)	-0.6434 (-0.9474, -0.3394)	-0.4982 (-0.8014, -0.1949)
Control-based [3]	2.4103 (0.1096)	2.5517 (0.1076)	3.0323 (0.1145)	-0.6220 (-0.9285, -0.3155)	-0.4807 (-0.7877, -0.1736)
Trimmed Mean +MI [4-1]	2.3074 (0.1086)	2.4878 (0.1080)	3.0376 (0.1136)	-0.7302 (-1.0381, -0.4224)	-0.5499 (-0.8576, -0.2421)
Trimmed Mean +MI [4-2]	2.3179 (0.1064)	2.4815 (0.1078)	3.0353 (0.1125)	-0.7174 (-1.0213, -0.4136)	-0.5538 (-0.8599, -0.2478)

[1] Source: Table 14.2.1.2.5 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.2.1.2.6 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Table 14.2.1.2.7 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data, including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-1] Source: Reviewer's analysis: Subjects with missing data due to AE and lack of efficacy are excluded (trimmed). Missing data due to reasons other than lack of efficacy and adverse event in all arms was imputed using a multiple imputation approach.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, AE or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

Table 15: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 24 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL-303				
Control-based [1]	3.2718 (0.1305)	3.3480 (0.1328)	3.9634 (0.1618)	-0.6916 (-1.0994, -0.2837)	-0.6154 (-1.0265, -0.2042)
Control-based [2]	3.3708 (0.1311)	3.4086 (0.1383)	3.9534 (0.1624)	-0.5826 (-0.9864, -0.1787)	-0.5447 (-0.9615, -0.1279)
Control-based [3]	3.3758 (0.1325)	3.4237 (0.1379)	3.9544 (0.1601)	-0.5786 (-0.9851, -0.1721)	-0.5307 (-0.9415, -0.1205)
Trimmed Mean +MI [4-1]	3.2762 (0.1308)	3.3342 (0.1325)	3.9982 (0.1601)	0.7219 (-1.1262, -0.3177)	-0.6639 (-1.0747, -0.2533)
Trimmed Mean +MI [4-2]	3.2662 (0.1309)	3.3263 (0.1341)	3.9768 (0.1594)	-0.7106 (-1.1143, -0.3069)	-0.6504 (-1.0558, -0.2450)
Study APL2-304					
Control-based [1]	3.0476 (0.1388)	3.2496 (0.1335)	4.0233 (0.1471)	-0.9757 (-1.3735, -0.5779)	-0.7737 (-1.1629, -0.3845)
Control-based [2]	3.1743 (0.1386)	3.3023 (0.1337)	4.0308 (0.1456)	-0.8565 (-1.2500, -0.4629)	-0.7285 (-1.1143, -0.3427)
Control-based [3]	3.1812 (0.1389)	3.3006 (0.1339)	4.0271 (0.1442)	-0.8459 (-1.2360, -0.4558)	-0.7265 (-1.1122, -0.3409)
Trimmed Mean +MI [4-1]	3.0080 (0.1380)	3.2153 (0.1315)	4.0271 (0.1440)	-1.0188 (-1.4101, -0.6276)	-0.8117 (-1.1930, -0.4306)
Trimmed Mean +MI [4-2]	3.0274 (0.1384)	3.2205 (0.1325)	4.0385 (0.1425)	-1.0111 (-1.4003, -0.6219)	-0.8179 (-1.1986, -0.4374)

[1] Source: Table 14.5.9.2.1 of the Applicant's Month 24 study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.5.9.2.2 of the Applicant's Month 24 study reports: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Table 14.5.9.2.3 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data, including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-1] Source: Reviewer's analysis: Subjects with missing data due to AE and lack of efficacy are excluded (trimmed). Missing data due to reasons other than lack of efficacy and adverse event in all arms was imputed using a multiple imputation approach.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, AE or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

Reviewer's remark:

[1]: In the first control-based analysis, to create a monotone missing data pattern, intermittent missing data in both arms was first imputed using a multiple imputation approach based on observed data within each treatment arm. Then, a controlled-base imputation (using observed data from the pooled sham arm) is applied to impute the missing data in the active arm due to AE and lack of efficacy. Given that there is substantial intermittent missing data and that very few subjects had missing data due to AE and lack of efficacy, this analysis is expected to provide comparable results to the primary efficacy analysis which implicitly imputed missing data.

[2]: The second control-based analysis followed the same steps as the first approach except that all missing data, regardless of reason for missingness, is imputed using the observed data

from the pooled sham arm in the second step. However, here also, substantial intermittent missing data is imputed using observed data within each treatment arm.

[3]: In this analysis, all missing data in both arms regardless of the pattern (monotone or otherwise) is imputed using observed data from the pooled sham arm.

[4-1]: In this analysis, all observed data for subjects who discontinued the study due to AE or lack of efficacy in both arms were trimmed. Missing data due to all other reasons were multiply imputed using the observed data within each treatment arm.

[4-2]: As noted in the disposition table, most subjects discontinued the study because they withdrew consent. Although the majority did so for reasons that appear to be unrelated to treatment, 3 subjects in the PM group and 1 subject in the SM group withdrew consent because of concerns about treatment through Month 18. Thus, in this analysis, all observed data for subjects who discontinued the study due to AE, lack of efficacy or who withdrew consent in both arms were trimmed. Missing data due to all other reasons were multiply imputed using the observed data within each treatment arm.

❑ Tipping Point Analysis Results

A tipping point analysis was first conducted by applying a set of shifting parameters to imputed data for subjects in the pegcetacoplan arms who discontinued the study due to adverse events or lack of efficacy. However, because most subjects discontinued the studies due to withdrawal of consent, a second tipping point analysis, where imputed data for subjects who withdrew consent for reasons that are assumed to be related to the efficacy or safety of the drug or injection (in addition to those reported due to lack of efficacy or adverse event) were also shifted, is conducted.

Recall, the treatment difference in the mean change from baseline at Month 12 was not statistically significant in Study APL2-303. However, the treatment differences in the mean change from baseline at Month 18 and Month 24 and the rate of GA growth (Slope through Month 18 and Month 24) were all statistically significant in both studies. For the latter, the tipping point, the shift that led to the treatment difference to no longer be statistically significant, was not reached for either of the two pegcetacoplan arms in both studies (Table 28--Table 39).

❑ Analysis Without Pooling the Sham Arms

Although there was no notable difference between the two sham arms with respect to pre-treatment baseline and demographic characteristics, some differences, including differences in missed visits, missing GA data, study discontinuation rates (including discontinuation due to adverse events) and adverse event rates are observed. For example:

- The proportion of subjects who discontinued the study due to adverse events was 9.2% in SM and 4.8% in SEOM.

- In Study APL2-303, the proportion of subjects with missing GA data at Month 12 was 32% in SM and 16.3% in SEOM. The corresponding figures at Month 18 were 24.7% vs 19.4%. Similarly, in APL2-304, the rates were 21.9% vs 12.7% at Month 12 and 29.5% vs 20.6% at Month 18. At Month 24, 23.7% (SM) and 18.4% (SEOM) in Study APL2-303 and 27.6% (SM) and 20.6% (SEOM) in Study APL2-304, had missing GA data.
- The proportion of subjects who died during the 24-month study period was 5.3% in SM and 2.4% in SEOM.

In response to the reviewer's information request to provide possible explanation on the observed discrepancy between the two sham arms, the Applicant stated that although the two studies were double masked to treatment assignment, treatment frequency (monthly [SM] vs every-other month [SEOM]) was known to investigators and subjects since enrollment into the study.

Per the Applicant, during the COVID-19 pandemic, sites were encouraged to follow the full schedule of assessments (based on their treatment group assignment). However, to reduce the pandemic exposure risk of subjects enrolled in the studies, a minimized schedule of assessment was followed. This included a less frequent number of assessments that did not require subjects in the SEOM treatment group to be seen for visits with no injection procedure (e.g., Month 1, Month 3). Per the Applicant, it is possible that the differences observed between SM and SEOM arms in missing visits, missing GA data, adverse event rates, and study discontinuation rates were driven by prior knowledge of the injection procedure visit, as well as the minimized assessment schedules implemented in the SEOM arm during the COVID-19 pandemic, thus leading to better compliance. Conversely, the greater treatment burden in the SM arm may have led to relatively lower compliance.

To evaluate the impact on the efficacy results of the observed differences between the two sham arms, the analyses of the protocol defined, and the DOP's preferred endpoints has been conducted without pooling the sham arms. Per this analysis, there is a notable difference in GA growth rate between the two sham arms; the SM arm had a slower GA growth rate compared to the SEOM arm. Consequently, while the treatment differences between the PEOM and SEOM are nominally significant in both studies, the treatment differences between PM and SM arms were nominally significant in Study APL2-304 only. Detailed summaries of the results are provided below.

▪ Analysis of the Protocol Defined Endpoint

The Applicant conducted the analysis of the mean change from baseline at Months 12, 18 and 24 comparing each dosing frequency to the corresponding sham arm (PM vs. SM and PEOM vs SEOM). In Study APL2-303, while there was only a slight difference in the observed mean change from baseline at Months 12, 18 and 24 between PM and PEOM arms, there was noticeable difference between the two sham arms. The SEOM arm had higher mean change

from baseline (worse) than the corresponding figure in the SM arm. Consequently, the difference between PM and SM is not nominally significant.

However, the difference between PEOM and SEOM is nominally significant. Recall, the treatment differences between each of the two pegcetacoplan arms against the pooled sham arm were not statistically significant in this study. Similarly, in Study APL2-304, the SEOM arm had a higher mean change from baseline compared to the SM arm. However, in line with the pooled analysis, in Study APL2-304, there was a nominally significance difference between each of the two pegcetacoplan arms against the corresponding sham arm (Table 16).

Table 16: Mean Change from Baseline in Total GA Area: Without Pooling Sham (mITT)

Parameters	LS mean (SE)				Difference (95.1% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Study APL2-303						
Month 12 [1]: Mean Change (SE)	1.7345 (0.0792)	1.7570 (0.0744)	1.8547 (0.1339)	2.0632 (0.1358)	-0.1202 (-0.4213, 0.1809)	-0.3062 (-0.6105, -0.0020)
Month 18 [2]: Mean Change (SE)	2.6218 (0.1007)	2.6337 (0.1032)	2.7712 (0.1897)	3.2140 (0.1970)	-0.1494 (-0.5678, 0.2689)	-0.5803 (-1.0177, -0.1428)
Month 24 [2]: Mean Change (SE)	3.2285 (0.1245)	3.3399 (0.1302)	3.6251 (0.2226)	3.2140 (0.1970)	-0.3966 (-0.8944, 0.1013)	-0.9630 (-1.5101, -0.4159)
Study APL2-304						
Month 12 [1]: Mean Change (SE)	1.5575 (0.0834)	1.6509 (0.0811)	1.8523 (0.0954)	2.0806 (0.1308)	-0.2948 (-0.5422, -0.0473)	-0.4298 (-0.7291, -0.1304)
Month 18 [2]: Mean Change (SE)	2.3512 (0.1069)	2.5168 (0.1087)	2.8540 (0.1334)	3.1579 (0.1851)	-0.5028 (-0.8375, -0.1680)	-0.6411 (-1.0601, -0.2221)
Month 24 [2]: Mean Change (SE)	3.1237 (0.1432)	3.2830 (0.1323)	3.8631 (0.1782)	4.1813 (0.2298)	-0.7395 (-1.1864, -0.2925)	-0.8983 (-1.4168 to -0.3799)

[1]: Source: Table 31 of the Applicant's study reports.

[2]: Source: Table 14.2.1.2.3 of the Applicant's study reports.

[3]: Source: Table 40 of the Applicant's Month 24 study reports.

▪ Analysis of the DOP's Preferred Endpoint (Slope)

The Applicant has also conducted the analysis of the slope endpoint without pooling the two sham arms. The observed results are consistent with the results observed for the protocol defined primary efficacy endpoint (Table 17).

Table 17: Mean Rate of GA Growth (Slope): Without Pooling Sham (mITT)

Parameters	LS mean (SE)				Difference (95.1% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Study APL2-303						
Month 12: Slope (SE) [1]	1.7623 (0.0762)	1.7494 (0.0737)	1.8425 (0.1206)	2.0725 (0.1333)	-0.0802 (-0.3604, 0.2000)	-0.3232 (-0.6223, -0.0240)
Month 18: Slope (SE) [2]	2.6449 (0.1013)	2.5999 (0.1026)	2.7896 (0.1821)	3.2032 (0.1989)	-0.1447 (-0.5533, 0.2639)	-0.6033 (-1.0424, -0.1642)
Month 24: Slope (SE) [3]	3.1761 (0.1362)	3.2034 (0.1331)	3.6065 (0.2198)	4.3156 (0.2551)	-0.4304 (-0.9369, 0.07610)	-1.1122 (-1.6763, -0.5480)
Study APL2-304						
Month 12: Slope (SE) [1]	1.5607 (0.0803)	1.6569 (0.0760)	1.8706 (0.0959)	2.0644 (0.1261)	-0.3099 (-0.5548, -0.0649)	-0.4075 (-0.6974, -0.1177)
Month 18: Slope (SE) [2]	2.3383 (0.1102)	2.4905 (0.10766)	2.7900 (0.12891)	3.1444 (0.1854)	-0.4517 (-0.7832, -0.1203)	-0.6539 (-1.0744, -0.2334)
Month 24: Slope (SE) [3]	3.0768	3.2459	3.7753	4.1566	-0.6985	-0.9106

	(0.1563)	(0.1350)	(0.1763)	(0.2291)	(-1.1582, -0.2389)	(-1.4321, -0.3892)
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[1] Source: Table 4.2.1.3.8.8 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 4.2.1.3.8.8 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 18 included.

[3] Source: Reviewer's Analysis. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 24 included.

□ Analyses Adjusting for Baseline Imbalances Observed Post-hoc

The Applicant conducted post-hoc analyses of the protocol defined as well as the DOP's preferred primary efficacy endpoints adjusting for selected baseline characteristics (prognostic factors) for which they state were major chance imbalances among the treatment arms. In both studies, the results from these analyses show that there is nominally significant difference between each of the two dosing frequencies of pegcetacoplan against the pooled sham with respect to both the protocol defined as well as the DOP's preferred primary efficacy endpoints (Table 18 and Table 19).

Table 18: Mean Change from Baseline in Total GA Area: Adjusted (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
	Study APL-303				
Month 12: Mean change (SE) [1]	1.7060 (0.0744)	1.7256 (0.0712)	2.0195 (0.0896)	-0.3135 (-0.5385, -0.0885)	-0.2940 (-0.5189, -0.0691)
Month 18: Mean change (SE) [2]	2.5845 (0.0967)	2.5788 (0.0951)	3.0722 (0.1292)	-0.4877 (-0.8024, -0.1729)	-0.4934 (-0.8098, -0.1770)
Month 24: Mean change (SE) [3]	3.1820 (0.1214)	3.2660 (0.1224)	4.0428 (0.1557)	-0.8608 (-1.2454, -0.4762)	-0.7768 (-1.1674, -0.3862)
Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
	Study APL2-304				
Month 12: Mean change (SE) [1]	1.5095 (0.0792)	1.6645 (0.0751)	2.0098 (0.0777)	-0.5003 (-0.7195, -0.2811)	-0.3453 (-0.5535, -0.1372)
Month 18: Mean change (SE) [2]	2.2695 (0.1030)	2.5321 (0.0984)	3.0692 (0.1074)	-0.7997 (-1.0949, -0.5045)	-0.5371 (-0.8183, -0.2560)
Month 24: Mean change (SE) [3]	3.0101 (0.1335)	3.2981 (0.1171)	4.0906 (0.1360)	-1.0805 (-1.4573, -0.7036)	-0.7924 (-1.1410, -0.4439)

[1] Source: Table 25 of the Applicant's study reports.

[2] Source: Table 14.2.1.1.2.1 of the Applicant's study reports.

[3] Source: Table 34 of the Applicant's Month 24 study reports.

Table 19: Mean Rate of GA Growth (Slope): Adjusted (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
	Study APL-303				
Month 12: Slope (SE) [1]	1.7431 (0.0712)	1.7276 (0.0699)	2.0160 (0.0830)	-0.2729 (-0.4879, -0.0578)	-0.2884 (-0.5026, -0.0741)
Month 18: Slope (SE) [2]	2.6113 (0.0959)	2.5656 (0.0953)	3.0924 (0.1258)	-0.4811 (-0.7921, -0.1702)	-0.5269 (-0.8379, -0.2158)
Month 24: Slope (SE) [3]	3.3304 (0.1201)	3.3137 (0.1211)	4.0995 (0.1545)	-0.7691 (-1.1525, -0.3856)	-0.7858 (-1.1724, -0.3993)
Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
	Study APL2-304				
Month 12: Slope (SE) [1]	1.5100 (0.0768)	1.6682 (0.0697)	2.0026 (0.0752)	-0.4925 (-0.7062, -0.2788)	-0.3343 (-0.5344, -0.1343)
Month 18: Slope (SE) [2]	2.2698	2.5179	3.0335	-0.7637	-0.5156

	(0.1061)	(0.0977)	(0.1072)	(-1.0627, -0.4647)	(-0.7971, -0.2342)
Month 24: Slope (SE) [3]	3.0218 (0.1374)	3.3192 (0.1212)	4.0542 (0.1341)	-1.0324 (-1.4113, -0.6535)	-1.0324 (-1.4113, -0.6535)

[1] Source: Table 28 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 14.2.1.3.8.1of the Applicant's study reports. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 18 included.

[3] Source: Table 37 of the Applicant's Month 24 study reports. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 24 included.

Per the Applicant, the individual sham groups are half the size of the pooled sham group and are more subject to chance differences. As an example, the Applicant pointed out that, in Study APL2-304, examination of the baseline characteristics revealed an imbalance between SM and SEOM arms on the baseline lesion location where a greater percentage of subjects in the SEOM group (35.3%) had a lesion without subfoveal involvement at baseline than in the SM group (22.9%). The Applicant also conducted the analyses of both the protocol defined and the DOP's preferred endpoints adjusting for selected baseline characteristics and without pooling the sham arms (Table 20).

Table 20: Mean Rate of GA Growth (Slope): Adjusted: Without Pooling Sham (mITT)

Parameters	LS mean (SE)				Difference (95.1% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Study APL2-303						
Month 12: Slope (SE) [1]	1.7408 (0.0712)	1.7256 (0.0698)	1.8814 (0.1053)	2.1431 (0.1249)	-0.1406 (-0.3922, 0.1110)	-0.4175 (-0.6986, -0.1363)
Month 18: Slope (SE) [2]	2.6104 (0.0960)	2.5654 (0.0952)	2.8591 (0.1613)	3.3172 (0.1866)	-0.2487 (-0.6187, 0.1212)	-0.7518 (-1.1630, -0.3407)
Month 24: Slope (SE) [3]	3.1524 (0.1218)	3.1369 (0.1259)	3.5654 (0.1933)	4.2727 (0.2228)	-0.4129 (-0.8623, 0.0364)	-1.1359 (-1.6470, -0.6247)
Study APL2-304						
Month 12: Slope (SE) [1]	1.5108 (0.0767)	1.6688 (0.0698)	1.9625 (0.0910)	2.0424 (0.1172)	-0.4517 (-0.6851, -0.2183)	-0.3736 (-0.6426, -0.1046)
Month 18: Slope (SE) [2]	2.2700 (0.1060)	2.5176 (0.0977)	2.9349 (0.1217)	3.1269 (0.1712)	-0.6649 (-0.9804, -0.3493)	-0.6093 (-0.9960, -0.2225)
Month 24: Slope (SE) [3]	2.8425 (0.1404)	3.1396 (0.1198)	3.7806 (0.1582)	3.9638 (0.2105)	-0.9381 (-1.3425, -0.5337)	-0.8242 (-1.3041, -0.3443)

[1] Source: Table 4.2.1.3.8.9 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 4.2.1.3.8.9 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 18 included.

[3] Source: Reviewer's Analysis. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 24 included.

❑ Identifying Potential Factors That Led to Difference in Magnitude of Treatment Effects Between PM Arms Across the Two Studies

Per the study results, the estimated mean change from baseline at Month 12 in the pooled sham arm is similar in the two studies. However, the magnitude of the observed treatment effect for the PM arm in Study APL2-303 is 50% lower than the magnitude observed in Study APL2-304. Although there does not appear to be noticeable difference in the demographic characteristics of

age, sex and ethnicity among subjects randomized to the PM arms across the two studies, there were some notable differences in baseline disease characteristics between subjects randomized to the PM arms across the two studies. Note, some of these characteristics were identified by the Applicant as potentially having effect on GA progression. These include foveal involvement, number of intermediate or large drusen >20, and whether GA was multi or unifocal. For example, compared to subjects in the PM arm in Study APL2-304, there were more subjects in the PM arm of study APL2-303 with multifocal GA lesion at baseline (73.1% vs 70.8%), more subjects with GA lesion at baseline with subfoveal involvement (64.2% vs. 57.4%) and fewer subjects with number of intermediate or large drusen at baseline of more than 20 units (28.8% vs. 46%).

As can be seen from the subgroup analyses, subjects with the baseline characteristics identified above are shown to have faster GA progressions. For example, in Study APL2-303, the mean change from baseline in GA area at Month 18 for sham randomized subjects with intermediate or large drusen at baseline of > 20 units was 2.5145 mm². The corresponding figure for sham randomized subjects with intermediate or large drusen at baseline of < 20 units was 3.573 mm² (faster GA growth). Therefore, the difference in GA progression across the PM arms of the two studies could be partly attributed to the difference in the number of subjects enrolled in the two studies with these disease characteristics at baseline. Also note, based on the results of the piecewise linear regression, the Applicant showed that the observed higher GA rate of progression in Study APL2-303 compared to Study APL2-304 was mostly driven by the higher progression observed in the Month 0 to 6 period. As time progressed, the difference between the PM arms across the two studies has reduced (Table 21).

Note, in addition to the chance imbalances in some baseline disease characteristics, there were some notable differences in treatment compliances between the two studies. For example, among subjects in the mITT population randomized to the PM arm in Study APL2-303, 16% have missed at least 5 of the 18 injections compared to 10% in the corresponding arm in Study APL2-304. The proportion of subjects who received all planned injections was also slightly lower for subjects randomized to the PM arm of Study APL2-304 (31.3%) compared to the corresponding arm in Study APL2-303 (33.7%). The difference in drug exposure might have also contributed to the discrepancy in the efficacy outcomes (See Section 3.3.1 for detailed drug exposure summary).

Table 21: Percentage Difference in Slope PM vs. Sham Pooled from a Piecewise Linear Regression

	APL2-304	APL2-303	Magnitude of APL2-303 Treatment Effect Relative to APL2-304 (%)
Estimates for Baseline to Month 6			
Unadjusted, PM vs. Sham Pooled	-22.8	-5.6	24.6
Covariate-Adjusted, PM vs. Sham Pooled	-27.0	-9.7	35.9
Estimates for Month 6 to Month 12			
Unadjusted, PM vs. Sham Pooled	-19.2	-17.3	90.1
Covariate-Adjusted, PM vs. Sham Pooled	-22.2	-20.4	91.9
Estimates for Month 12 to Month 18			
Unadjusted, PM vs. Sham Pooled	-22.0	-14.2	64.5
Covariate-Adjusted, PM vs. Sham Pooled	-26.3	-17.0	64.6
Estimates for Month 18 to Month 24 (available data as included in NDA)			
Unadjusted, PM vs. Sham Pooled	-30.0	-24.7	82.3
Covariate-Adjusted, PM vs. Sham Pooled	-32.1	-26.0	81.0

Source: Table 2 of the Applicant's response to information request (IR) submitted on 13/09/2022. Unadjusted and covariate adjusted refers to results with or without adjusting for baseline characteristics with major imbalance.

C. Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of the two studies are changes from baseline at Month 24 in monocular maximum reading speed, FRI index score, and NL-BCVA score. For each endpoint, the analysis was conducted using a similar MMRM that was used for the protocol defined primary efficacy endpoint based on all observed data on the mITT population. From each model, the least squares mean change from baseline for each treatment arm, the differences between treatment arms and the associated 2-sided 95.1% confidence intervals are provided. Per the study results summarized below, none of the differences observed between each dosing frequency of pegcetacoplan and the pooled sham with respect to these secondary efficacy endpoints are statistically significant.

■ Monocular Maximum Reading Speed (MMRS)

Table 22: Mean Change from Baseline in MMRS at Month 24 (mITT)

Study	LS mean (SE)			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	-22.897 (4.1171)	-25.532 (2.7676)	-22.355 (2.9341)	-0.542 (-9.922, 8.838)	-3.177 (-10.619, 4.265)
Study APL2-304	-22.446 (3.0329)	-17.533 (3.2886)	-16.211 (3.8129)	-6.235 (-15.182, 2.712)	-1.322 (-10.562, 7.918)

Source: Table 51 (APL2-303) and Table 50 (APL2-304) of the Applicant's Month 24 study reports.

■ FRI Index Score

Table 23: Mean Change from Baseline in FRI Index Score at Month 24 (mITT)

Study	LS mean (SE)			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	-0.408 (0.0570)	-0.371 (0.0562)	-0.360 (0.0601)	0.048 (-0.204, 0.108)	-0.011 (-0.163, 0.142)
Study APL2-304	-0.287 (0.0563)	-0.379 (0.0536)	-0.273 (0.0554)	-0.015 (-0.162, 0.133)	-0.106 (-0.252, 0.039)

Source: Table 52 (APL2-303) and Table 51 (APL2-304) of the Applicant's Month 24 study reports.

- NL-BCVA Score

Table 24: Mean Change from Baseline in FRI Index Score at Month 24 (mITT)

Study	LS mean (SE)			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	-8.126 (1.0182)	-8.947 (1.0322)	-6.217 (1.0167)	-1.909 (-4.701, 0.833)	-2.730 (-5.565, 0.105)
Study APL2-304	-7.477 (1.0512)	-8.526 (1.0525)	-7.660 (1.0734)	0.183 (-2.724, 3.090)	-0.866 (-3.793, 2.062)

Source: Table 53 (APL2-303) and Table 52 (APL2-304) of the Applicant's Month 24 study reports.

3.3 Evaluation of Safety

This section presents treatment exposure and descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), using MedDRA 20.1 dictionary derived term, from Study APL2-303 and Study APL2-304. These summaries are provided for the safety analysis population, which is defined in the SAPs as all randomized patients who receive at least 1 dose of study medication. The safety analysis population is comprised of 620 subjects in Study APL2-303 [PM (206); PEOM (208); Pooled sham (206: 102 SM and 104 SEOM)], and 636 subjects in Study APL2-304 [PM (213); PEOM (212); Pooled sham (211: 105 SM and 106 SEOM subjects)].

3.3.1 Extent of Treatment Exposure

Per the study protocol, during the 24 months, subjects randomized to the monthly dosing frequencies (PM and SM) were to receive up to 24 injections, whereas those randomized to every other month dosing frequency (PEOM and SEOM) were to receive up to 12 injections. In both studies, the percentage of subjects who received the maximum number of planned injections for 24 months was relatively low. This appears to be more pronounced in the monthly injections raising the issue of treatment compliance. Per the Applicant, the main reason for missed injections was the disruption caused by the COVID-19 pandemic. Detailed exposure summary is provided below.

▪ Month 12 cut-off

In Study APL2-303, the percentage of subjects who received the maximum allowed number of injections was (PM: 40.8%), (PEOM: 60.5%), (SM: 35.1%), and (SEOM: 66%). The corresponding figures in Study APL2-304 were (PM: 40.1%), (PEOM: 67.3%), (SM: 39.4%), and (SEOM: 57.8%). In Study APL2-303, the Mean (SD) number of injections was 10.2 (2.24), 5.3 (1.05), 10.0 (2.54), and 5.4 (0.97) for the PM, PEOM, SM and SEOM groups, respectively. The corresponding figures in Study APL2-304 were 10.2 (2.31), 5.4 (1.12), 10.1 (2.55), and 5.3 (0.92) for the PM, PEOM, SM and SEOM groups, respectively.

▪ Month 18 cut-off

In Study APL2-303, the percentage of subjects who received the maximum allowed number of injections (did not miss any injection) was (PM: 31.3%), (PEOM: 51.7%), (SM: 30.9%), and

(SEOM: 57.1%). The corresponding figures in Study APL2-304 were (PM: 33.7%), (PEOM: 60.0%), (SM: 32.4%), and (SEOM: 52%).

In Study APL2-303, the [Mean (SD), min, max] number of injections of was [14.7 (4.03), 1, 18], [7.7 (1.87), 1, 10], [14.6 (4.29), 2, 18] and [7.8 (1.8), 1, 9] for the PM, PEOM, SM and SEOM groups, respectively. In Study APL2-304, the [Mean (SD), min, max] number of injections was [14.8 (4.08), 2, 18], [7.9 (1.97), 1, 9], [14.4 (4.58), 0, 18], [7.9 (1.59), 2, 9] for the PM, PEOM, SM and SEOM groups, respectively.

▪ Month 24 cut-off

In Study APL2-303, the percentage of subjects who received the maximum allowed number of injections (did not miss any injection) was (PM: 18.4%), (PEOM: 39.9%), (SM: 22.5%), and (SEOM: 43.5%). The corresponding figures in Study APL2-304 were (PM: 19.2%), (PEOM: 21.9%), (SM: 32.4%), and (SEOM: 37.7%).

In Study APL2-303, the [Mean (SD)] number of injections of was [18.3 (6.57)], [9.8 (3.13)], [18.2 (7.13)] and [9.8 (3.37)] for the PM, PEOM, SM and SEOM groups, respectively. In Study APL2-304, the [Mean (SD)] number of injections was [18.1 (7.03)], [9.9 (3.30)], [18.3 (6.88)] and [9.9 (2.99)] for the PM, PEOM, SM and SEOM groups, respectively.

3.3.2 Adverse Events

The overall adverse event summary for the pooled data up to Month 24 is presented in Table 25. A higher percentage of subjects in the two pegcetacoplan arms reported at least one ocular adverse event compared to the sham arms (61.6% in PM, 55% in PEOM, 46.4% in SM and 46.2% in SEOM). In addition, a slightly higher proportion of subjects in the PM pegcetacoplan arm reported at least one serious adverse event compared to the PEOM as well as the sham arms (34.8% in PM, 25.5% in PEOM, 29% in SM and 24.8% in SEOM).

The proportion of subjects who died during the 24 month was 6.7% in PM, 3.6% in PEOM, 5.3% in SM and 2.4% in SEOM. The proportion of subjects who discontinued the study due to adverse events was 11.2% in PM, 6.9% in PEOM, 9.2% in SM and 4.8% in SEOM. Note, most of the adverse events that led to treatment discontinuation were non-ocular in nature. Also note, the differences in the observed incidence rates in the two pegcetacoplan arms suggest that more frequent injection leads to increased adverse events (Table 25).

Table 25: Overall Summary of Adverse Events (Up to Month 24)

	PM (N=419)	PEOM (N=420)	Pegcetacoplan pooled (N = 839)	SM (N=207)	SEOM (N=210)	Sham pooled (N=417)
All AE	370 (88.3)	367 (87.4)	737 (87.8)	166 (80.2)	178 (84.8)	344 (82.5)
Ocular AE	258 (61.6)	231 (55.0)	489 (58.3)	96 (46.4)	97 (46.2)	193 (46.3)
All Serious AE (SAE)	146 (34.8)	107 (25.5)	253 (30.2)	60 (29.0)	52 (24.8)	112 (26.9)
Ocular SAE	2 (0.5)	1 (0.2)	3 (0.4)	2 (1.0)	0	2 (0.5)
Death	28 (6.7)	15 (3.6)	43 (5.1)	11 (5.3)	5 (2.4)	16 (3.8)

AEs leading to treatment discontinuation	47 (11.2)	32 (7.6)	79 (9.4)	19 (9.2)	9 (4.3)	28 (6.7)
AEs leading to study discontinuation	47 (11.2)	29 (6.9)	76 (9.1)	19 (9.2)	10 (4.8)	29 (7.0)

Source: Adapted from Table 14.3.1.1.1a and Table 14.3.1.1.3a of the Applicant's Month 24 study reports. AE: Adverse event.

The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms (PM, PEOM) were: vitreous floaters (9.8%, 6.9%), Neovascular age-related macular degeneration (9.8%, 5.7%), conjunctival haemorrhage (8.1%; 8.1%), visual acuity reduced (7.9%, 6.4%) and eye pain (7.2%, 5.7%). The incidence rate of these adverse events in the sham arms (SM, SEOM) were vitreous floaters (1.4%, 1.0%), Neovascular age-related macular degeneration (1.9%, 1.9%), conjunctival haemorrhage (2.4%, 4.8%), visual acuity reduced (7.7%, 5.7%) and eye pain (6.3%, 6.7%; Table 26).

Table 26: Summary of Ocular Adverse Events in the Study Eye (Up to Month 24)

	PM (N =419) n (%)	PEOM (N=420)	Pegcetacoplan pooled (N=839) n (%)	SM (N=207) n (%)	SEOM (N = 210) n (%)	Sham pooled (N=417) n (%)
Vitreous floaters	41 (9.8)	29 (6.9)	70 (8.3)	3 (1.4)	2 (1.0)	5 (1.2)
Conjunctival haemorrhage	34 (8.1)	34 (8.1)	68 (8.1)	5 (2.4)	10 (4.8)	15 (3.6)
Neovascular age-related macular degeneration	41 (9.8)	24 (5.7)	65 (7.7)	4 (1.9)	4 (1.9)	8 (1.9)
Visual acuity reduced	33 (7.9)	27 (6.4)	60 (7.2)	16 (7.7)	12 (5.7)	28 (6.7)
Eye pain	30 (7.2)	24 (5.7)	54 (6.4)	13 (6.3)	14 (6.7)	27 (6.5)
Dry eye	23 (5.5)	20 (4.8)	43 (5.1)	8 (3.9)	9 (4.3)	17 (4.1)
Vitreous detachment	15 (3.6)	25 (6.0)	40 (4.8)	8 (3.9)	6 (2.9)	14 (3.4)
Retinal haemorrhage	18 (4.3)	21 (5.0)	39 (4.6)	5 (2.4)	7 (3.3)	12 (2.9)
Punctate keratitis	23 (5.5)	8 (1.9)	31 (3.7)	2 (1.0)	1 (0.5)	3 (0.7)
Posterior capsule opacification	15 (3.6)	15 (3.6)	30 (3.6)	5 (2.4)	6 (2.9)	11 (2.6)
Cataract	16 (3.8)	13 (3.1)	29 (3.5)	8 (3.9)	8 (3.8)	16 (3.8)
Eye irritation	18 (4.3)	10 (2.4)	28 (3.3)	10 (4.8)	10 (4.8)	20 (4.8)
Low luminance best-corrected visual acuity decreased	15 (3.6)	13 (3.1)	28 (3.3)	7 (3.4)	8 (3.8)	15 (3.6)
Visual impairment	13 (3.1)	13 (3.1)	26 (3.1)	6 (2.9)	6 (2.9)	12 (2.9)
Blepharitis	9 (2.1)	17 (4.0)	26 (3.1)	4 (1.9)	5 (2.4)	9 (2.2)
Vision blurred	13 (3.1)	10 (2.4)	23 (2.7)	7 (3.4)	9 (4.3)	16 (3.8)
Foreign body sensation in eyes	13 (3.1)	10 (2.4)	23 (2.7)	4 (1.9)	3 (1.4)	7 (1.7)
Choroidal neovascularisation	12 (2.9)	4 (1.0)	16 (1.9)	4 (1.9)	1 (0.5)	5 (1.2)
Ocular hyperaemia	9 (2.1)	5 (1.2)	14 (1.7)	6 (2.9)	1 (0.5)	7 (1.7)
Photopsia	7 (1.7)	6 (1.4)	13 (1.5)	2 (1.0)	1 (0.5)	3 (0.7)
Ocular discomfort	8 (1.9)	4 (1.0)	12 (1.4)	1 (0.5)	2 (1.0)	3 (0.7)
Lacrimation increased	6 (1.4)	6 (1.4)	12 (1.4)	5 (2.4)	3 (1.4)	8 (1.9)
Dry age-related macular degeneration	6 (1.4)	6 (1.4)	12 (1.4)	4 (1.9)	2 (1.0)	6 (1.4)
Eye pruritus	6 (1.4)	6 (1.4)	12 (1.4)	3 (1.4)	3 (1.4)	6 (1.4)

Vitreous haemorrhage	8 (1.9) 9	3 (0.7) 3	11 (1.3)	0	0	0
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Source: Adapted from Table 14.3.1.2.1a of the Applicant's Month 24 study reports.

❑ Adverse Events of Special Interest

The Applicant provided summaries of adverse events of special interest, namely, endophthalmitis, intraocular inflammations and exudative AMD. Per the study results, no subject reported endophthalmitis in the sham arms while 5 (0.6%) subjects in the two pegcetacoplan arms combined [2 in the PM and 3 in the PEOM arm] reported endophthalmitis. The percentage of subjects with intraocular inflammations was 3.8% in the PM arm and 1.9% in the PEOM arm. One subjects in SEOM arm reported intraocular inflammations.

A higher percentage of subjects in the pegcetacoplan pooled group (9.4%) than in the sham pooled group (3.1%) had an exudative AMD adverse event in the study eye. Subjects in the PM (12.2%) group had a higher incidence of exudative AMD adverse events in the study eye than in the PEOM (6.7%) group (Table 27).

Table 27: Summary of Ocular Adverse Events of Special Interest in the Study Eye (Up to Month 24)

	PM (N=419) n (%)	PEOM (N=420)	Pegcetacoplan pooled (N=839) n (%)	SM (N=207) n (%)	SEOM (N = 210) n (%)	Sham pooled (N=417) n (%)
Endophthalmitis	2 (0.5)	3 (0.7)	5 (0.6)	0	0	0
Intraocular inflammations	16 (3.8)	8 (1.9)	24 (2.9)	0	1 (0.5)	1 (0.2)
Exudative AMD	51 (12.2)	28 (6.7)	79 (9.4)	8 (3.9)	5 (2.4)	13 (3.1)

Source: Adapted from Table 14.3.1.14.1a of the Applicant's Month 24 study reports.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses for each individual study separately are presented in Figure 4--Figure 16. The subgroup analyses are conducted using the method of analysis used for the primary efficacy endpoint. The subgroup results are generally consistent with the Applicant's primary efficacy analysis results.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In this review, issues related to missing data and pooling of the two the sham arms in the evaluation of efficacy were encountered. First, the amount of missing data, i.e., subjects who did not have efficacy measurements reported at the primary analysis time points, i.e., Month12, 18 and 24, is relatively very high. Specifically, approximately 20-22% of subjects randomized to the two pegcetacoplan arms (with more subjects in the PM arm) had missing GA data at Month 12. At the Month 24 visit, 30% and 33% of subjects randomized to the PM arm in Study APL2-303, and Study APL2-304, respectively had missing GA data.

Second, the protocol defined as well as the DOP's primary efficacy endpoints were conducted by comparing each pegcetacoplan arm to the pooled sham arm. However, notable differences between the SM and SEOM arms in missing visits, missing GA data, adverse event rates, and study discontinuation rates were observed. Besides, subjects randomized to the SEOM arm had a faster GA progression compared to those in SM arm. Therefore, the observed favorable differences between the two pegcetacoplan arms and the pooled sham arm might be mostly driven by the observed faster GA growth rate in the SEOM arm.

5.2 Collective Evidence

The Applicant's analyses of the protocol defined primary efficacy endpoint provided statistically significant (Study APL2-304) and numerically favorable (Study APL2-303) results for the two pegcetacoplan arms. The analyses of the DOP's preferred primary efficacy endpoint evaluated using data through Month 18 and through Month 24 provided results in favor of the two pegcetacoplan arms in both studies. The analyses of the protocol defined as well as DOP's primary efficacy endpoints under different missing data handling methods are generally consistent with the primary analysis findings. Treatment comparisons with respect to secondary efficacy endpoints did not result in any meaningful differences between the two pegcetacoplan arms and the pooled sham arm.

The incidence of adverse events was higher in the two pegcetacoplan arms especially in the PM arm, compared to the pooled sham. The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms were vitreous floaters, Neovascular age-related macular degeneration, conjunctival hemorrhage, and eye pain. Also note, a higher incidence of adverse events of special interest, namely, intraocular inflammations and exudative AMD, were reported in the two pegcetacoplan arms compared to the pooled sham.

In both studies, less than 20% of subjects in the PM arm had received the 24 planned injections during the 24-month study period. This raises potential treatment compliance issues in the real world, and the potential for underestimation of incidence of adverse events with a full treatment regimen.

5.3 Conclusions and Recommendation

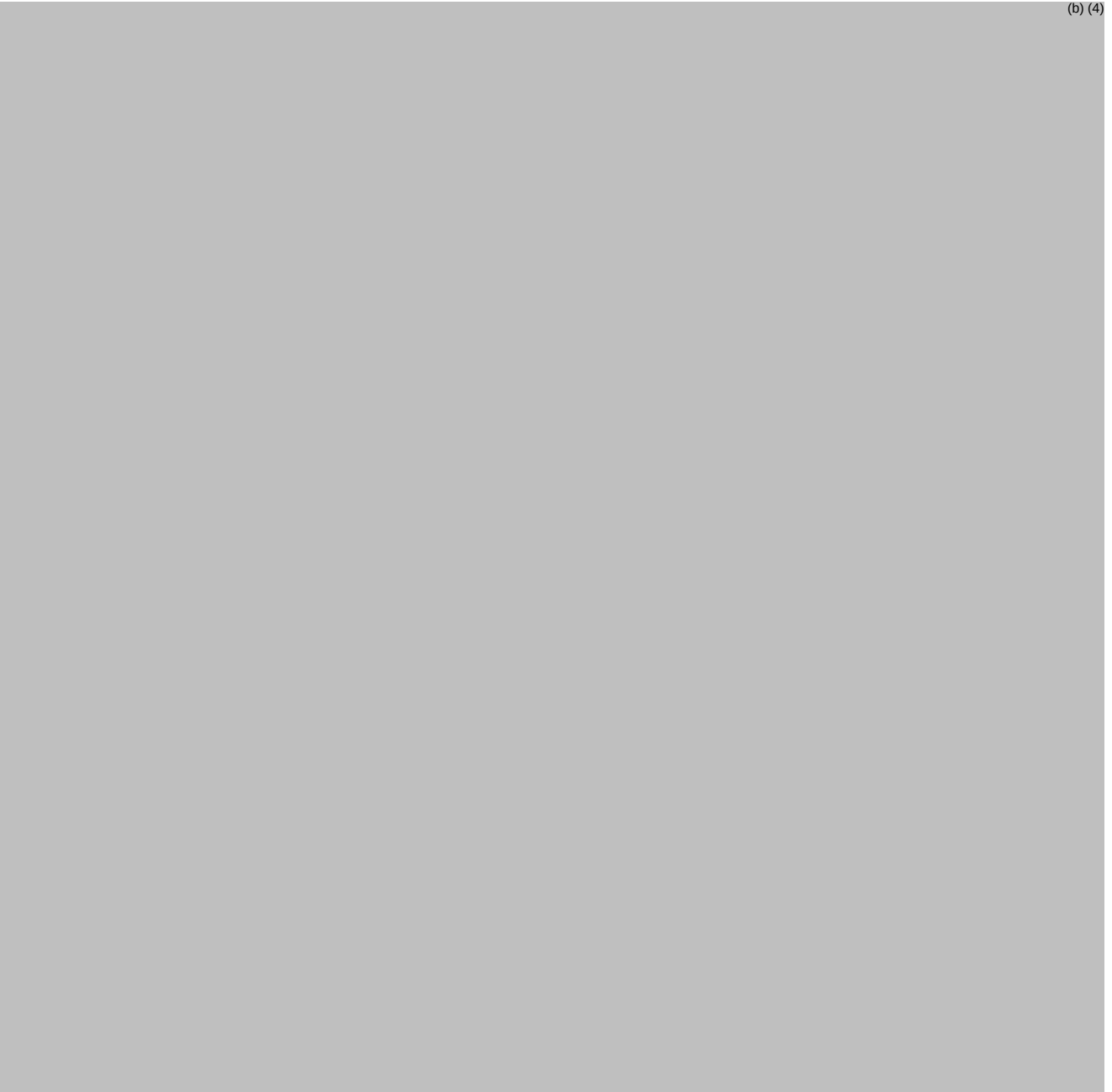
Overall, the results of the Applicant's and the reviewer's analyses in this review provide evidence to support the efficacy of pegcetacoplan for the treatment of GA secondary to AMD. Safety wise, incidence of adverse events, including adverse events of special interest (intraocular inflammations and exudative AMD), were higher in the two pegcetacoplan arms; with more adverse events reported for the PM arm than the PEOM arm. Therefore, the final determination for the approval of this drug, and the selection of the to be marketed dosing frequency should be made based on the totality of evidence, taking the absence of alternative treatment for this indication, and the potential safety and compliance issues into account.

5.4 Labeling Recommendations

In Section 14 of the drug labeling, the Applicant presented the summary results for the rate of GA growth area estimated based on the piecewise regression. For this analysis, a linear model with knots at Months 6, 12, 18 was fitted. The mean rate of GA growth at Month 24 is estimated as the average of the piecewise slopes for each 6-month period. Note, the mean rate of GA growth based on a linear model (with no knots) is numerically equivalent to the value estimated based on the piecewise regression model. This reviewer does not object to the presentation of the results based on the piecewise regression model provided the information is deemed relevant to the prescribing physician by the Clinical review team.

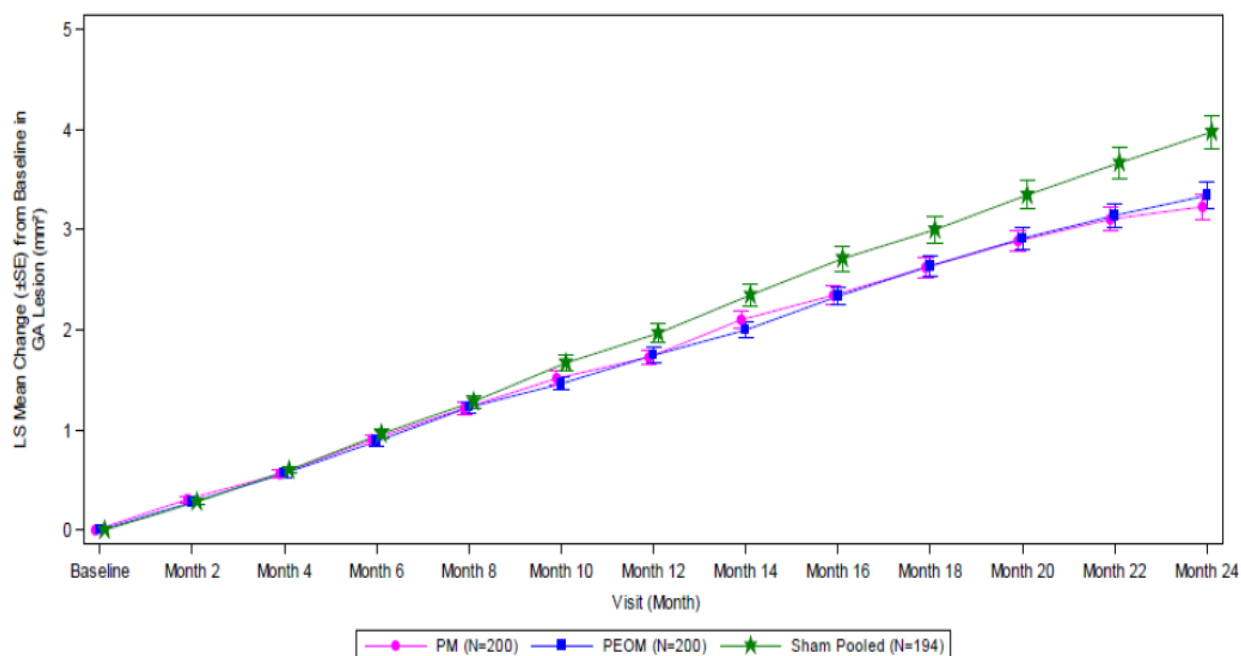
The Applicant has also included the following in Section 14 of the label:

(b) (4)



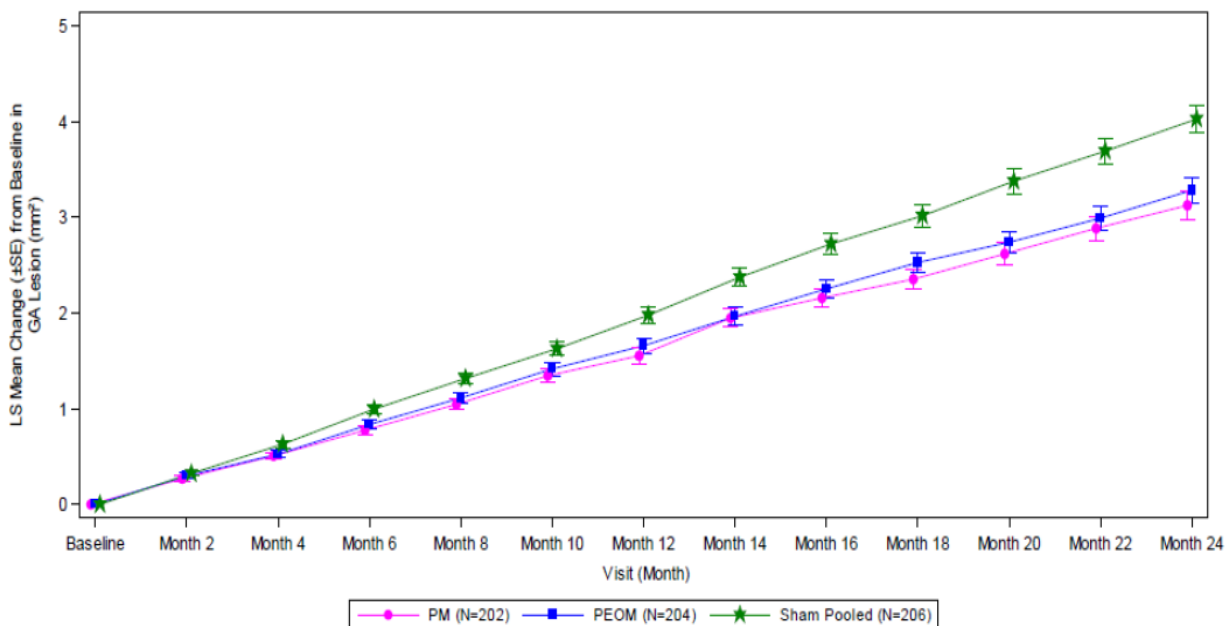
6 Appendix A: Selected Efficacy and Safety Summaries (APL2-303 and APL2-304)

Figure 3: Plot of Mean Change from Baseline Total GA Area (Study APL2-303)



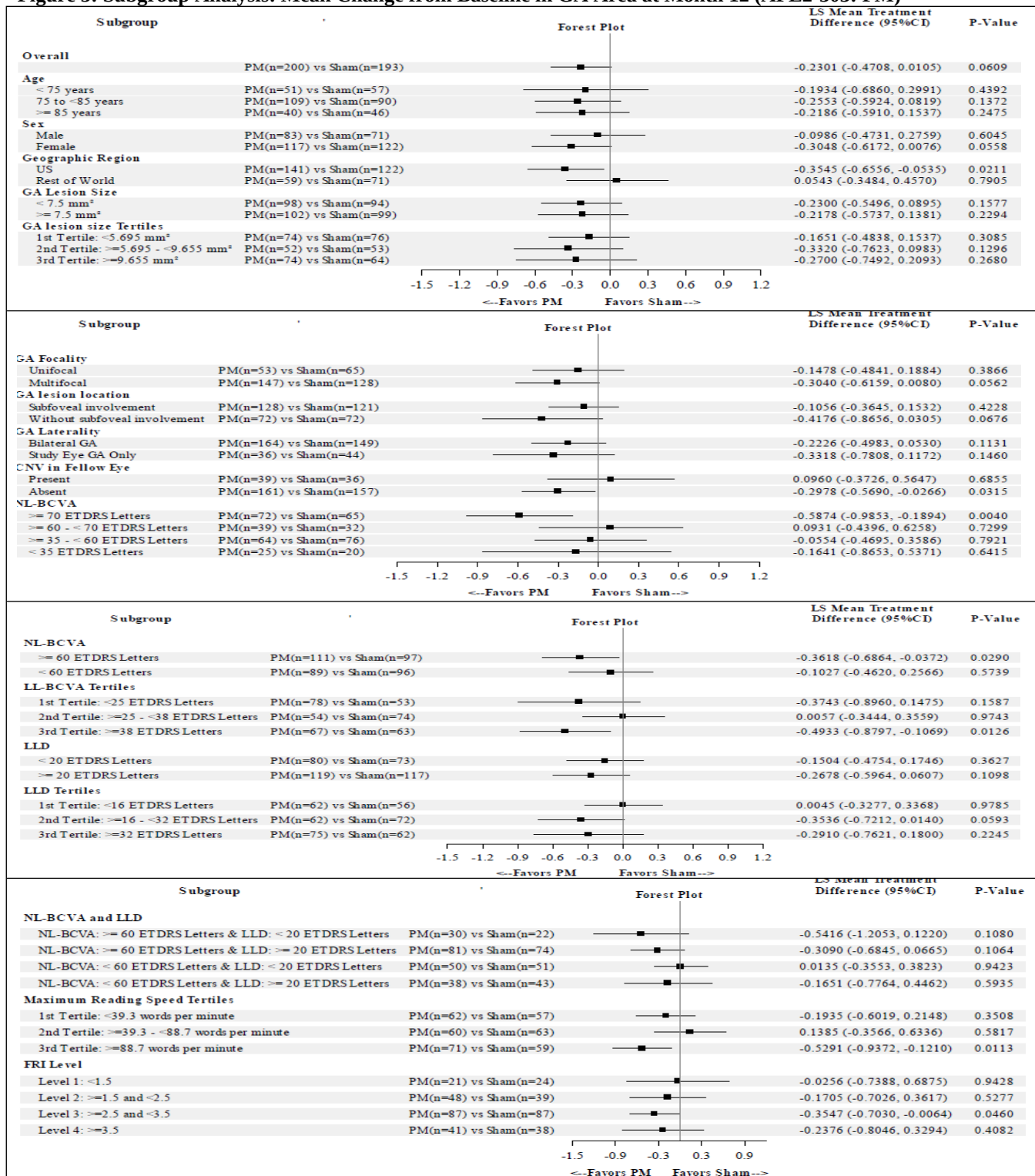
Source: Figure 4 of the Applicant's Month 24 study report

Figure 4: Plot of Mean Change from Baseline Total GA Area (Study APL2-304)



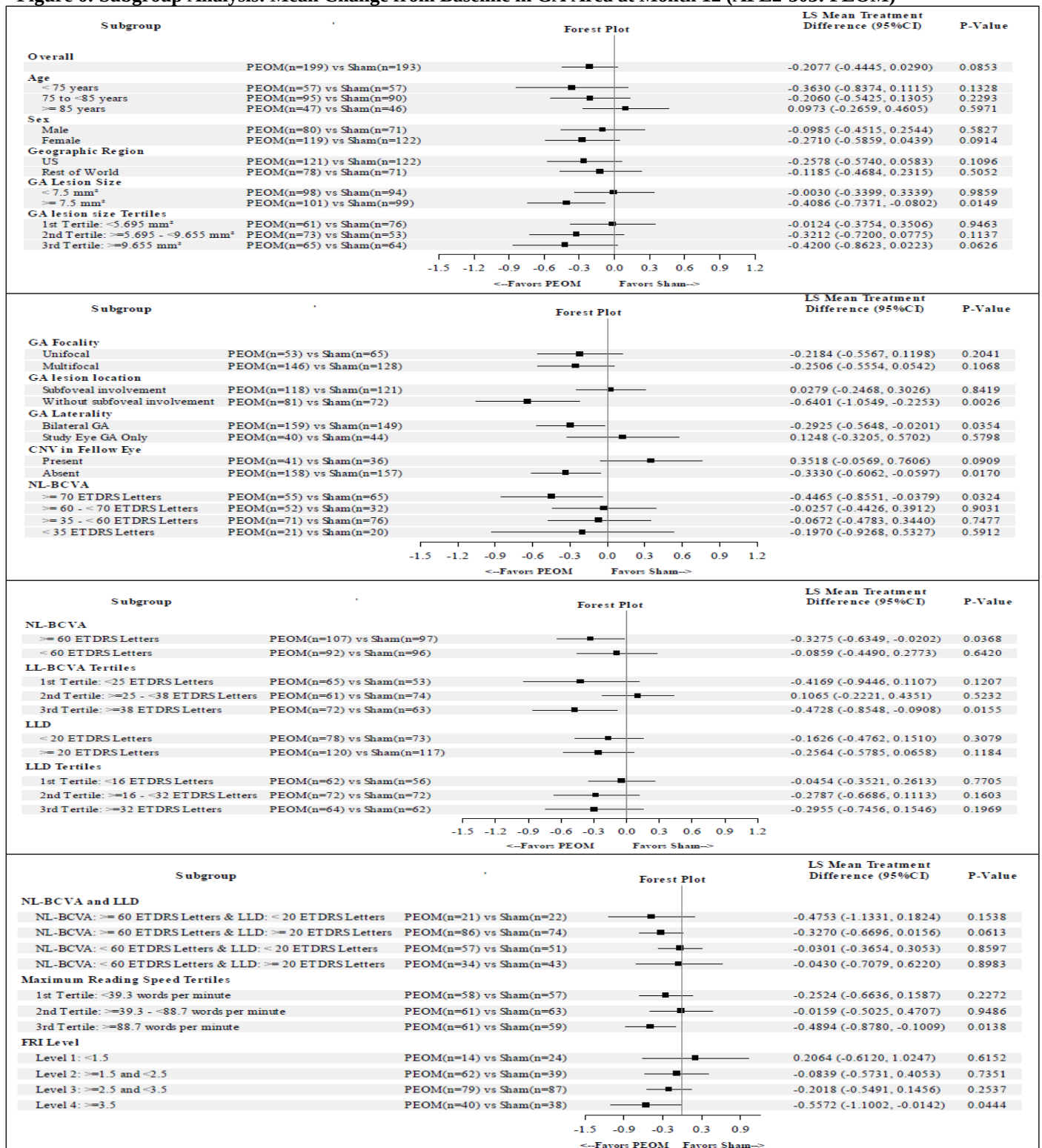
Source: Figure 4 of the Applicant's Month 24 study report

Figure 5: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-303: PM)



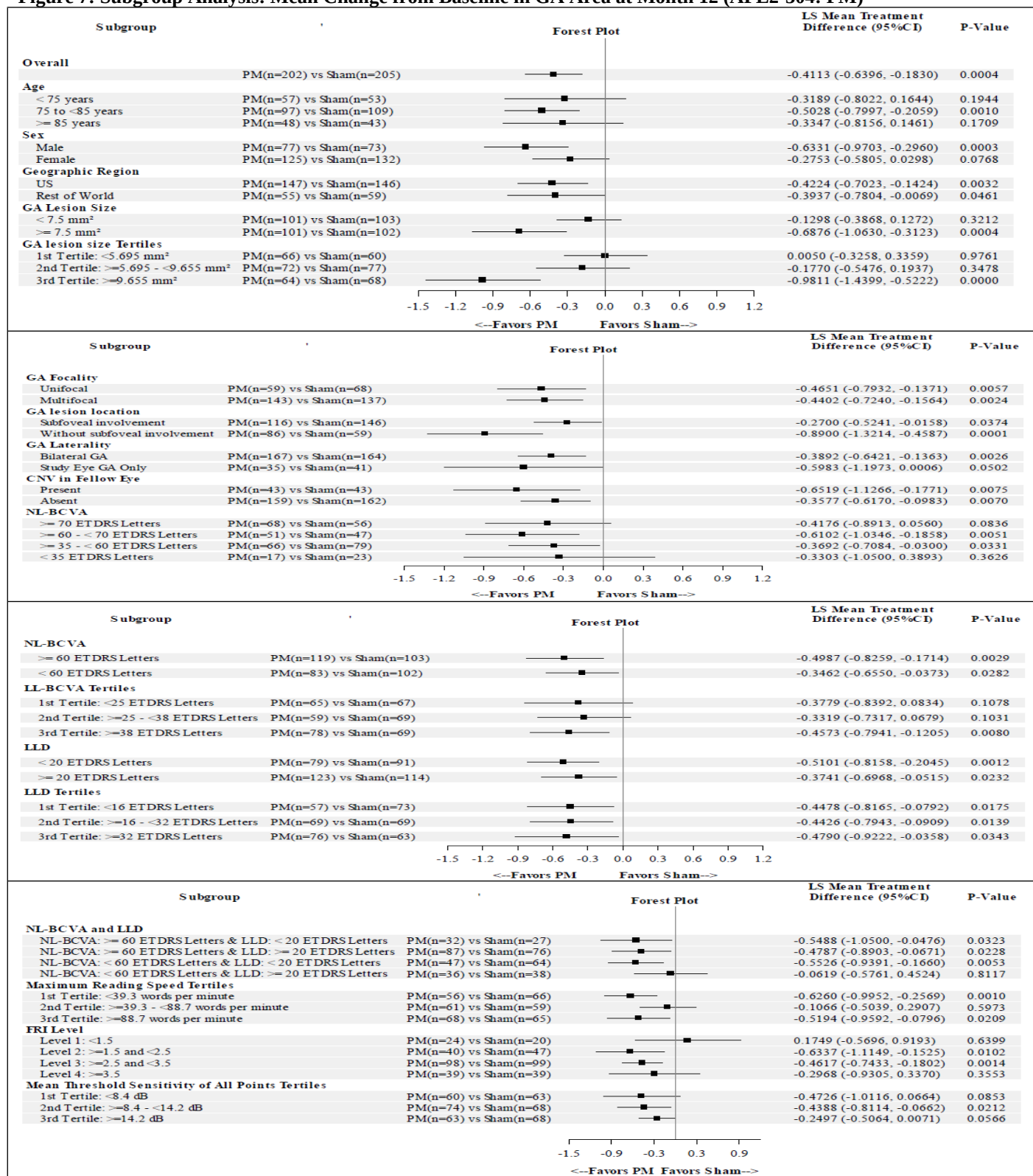
Source: Figure 6 of the Applicant's study report.

Figure 6: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-303; PEOM)



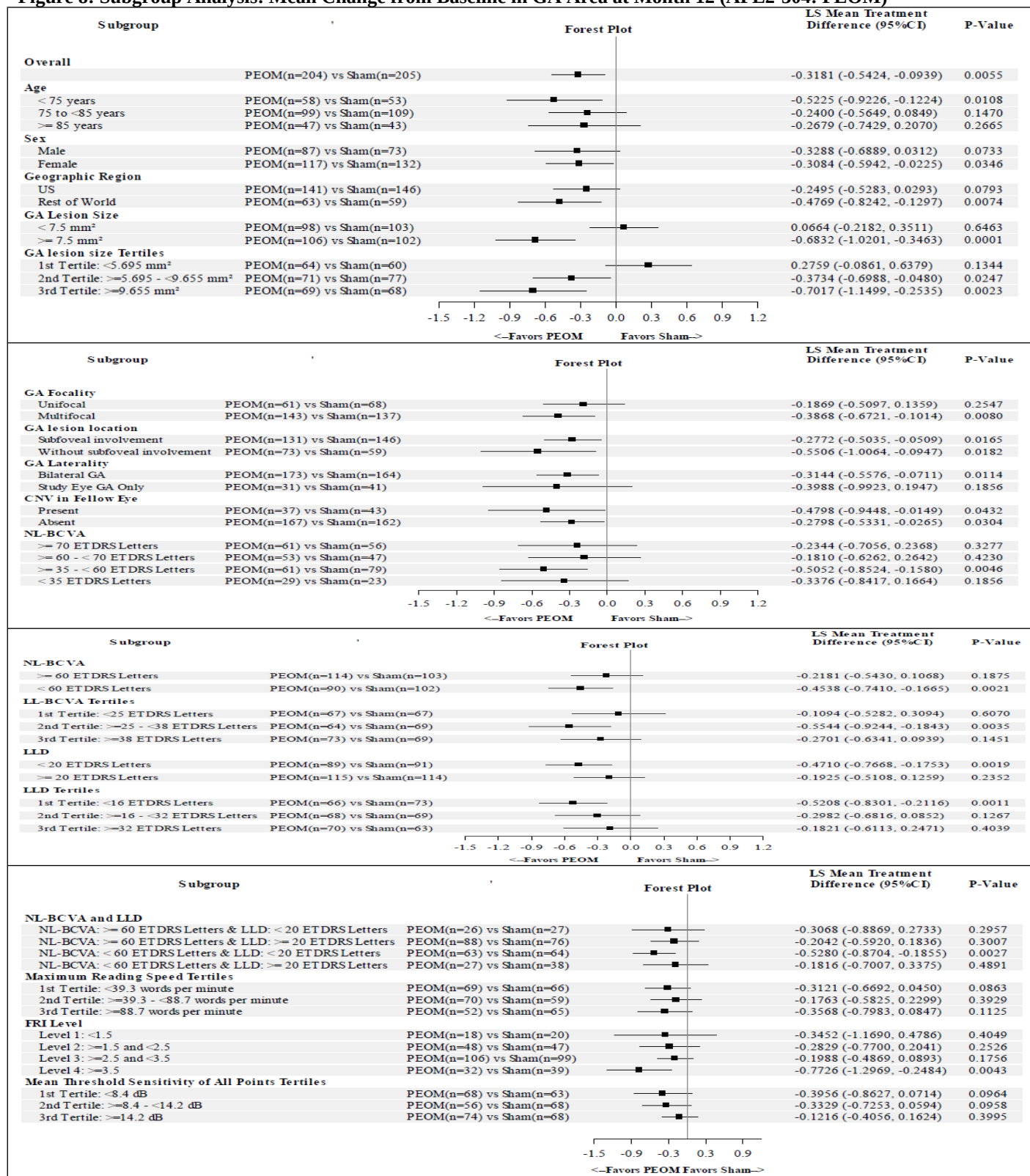
Source: Figure 7 of the Applicant's study report.

Figure 7: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-304: PM)



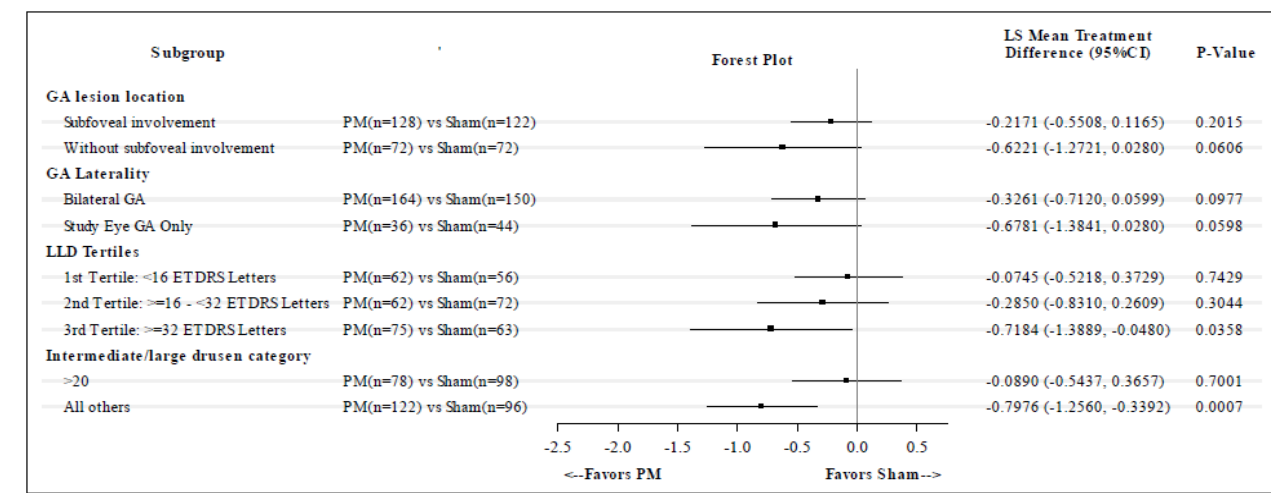
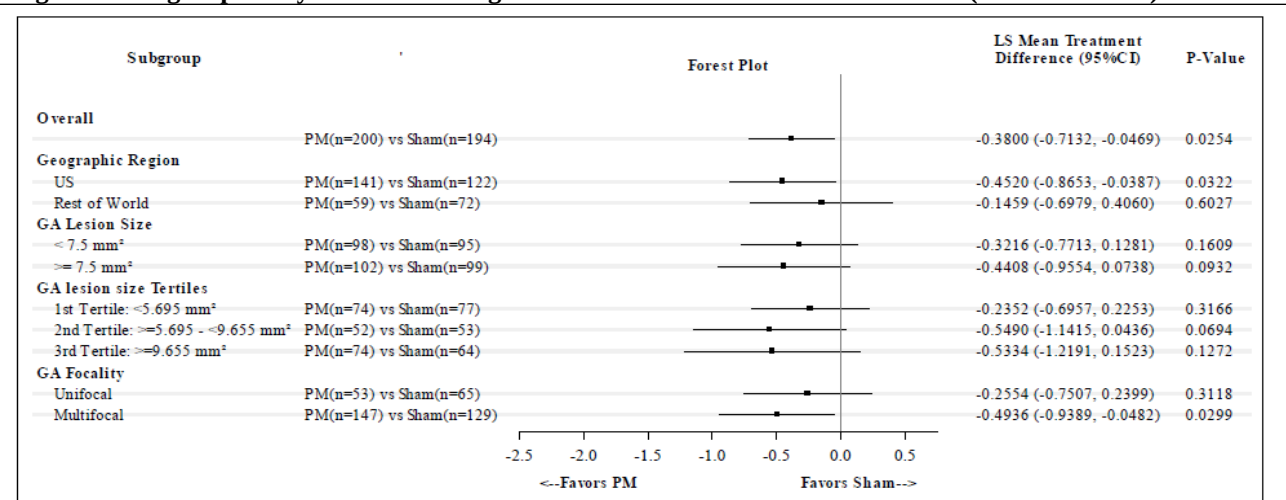
Source: Figure 6 of the Applicant's study report.

Figure 8: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-304: PEOM)



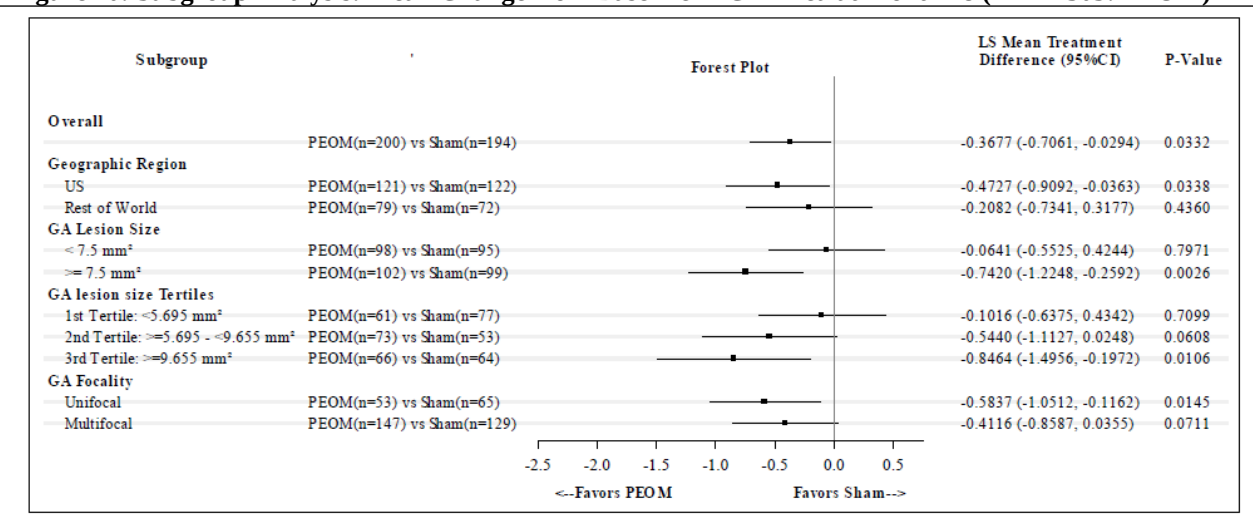
Source: Figure 7 of the Applicant's study report.

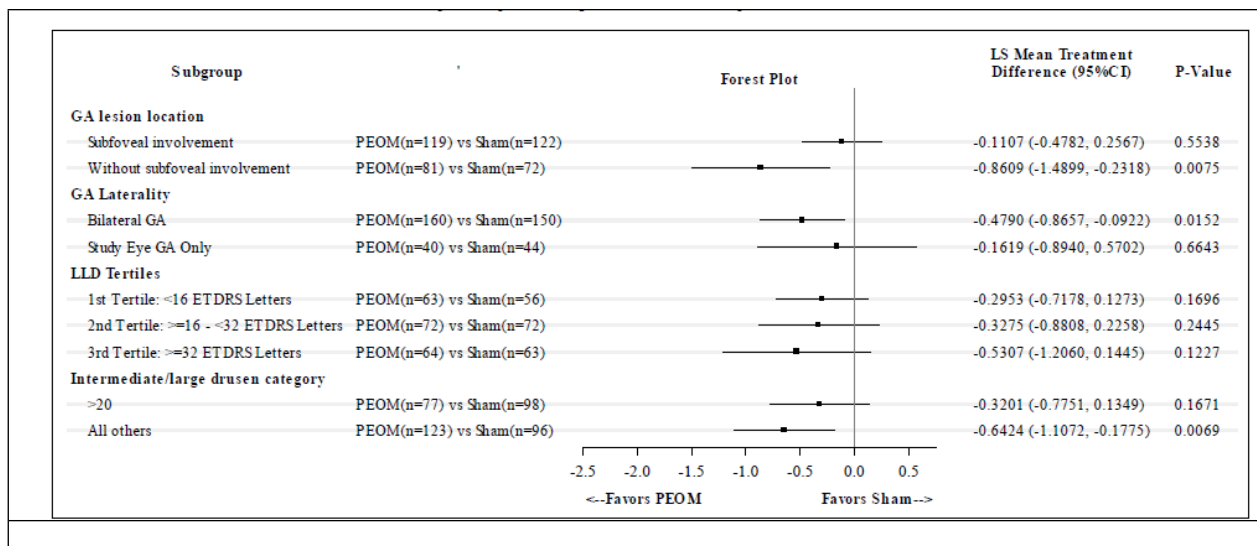
Figure 9: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-303: PM)



Source: Figure 14.2.1.4.1 of the Applicant's study report.

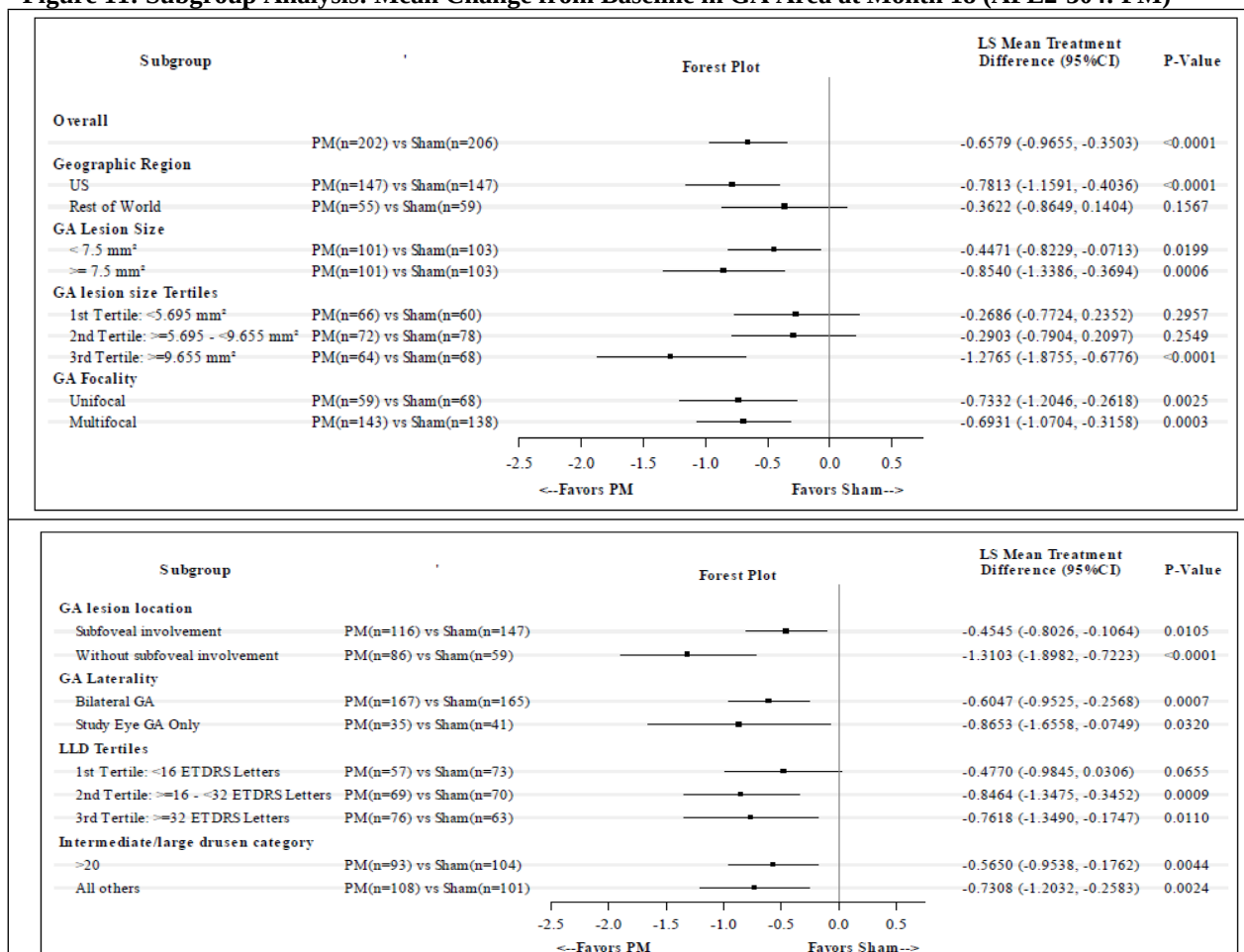
Figure 10: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-303: PEOM)





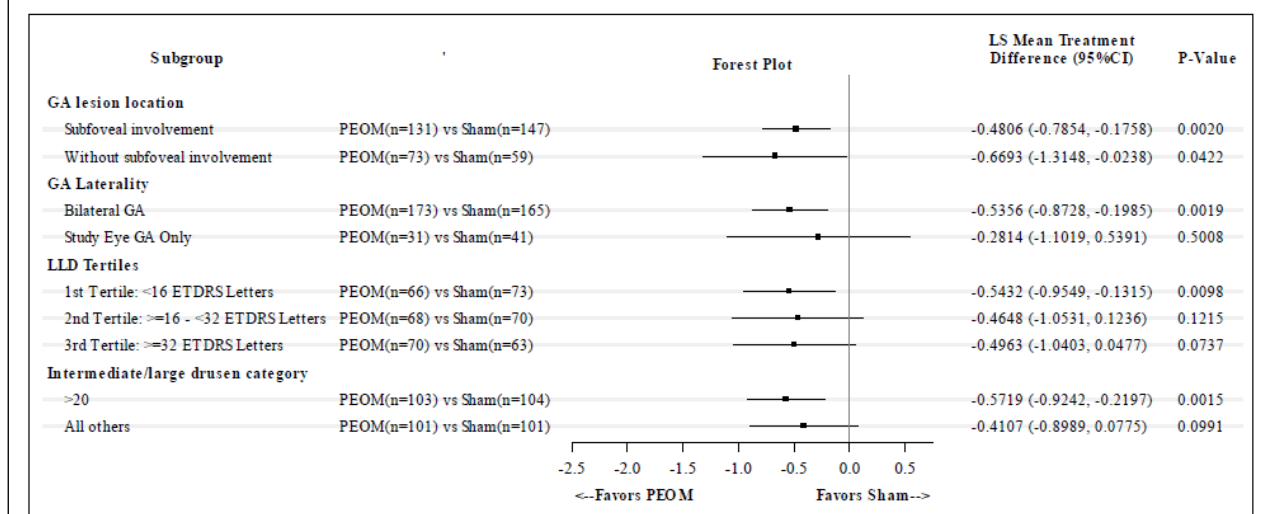
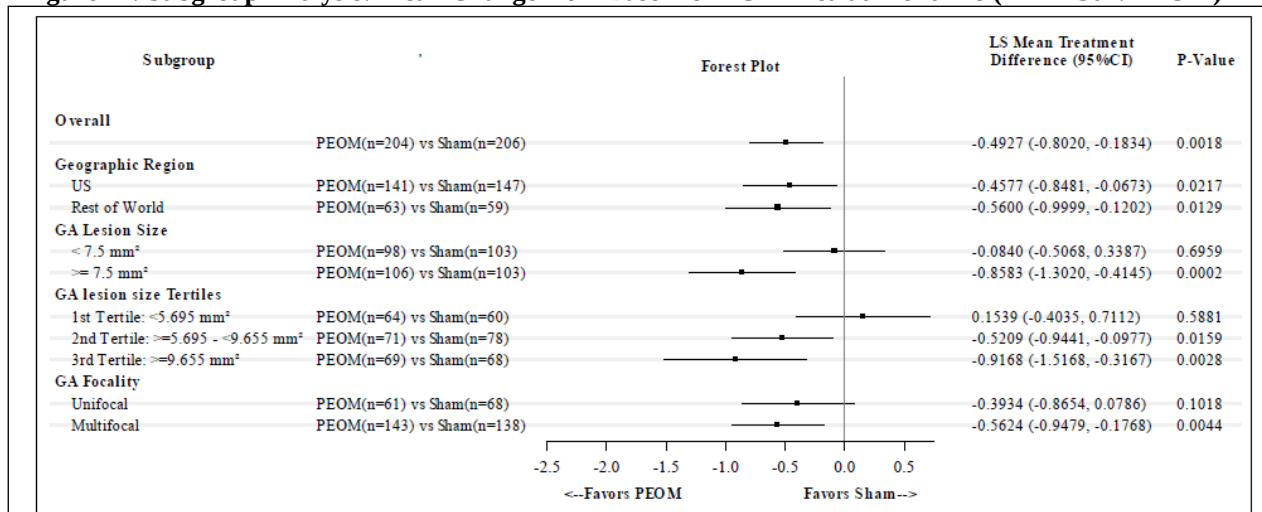
Source: Figure 14.2.1.4.1 of the Applicant's study report.

Figure 11: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-304: PM)



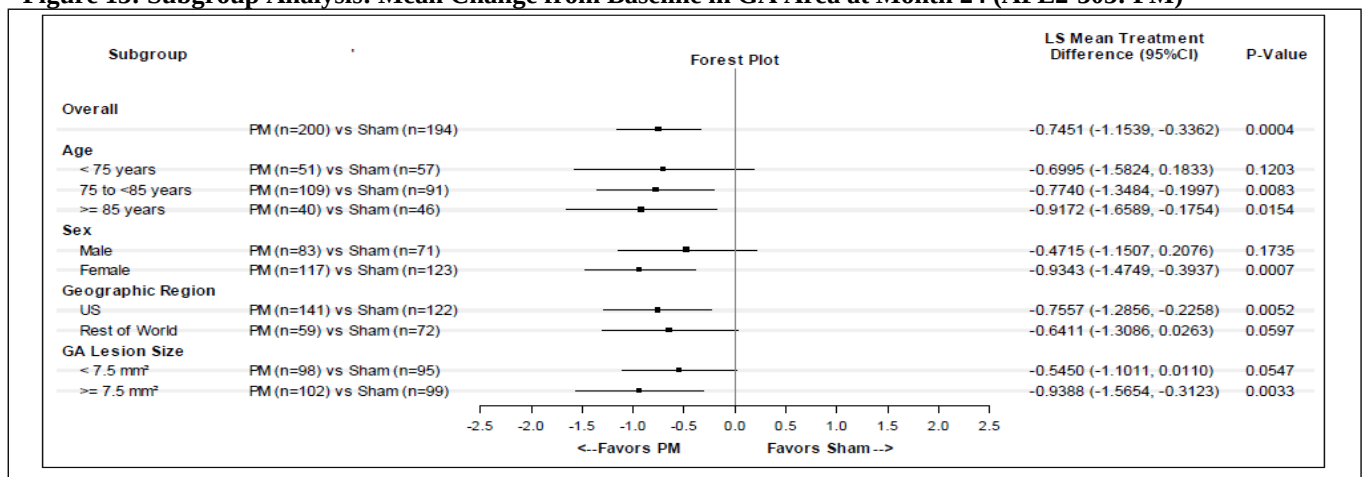
Source: Figure 14.2.1.4.1 of the Applicant's study report.

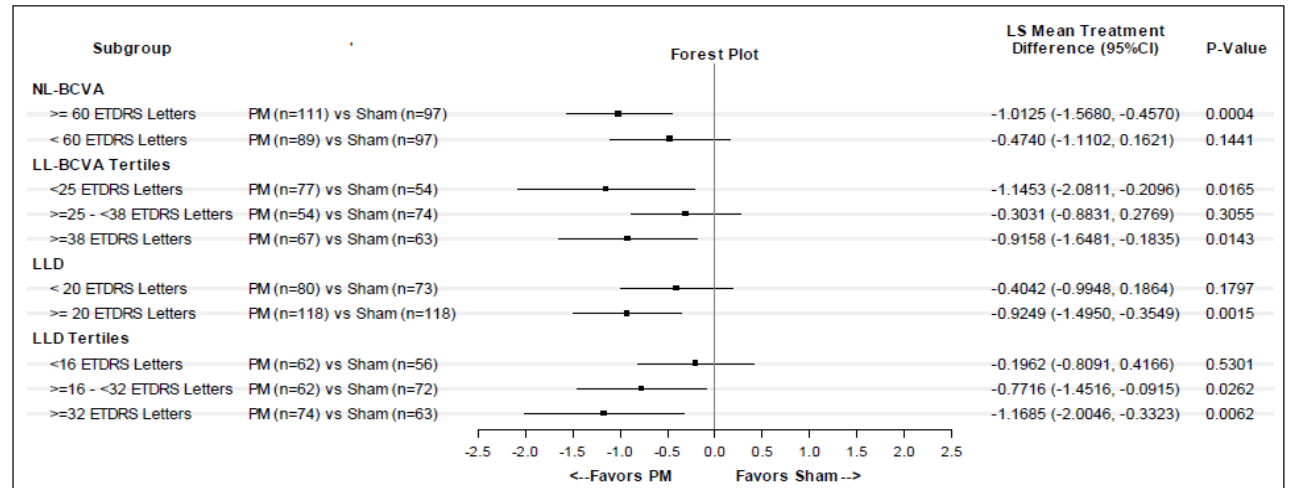
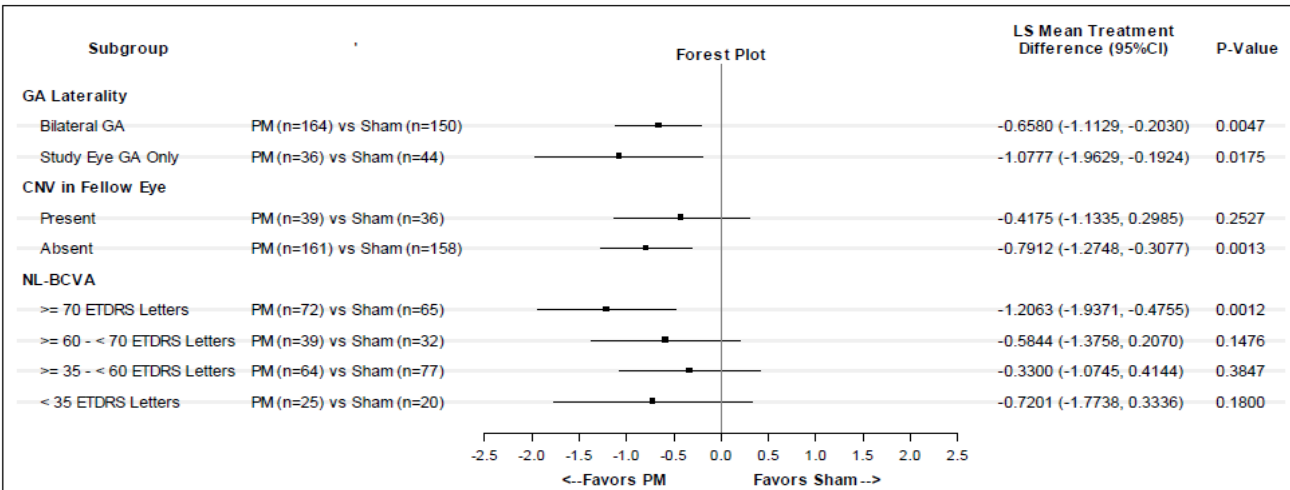
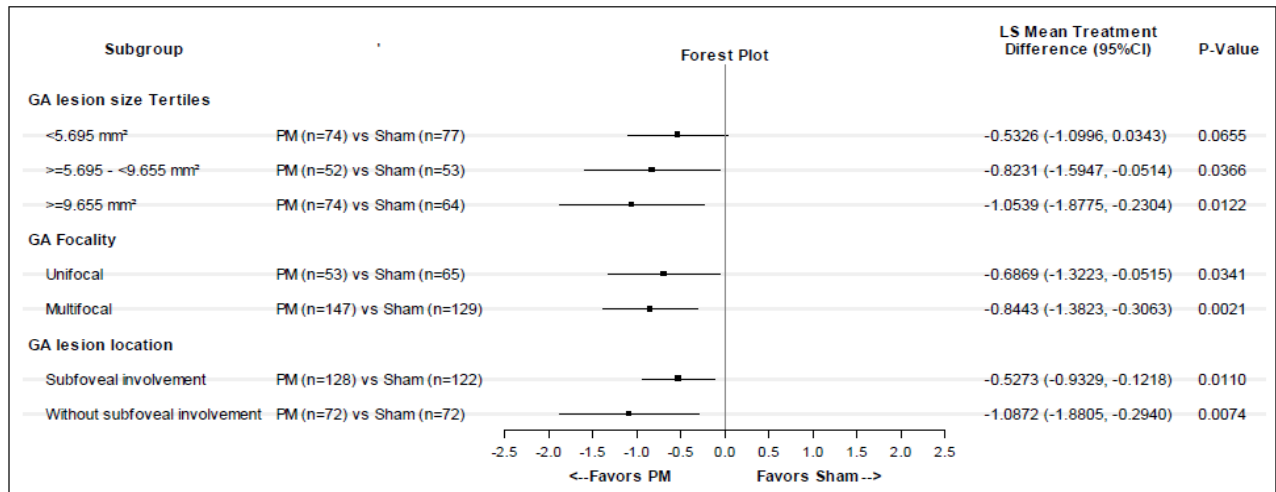
Figure 12: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-304: PEOM)

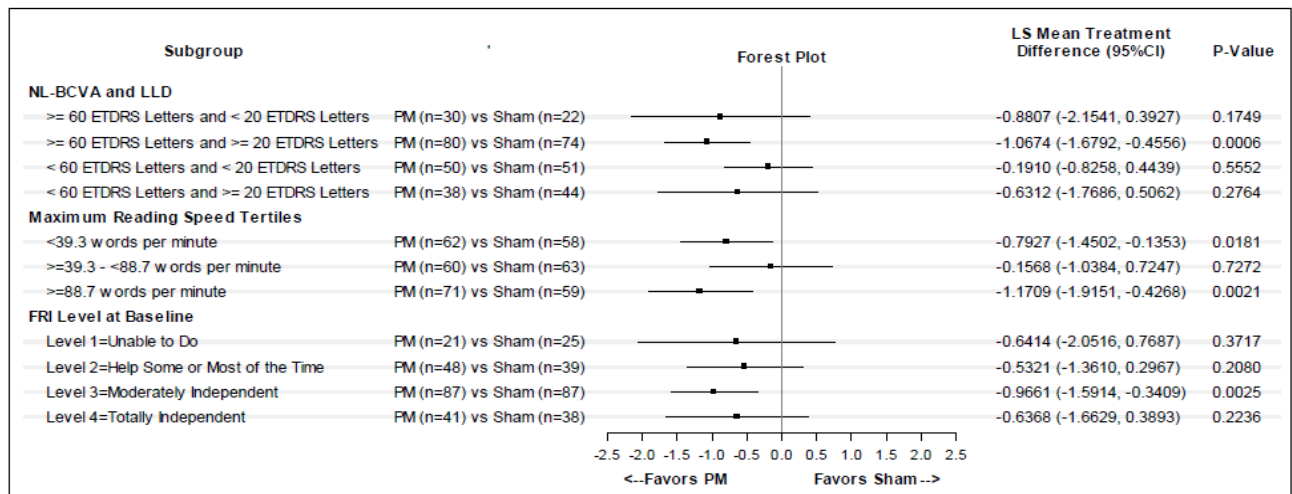


Source: Figure 14.2.1.4.1 of the Applicant's study report.

Figure 13: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 24 (APL2-303: PM)

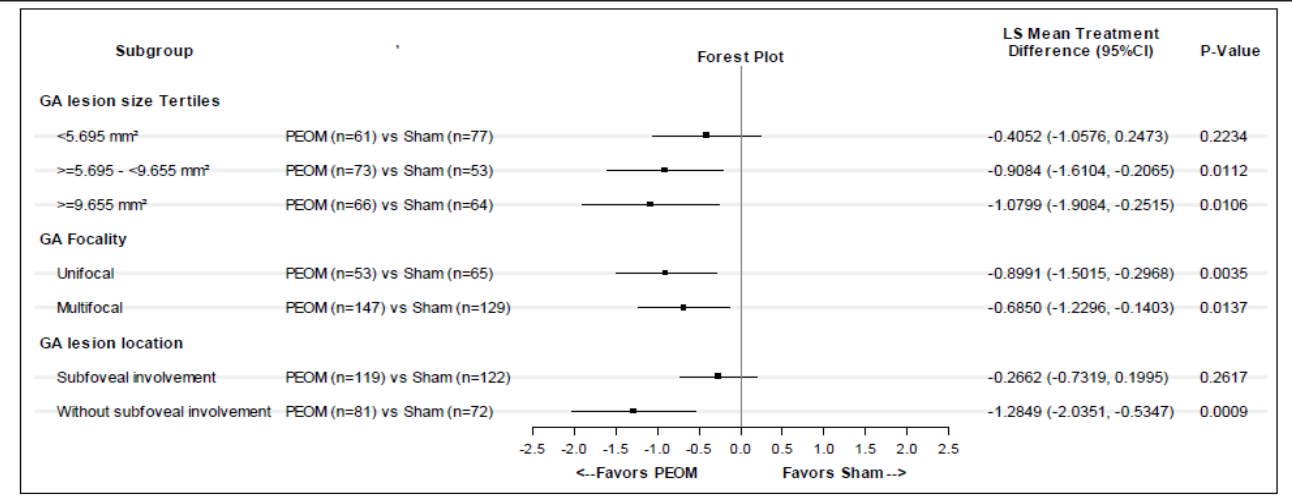
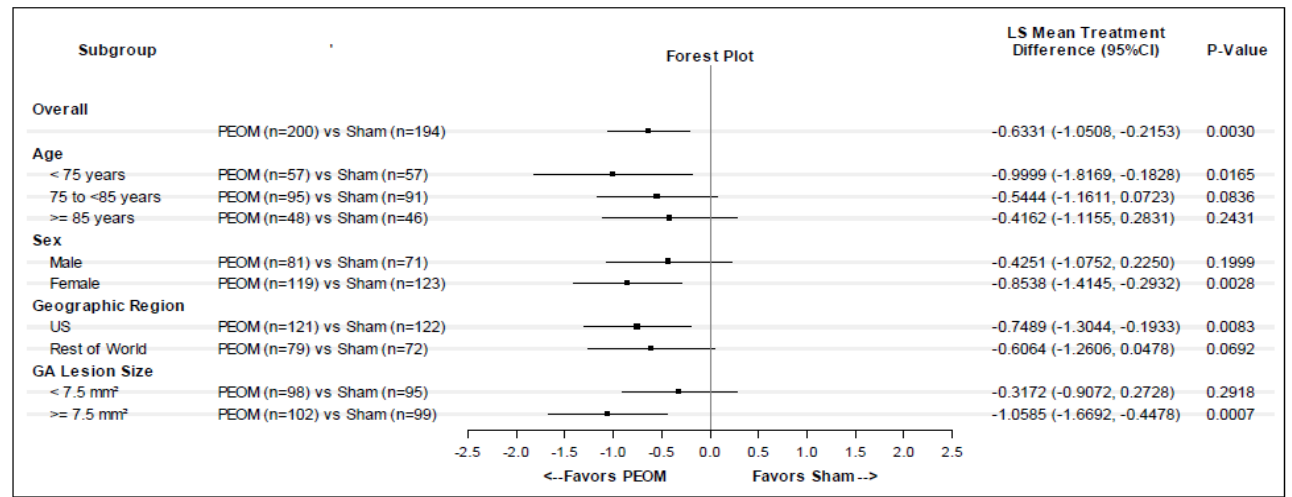


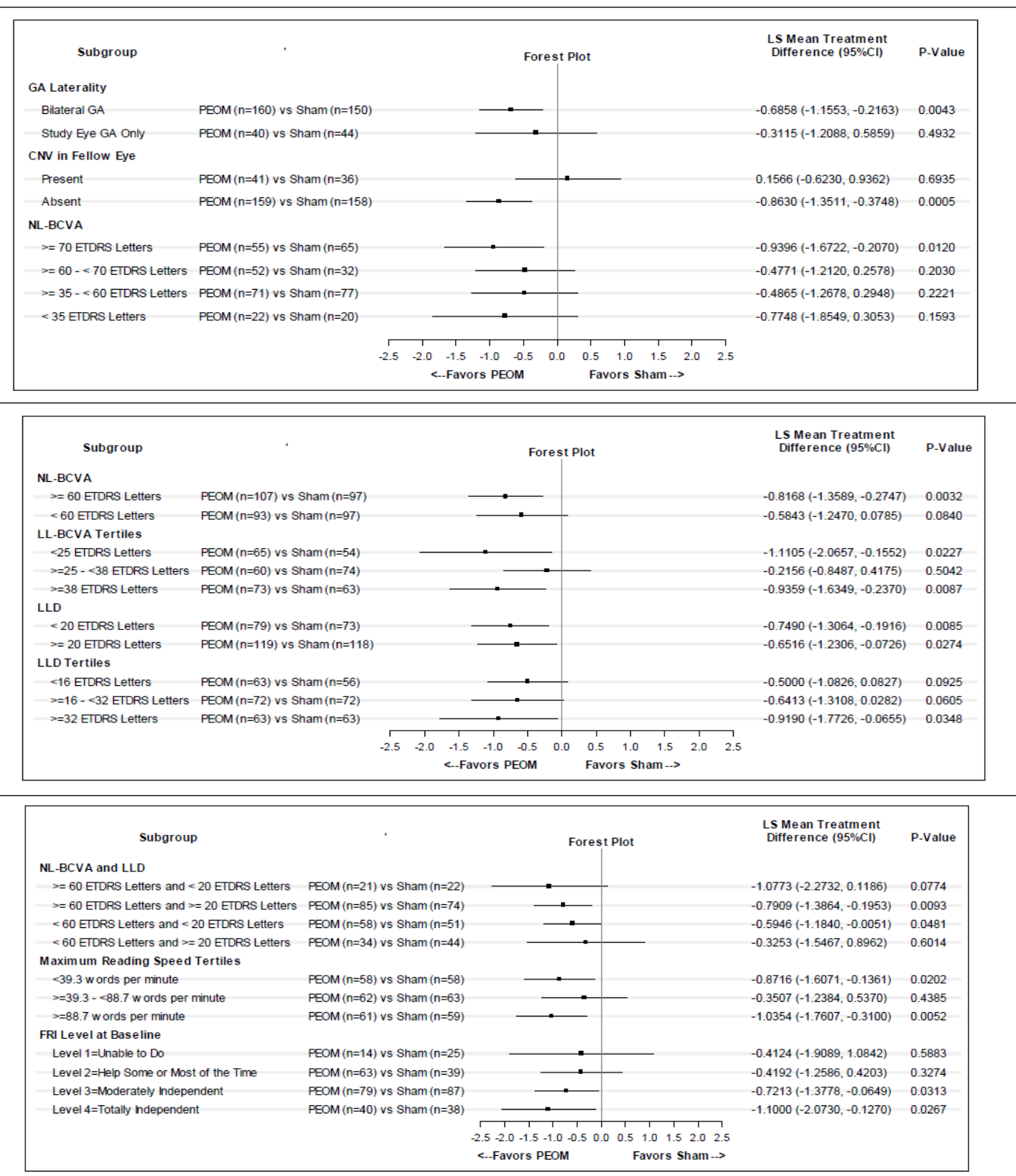




Source: Figure 6 of the Applicant's Month 24 study report.

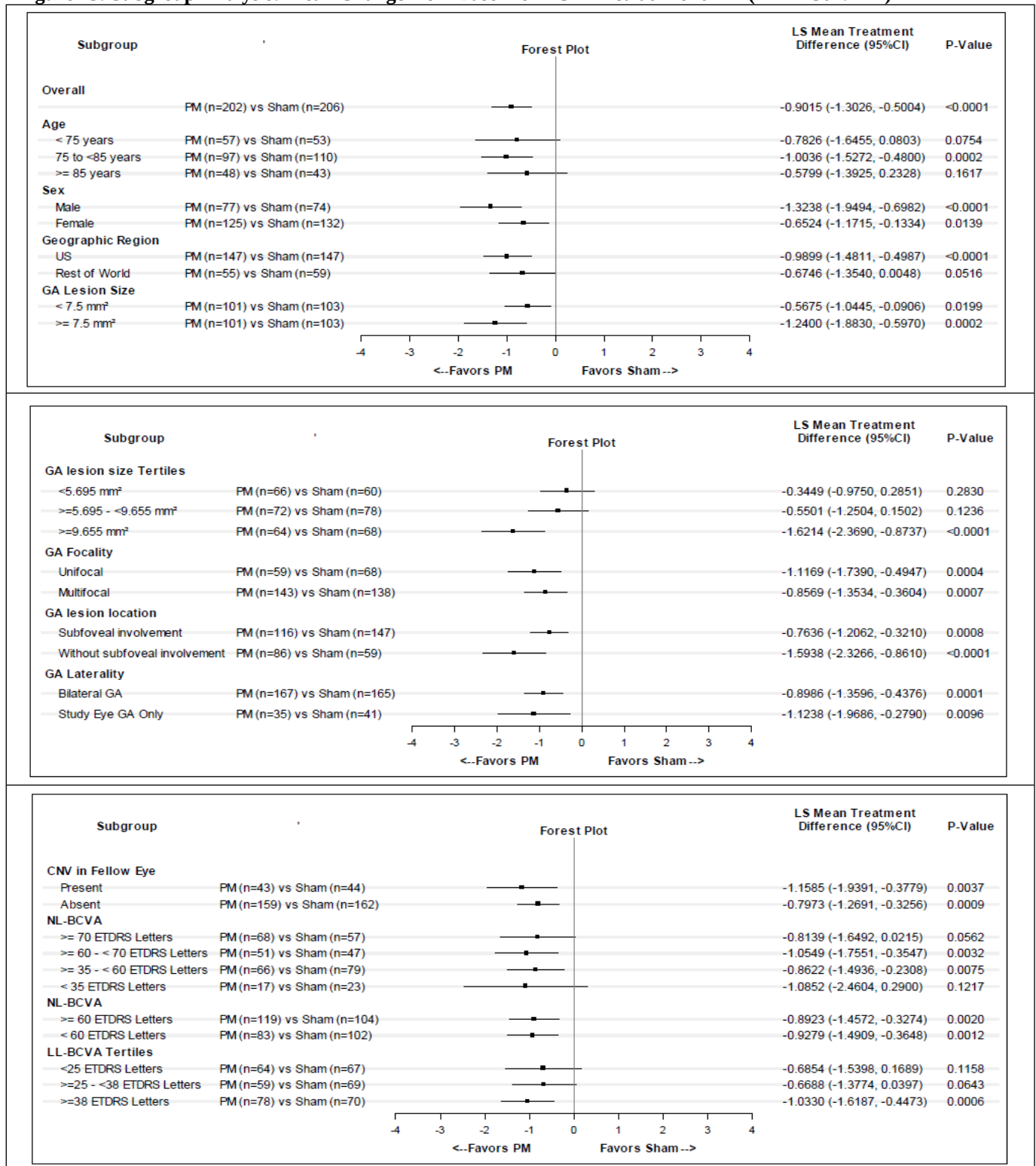
Figure 14: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 24 (APL2-303: PEOM)

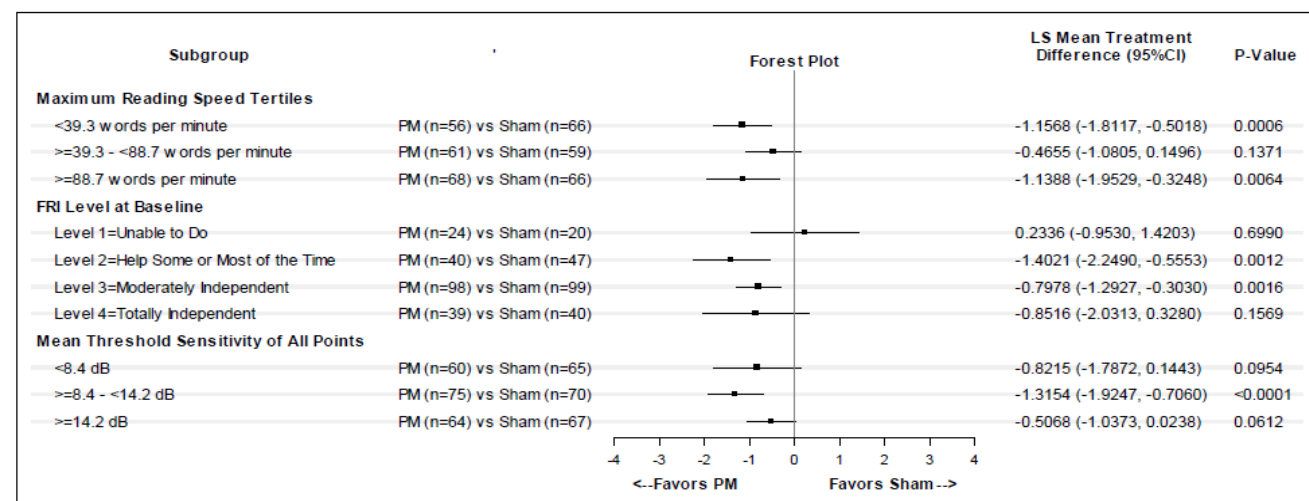
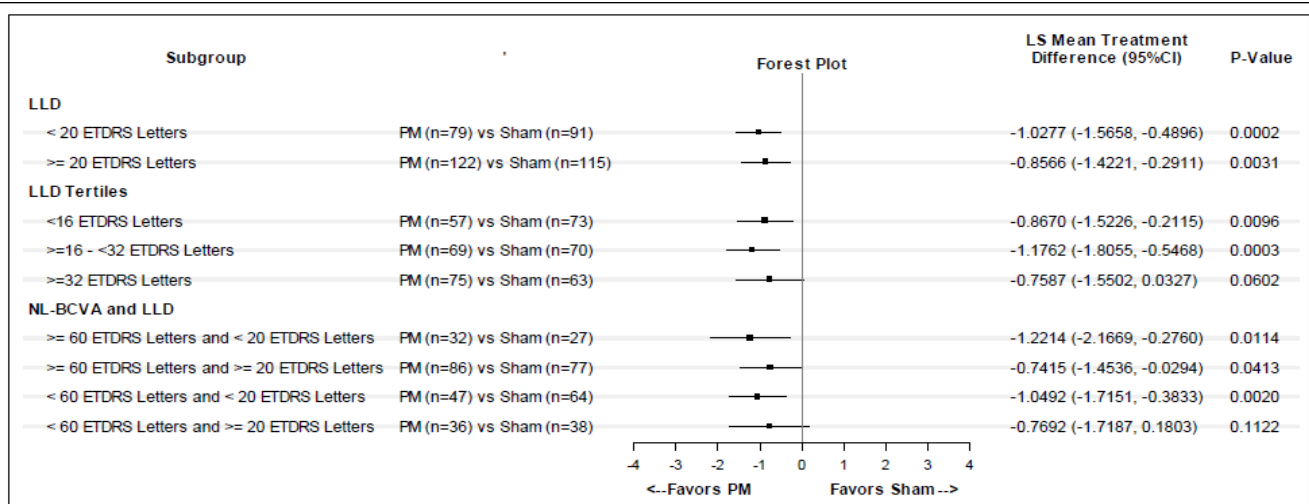




Source: Figure 7 of the Applicant's Month 24 study report.

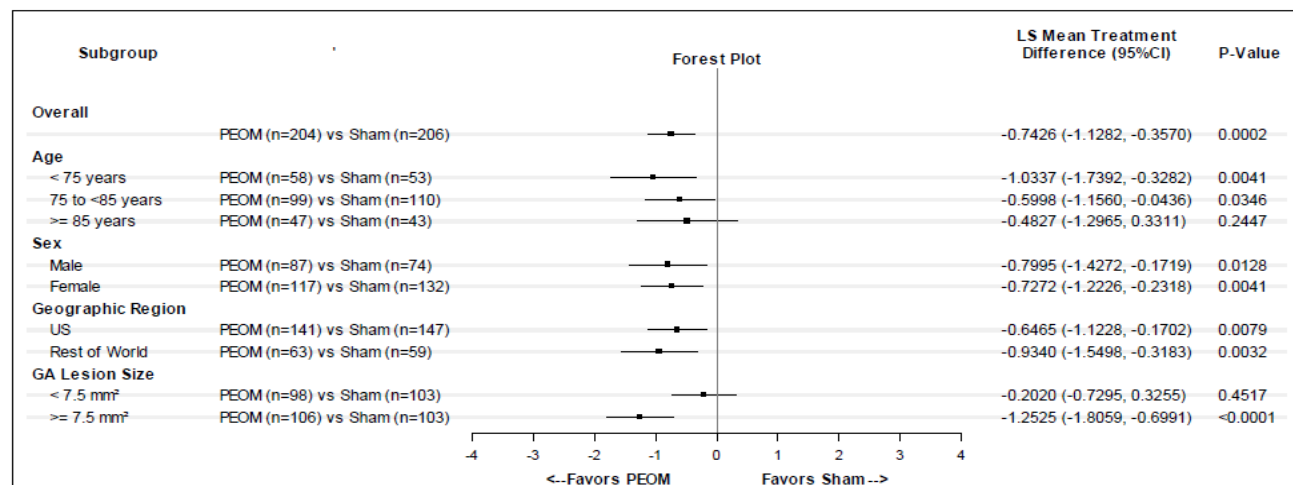
Figure 15: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 24 (APL2-304: PM)

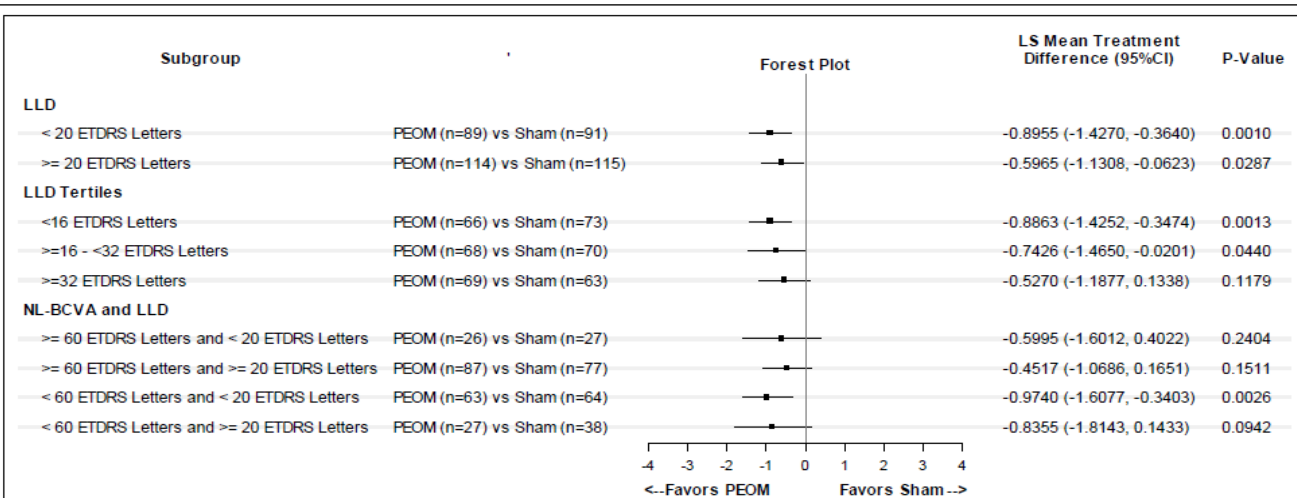
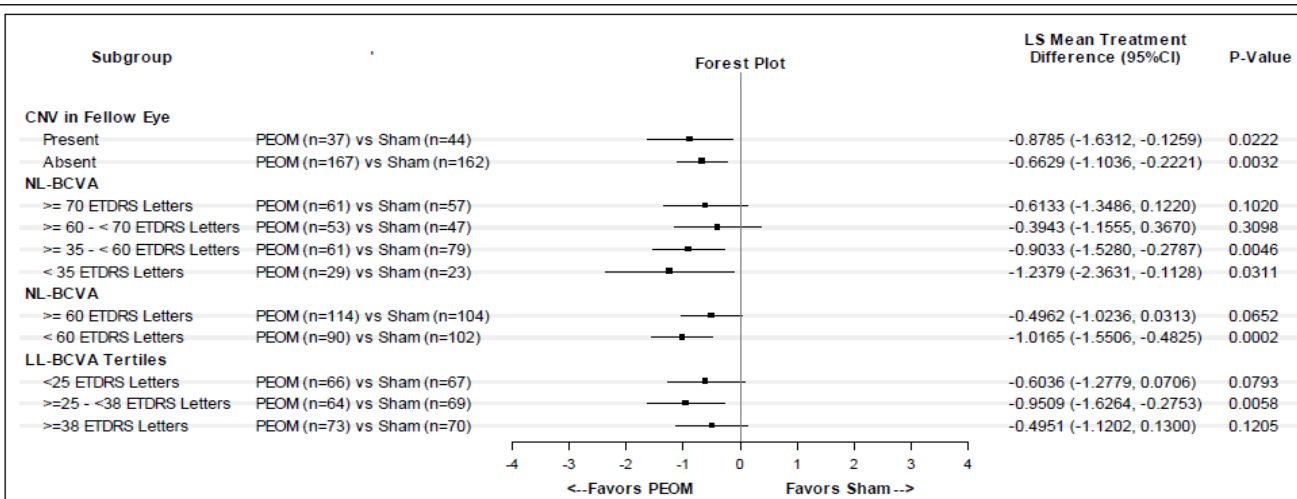
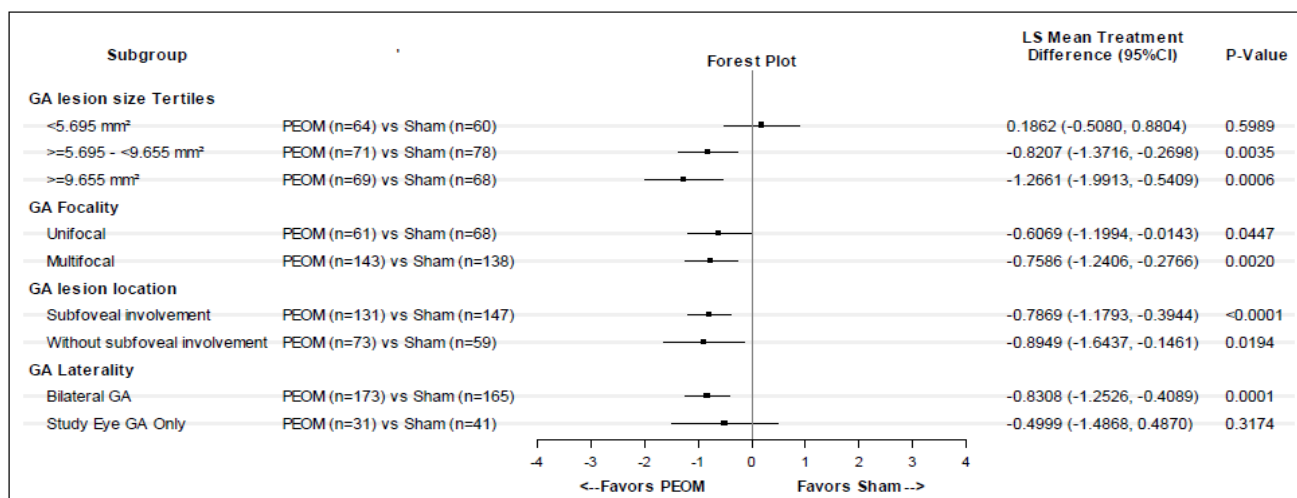


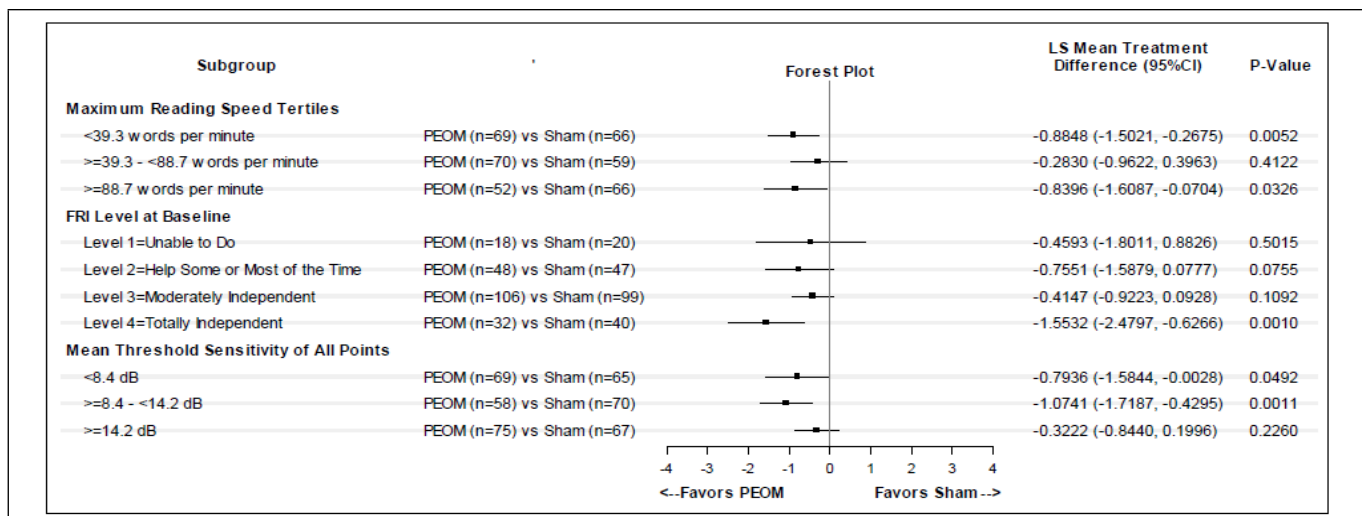


Source: Figure 6 of the Applicant's Month 24 study report.

Figure 16: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 24 (APL2-304: PEOM)







Source: Figure 7 of the Applicant's Month 24 study report.

Table 28: Tipping Point Analyses of Mean Change from Baseline at Month 12 (APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2292	(-0.4682, 0.0097)	0.0601
	0.12	-0.2281	(-0.4669, 0.0106)	0.0611
	0.18	-0.2268	(-0.4649, 0.0113)	0.0620
	0.24	-0.2230	(-0.4624, 0.0164)	0.0679
	0.30	-0.2209	(-0.4600, 0.0182)	0.0702
	0.36	-0.2173	(-0.4563, 0.0217)	0.0748
	0.42	-0.2143	(-0.4531, 0.0245)	0.0786
	0.48	-0.2127	(-0.4515, 0.0260)	0.0808
	0.54	-0.2069	(-0.4458, 0.0321)	0.0898
	0.60	-0.2081	(-0.4478, 0.0316)	0.0888
	0.66	-0.2042	(-0.4435, 0.0351)	0.0944
PEOM vs Sham Pooled	0.06	-0.2129	(-0.4460, 0.0203)	0.0735
	0.12	-0.2109	(-0.4445, 0.0227)	0.0768
	0.18	-0.2104	(-0.4443, 0.0234)	0.0778
	0.24	-0.2073	(-0.4415, 0.0268)	0.0827
	0.30	-0.2041	(-0.4380, 0.0298)	0.0872
	0.36	-0.2010	(-0.4346, 0.0325)	0.0916
	0.42	-0.1992	(-0.4329, 0.0344)	0.0946
	0.48	-0.1980	(-0.4327, 0.0367)	0.0983
	0.54	-0.1931	(-0.4275, 0.0414)	0.1065
	0.60	-0.1921	(-0.4274, 0.0431)	0.1094
	0.66	-0.1911	(-0.4261, 0.0438)	0.1109
	0.72	-0.1867	(-0.4207, 0.0474)	0.1180

Source: Table 14.2.1.2.2 of the Applicant's study report. The shift parameters were applied to imputed data due to AE or Lack of efficacy.

Table 29: Tipping Point Analyses of Mean Change from Baseline at Month 12 [2] (APL2-303)

	Estimate of LS Mean	
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Treatment Comparison	Shift Parameter	Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2276	(-0.4661, 0.0110)	0.0615
	0.12	-0.2335	(-0.4744, 0.0074)	0.0575
	0.18	-0.2293	(-0.4688, 0.0102)	0.0606
	0.24	-0.2306	(-0.4698, 0.0087)	0.0589
	0.30	-0.2320	(-0.4704, 0.0065)	0.0565
	0.36	-0.2314	(-0.4715, 0.0087)	0.0589
	0.42	-0.2242	(-0.4635, 0.0151)	0.0663
	0.48	-0.2263	(-0.4667, 0.0141)	0.0650
	0.54	-0.2295	(-0.4686, 0.0096)	0.0599
	0.60	-0.2256	(-0.4632, 0.0120)	0.0628
	0.66	-0.2202	(-0.4595, 0.0190)	0.0712
PEOM vs Sham Pooled	0.06	-0.2121	(-0.4452, 0.0209)	0.0745
	0.12	-0.2140	(-0.4477, 0.0197)	0.0727
	0.18	-0.2142	(-0.4496, 0.0213)	0.0746
	0.24	-0.2123	(-0.4453, 0.0206)	0.0740
	0.30	-0.2089	(-0.4431, 0.0253)	0.0804
	0.36	-0.2084	(-0.4422, 0.0254)	0.0807
	0.42	-0.2088	(-0.4415, 0.0239)	0.0786
	0.48	-0.2081	(-0.4430, 0.0268)	0.0826
	0.54	-0.2076	(-0.4431, 0.0279)	0.0840
	0.60	-0.2060	(-0.4397, 0.0277)	0.0840
	0.66	-0.2027	(-0.4373, 0.0319)	0.0903
	0.72	-0.2026	(-0.4366, 0.0314)	0.0897

Source: Table 14.2.1.2.1 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 30: Tipping Point Analyses of Rate of GA Growth (Slope: Month 12: APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2078	(-0.4388, 0.0232)	0.0779
	0.12	-0.2131	(-0.4457, 0.0196)	0.0726
	0.18	-0.2097	(-0.4433, 0.0239)	0.0785
	0.24	-0.2118	(-0.4429, 0.0193)	0.0724
	0.30	-0.2137	(-0.4455, 0.0181)	0.0708
	0.36	-0.2138	(-0.4469, 0.0192)	0.0721
	0.42	-0.2065	(-0.4391, 0.0261)	0.0819
	0.48	-0.2090	(-0.4414, 0.0234)	0.0780
	0.54	-0.2085	(-0.4406, 0.0237)	0.0784
	0.60	-0.2077	(-0.4389, 0.0236)	0.0784
	0.66	-0.2040	(-0.4376, 0.0296)	0.0869
PEOM vs Sham Pooled	0.06	-0.2216	(-0.4491, 0.0060)	0.0563
	0.12	-0.2243	(-0.4534, 0.0049)	0.0551
	0.18	-0.2235	(-0.4539, 0.0069)	0.0573
	0.24	-0.2227	(-0.4504, 0.0050)	0.0552
	0.30	-0.2193	(-0.4489, 0.0102)	0.0611
	0.42	-0.2193	(-0.4483, 0.0098)	0.0606
	0.48	-0.2199	(-0.4493, 0.0094)	0.0602
	0.54	-0.2173	(-0.4476, 0.0130)	0.0644
	0.60	-0.2171	(-0.4462, 0.0121)	0.0634
	0.66	-0.2147	(-0.4451, 0.0157)	0.0677
	0.72	-0.2135	(-0.4429, 0.0159)	0.0681

Source: Table 14.2.1.3.15 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 31: Tipping Point Analyses of Mean Change from Baseline at Month 12 (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4084	(-0.6376, -0.1792)	0.0005
	0.12	-0.4044	(-0.6332, -0.1757)	0.0005
	0.18	-0.4036	(-0.6319, -0.1754)	0.0005
	0.24	-0.3970	(-0.6255, -0.1685)	0.0007
	0.30	-0.3942	(-0.6229, -0.1654)	0.0007
	0.36	-0.3885	(-0.6173, -0.1598)	0.0009
	0.42	-0.3865	(-0.6151, -0.1579)	0.0009
	0.48	-0.3841	(-0.6127, -0.1555)	0.0010
	0.54	-0.3790	(-0.6079, -0.1501)	0.0012
	0.60	-0.3752	(-0.6041, -0.1463)	0.0013
	0.66	-0.3718	(-0.6012, -0.1424)	0.0015
	0.72	-0.3672	(-0.5964, -0.1380)	0.0017
PEOM vs Sham Pooled	0.06	-0.3140	(-0.5386, -0.0894)	0.0061
	0.12	-0.3113	(-0.5363, -0.0864)	0.0067
	0.18	-0.3091	(-0.5343, -0.0839)	0.0072
	0.24	-0.3071	(-0.5317, -0.0826)	0.0073
	0.30	-0.3046	(-0.5295, -0.0797)	0.0079
	0.36	-0.3005	(-0.5253, -0.0756)	0.0088
	0.42	-0.2995	(-0.5244, -0.0745)	0.0091
	0.48	-0.2971	(-0.5224, -0.0718)	0.0097
	0.54	-0.2957	(-0.5207, -0.0706)	0.0100
	0.60	-0.2922	(-0.5174, -0.0671)	0.0110
	0.66	-0.2906	(-0.5159, -0.0652)	0.0115
	0.72	-0.2878	(-0.5132, -0.0624)	0.0123

Source: Table 14.2.1.2.2 of the Applicant's study report. The shift parameters were applied to imputed data due to AE or Lack of efficacy.

Table 32: Tipping Point Analyses of Mean Change from Baseline at Month 12 [2] (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4173	(-0.6476, -0.1870)	0.0004
	0.12	-0.4142	(-0.6426, -0.1859)	0.0004
	0.18	-0.4101	(-0.6387, -0.1814)	0.0004
	0.24	-0.4131	(-0.6407, -0.1855)	0.0004
	0.30	-0.4057	(-0.6343, -0.1771)	0.0005
	0.36	-0.4062	(-0.6344, -0.1781)	0.0005
	0.42	-0.4025	(-0.6319, -0.1732)	0.0006
	0.48	-0.4004	(-0.6294, -0.1713)	0.0006
	0.54	-0.4052	(-0.6348, -0.1755)	0.0005
	0.60	-0.4054	(-0.6366, -0.1742)	0.0006
	0.66	-0.4011	(-0.6281, -0.1741)	0.0005
	0.72	-0.4037	(-0.6323, -0.1750)	0.0005
PEOM vs Sham Pooled	0.06	-0.3226	(-0.5444, -0.1008)	0.0044
	0.12	-0.3154	(-0.5396, -0.0913)	0.0058
	0.18	-0.3112	(-0.5354, -0.0869)	0.0065
	0.24	-0.3154	(-0.5398, -0.0909)	0.0059
	0.30	-0.3115	(-0.5364, -0.0866)	0.0066
	0.36	-0.3128	(-0.5385, -0.0871)	0.0066
	0.42	-0.3066	(-0.5320, -0.0812)	0.0077
	0.48	-0.3044	(-0.5292, -0.0795)	0.0080
	0.54	-0.3111	(-0.5364, -0.0858)	0.0068
	0.60	-0.3089	(-0.5344, -0.0835)	0.0072

	0.66	-0.3070	(-0.5329, -0.0811)	0.0077
	0.72	-0.3059	(-0.5305, -0.0813)	0.0076

Source: Table 14.2.1.2.1 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 33: Tipping Point Analyses of Rate of GA Growth (Slope: Month 12: APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4095	(-0.6344, -0.1847)	0.0004
	0.12	-0.4076	(-0.6319, -0.1834)	0.0004
	0.18	-0.4058	(-0.6285, -0.1830)	0.0004
	0.24	-0.4078	(-0.6282, -0.1874)	0.0003
	0.30	-0.4005	(-0.6240, -0.1770)	0.0004
	0.36	-0.4019	(-0.6260, -0.1777)	0.0004
	0.42	-0.3963	(-0.6199, -0.1727)	0.0005
	0.48	-0.3953	(-0.6185, -0.1721)	0.0005
	0.54	-0.3998	(-0.6228, -0.1769)	0.0004
	0.60	-0.3999	(-0.6259, -0.1738)	0.0005
	0.66	-0.3977	(-0.6207, -0.1747)	0.0005
PEOM vs Sham Pooled	0.72	-0.3972	(-0.6218, -0.1725)	0.0005
	0.06	-0.3179	(-0.5330, -0.1028)	0.0038
	0.12	-0.3123	(-0.5299, -0.0947)	0.0049
	0.18	-0.3112	(-0.5292, -0.0932)	0.0051
	0.24	-0.3129	(-0.5296, -0.0962)	0.0047
	0.30	-0.3097	(-0.5272, -0.0922)	0.0053
	0.36	-0.3110	(-0.5294, -0.0927)	0.0052
	0.42	-0.3057	(-0.5238, -0.0877)	0.0060
	0.48	-0.3031	(-0.5202, -0.0861)	0.0062
	0.54	-0.3090	(-0.5268, -0.0913)	0.0054
	0.60	-0.3085	(-0.5267, -0.0902)	0.0056
	0.66	-0.3071	(-0.5261, -0.0881)	0.0060
	0.72	-0.3040	(-0.5221, -0.0859)	0.0063

Source: Table 14.2.1.3.15 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 34: Tipping Point Analyses of Mean Change from Baseline at Month 18 (APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.3851	(-0.7213, -0.0488)	0.0248
	0.18	-0.3684	(-0.7017, -0.0350)	0.0303
	0.27	-0.3801	(-0.7144, -0.0457)	0.0259
	0.36	-0.3734	(-0.7083, -0.0386)	0.0288
	0.45	-0.3673	(-0.6972, -0.0374)	0.0291
	0.54	-0.3622	(-0.6931, -0.0314)	0.0319
	0.63	-0.3546	(-0.6901, -0.0191)	0.0383
	0.72	-0.3634	(-0.6986, -0.0282)	0.0336
	0.81	-0.3553	(-0.6861, -0.0244)	0.0353
	0.90	-0.3499	(-0.6829, -0.0170)	0.0394
	0.99	-0.3484	(-0.6817, -0.0151)	0.0405
PEOM vs Sham Pooled	1.08	-0.3372	(-0.6711, -0.0033)	0.0477
	0.09	-0.3828	(-0.7200, -0.0455)	0.0261
	0.18	-0.3691	(-0.7029, -0.0353)	0.0302
	0.27	-0.3762	(-0.7101, -0.0422)	0.0273
	0.36	-0.3715	(-0.7060, -0.0370)	0.0295
	0.45	-0.3701	(-0.7003, -0.0400)	0.0280
	0.54	-0.3639	(-0.6976, -0.0303)	0.0325

	0.63	-0.3615	(-0.6977, -0.0252)	0.0351
	0.72	-0.3664	(-0.6990, -0.0339)	0.0308
	0.81	-0.3589	(-0.6917, -0.0262)	0.0345
	0.90	-0.3522	(-0.6861, -0.0183)	0.0387
	0.99	-0.3479	(-0.6817, -0.0141)	0.0411
	1.08	-0.3473	(-0.6819, -0.0126)	0.0420

Source: Table 14.2.1.2.2 of the Response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 35: Tipping Point Analyses of Rate of GA Growth (Slope: Month 18 [2]; APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.3735	(-0.7037, -0.0432)	0.0267
	0.18	-0.3560	(-0.6856, -0.0265)	0.0342
	0.27	-0.3673	(-0.6950, -0.0395)	0.0281
	0.36	-0.3589	(-0.6884, -0.0293)	0.0328
	0.45	-0.3537	(-0.6791, -0.0283)	0.0331
	0.54	-0.3483	(-0.6749, -0.0218)	0.0366
	0.63	-0.3426	(-0.6731, -0.0120)	0.0422
	0.72	-0.3507	(-0.6812, -0.0201)	0.0376
	0.81	-0.3436	(-0.6706, -0.0166)	0.0395
	0.90	-0.3380	(-0.6661, -0.0099)	0.0435
	0.99	-0.3366	(-0.6643, -0.0089)	0.0441
PEOM vs Sham Pooled	1.08	-0.3250	(-0.6549, 0.0049)	0.0535
	0.09	-0.4147	(-0.7479, -0.0816)	0.0147
	0.18	-0.4009	(-0.7328, -0.0690)	0.0179
	0.27	-0.4068	(-0.7378, -0.0759)	0.0160
	0.36	-0.4008	(-0.7328, -0.0688)	0.0180
	0.45	-0.3989	(-0.7262, -0.0716)	0.0169
	0.54	-0.3952	(-0.7250, -0.0654)	0.0188
	0.63	-0.3915	(-0.7243, -0.0586)	0.0212
	0.72	-0.3986	(-0.7279, -0.0693)	0.0177
	0.81	-0.3913	(-0.7204, -0.0623)	0.0198
	0.90	-0.3859	(-0.7166, -0.0553)	0.0222
	0.99	-0.3791	(-0.7095, -0.0488)	0.0245
	1.08	-0.3789	(-0.7116, -0.0463)	0.0256

Source: Table 14.2.1.3.15 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 36: Tipping Point Analyses of Mean Change from Baseline at Month 18 (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.6569	(-0.9635, -0.3502)	<0.0001
	0.18	-0.6539	(-0.9609, -0.3469)	<0.0001
	0.27	-0.6511	(-0.9610, -0.3413)	<0.0001
	0.36	-0.6541	(-0.9612, -0.3469)	<0.0001
	0.45	-0.6521	(-0.9618, -0.3425)	<0.0001
	0.54	-0.6514	(-0.9578, -0.3449)	<0.0001
	0.63	-0.6536	(-0.9606, -0.3465)	<0.0001
	0.72	-0.6418	(-0.9520, -0.3316)	<0.0001
	0.81	-0.6368	(-0.9425, -0.3312)	<0.0001
	0.90	-0.6371	(-0.9458, -0.3284)	<0.0001
	0.99	-0.6405	(-0.9522, -0.3288)	<0.0001
PEOM vs Sham Pooled	1.08	-0.6311	(-0.9388, -0.3234)	<0.0001
	0.09	-0.4923	(-0.8014, -0.1833)	0.0018
	0.18	-0.4870	(-0.7955, -0.1786)	0.0020

	0.27	-0.4916	(-0.8014, -0.1818)	0.0019
	0.36	-0.4882	(-0.7953, -0.1811)	0.0018
	0.45	-0.4812	(-0.7907, -0.1717)	0.0023
	0.54	-0.4815	(-0.7908, -0.1721)	0.0023
	0.63	-0.4855	(-0.7927, -0.1783)	0.0020
	0.72	-0.4755	(-0.7817, -0.1693)	0.0023
	0.81	-0.4718	(-0.7792, -0.1644)	0.0026
	0.90	-0.4699	(-0.7772, -0.1626)	0.0027
	0.99	-0.4681	(-0.7754, -0.1609)	0.0028
	1.08	-0.4659	(-0.7753, -0.1565)	0.0032

Source: Table 14.2.1.2.2 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE.

Table 37: Tipping Point Analyses of Rate of GA Growth (Slope: Month 18 [2]; APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.7115	(-1.0132, -0.4098)	<0.0001
	0.18	-0.7080	(-1.0094, -0.4067)	<0.0001
	0.27	-0.7068	(-1.0171, -0.3965)	<0.0001
	0.36	-0.7086	(-1.0118, -0.4055)	<0.0001
	0.45	-0.7047	(-1.0118, -0.3977)	<0.0001
	0.54	-0.7054	(-1.0090, -0.4018)	<0.0001
	0.63	-0.7057	(-1.0105, -0.4010)	<0.0001
	0.72	-0.6957	(-1.0044, -0.3869)	<0.0001
	0.81	-0.6901	(-0.9935, -0.3866)	<0.0001
	0.90	-0.6881	(-0.9953, -0.3808)	<0.0001
	0.99	-0.6963	(-1.0073, -0.3853)	<0.0001
	1.08	-0.6835	(-0.9855, -0.3814)	<0.0001
PEOM vs Sham Pooled	0.09	-0.5354	(-0.8396, -0.2311)	0.0006
	0.18	-0.5317	(-0.8361, -0.2272)	0.0006
	0.27	-0.5341	(-0.8418, -0.2264)	0.0007
	0.36	-0.5305	(-0.8338, -0.2272)	0.0006
	0.45	-0.5233	(-0.8289, -0.2176)	0.0008
	0.54	-0.5250	(-0.8303, -0.2196)	0.0008
	0.63	-0.5282	(-0.8318, -0.2247)	0.0006
	0.72	-0.5173	(-0.8187, -0.2159)	0.0008
	0.81	-0.5143	(-0.8188, -0.2098)	0.0009
	0.90	-0.5130	(-0.8165, -0.2094)	0.0009
	0.99	-0.5122	(-0.8155, -0.2089)	0.0009
	1.08	-0.5095	(-0.8150, -0.2039)	0.0011

Source: Table 14.2.1.3.15 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 38: Tipping Point Analyses of Rate of GA Growth (Slope: Month 24 [2]; APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.12	-0.6783	(-1.0772, -0.2794)	0.0009
	0.24	-0.6809	(-1.0824, -0.2794)	0.0009
	0.36	-0.6624	(-1.0635, -0.2614)	0.0012
	0.48	-0.6254	(-1.0329, -0.2179)	0.0026
	0.60	-0.6182	(-1.0207, -0.2156)	0.0026
	0.72	-0.6015	(-1.0037, -0.1993)	0.0034
	0.84	-0.5713	(-0.9741, -0.1685)	0.0054
	0.96	-0.5589	(-0.9629, -0.1550)	0.0067
	1.08	-0.5452	(-0.9487, -0.1417)	0.0081
	1.20	-0.5251	(-0.9252, -0.1251)	0.0101

PEOM vs Sham Pooled	1.32	-0.5140	(-0.9162, -0.1118)	0.0123
	1.44	-0.5035	(-0.9078, -0.0993)	0.0146
	0.12	-0.6293	(-1.0349, -0.2236)	0.0024
	0.24	-0.6168	(-1.0214, -0.2122)	0.0028
	0.36	-0.6005	(-1.0099, -0.1911)	0.0040
	0.48	-0.5847	(-0.9883, -0.1811)	0.0045
	0.60	-0.5712	(-0.9776, -0.1647)	0.0059
	0.72	-0.5573	(-0.9658, -0.1489)	0.0075
	0.84	-0.5416	(-0.9488, -0.1343)	0.0092
	0.96	-0.5314	(-0.9401, -0.1227)	0.0108
	1.08	-0.5040	(-0.9150, -0.0930)	0.0162
	1.20	-0.5024	(-0.9093, -0.0955)	0.0155
	1.32	-0.4857	(-0.8954, -0.0761)	0.0201
	1.44	-0.4850	(-0.8943, -0.0758)	0.0202

Source: Table 14.5.9.2.4 of the Applicant's Month 24 study reports. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 39: Tipping Point Analyses of Rate of GA Growth (Slope: Month 24 [2]; APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.12	-0.9942	(-1.3809, -0.6074)	<0.0001
	0.24	-0.9799	(-1.3772, -0.5827)	<0.0001
	0.36	-0.9582	(-1.3488, -0.5676)	<0.0001
	0.48	-0.9354	(-1.3310, -0.5398)	<0.0001
	0.60	-0.9198	(-1.3073, -0.5323)	<0.0001
	0.72	-0.8971	(-1.2875, -0.5066)	<0.0001
	0.84	-0.8683	(-1.2531, -0.4835)	<0.0001
	0.96	-0.8562	(-1.2465, -0.4659)	<0.0001
	1.08	-0.8422	(-1.2319, -0.4524)	<0.0001
	1.20	-0.8265	(-1.2221, -0.4309)	<0.0001
	1.32	-0.8082	(-1.1966, -0.4197)	<0.0001
PEOM vs Sham Pooled	1.44	-0.8000	(-1.1998, -0.4002)	<0.0001
	0.12	-0.7993	(-1.1774, -0.4212)	<0.0001
	0.24	-0.7905	(-1.1720, -0.4089)	<0.0001
	0.36	-0.7775	(-1.1572, -0.3978)	<0.0001
	0.48	-0.7750	(-1.1566, -0.3934)	<0.0001
	0.60	-0.7472	(-1.1249, -0.3696)	0.0001
	0.72	-0.7386	(-1.1216, -0.3556)	0.0002
	0.84	-0.7203	(-1.0966, -0.3439)	0.0002
	0.96	-0.7056	(-1.0922, -0.3191)	0.0003
	1.08	-0.7058	(-1.0851, -0.3265)	0.0003
	1.20	-0.6840	(-1.0709, -0.2970)	0.0005
	1.32	-0.6802	(-1.0628, -0.2976)	0.0005
	1.44	-0.6635	(-1.0483, -0.2786)	0.0007

Source: Table 14.5.9.2.4 of the Applicant's Month 24 study reports. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 40: Patient Disposition Without Pooling Sham (Month 12: Study APL2-303: ITT)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacopla n pooled (N = 425) n (%)	SM (N = 106) n (%)	SEOM (N = 106) n (%)	Sham pooled (N = 212) n (%)	Total (N = 637) n (%)
Randomized, n	206	208	414	102	105	207	621
Completed treatment through Month 12, n (%)	182 (88.3)	188 (90.4)	370 (89.4)	89 (87.3)	90 (85.7)	179 (86.5)	549 (88.4)
Continued in the study to Month 12 after treatment discontinuation, n (%)	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Completed study through Month 12, n (%)	183 (88.8)	188 (90.4)	371 (89.6)	89 (87.3)	90 (85.7)	179 (86.5)	550 (88.6)
Discontinued from treatment through Month 12 ^a , n (%)	24 (11.7)	20 (9.6)	44 (10.6)	13 (12.7)	14 (13.3)	27 (13.0)	71 (11.4)
Primary reason for discontinuation from treatment prior to Month 12							
Adverse event	1 (0.5)	4 (1.9)	5 (1.2)	5 (4.9)	1 (1.0)	6 (2.9)	11 (1.8)
Lost to follow-up	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	15 (7.3)	9 (4.3)	24 (5.8)	6 (5.9)	8 (7.6)	14 (6.8)	38 (6.1)
Pregnancy	0	0	0	0	0	0	0
Death ^b	5 (2.4)	0	5 (1.2)	0	2 (1.9)	2 (1.0)	7 (1.1)
Because of COVID-19 impact ^c	1 (0.5)	6 (2.9)	7 (1.7)	2 (2.0)	3 (2.9)	5 (2.4)	12 (1.9)
Other ^d	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Completed study through Month 12, n (%)	184 (86.4)	190 (89.6)	374 (88.0)	95 (89.6)	96 (90.6)	191 (90.1)	565 (88.7)
Discontinued from study through Month 12, n (%)	29 (13.6)	22 (10.4)	51 (12.0)	11 (10.4)	10 (9.4)	21 (9.9)	72 (11.3)
Primary reason for discontinuation from study prior to Month 12, n (%)							
Adverse event	1 (0.5)	4 (1.9)	5 (1.2)	4 (3.9)	1 (1.0)	5 (2.4)	10 (1.6)
Lost to follow-up	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	15 (7.3)	10 (4.8)	25 (6.0)	6 (5.9)	9 (8.6)	15 (7.2)	40 (6.4)
Pregnancy	0	0	0	0	0	0	0
Death ^b	5 (2.4)	0	5 (1.2)	1 (1.0)	2 (1.9)	3 (1.4)	8 (1.3)
Due to COVID-19 impact ^c	1 (0.5)	6 (2.9)	7 (1.7)	2 (2.0)	3 (2.9)	5 (2.4)	12 (1.9)
Other	0	0	0	0	0	0	0

Source: Table 12 of the Applicant's study report.

a Includes reasons for subjects who discontinued from treatment only and those who discontinued from treatment and study.

b Two subjects in the PEOM group (Subject (b) (6) and Subject (b) (6)) were incorrectly reported as having discontinued because of an AE. These have been corrected in the APL2-303 CSR erratum to death as the reason for discontinuation.

c Any discontinuation due to COVID-19 impact except for adverse event of COVID-19. Instances of adverse event of COVID-19 were captured under the adverse event category.

d Subject (b) (6) (PEOM group) was incorrectly reported as discontinuing treatment because of 'other.' This has been corrected in the APL2-303 CSR erratum to reflect that the subject withdrew consent and should not have been reported as discontinuing treatment for other reasons.

Table 41: Patient Disposition Without Pooling Sham (Month 12: Study APL2-304: ITT)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacopla n pooled (N = 425)	SM (N = 106) n (%)	SEOM (N = 106) n (%)	Sham pooled (N = 212) n (%)	Total (N = 637) n (%)
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			n (%)				
Randomized, n	213	212	425	106	106	212	637
Completed treatment through Month 12, n (%)	183 (85.9)	188 (88.7)	371 (87.3)	95 (89.6)	96 (90.6)	191 (90.1)	562 (88.2)
Discontinued from treatment prior to Month 12, n (%)	29 (13.6)	24 (11.3)	53 (12.5)	11 (10.4)	10 (9.4)	21 (9.9)	74 (11.6)
Continued in the study to Month 12 after treatment discontinuation, n (%)	1 (0.5)	2 (0.9)	3 (0.7)	0	0	0	3 (0.5)
Not treated, n (%)	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Primary reason for discontinuation from treatment prior to Month 12 ^a							
Adverse event	3 (1.4)	7 (3.3)	10 (2.4)	1 (0.9)	1 (0.9)	2 (0.9)	12 (1.9)
Lost to follow-up	2 (0.9)	1 (0.5)	3 (0.7)	0	1 (0.9)	1 (0.5)	4 (0.6)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	13 (6.1)	11 (5.2)	24 (5.6)	5 (4.7)	4 (3.8)	9 (4.2)	33 (5.2)
Pregnancy	0	0	0	0	0	0	0
Death	7 (3.3)	3 (1.4)	10 (2.4)	4 (3.8)	0	4 (1.9)	14 (2.2)
Because of COVID impact ^b	4 (1.9)	2 (0.9)	6 (1.4)	1 (0.9)	4 (3.8)	5 (2.4)	11 (1.7)
Other	0	0	0	0	0	0	0
Completed study through Month 12, n (%)	184 (86.4)	190 (89.6)	374 (88.0)	95 (89.6)	96 (90.6)	191 (90.1)	565 (88.7)
Discontinued from study prior to Month 12, n (%)	29 (13.6)	22 (10.4)	51 (12.0)	11 (10.4)	10 (9.4)	21 (9.9)	72 (11.3)
Primary reason for discontinuation from study prior to Month 12, n (%)							
Adverse event	3 (1.4)	5 (2.4)	8 (1.9)	1 (0.9)	1 (0.9)	2 (0.9)	10 (1.6)
Lost to follow-up	2 (0.9)	1 (0.5)	3 (0.7)	0	1 (0.9)	1 (0.5)	4 (0.6)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	14 (6.6)	11 (5.2)	25 (5.9)	5 (4.7)	4 (3.8)	9 (4.2)	34 (5.3)
Pregnancy	0	0	0	0	0	0	0
Death	7 (3.3)	3 (1.4)	10 (2.4)	4 (3.8)	0	4 (1.9)	14 (2.2)
Because of COVID impact ^b	3 (1.4)	2 (0.9)	5 (1.2)	1 (0.9)	4 (3.8)	5 (2.4)	10 (1.6)
Other	0	0	0	0	0	0	0

Source: Table 12 of the Applicant's study reports. a Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study. b Any discontinuation because of COVID impact except for adverse event of COVID. Instances of adverse event of COVID are captured under the adverse event category.

Table 42: Baseline and Demographic Characteristics Without Pooling Sham (Study APL-303)

	PM (N = 202)	PEOM (N=205)	Pegcetacoplan pooled (N = 407)	SM (N = 104)	SEOM (N = 102)	Sham pooled (N = 206)	Total (N = 613)
Sex, n (%)							
Female	118 (58.7)	120 (60.0)	238 (59.4)	61 (62.9)	61 (62.9)	122 (62.9)	360 (60.5)
Male	83 (41.3)	80 (40.0)	163 (40.6)	36 (37.1)	36 (37.1)	72 (37.1)	235 (39.5)
Age, years							
Mean (SD)	78.7 (6.91)	79.2 (7.07)	78.9 (6.99)	79.0 (7.35)	78.2 (7.25)	78.6 (7.29)	78.8 (7.08)
Minimum, maximum	60, 93	61, 93	60, 93	61, 94	61, 96	61, 96	60, 96
Age group, n (%)							

<65 years	5 (2.5)	6 (3.0)	11 (2.7)	3 (3.1)	5 (5.2)	8 (4.1)	19 (3.2)
≥65-<75 years	46 (22.9)	51 (25.5)	97 (24.2)	26 (26.8)	23 (23.7)	49 (25.3)	146 (24.5)
≥75-<85 years	110 (54.7)	95 (47.5)	205 (51.1)	40 (41.2)	50 (51.5)	90 (46.4)	295 (49.6)
≥85 years	40 (19.9)	48 (24.0)	88 (21.9)	28 (28.9)	19 (19.6)	47 (24.2)	135 (22.7)
Geographic region, n (%)							
US	142 (70.6)	122 (61.0)	264 (65.8)	63 (64.9)	59 (60.8)	122 (62.9)	386 (64.9)
ROW	59 (29.4)	78 (39.0)	137 (34.2)	34 (35.1)	38 (39.2)	72 (37.1)	209 (35.1)
Country, n(%)							
US	142 (70.6)	122 (61.0)	264 (65.8)	63 (64.9)	59 (60.8)	122 (62.9)	386 (64.9)
Argentina	18 (9.0)	21 (10.5)	39 (9.7)	10 (10.3)	8 (8.2)	18 (9.3)	57 (9.6)
Brazil	9 (4.5)	13 (6.5)	22 (5.5)	2 (2.1)	8 (8.2)	10 (5.2)	32 (5.4)
France	12 (6.0)	13 (6.5)	25 (6.2)	3 (3.1)	4 (4.1)	7 (3.6)	32 (5.4)
Germany	3 (1.5)	4 (2.0)	7 (1.7)	5 (5.2)	5 (5.2)	10 (5.2)	17 (2.9)
UK	4 (2.0)	6 (3.0)	10 (2.5)	3 (3.1)	3 (3.1)	6 (3.1)	16 (2.7)
Poland	2 (1.0)	7 (3.5)	9 (2.2)	2 (2.1)	3 (3.1)	5 (2.6)	14 (2.4)
Czech Republic	2 (1.0)	7 (3.5)	9 (2.2)	1 (1.0)	3 (3.1)	4 (2.1)	13 (2.2)
Australia	3 (1.5)	1 (0.5)	4 (1.0)	1 (1.0)	3 (3.1)	4 (2.1)	8 (1.3)
Canada	2 (1.0)	1 (0.5)	3 (0.7)	4 (4.1)	0	4 (2.1)	7 (1.2)
Israel	0	4 (2.0)	4 (1.0)	2 (2.1)	0	2 (1.0)	6 (1.0)
Italy	2 (1.0)	1 (0.5)	3 (0.7)	0	0	0	3 (0.5)
Spain	1 (0.5)	0	1 (0.2)	1 (1.0)	1 (1.0)	2 (1.0)	3 (0.5)
New Zealand	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Race, n (%)							
White	187 (93.0)	185 (92.5)	372 (92.8)	94 (96.9)	93 (95.9)	187 (96.4)	559 (93.9)
Not Reported	12 (6.0)	10 (5.0)	22 (5.5)	3 (3.1)	3 (3.1)	6 (3.1)	28 (4.7)
Missing	1 (0.5)	1 (0.5)	2 (0.5)	0	1 (1.0)	1 (0.5)	3 (0.5)
Black or African American	1 (0.5)	1 (0.5)	2 (0.5)	0	0	0	2 (0.3)
Asian	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Multiple	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Unknown	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Ethnicity, n (%)							
Hispanic or Latino	32 (15.9)	34 (17.0)	66 (16.5)	13 (13.4)	16 (16.5)	29 (14.9)	95 (16.0)
Not Hispanic or Latino	158 (78.6)	151 (75.5)	309 (77.1)	82 (84.5)	77 (79.4)	159 (82.0)	468 (78.7)
Not reported ^a	10 (5.0)	11 (5.5)	21 (5.2)	2 (2.1)	4 (4.1)	6 (3.1)	27 (4.5)
Unknown	0	3 (1.5)	3 (0.7)	0	0	0	3 (0.5)
Missing	1 (0.5)	1 (0.5)	2 (0.5)	0	0	0	2 (0.3)
Tobacco use history, n (%)							
Ever	103 (51.2)	100 (50.0)	203 (50.6)	43 (44.3)	43 (44.3)	86 (44.3)	289 (48.6)
Never	98 (48.8)	100 (50.0)	198 (49.4)	54 (55.7)	54 (55.7)	108 (55.7)	306 (51.4)

Source: Table 14 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Australia, Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

Table 43: Baseline and Demographic Characteristics Without Pooling Sham (Study APL-304)

	PM (N = 202)	PEOM (N=205)	Pegcetacopla n pooled (N = 407)	SM (N = 104)	SEOM (N = 102)	Sham pooled (N = 206)	Total (N = 613)
Sex, n (%)							
Female	125 (61.9)	117 (57.1)	242 (59.5)	64 (61.5)	69 (67.6)	133 (64.6)	375 (61.2)
Male	77 (38.1)	88 (42.9)	165 (40.5)	40 (38.5)	33 (32.4)	73 (35.4)	238 (38.8)
Age, years							
Mean (SD)	78.8 (7.24)	78.1 (7.74)	78.4 (7.49)	78.4 (7.38)	78.8 (7.18)	78.6 (7.26)	78.5 (7.41)
Minimum, maximum	61, 95	60, 100	60, 100	60, 93	63, 92	60, 93	60, 100
Age group, n (%)							
<65 years	5 (2.5)	9 (4.4)	14 (3.4)	6 (5.8)	3 (2.9)	9 (4.4)	23 (3.8)
≥65-<75 years	52 (25.7)	50 (24.4)	102 (25.1)	23 (22.1)	22 (21.6)	45 (21.8)	147 (24.0)
≥75-<85 years	97 (48.0)	99 (48.3)	196 (48.2)	54 (51.9)	55 (53.9)	109 (52.9)	305 (49.8)
≥85 years	48 (23.8)	47 (22.9)	95 (23.3)	21 (20.2)	22 (21.6)	43 (20.9)	138 (22.5)
Geographic region, n (%)							
US	147 (72.8)	142 (69.3)	289 (71.0)	73 (70.2)	74 (72.5)	147 (71.4)	436 (71.1)
Rest of world	55 (27.2)	63 (30.7)	118 (29.0)	31 (29.8)	28 (27.5)	59 (28.6)	177 (28.9)
Country, n(%)							
US	147 (72.8)	142 (69.3)	289 (71.0)	73 (70.2)	74 (72.5)	147 (71.4)	436 (71.1)
France	12 (5.9)	14 (6.8)	26 (6.4)	5 (4.8)	10 (9.8)	15 (7.3)	41 (6.7)
Australia	9 (4.5)	14 (6.8)	23 (5.7)	6 (5.8)	4 (3.9)	10 (4.9)	33 (5.4)
Germany	7 (3.5)	8 (3.9)	15 (3.7)	6 (5.8)	5 (4.9)	11 (5.3)	26 (4.2)
Czech Republic	9 (4.5)	7 (3.4)	16 (3.9)	3 (2.9)	2 (2.0)	5 (2.4)	21 (3.4)
Poland	5 (2.5)	5 (2.4)	10 (2.5)	5 (4.8)	4 (3.9)	9 (4.4)	19 (3.1)
Italy	3 (1.5)	3 (1.5)	6 (1.5)	2 (1.9)	1 (1.0)	3 (1.5)	9 (1.5)
UK	1 (0.5)	4 (2.0)	5 (1.2)	3 (2.9)	1 (1.0)	4 (1.9)	9 (1.5)
Israel	3 (1.5)	2 (1.0)	5 (1.2)	1 (1.0)	0	1 (0.5)	6 (1.0)
Netherlands	3 (1.5)	1 (0.5)	4 (1.0)	0	0	0	4 (0.7)
New Zealand	1 (0.5)	2 (1.0)	3 (0.7)	0	1 (1.0)	1 (0.5)	4 (0.7)
Spain	1 (0.5)	3 (1.5)	4 (1.0)	0	0	0	4 (0.7)
Brazil	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Race, n (%)							
Asian	3 (1.5)	1 (0.5)	4 (1.0)	0	2 (2.0)	2 (1.0)	6 (1.0)
Black or African	2 (1.0)	0	2 (0.5)	0	0	0	2 (0.3)
White	185 (91.6)	189 (92.2)	374 (91.9)	96 (92.3)	91 (89.2)	187 (90.8)	561 (91.5)
Unknown	0	1 (0.5)	1 (0.2)	3 (2.9)	0	3 (1.5)	4 (0.7)
Not reported	12 (5.9)	12 (5.9)	24 (5.9)	5 (4.8)	9 (8.8)	14 (6.8)	38 (6.2)
Missing	0	2 (1.0)	2 (0.5)	0	0	0	2 (0.3)
Ethnicity, n (%)							
Hispanic or Latino	4 (2.0)	7 (3.4)	11 (2.7)	4 (3.8)	0	4 (1.9)	15 (2.4)
Not Hispanic or Latino	184 (91.1)	186 (90.7)	370 (90.9)	93 (89.4)	94 (92.2)	187 (90.8)	557 (90.9)
Not reported	14 (6.9)	12 (5.9)	26 (6.4)	7 (6.7)	8 (7.8)	15 (7.3)	41 (6.7)
Unknown	0	0	0	0	0	0	0
Tobacco use history, n (%)							
Ever	108 (53.5)	95 (46.3)	203 (49.9)	54 (51.9)	49 (48.0)	103 (50.0)	306 (49.9)
Never	94 (46.5)	110 (53.7)	204 (50.1)	50 (48.1)	53 (52.0)	103 (50.0)	307 (50.1)

Source: Table 14 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

Table 44: Breakdown of Subjects Who Withdrew Consent (Study APL-303)

	Baseline up to Month 12					Baseline up to Month 18					Post-Month 12 up to Month 18				
	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207
Reason for consent withdrawal															
All reasons	14 (6.8%)	10 (4.8%)	6 (5.9%)	8 (7.6%)	14 (6.8%)	24 (11.7%)	14 (6.7%)	6 (5.9%)	11 (10.5%)	17 (8.2%)	10 (4.9%)	4 (1.9%)	0	3 (2.9%)	3 (1.4%)
Poor general health	4	1	0	2	2	5	2	0	2	2	1	1	0	0	0
Travel to site too difficult or moved away	1	2	2	2	4	4	3	2	3	5	3	1	0	1	1
Study burden	2	3	1	2	3	5	4	1	2	3	3	1	0	0	0
Personal reasons	2	2	0	1	1	3	2	0	1	1	1	0	0	0	0
Concerns about study procedures	0	1	1	1	2	0	1	1	2	3	0	0	0	1	1
Concerns about treatment	2	0	1	0	1	3	0	1	0	1	1	0	0	0	0
Reason not specified	3	1	1	0	1	4	2	1	1	2	1	1	0	1	1

Abbreviations: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.
Source: Table 5; Study APL2-303 Table 14.1.2.2.2.

Table 45: Breakdown of Subjects Who Withdrew Consent (Study APL-304)

	Baseline up to Month 12					Baseline up to Month 18					Post-Month 12 up to Month 18				
	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212
Reason for consent withdrawal															
Any reason	13 (6.1%)	12 (5.7%)	5 (4.7%)	4 (3.8%)	9 (4.2%)	21 (9.9%)	14 (6.6%)	8 (7.5%)	6 (5.7%)	14 (6.6%)	8 (3.8%)	2 (0.9%)	3 (2.8%)	2 (1.9%)	5 (2.4%)
Study burden	4	2	1	1	2	7	2	2	2	4	3	0	1	1	2
Poor general health	2	3	1	1	2	4	3	2	2	4	2	0	1	1	2
Concerns about treatment	3	2	0	0	0	3	2	0	0	0	0	0	0	0	0
Travel to site too difficult or moved away	1	1	1	1	2	2	1	2	1	3	1	0	1	0	1
Personal reasons	1	0	1	1	2	1	0	1	1	2	0	0	0	0	0
Missed too many visits (COVID-19 pandemic)	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Reason not specified	2	4	1	0	1	3	6	1	0	1	1	2	0	0	0

Abbreviations: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.
Source: Table 4; Study APL2-304 Table 14.1.2.2.2.

Table 46: Number of Subjects Included in the Analyses Populations (APL2-303)

Populations	PM	PEOM	Pegcetacoplan Pooled	SM	SEOM	Sham Pooled	Total
	(N=206)	(N=208)	(N=414)	(N=102)	(N=105)	(N=207)	(N=621)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intent-to-treat (ITT)	206 (100)	208 (100)	414 (100)	102 (100)	105 (100)	207 (100)	621 (100)
Modified ITT	201 (97.6)	200 (96.2)	401 (96.9)	97 (95.1)	97 (92.4)	194 (93.7)	595 (95.8)
Excluded from mITT	5 (2.4)	8 (3.8)	13 (3.1)	5 (4.9)	8 (7.6)	13 (6.3)	26 (4.2)
No post-baseline value of GA lesion area in the study eye	5 (2.4)	8 (3.8)	13 (3.1)	5 (4.9)	7 (6.7)	12 (5.8)	25 (4.0)
No injection of pegcetacoplan or Sham	0	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)
Per protocol (PP) set	155 (75.2)	163 (78.4)	318 (76.8)	71 (69.6)	80 (76.2)	151 (72.9)	469 (75.5)
Safety Set	206 (100)	208 (100)	414 (100)	102 (100)	104 (99.0)	206 (99.5)	620 (99.8)

Source: Table 14.1.2.1 of the Applicant's study report.

Table 47: Number of Subjects Included in the Analyses Populations (APL2-304)

Populations	PM	PEOM	Pegcetacoplan Pooled	SM	SEOM	Sham Pooled	Total
	(N=213)	(N=212)	(N=425)	(N=106)	(N=106)	(N=212)	(N=637)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intent-to-treat (ITT)	213 (100)	212 (100)	425 (100)	106 (100)	106 (100)	212 (100)	637 (100)
Modified ITT (mITT)	202 (94.8)	205 (96.7)	407 (95.8)	104 (98.1)	102 (96.2)	206 (97.2)	613 (96.2)
Excluded from mITT	11 (5.2)	7 (3.3)	18 (4.2)	2 (1.9)	4 (3.8)	6 (2.8)	24 (3.8)
No post-baseline value of GA lesion area in the study eye	10 (4.7)	7 (3.3)	17 (4.0)	2 (1.9)	4 (3.8)	6 (2.8)	23 (3.6)
No injection of pegcetacoplan or Sham	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Per protocol (PP) set	51 (23.9)	35 (16.5)	86 (20.2)	25 (23.6)	23 (21.7)	48 (22.6)	134 (21.0)
Safety Set	213 (100)	212 (100)	425 (100)	105 (99.1)	106 (100)	211 (99.5)	636 (99.8)

Source: Table 14.1.2.1 of the Applicant's study report.

Table 48: Summary of Specific Reasons for Exclusion from the mITT

	APL2-303			APL2-304		
	PM	PEOM	Sham pooled	PM	PEOM	Sham pooled
Intent-to-treat set	N=206	N=208	N=207	N = 213	N = 212	N = 212
Exclusion from mITT set, n (%)	5 (2.4)	8 (3.8)	13 (6.3)	11 (5.2)	7 (3.3)	6 (2.8)
Reason for no postbaseline GA area assessment						
Withdrew consent	3	2	6	4	2	2
Lost to follow-up	0	0	0	2	1	1
COVID impact leading to missed visits or discontinuation	1	3	4	2	1	2
Death	1	0	0	1	2	0
AE leading to discontinuation	0	2	2	1	1	0
GA area could not be measured	0	1	0	0	0	1

Source: Table 3 of the Applicant's response to IR submitted on 07/11/2022.

Table 49: Applicant's Analyses of Mean rate of GA growth (Slope at Month 12; Piecewise linear model)

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Number of subjects included in the model	202	204	205	200	199	193	84	78	80
Estimates for baseline to Month 6									
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7728 (0.04559)	0.8208 (0.04350)	0.9794 (0.04619)	0.8989 (0.04775)	0.8849 (0.04489)	0.9468 (0.04800)	0.8281 (0.10292)	0.9852 (0.10466)	0.9850 (0.10167)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6833-0.8624	0.7354-0.9062	0.8887-1.0701	0.8051-0.9926	0.7967-0.9730	0.8525-1.0411	0.6253 - 1.0309	0.7790- 1.1915	0.7846 - 1.1854
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.2065 (-0.3339 to -0.0792)	-0.1586 (-0.2838 to -0.0333)	NA	-0.0479 (-0.1812 to 0.0853)	-0.0619 (-0.1910 to -0.0672)	NA	-0.1569 (-0.4420 to 0.1282)	0.0002 (-0.2874 to -0.2878)	NA
Percentage difference in slope of GA lesion area	-21.1%	-16.2%	NA	-5.1%	-6.5%	NA	-15.9%	0.0%	NA

growth vs sham pooled group									
P value vs sham pooled group	.0015	.0132	NA	.4801	.3468	NA	.2793	.9990	NA
Estimates for Month 6 to Month 12									
Slope (SE) of GA lesion area growth (mm ² /6 months)	0.7924 (0.05685)	0.8393 (0.05403)	0.9913 (0.04909)	0.8538 (0.05116)	0.8611 (0.05047)	1.0292 (0.05967)	0.5656 (0.09824)	0.7221 (0.10437)	1.0764 (0.09767)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6807-0.9041	0.7331-0.9454	0.8949-1.0877	0.7533-0.9543	0.7620-0.9602	0.9120-1.1463	0.3718-0.7594	0.5162-0.9280	0.8837-1.2691
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1989 (-0.3463 to -0.0515)	-0.1520 (-0.2955 to -0.0086)	NA	-0.1754 (-0.3299 to -0.0209)	-0.1681 (-0.3217 to -0.0145)	NA	-0.5108 (-0.7841 to -0.2376)	-0.3543 (-0.6363 to -0.0723)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-20.1%	-15.3%	NA	-17.0%	-16.3%	NA	-47.5%	-32.9%	NA
P value vs sham pooled group	.0083	.0379	NA	.0262	.0320	NA	.0003	.0141	NA
Estimates for baseline to Month 12									
Average slope (SE) of GA lesion area growth, mm ² /12 months	1.5652 (0.08236)	1.6601 (0.07785)	1.9707 (0.07965)	1.7527 (0.07606)	1.7460 (0.07420)	1.9760 (0.09260)	1.3937 (0.16305)	1.7074 (0.16950)	2.0614 (0.16228)
95% CI of slope of GA lesion area growth, mm ² /12 months	1.4035-1.7270	1.5072-1.8130	1.8142-2.1271	1.6033-1.9021	1.6002-1.8917	1.7941-2.1578	1.0723-1.7152	1.3733-2.0415	1.7415-2.3814
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /12 months	-0.4054 (-0.6304 to -0.1805)	-0.3106 (-0.5299 to -0.0913)	NA	-0.2233 (-0.4588 to 0.0122)	-0.2300 (-0.4630 to -0.0030)	NA	-0.6677 (-1.1213 to -0.2142)	-0.3541 (-0.8167 to 0.1085)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-20.6%	-15.8%	NA	-11.3%	-11.6%	NA	-32.4%	-17.2%	NA
P value vs sham pooled group	.0004	.0056	NA	.0631	.0530	NA	.0041	.1328	NA

Source: Table 10 of the Applicants Clinical efficacy summary. This model includes knots at Month 6.

Table 50: Mean rate of GA growth (Slope at Month 18; Piecewise linear model: APL2-303)

	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)
Number of subjects included in the model	200	200	194
Estimates for baseline to Month 6			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.9059 (0.04709)	0.8814 (0.04689)	0.9599 (0.04998)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.8136-0.9982	0.7895-0.9734	0.8619-1.0579
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.0540 (-0.1889 to 0.0809)	-0.0785 (-0.2129 to 0.0560)	NA
Percentage difference in slope of GA lesion	-5.6%	-8.2%	NA

area growth vs sham pooled group			
<i>P</i> value vs sham pooled group	.4324	.2526	NA
Annual GA lesion area growth rate	1.8118	1.7629	1.9198
95% CI of annual GA lesion area growth rate	1.6271-1.9964	1.5790-1.9467	1.7238-2.1158
Estimates for Month 6 to Month 12			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8364 (0.05058)	0.8470 (0.05102)	1.0106 (0.06118)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7373-0.9356	0.7469-0.9470	0.8906-1.1305
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1741 (-0.3298 to -0.0184)	-0.1636 (-0.3200 to -0.0072)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-17.2%	-16.2%	NA
<i>P</i> value vs sham pooled group	.0284	.0404	NA
Annual GA lesion area growth rate	1.6728	1.6939	2.0211
95% CI of annual GA lesion area growth rate	1.4745-1.8712	1.4939-1.8940	1.7813-2.2610
Estimates for Month 12 to Month 18			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8975 (0.05097)	0.8673 (0.05188)	1.0555 (0.05835)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7976-0.9975	0.7656-0.9690	0.9411-1.1699
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1579 (-0.3100 to -0.0058)	-0.1881 (-0.3415 to -0.0348)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-15.0%	-17.8%	NA
<i>P</i> value vs sham pooled group	.0418	.0162	NA
Annual GA lesion area growth rate	1.7951	1.7347	2.1109
95% CI of annual GA lesion area growth rate	1.5952-1.9949	1.5312-1.9381	1.8821-2.3397
Estimates for baseline to Month 18			
Average slope (SE) of GA lesion area growth, mm ² /18 months	2.6398 (0.09993)	2.5957 (0.10283)	3.0259 (0.13892)
95% CI of slope of GA lesion area growth, mm ² /18 months	2.4439-2.8358	2.3941-2.7973	2.7536-3.2983
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /18 months	-0.3861 (-0.7217 to -0.0505)	-0.4302 (-0.7691 to -0.0912)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-12.8%	-14.2%	NA
<i>P</i> value vs sham pooled group	.0242	.0129	NA

Source: Table 4 of the Applicants Post 12-month Study report. Annual Growth Rate was calculated as the slope for time period multiplied by 2. Model includes treatment + baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + time (continuous) + time spline at month 6 (continuous) + time spline at month 12 (continuous) + presence of CNV in the fellow eye (yes or no) + time (continuous) x treatment + time spline at month 6 (continuous) x treatment + time spline at month 12 (continuous) x treatment + baseline GA lesion area x time (continuous) + baseline GA lesion area x time spline at month 6 (continuous) + baseline GA lesion area x time spline at month 12 (continuous). A heterogeneous autoregressive covariance matrix is used to model the within-subject errors.

Table 51: Mean rate of GA growth (Slope at Month 18; Piecewise linear model: APL2-304)

	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)
Number of subjects included in the model	202	204	206
Estimates for baseline to Month 6			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7607 (0.04630)	0.8221 (0.04344)	0.9839 (0.04670)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6699-0.8515	0.7369-0.9072	0.8923-1.0754
Difference (95% CI) in slope of GA lesion area growth (vs sham pooled), mm ² /6 months	-0.2232 (-0.3521 to -0.0943)	-0.1618 (-0.2875 to -0.0361)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-22.7%	-16.4%	NA
P value vs sham pooled group	.0007	.0116	NA
Annual GA lesion area growth rate	1.5214	1.6442	1.9677
Estimates for Month 6 to Month 12			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7865 (0.05997)	0.8167 (0.05683)	0.9710 (0.05164)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6689-0.9040	0.7053-0.9281	0.8698-1.0723
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1846 (-0.3396 to -0.0295)	-0.1543 (-0.3051 to -0.0036)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-19.0%	-15.9%	NA
P value vs sham pooled group	.0197	.0448	NA
Annual GA lesion area growth rate	1.5729	1.6334	1.9420
95% CI of annual GA lesion area growth rate	1.3378-1.8080	1.4105-1.8562	1.7395-2.1445
Estimates for Month 12 to Month 18			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8039 (0.05075)	0.8600 (0.05035)	1.0257 (0.05423)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7044-0.9034	0.7613-0.9588	0.9194-1.1321
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.2218 (-0.3674 to -0.0763)	-0.1657 (-0.3109 to -0.0205)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-21.6%	-16.2%	NA
P value vs sham pooled group	.0028	.0253	NA
Annual GA lesion area growth rate	1.6078	1.7201	2.0515
95% CI of annual GA lesion area growth rate	1.4088-1.8068	1.5227-1.9175	1.8389-2.2641
Estimates for baseline to Month 18			

Average slope (SE) of GA lesion area growth, mm ² /182 months	2.3510 (0.10991)	2.4988 (0.10878)	2.9806 (0.11508)
95% CI of slope of GA lesion area growth, mm ² /18 months	2.1356-2.5665	2.2855-2.7121	2.7550-3.2062
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /18 months	-0.6296 (-0.9414 to -0.3177)	-0.4818 (-0.7928 to -0.1708)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-21.1%	-16.2%	NA
P value vs sham pooled group	<.0001	.0024	NA

Source: Table 4 of the Applicants Post 12-month Study report. Annual Growth Rate was calculated as the slope for time period multiplied by 2. Model includes treatment + baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + time (continuous) + time spline at month 6 (continuous) + time spline at month 12 (continuous) + presence of CNV in the fellow eye (yes or no) + time (continuous) x treatment + time spline at month 6 (continuous) x treatment + time spline at month 12 (continuous) x treatment + baseline GA lesion area x time (continuous) + baseline GA lesion area x time spline at month 6 (continuous) + baseline GA lesion area x time spline at month 12 (continuous). A heterogeneous autoregressive covariance matrix is used to model the within-subject errors.

Table 52: Mean rate of GA growth (Slope at Month 24; Piecewise linear model: APL2-303)

	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)
Number of subjects included in the model	201	201	195
Estimates for baseline to Month 6			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8917 (0.04546)	0.8738 (0.04340)	0.9876 (0.04596)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.8026- 0.9809	0.7887-0.9589	0.8975-1.0777
Difference (95% CI) in slope of GA lesion area growth (versus sham pooled), mm ² /6 months	-0.0959 (-0.2223 to 0.0305)	-0.1139 (-0.2377 to 0.0100)	N/A
Percentage difference in slope of GA lesion area growth (versus sham pooled)	-9.7%	-11.5%	N/A
P value vs sham pooled group	.1369	.0717	
Annual GA lesion area growth rate	1.7835	1.7476	1.9753
95% CI of annual GA lesion area growth rate	1.6052-1.9617	1.5774-1.9177	1.7951-2.1555
Estimates for month 6 to month 12			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8307 (0.04881)	0.8347 (0.05100)	1.0403 (0.05935)
95% CI of slope of GA lesion area growth, mm ² /6 months	(0.7350-0.9264)	(0.7347-0.9347)	(0.9240-1.1567)
Difference (95% CI) in slope of GA	-0.2096	-0.2056	N/A

lesion area growth (versus sham pooled), mm ² /6 months	(-0.3601 to -0.0591)	(-0.3607 to -0.0505)	
Percentage difference in slope of GA lesion area growth (versus sham pooled)	-20.1%	-19.8%	N/A
P value vs sham pooled group	.0063	.0094	N/A
Annual GA lesion area growth rate	1.6614	1.6695	2.0806
95% CI of annual GA lesion area growth rate	1.4701-1.8528	1.4695-1.8694	1.8480-2.3133
Estimates for month 12 to month 18			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8989 (0.05019)	0.8654 (0.04785)	1.0817 (0.05349)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.8005-0.9973	0.7716-0.9592	0.9768-1.1865
Difference (95% CI) in slope of GA lesion area growth (versus sham pooled), mm ² /6 months	-0.1827 (-0.3275 to -0.0380)	-0.2163 (-0.3570 to -0.0756)	NA
Percentage difference in slope of GA lesion area growth (versus sham pooled)	-16.9%	-20.0%	NA
P value vs sham pooled group	.0134	.0026	NA
Annual GA lesion area growth rate	1.7979	1.7308	2.1633
95% CI of annual GA lesion area growth rate	1.6011-1.9946	1.5432-1.9184	1.9536-2.3730
Estimates for Month 18 to Month 24			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.6261 (0.06722)	0.6787 (0.05291)	0.9870 (0.05394)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.4943-0.7579	0.5750-0.7824	0.8813-1.0928
Difference (95% CI) in slope of GA lesion area growth (versus sham pooled), mm ² /6 months	-0.3609 (-0.5259 to -0.1959)	-0.3083 (-0.4562 to -0.1604)	NA
Percentage difference in slope of GA lesion area growth (versus sham pooled)	-36.6%	-31.2%	NA
P value vs sham pooled group	<.0001	<.0001	NA
Annual GA lesion area growth rate	1.2522	1.3574	1.9741
95% CI of annual GA lesion area growth rate	0.9886-1.5158	1.1499-1.5648	1.7626-2.1855
Estimates for baseline to Month 24			

Average slope (SE) of GA lesion area growth, mm ² /24 months ^a	3.2475 (0.12147)	3.2526 (0.12264)	4.0967 (0.15553)
95% CI of slope of GA lesion area growth, mm ² /24 months	3.0093-3.4856	3.0122-3.4930	3.7918-4.4016
Difference (95% CI) in slope of GA lesion area growth (versus sham pooled), mm ² /24 months	-0.8492 -1.2356 to -0.4627	-0.8440 -1.2335 to -0.4545	NA
Percentage difference in slope of GA lesion area growth (versus sham pooled)	-20.7%	-20.6%	NA
<i>P</i> value vs sham pooled group	<.0001	<.0001	NA

Source: Table 38 of the Applicants Month 24 study report

Table 53: Mean rate of GA growth (Slope at Month 24; Piecewise linear model: APL2-304)

	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)
Percentage difference in slope of GA lesion area growth vs sham pooled group	-19.2%	-15.7%	NA
<i>P</i> value vs sham pooled group	.0181	.0467	NA
Annual GA lesion area growth rate	1.5696	1.6368	1.9421
95% CI of annual GA lesion area growth rate	1.3360-1.8032	1.4149-1.8587	1.7396-2.1445
Estimates for month 12 to month 18			
Slope (SE) of GA lesion area growth (mm ² /6 months)	0.8004 (0.05034)	0.8682 (0.04959)	1.0269 (0.05288)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7017-0.8991	0.7710-0.9654	0.9232-1.1305
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.2265 (-0.3696 to -0.0834)	-0.1586 (-0.3009 to -0.0164)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-22.1%	-15.4%	NA

<i>P</i> value vs sham pooled group	.0019	.0288	NA
Annual GA lesion area growth rate	1.6007	1.7365	2.0538
95% CI of annual GA lesion area growth rate	1.4034-1.7981	1.5420-1.9309	1.8464-2.2611
Estimates for month 18 to month 24			
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6313-0.8921	0.6642-0.8356	0.8816-1.1100
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	−0.2341 (−0.4071 to −0.0611)	−0.2459 (−0.3886 to −0.1031)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−23.5%	−24.7%	NA
<i>P</i> value vs sham pooled group	.0080	.0007	NA
Annual GA lesion area growth rate	1.5234	1.4998	1.9916
95% CI of annual GA lesion area growth rate	1.2626-1.7841	1.3284-1.6713	1.7632-2.2199
Estimates for baseline to month 24			
Average slope (SE) of GA lesion area growth, mm ² /24 months ^a	3.1073 (0.14841)	3.2586 (0.13420)	3.9775 (0.14310)
95% CI of slope of GA lesion area growth, mm ² /24 months	2.8164-3.3982	2.9955-3.5217	3.6970-4.2580
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /24 months	−0.8702 (−1.2740 to −0.4664)	−0.7189 (−1.1039 to −0.3339)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	−21.9%	−18.1%	NA

<i>P</i> value vs sham pooled group	<.0001	.0003	NA
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Source: Table 36 of the Applicants Month 24 study report

7. Appendix B: Summary of Additional Study: POT-CP12164

In addition to the two pivotal studies, the Applicant conducted and presented the results from a Phase 2, prospective, multicenter, randomized, single-masked, sham injection study. The primary objective of this study was to assess the safety, tolerability, and evidence of activity of pegcetacoplan in patients with GA secondary to AMD. This section presents the results of this study.

Executive Summary

This was a Phase 2, multicenter, randomized, single-masked, sham-controlled study. In this study, a total of 246 subjects were randomized in an approximately 2:2:1:1 ratio to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively. Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

The primary efficacy endpoint for this study was defined as the annual growth rate of GA area in the study eye as measured by the mean change from baseline in square root area of GA lesion at Month 12. Per the study results, there was a statistically significant difference in the annual rate of growth in square root GA area in favor of both dosing frequencies compared to the sham group [(PM vs Sham, $P=0.008$); (PEOM vs Sham; $P=0.0630$); Table 54).

Table 54: Annual Growth Rate in CFB Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.025)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean	0.20 to 0.30	0.23 to 0.33	0.30 to 0.40
Difference in LS mean (95% CI) versus sham pooled group, mm	-0.10 (-0.16 to -0.03)	-0.07 (-0.14 to 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA
P value versus sham pooled group	.008	.063	NA
Difference in LS mean (95% CI) versus PEOM group	-0.03 (-0.10 to 0.04)	NA	NA
P value versus PEOM group	.444	NA	NA

Source: Table 19 of the Applicant's study reports.

Regarding safety, the incidence of ocular adverse events was higher in the two pegcetacoplan arms compared to the sham arm. The percentage of subjects with ocular adverse events was 58.2% in the PM group, 50.7% in the PEOM group, 42.0% in SM group, and 40.5% in the SEOM group (41.2% for the Pooled sham group). The most frequently reported ocular adverse events in the PM group were vitreous floaters (8.4%), neovascular age-related macular degeneration (8.4%) and conjunctival haemorrhage (7.6%). The corresponding figures in the

PEOM group were vitreous floaters (6.4%), neovascular age-related macular degeneration (5.5%) and conjunctival haemorrhage (6.9%). The incidence of these events in the pooled sham group was vitreous floaters (1.0%), neovascular age-related macular degeneration (1.9%) and conjunctival haemorrhage (3.1%).

Reviewer's remark: In Study POT-CP121614, the subject, and assessors (i.e., photographer[s] and visual acuity technicians) were masked to the specific treatment being administered. However, the investigators and study site personnel not performing assessments of efficacy variables were unmasked to treatment assignment. Regarding efficacy, the square root of GA area was used; and treatment comparisons were conducted at a 10% level of significance. Note, the Division informed the Applicant that this study could be considered as an adequate and well-controlled study.

❑ Study Design and Endpoints

▪ Study Design

Study POT-CP121614 was prospective, multicenter, randomized, single-masked, sham-injection controlled study. This study was designed to evaluate the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD. To be eligible for these studies, patients had to meet the following ocular inclusion criteria for the study eye:

- Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
- The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
 - o Total GA area must be ≥ 2.5 and ≤ 17.5 mm² (1 and 7 disk areas respectively).
 - o If GA is multifocal, at least 1 focal lesion must be ≥ 1.25 mm² (0.5 disk areas).
 - o The entire GA lesion must be completely visualized on the macula centered image.
 - o Presence of any pattern of hyper autofluorescence in the junctional zone of GA.

▪ Randomization and Treatment

In this study, 246 subjects were randomized in a 2:2:1:1 randomization ratio to the four study treatments:

- Pegcetacoplan monthly (PM): Pegcetacoplan 15 mg/0.1 mL monthly for 24 months.

- Pegcetacoplan every other month (PEOM): Pegcetacoplan 15 mg/0.1 mL every other month for 24 months.
- Sham monthly (SM): Sham injection monthly for 24 months.
- Sham every other month (SEOM): Sham injection every other month for 24 months.

Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

▪ Efficacy Endpoints

The protocol defined primary efficacy endpoint was annual growth rate of GA area in the study eye as measured by the mean change from baseline in square root area of GA lesion at Month 12 based on fundus autofluorescence photographs (FAF).

□ Statistical Methods

In this study, all statistical tests were 2-sided at the 0.1 level of significance. There were no adjustments for multiple comparisons.

Analysis Populations

The studies defined the following analysis populations:

- The intent-to-treat (ITT): The ITT set includes all randomized subjects who received at least 1 injection of study medication. Each subject was included in their randomized treatment group even if they received the wrong study medication.
- The modified ITT (mITT): The mITT includes all randomized subjects who received at least 1 injection of study medication and who had at least 1 visit at or after Month 2 where primary efficacy data were collected; Month 2 was the first visit on-treatment where lesion area was measured.
- The per-protocol (PP): The PP set includes all subjects in the mITT population who did not violate any inclusion or exclusion criteria and did not deviate from the protocol in a way that could influence their efficacy assessment. Subjects were excluded if they:
 - Received less than 75% of their expected injections prior to Month 12
 - For subjects receiving monthly injections: less than 9 injections
 - For subjects receiving EOM injections: less than 4 injections
 - Received the incorrect study medication at any time point throughout the study.

Analysis Methods

▪ Primary Analyses

The primary efficacy analysis was conducted using a mixed effects model for repeated measures (MMRM). The model included the fixed effects of treatment (3 groups: PM, PEOM and Sham), baseline square root area for GA lesion, visit (2, 6 and 12 months), treatment by visit interaction, visit by baseline interaction and treatment by baseline interaction. An unstructured covariance structure was used to model the within subject error.

▪ Sensitivity and Supplemental Analyses

Per the Applicant, the robustness of the primary analysis was evaluated by repeating the primary analysis with the PP population. In addition, the following sensitivity analyses were conducted using the mITT population:

- A MMRM analysis including only data which is within a specific time period of the last injection. In this analysis, month 6 data were to be included if a subject was dosed on or after Month 4, and Month 12 were to be included if a subject was dosed on or after Month 8. All Month 2 data was included, as the criteria to be included in the mITT population requires a subject to have had at least one dose of study medication.
- An analysis using the last observed carried forward (LOCF) method for handling missing data. In this analysis, all available Month 12 data was included, and missing data was replaced using LOCF method. An analysis of Covariance (ANCOVA) model was fitted for the Month 12 change from baseline in square root area for GA lesion, that includes baseline as a covariate and treatment (3 groups: PM, PEOM and Sham).
- Completer analysis i.e., observed data for those subjects who complete the treatment period (for subjects receiving monthly injections this will be 12 injections and for subjects receiving EOM injections this will be 6 injections) and have their Month 12 assessment. The analysis model was the same as for the primary analysis.

❑ Patient Disposition and Demographic and Baseline Characteristics

▪ Patient Disposition

As can be seen, the proportion of subjects who discontinued the study and/or treatment is higher in the two dosing frequencies of pegcetacoplan compared to the sham arm. The main reason for study discontinuation was adverse event. Note, almost four times more subjects in the PM arm compared to the pooled sham arm discontinued the study due to adverse event. Two subjects each in PEOM and pooled sham arms died (Table 55).

Table 55: Patient Disposition (POT-CP121614: ITT)

	PM	PEOM	Sham Pooled	Total

	(N=86)	(N=79)	(N=81)	(N=246)
Randomized	86	79	81	246
Completed treatment	52 (60.5)	60 (75.9)	69 (85.2)	181 (73.6)
Completed study	65 (75.6)	64 (81.0)	69 (85.2)	198 (80.5)
Withdrawn from treatment	34 (39.5)	19 (24.1)	12 (14.8)	65 (26.4)
Withdrawn from study	21 (24.4)	15 (19.0)	12 (14.8)	48 (19.5)
Primary reason for withdrawal from treatment				
Adverse Event	17 (19.8)	5 (6.3)	4 (4.9)	26 (10.6)
Investigator's decision	5 (5.8)	1 (1.3)	0	6 (2.4)
Sponsor's decision	1 (1.2)	0	1 (1.2)	2 (0.8)
Subject request	6 (7.0)	5 (6.3)	3 (3.7)	14 (5.7)
Death	0	2 (2.5)	2 (2.5)	4 (1.6)
Other	5 (5.8)	6 (7.6)	2 (2.5)	13 (5.3)
Primary reason for withdrawal from study				
Adverse Event	6 (7.0)	3 (3.8)	4 (4.9)	13 (5.3)
Withdrawal by subject	9 (10.5)	9 (11.4)	3 (3.7)	21 (8.5)
Investigator's decision	2 (2.3)	0	0	2 (0.8)
Lost to follow-up	1 (1.2)	1 (1.3)	0	2 (0.8)
Death	2 (2.3)	2 (2.5)	4 (4.9)	8 (3.3)
Other	1 (1.2)	0	1 (1.2)	2 (0.8)

Source: Table 7 of the Applicant's Study report.

▪ **Baseline and Demographic Characteristics**

There were no significant baseline imbalances between the three arms in the demographics of age, gender, or race. In all arms, there were more female participants than male participants; and most of the study participants were White and over the age of 65 years. Black and Asian subjects appear to be severely under-represented, comprising of only 1.2% each in the ITT subjects (Table 56).

Table 56: Baseline and Demographic Characteristics (POT-CP121614: ITT)

	PM (N=86)	PEOM (N=79)	Sham Pooled (N=81)	Total (N=246)
Sex				
Female	55 (64.0)	50 (63.3)	49 (60.5)	154 (62.6)
Male	31 (36.0)	29 (36.7)	32 (39.5)	92 (37.4)
Age, years				
Mean (SD)	79.6 (7.51)	81.0 (7.55)	78.4 (7.43)	79.7 (7.54)
Minimum, maximum	63, 95	60, 97	60, 96	60, 97
<65 years	2 (2.3)	1 (1.3)	3 (3.7)	6 (2.4)
≥65-<75 years	21 (24.4)	14 (17.7)	21 (25.9)	56 (22.8)
≥75-<85 years	38 (44.2)	37 (46.8)	40 (49.4)	115 (46.7)
≥85 years	25 (29.1)	27 (34.2)	17 (21.0)	69 (28.0)
Country				
Australia	12 (14.0)	11 (13.9)	12 (14.8)	35 (14.2)
New Zealand	3 (3.5)	3 (3.8)	4 (4.9)	10 (4.1)
US	71 (82.6)	65 (82.3)	65 (80.2)	201 (81.7)
Race				

Asian	1 (1.2)	0	0	1 (0.4)
Black or African American	1 (1.2)	1 (1.3)	0	2 (0.8)
White	84 (97.7)	76 (96.2)	81 (100.0)	241 (98.0)
Other	0	2 (2.5)	0	2 (0.8)
Ethnicity				
Hispanic or Latino	2 (2.3)	1 (1.3)	2 (2.5)	5 (2.0)
Not Hispanic or Latino	81 (94.2)	76 (96.2)	77 (95.1)	234 (95.1)
Not reported	2 (2.3)	0	0	2 (0.8)
Unknown	1 (1.2)	2 (2.5)	2 (2.5)	5 (2.0)

Source: Table 10 of the Applicant's Study report.

❑ **Results And Conclusions**

▪ **Primary Efficacy Analysis Results**

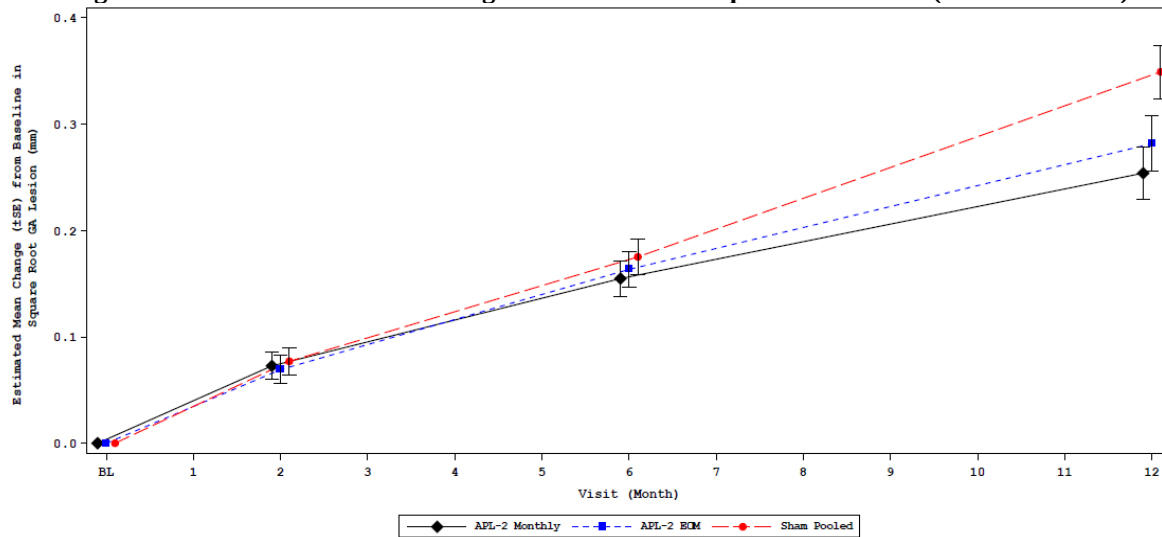
The Applicant reports that there was a statistically significant difference in the annual rate of growth in square root GA area in favor of both dosing frequencies compared to the sham group ([(PM vs Sham, $P=0.008$); (PEOM vs Sham; $P=0.0630$); Table 57).

Table 57: Change from Baseline in Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.025)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean	0.20 to 0.30	0.23 to 0.33	0.30 to 0.40
Difference in LS mean (95% CI) versus sham pooled group, mm	-0.10 (-0.16 to -0.03)	-0.07 (-0.14 to 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA
P value versus sham pooled group	.008	.063	NA
Difference in LS mean (95% CI) versus PEOM group	-0.03 (-0.10 to 0.04)	NA	NA
P value versus PEOM group	.444	NA	NA

Source: Table 19 of the study reports.

Figure 17: Mean Plot of Mean Change from Baseline in Square Root of GA (POT-CP121614)



Source: Figure 1 of the study report.

■ Sensitivity Analysis Results

Recall, the Applicant conducted sensitivity analyses to evaluate the robustness of the primary efficacy analysis results. The results of the sensitivity analyses are generally consistent with the primary efficacy analysis results.

Table 58: Change from Baseline in Square Root GA (POT-CP121614: Per Protocol)

Statistic	PM (N = 66)	PEOM (N = 71)	Sham pooled (N = 73)
n included in the model	66	71	73
LS mean (SE), mm	0.26 (0.027)	0.28 (0.027)	0.35 (0.025)
95% CI of LS mean, mm	0.21, 0.31	0.22, 0.33	0.30, 0.40
Difference (95% CI) in LS mean from sham pooled group, mm	-0.09 (-0.16, -0.02)	-0.07 (-0.15, 0)	NA
Percentage difference in LS mean from sham pooled group	-26%	-20%	NA

Source: Table 21 of the Applicant's study report.

Table 59: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.026)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean, mm	0.20, 0.30	0.23, 0.33	0.30, 0.40
Difference (95% CI) in LS mean from sham pooled group, mm	-0.10 (-0.17, -0.03)	-0.07 (-0.14, 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA

Source: Table 22 of the Applicant's study report.

Table 60: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT: LOCF)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.34 (0.032)	0.36 (0.033)	0.45 (0.033)
95% CI of LS mean, mm	0.28, 0.40	0.29, 0.42	0.39, 0.51
Difference (95% CI) in LS mean from sham pooled group, mm	-0.11 (-0.20, -0.02)	-0.09 (-0.19, 0)	NA
Percentage difference in LS mean from sham pooled group	-24%	-20%	NA

Source: Table 23 of the Applicant's study report. LOCF: Last observation carried forward.

Table 61: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT: CC)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	49	54	64
LS mean (SE), mm	0.25 (0.031)	0.28 (0.029)	0.36 (0.027)
95% CI of LS mean, mm	0.19, 0.31	0.22, 0.34	0.30, 0.41
Difference (95% CI) in LS mean from sham pooled group, mm	-0.10 (-0.18, -0.02)	-0.08 (-0.16, 0)	NA
Percentage difference in LS mean from sham pooled group	-28%	-22%	NA

Source: Table 24 of the Applicant's study report. CC: Complete cases.

☐ **Safety Summary**

☐ **Extent of Treatment Exposure**

The mean numbers of injections in the sham-treated groups (11.6 injections in the SM group and 6.6 injections in the SEOM group) were higher than in their pegcetacoplan-treated counterparts (10.5 injections in the PM group and 6.2 injections in the PEOM group). The proportion of subjects who received all planned injection was 45.3% in the PM group and 70.9% in the PEOM group. The corresponding figures in the sham arms were 61.0% (SM) and 80.0% (SEOM), respectively.

Table 62: Summary of Drug Exposure (POT-CP121614: ITT)

Statistic	PM (N = 86)	PEOM (N = 79)	SM (N = 41)	SEOM (N = 40)
n	86	79	41	40
Mean (SD) number of injections	10.5 (3.51)	6.2 (1.58)	11.6 (2.67)	6.6 (1.25)
Median number of injections	12.0	7.0	13.0	7.0
Minimum, maximum number of injections	1, 13	1, 8	2, 13	1, 8
Number (%) of subjects who received all planned injections	39 (45.3)	56 (70.9)	25 (61.0)	32 (80.0)

Source: Table 48 of the Applicant's study report

▪ **Adverse Events**

The incidence of ocular adverse events was higher in the two pegcetacoplan arms compared to the sham arm. The percentage of subjects with ocular adverse events was 58.2% in the PM group, 50.7% in the PEOM group, 42.0% in SM group, and 40.5% in the SEOM group (41.2% for the Pooled sham group;). The most frequently reported ocular adverse events in the PM group were vitreous floaters (8.4%), neovascular age-related macular degeneration (8.4%) and conjunctival haemorrhage (7.6%). The corresponding figures in the PEOM group were vitreous floaters (6.4%), neovascular age-related macular degeneration (5.5%) and conjunctival haemorrhage (6.9%). The incidence of these events in the pooled sham group was vitreous floaters (1.0%), neovascular age-related macular degeneration (1.9%) and conjunctival haemorrhage (3.1%;).

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA217171
Product Name:	Pegcetacoplan
Indication(s):	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
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1 EXECUTIVE SUMMARY

This is a statistical review of the New Drug Application (NDA) submitted by Apellis Pharmaceuticals, Inc. (Applicant) for intravitreal (IVT) pegcetacoplan therapy (pegcetacoplan). The proposed indication is for the treatment of adult subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The primary objective of this review is to evaluate whether the safety and efficacy results in the two identically designed pivotal Phase 3 studies, APL2-303 and APL2-304, submitted in this NDA, support the proposed indication.

The two studies were 24-month, multicenter, double-masked, randomized, parallel-group, sham-controlled, studies. The primary objective of these studies was to evaluate the safety and efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD. The main efficacy outcome of interest was the total area of GA lesions in the study eye measured by fundus autofluorescence (FAF) images. Six-hundred twenty-one subjects in Study APL2-303 and 637 subjects in Study APL2-304 were randomized in an approximately 2:2:1:1 ratio to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively. Randomization was stratified according to GA lesion area at screening ($<7.5 \text{ mm}^2$; $\geq 7.5 \text{ mm}^2$), and presence of choroidal neovascularization (CNV) in the fellow eye. Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

The protocol defined primary efficacy endpoint of these studies was the mean change from baseline in total area of GA at Month 12 in the study eye. However, for this indication, the Division of Ophthalmology Products (DOP) recommends the mean rate of GA growth (Slope) as the primary efficacy endpoint. This requirement has been communicated to the Applicant on multiple occasions during the review process.

The primary efficacy analysis of the mean change from baseline was conducted based on a mixed effects model for repeated measures (MMRM). The analysis for the DOP preferred endpoint, mean rate of GA growth (Slope), was conducted based on a linear mixed effects model (See 3.2.2.3 for details). For each analysis, a fixed-sequence testing procedure was used to control the overall Type I error rate due to the comparison of the two dosing frequencies of pegcetacoplan against the pooled sham. In this procedure, the comparison between PM and the pooled sham arm was tested first, and the comparison between PEOM and the pooled sham arm was to be tested only if the difference between PM and pooled sham was statistically significant.

The Applicant's findings for the protocol defined primary efficacy endpoint provided statistically significant evidence in favor of both pegcetacoplan arms against the pooled sham arm in Study APL2-304. However, the corresponding treatment differences between each pegcetacoplan arm and the pooled sham arm were not statistically significant in Study APL2-303 [(PM vs Sham; $p\text{-value}=0.0609$, (PEOM vs Sham, $p\text{-value}=0.0853$); Table 1 and Table 3]. The Applicant also presented results from the analysis of the protocol defined primary efficacy endpoint across various patient subgroups and under different missing data handling methods. Results from these analyses are generally consistent with the primary analysis findings.

Table 1: Summary of Mean Change from Baseline in Total GA Area at Month 12 (mITT)

Study	LS mean (SE)			Difference (95% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	1.733 (0.079)	1.756 (0.074)	1.964 (0.095)	-0.2301 (-0.470, 0.010)	-0.2077 (-0.444, 0.029)
Study APL2-304	1.557 (0.083)	1.650 (0.081)	1.968 (0.082)	-0.4113 (-0.639, -0.183)	-0.3181 (-0.542, -0.093)

Source: Table 24 of the Applicant's study reports.

As noted earlier, for this indication, the DOP considers the mean rate of GA growth (Slope) as the primary efficacy endpoint. Although the Applicant has not explicitly specified the Slope as the primary endpoint in the protocol and statistical analysis plan, they nonetheless presented the results for this endpoint in the study reports. The Applicant's findings for the Slope endpoint based on data collected through Month 12 mirrored the results observed for the protocol defined primary efficacy endpoint, such that, differences between each of the two dosing frequencies of pegcetacoplan against pooled sham in annual growth rates were nominally significant in Study APL2-304 but not in Study APL2-303 (Table 2).

However, in both studies, the analysis of the mean rate of GA growth (Slope) through Month 18 provided statistically significant differences between each dosing frequency of pegcetacoplan and the pooled sham. Note, in Study APL2-303, the PEOM arm has resulted in numerically lower mean GA progression rate compared to the PM arm. Conversely, in Study APL2-304, the PM arm resulted in numerically lower mean GA progression rate compared to the PEOM arm (Table 2).

Table 2: Summary of Mean Rate of GA Growth (Slope; mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Month 12: Slope (SE) [1]	1.762 (0.0762)	1.749 (0.0737)	1.959 (0.0905)	-0.197 (-0.430, 0.035)	-0.210 (-0.439, 0.019)
Month 18: Slope (SE) [2]	2.644 (0.1013)	2.600 (0.1026)	3.001 (0.1361)	-0.356 (-0.689, -0.023)	-0.401 (-0.735, -0.067)
Study APL2-304					
Month 12: Slope (SE) [1]	1.560 (0.0802)	1.656 (0.0760)	1.968 (0.0797)	-0.407 (-0.629, -0.185)	-0.311 (-0.529, -0.094)
Month 18: Slope (SE) [2]	2.338 (0.1101)	2.490 (0.1076)	2.9708 (0.1144)	-0.632 (-0.943, -0.320)	-0.480 (-0.789, -0.171)

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

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

Also note, the estimated effect in the pooled sham arm is fairly similar across the two studies. However, the magnitude of the observed treatment effect in Study APL2-303 for the two pegcetacoplan arms (notably for the PM arm) is substantially lower than the corresponding figure in Study APL2-304. Although there does not appear to be noticeable difference in the demographic characteristics of age, sex and ethnicity among subjects randomized to the PM arms across the two studies, there were some differences in baseline disease characteristics between subjects randomized to the PM arms across the two studies. Some of these characteristics were identified by the Applicant as potentially having effect on GA progression. Besides, there was a slight difference in the rate of treatment compliance between subjects randomized to the PM arms across the two studies.

Regarding safety, a higher percentage of subjects in the two pegcetacoplan arms reported at least one ocular adverse event compared to the sham arms (58% in PM, 51% in PEOM, 42% in SM and 41% in SEOM). The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms (PM, PEOM) were: vitreous floaters (8.5%, 6.4%), Neovascular age-related macular degeneration (8.4%, 5.5%), conjunctival haemorrhage (7.6%; 6.9%), and eye pain (6.4%, 5.2%). The incidence rate of these adverse events in the sham arms (SM, SEOM) were vitreous floaters (1.0%, 1.0%), Neovascular age-related macular degeneration (1.9%, 1.9%), conjunctival haemorrhage (2.4%, 3.8%), and eye pain (5.8%, 6.2%). In addition, a slightly higher proportion of subjects in the PM pegcetacoplan arm reported at least one serious adverse event compared to the PEOM as well as the sham arms (28% in PM, 21% in PEOM, 25% in SM and 19% in SEOM). The proportion of subjects who died during the 18-month study period was 4.8% in PM, 2.6% in PEOM, 4.8% in SM and 1.4% in SEOM. The proportion of subjects who discontinued the study due to adverse events was 7.2% in PM, 4.8% in PEOM, 8.2% in SM and 2.4% in SEOM. Most of the adverse events that led to treatment discontinuation were non-ocular in nature. Note, the safety summaries presented here are for the 18-month treatment period. Based on the drug exposure summary (See Section 3.3.1), only a third of the subjects in the PM arm received the total allowed 18 injections during the 18-month period. Therefore, it is possible that the actual incidence of adverse events with a full treatment regimen might be higher.

Overall, the results of the primary efficacy analyses in the two pivotal studies coupled with supportive evidence from the Phase 2 study (see Appendix) demonstrated the efficacy of pegcetacoplan for the treatment of GA secondary to AMD. Safety wise, compared to sham, incidence of adverse events, including adverse events of special interest (intraocular inflammations and exudative AMD), were higher in the two peregctogol arms; with more adverse events reported in subjects randomized to the PM arm. Therefore, the final determination for the approval of this drug, including the selection of the to-be-marketed dosing frequency, should be made based on the totality of evidence, taking the absence of alternative treatment for this indication and the potential safety issues into account.

2 INTRODUCTION

This is a statistical review of the NDA submitted by Apellis Pharmaceuticals, Inc., referred to as the Applicant on May 26, 2022, for intravitreal (IVT) pegcetacoplan therapy (pegcetacoplan). The proposed indication is for the treatment of GA secondary to AMD. The primary evidence of efficacy and safety for this NDA comes from two identically designed pivotal Phase 3 studies (Studies APL2-303 and APL2-304). The two studies were conducted across multiple sites located in the US and elsewhere (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Israel, Italy, the Netherlands, New Zealand, Poland, Spain, and the UK). Study APL2-303 enrolled 621 subjects in 122 study sites, of which, 400 (64.4%) subjects were enrolled in sites located within the United States (US). Similarly, Study APL2-304 enrolled 637 subjects, of which, 453 (71.1%) subjects were enrolled in sites located within the US.

The Applicant proposes to include findings from Study APL2-303 and Study APL2-304 into the “Clinical Studies” (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of intravitreal (IVT) pegcetacoplan therapy in the treatment of adult patients with GA secondary to AMD. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology Products (DOP) if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant’s summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

Per the Applicant, a major contributing factor to the pathogenesis of GA appears to be overactivation of the complement cascade (part of the body’s immune system), resulting in chronic inflammation, cell dysregulation, and retinal cell death. The Applicant states that peptide moieties of pegcetacoplan molecule bind to complement C3 and C3b resulting in broad inhibition of complement activation.

Per the Applicant, although there is treatment for exudative AMD, also known as wet (neovascular) AMD, with anti-vascular endothelial growth factor (VEGF) therapies, no approved therapy exists for GA, which is usually bilateral and relentlessly progressive. The Applicant is therefore developing pegcetacoplan for the treatment of GA secondary to AMD.

2.1.2 History of Drug Development

The protocols (original and amendments) and the statistical analysis plans (SAPs) for Studies APL2-304 and APL2-303 were reviewed under IND124784. The Applicant had a series of discussions with the DOP to reach agreement on the development program for IVT pegcetacoplan. The summary of the relevant interactions between the Applicant and the DOP is provided below:

- On 12/05/2017, the Applicant had a Type B end-of-Phase 2 meeting with the DOP. The objective of the meeting was to obtain agreement on the design of the two Phase 3 protocols. In response to the Applicant's question regarding the primary efficacy endpoint, the Division agreed that the primary endpoint of the mean rate of growth from baseline to month 12, measured as the total area of the GA lesion is acceptable. The Division also recommended the Applicant to evaluate the data upon completion of the trial to determine the best model to describe the total area growth over time. The Division requested the Applicant to clearly specify the proposed mixed effects model and the missing data method they planned to conduct based on the multiple imputation approach.
- On 03/01/2021, the Applicant had a Type C meeting with the DOP. The objective of the meeting was to discuss the statistical analysis strategy and pooling proposals for the Phase 3 studies for pegcetacoplan. The Division provided feedback on the SAPs. The Applicant incorporated the feedbacks and submitted an updated SAP.
- On 11/09/2021, The Division informed the Applicant that Studies APL2-303 and APL2-304 appeared to be adequate and well controlled, although the final determination will be a review issue. The Division recommended analysis of the mean rate of change from baseline in total GA lesion area using fundus autofluorescence (FAF) for the primary endpoint.
- On 01/21/2022, the Applicant had a Type B Pre-NDA meeting with the DOP. The Division recommended the Applicant to 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 the Applicant's plan to include Month 12 clinical study reports (CSRs) in the initial NDA, full data sets through Month 18, brief summaries of key findings at Month 18, and brief summaries of pertinent data beyond Month 18.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary for the protocol defined primary efficacy endpoint, mean change from baseline in total GA area at Month 12, is presented in Table 3.

Table 3: Efficacy Summaries of APL2-303 and APL2-304

Design	Treatment (Sample size)	Endpoint/Analysis	Applicant's findings ²
APL2-303 ¹ MC, RD, DB, PG, SC	▪ PM (N=206) ▪ PEOM (N=208) ▪ SM (N=102) ▪ SEOM (N=105)	Primary Endpoint: Mean change from baseline (CFB) in total area of GA lesion(s) in the study eye at Month 12. The primary efficacy analysis provided the least squares (LS) mean difference between each of the two dosing frequencies of pegcetacoplan (PM and PEOM) and the sham group and its two-sided 95% CI using a MMRM. The	The study did not meet its primary objective of demonstrating the statistical superiority of either of the two dosing frequencies against sham at the prespecified significance level (0.0496). The difference in LS mean

		primary efficacy analysis was conducted based on modified intent to treat population (mITT). Multiplicity was controlled for the primary endpoint using a fixed sequencing approach where the comparison between PM and sham pooled was tested and if statistically significant, the comparison between PEOM and sham pooled was tested.	CFB (95% CI, P-value) between the PM group and the sham pooled group was -0.2301mm^2 $[-0.4708, 0.0105]$; $P=0.0609$. The difference (95% CI; P-value) between the PEOM group and Sham group was -0.2207mm^2 $[-0.4445, 0.0290]$; $P=0.0853$.
APL2-304 ¹ MC, RD, DB, PG, SC	- PM (N=213) - PEOM (N=212) - SM (N=106) - SEOM (N=106)	Primary Endpoint: Mean change from baseline (CFB) in total area of GA lesion(s) in the study eye at Month 12. The primary efficacy analysis provided the least squares (LS) mean difference between each of the two dosing frequencies of pegcetacoplan (PM and PEOM) and the sham group and its two-sided 95% CI using a MMRM. The primary efficacy analysis was conducted based on modified intent to treat population (mITT). Multiplicity was controlled for the primary endpoint using a fixed sequencing approach where the comparison between PM and sham pooled was tested and if statistically significant, the comparison between PEOM and sham pooled was tested.	The study met its primary objective of demonstrating the statistical superiority of both dosing frequencies against sham at the prespecified significance level (0.0496). The difference in LS mean CFB (95% CI, P-value) between the PM group and the sham pooled group was -0.4113mm^2 $[-0.6396, -0.1830]$; $P=0.0004$. The difference (95% CI; P-value) between the PEOM group and sham group was -0.3181mm^2 $[-0.5424, -0.0939]$; $P=0.0055$.

Source: Applicant's study reports. ¹ MC: Multi -center, RD: Randomized, DB: Double-blind, PG: Parallel-group, SC: Sham-controlled. ² The studies anticipated four unmasked reviews of safety data by the data safety monitoring committee (DSMC). Because some of the safety outcomes are also related to efficacy, the DOP recommended an alpha adjustment of 0.0001 for each of the 4 independent data monitoring committee unmasked data reviews that occurred before the primary analysis. Therefore, hypothesis testing in each study was performed at a 2-sided $\alpha=0.0496$ (0.05-0004).

2.2 Data Sources

This NDA application was submitted electronically and includes full study reports as well as standardized datasets using SDTM and ADaM formats that are relevant for the analyses of studies APL2-303 and APL2-304 presented in this review. Datasets and corresponding definition files can be found at the following location:

<\\CDSESUB1\evsprod\NDA217171\0001\m5>

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt contains the demographic and disposition data.
- adga.xpt contains the GA area efficacy data.
- adae.xpt contains the adverse event data.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the NDA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of studies APL2-303 and APL2-304 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Studies APL2-303 and APL2-304 were multicenter, double-masked, randomized, parallel-group, sham-controlled, studies. These studies were designed to evaluate the safety and efficacy of pegcetacoplan compared with sham injection in subjects with GA secondary to AMD. To be eligible for these studies, patients had to meet the following ocular inclusion criteria for the study eye:

- Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
- The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
 - o Total GA area must be ≥ 2.5 and ≤ 17.5 mm² (1 and 7 disk areas respectively).
 - o If GA is multifocal, at least 1 focal lesion must be ≥ 1.25 mm² (0.5 disk areas), with the overall aggregate area of GA as specified above.
 - o The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any areas of peripapillary atrophy.
 - o Presence of any pattern of hyper autofluorescence in the junctional zone of GA.
- Normal luminance best corrected visual acuity of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent).

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

3.2.1.2 Randomization and Treatment

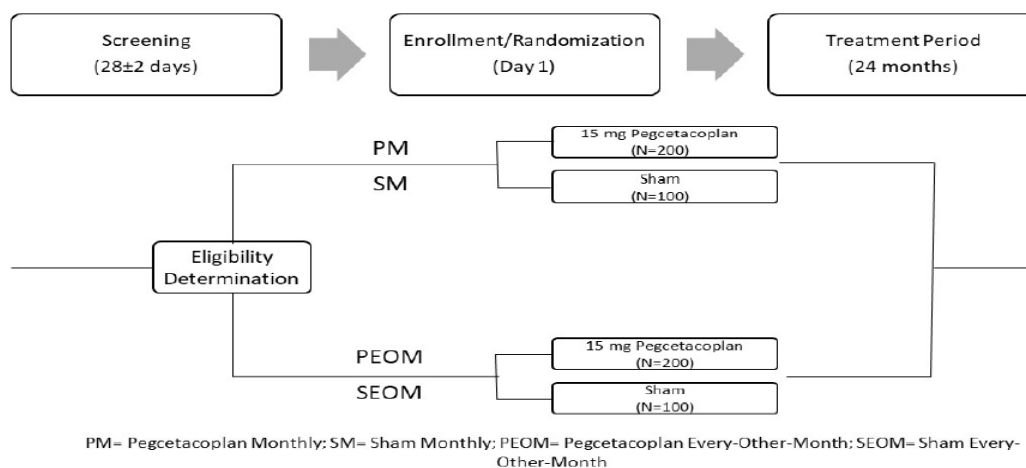
Both studies used a 2:2:1:1 randomization ratio for allocating eligible patients to the four study arms:

- Pegcetacoplan monthly (PM): Pegcetacoplan 15 mg/0.1 mL monthly for 24 months.
- Pegcetacoplan every other month (PEOM): Pegcetacoplan 15 mg/0.1 mL every other month for 24 months.
- Sham monthly (SM): Sham injection monthly for 24 months.
- Sham every other month (SEOM): Sham injection every other month for 24 months.

Per the Applicant, the procedure for sham injection was the same as that used for IVT pegcetacoplan injection but no actual injection occurred. Randomization was stratified according to GA lesion area at screening ($<7.5 \text{ mm}^2$; $\geq 7.5 \text{ mm}^2$), and presence of choroidal neovascularization (CNV) in the fellow eye. Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

The total duration of both studies was 24 Weeks. For the first 12 months, all randomized subjects were to return every month to the clinical site for assessments and additional pegcetacoplan or sham injections according to their randomization scheme. From Month 12 onwards, subjects were to return to the clinical site based on their randomized treatment schedule (monthly or every other month) and will follow the treatment regimen and assessments outlined in the visit schedule until Month 24 (See Study design schema in Figure 1).

Figure 1: Study Design Schema



3.2.1.3 Efficacy Endpoints

The protocol defined primary efficacy endpoint of these studies was the mean change from baseline in total GA area at Month 12. However, the DOP recommend the Applicant to use the mean rate of growth (Slope) as the primary efficacy endpoint.

Reviewer's remark: The requirement to use the mean rate of GA growth (Slope) as a primary efficacy endpoint was communicated to the Applicant on multiple occasions during the review process. For example, at the end of Phase 2 meeting (12/05/2017), the Division recommended the primary efficacy endpoint to be the mean rate of GA growth evaluated based on the best linear fit. In addition, at the Type-C meeting (3/1/2021), the Division had stated that the magnitude of change observed at Month 12 will not be clinically relevant for this indication and recommended the endpoint to be based on a rate of change. Furthermore, at the Type-A meeting held on 11/18/2021, the DOP stated the following: "Analysis of the mean rate change of growth from baseline through all available measurements, measured as the total area of the GA lesion using fundus autofluorescence is recommended for the primary endpoint."

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, the primary estimand and methods to deal with missing data and intercurrent events and statistical analyses presented in this review that are performed by the Applicant, as described in the SAPs for studies APL2-303 and APL2-304, as well as independent analyses performed by the statistical reviewer.

3.2.2.1 Statistical Hypotheses and Sample size

□ Hypothesis Testing

The primary null and alternative hypotheses related to the protocol defined primary efficacy endpoint for the comparison of each dosing frequency against the pooled sham can be mathematically stated as follows:

$$H_{01}: \mu_{pm} = \mu_{sham}$$

$$H_{a1}: \mu_{pm} \neq \mu_{sham}$$

And

$$H_{02}: \mu_{peom} = \mu_{sham}$$

$$H_{a2}: \mu_{peom} \neq \mu_{sham}$$

where μ_{pm} , μ_{peom} , and μ_{sham} are the mean change from baseline in total GA area at Month 12 in the PM, PEOM and the pooled sham arms, respectively. To adjust for multiplicity due to the test of the two pegcetacoplan arms, a sequential testing procedure was used. In this procedure, the superiority of PM against pooled sham was tested first, followed by the comparison of PEOM against pooled sham. The study will be considered positive if the first hypothesis (H_{01}) is rejected.

Reviewer's remark: The hypotheses formulated above could also be used for the DOP's recommended endpoint, the mean rate of growth (slope), with μ_{pm} , μ_{peom} , and μ_{sham} now representing the rate of growth (slopes) in total GA area at Month 12/18 in the PM, PEOM and the pooled sham arms, respectively.

Reviewer's remark: The studies anticipated four unmasked reviews of safety data by the data safety monitoring committee (DSMC). Because some of the safety outcomes are also related to efficacy, the DOP recommended an alpha adjustment of 0.0001 for each of the 4 independent data monitoring committee unmasked data reviews that occurred before the primary analysis. Therefore, hypothesis testing in each study was performed at a 2-sided $\alpha=0.0496$ (0.05-0004).

□ Sample Size

In both studies, a total of approximately 600 subjects were to be randomized in a 2:2:1:1 ratio to receive treatment with PM, PEOM, SM, or SEOM. This sample size assumed an annual growth rate in GA lesion area of 1.47, 1.70 and 2.13 mm²/year for PM, PEOM and Sham-Pooled groups, respectively. These values were estimated from the results of a Phase 2 trial of pegcetacoplan. Based on the same Phase 2 trial data, a standard deviation (common for all arms) of the lesion growth was assumed to be 1.50 mm².

3.2.2.2 Analysis Populations

The studies defined the following analysis populations:

- The intent-to-treat (ITT): The ITT set includes all randomized subjects. Subjects were to be analyzed in the treatment arm assigned at randomization with the 2 sham treatment arms being combined into a single 'control' group.
- The modified ITT (mITT): The mITT set includes all randomized subjects who receive at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline value of GA lesion in the study eye as assessed by FAF. The primary efficacy analysis is conducted based on the mITT population.
- The per-protocol (PP): The PP set includes all ITT subjects who follow the protocol without any major deviation(s) that could impact the integrity of the data.

Reviewer's remark: The analysis based on the mITT population excluded randomized and treated subjects from each arm. Upon request by the statistical reviewer, the Applicant conducted a sensitivity analysis incorporating the subjects excluded from the mITT population. The result of this analysis provided numerically favorable results for the active treatment.

3.2.2.3 Analysis Methods

A. Primary Analyses

☐ Analysis of the Protocol Defined Primary Efficacy Endpoint

Per the Applicant, the primary scientific research question of interest in the two studies was to assess the effect of pegcetacoplan compared with that of sham at Month 12 regarding the impact on GA lesion progression under real-life conditions following the ITT principle. The Applicant provided the following attributes of the primary estimand:

- Population: GA subjects defined through inclusion and exclusion criteria in the mITT population.
- Treatment conditions: The treatment regimen of interest in this study is PM, PEOM, and Sham.
- Variable (or endpoint): Change in total area of GA lesions in the study eye from baseline measured by FAF to Month 12.
- The intercurrent events listed below were to be handled with a treatment policy strategy whereby any measured value would be used as is.
 - o Treatment discontinuation
 - o Lost to follow up
 - o Withdrawal from the study
- Missing data resulting from these intercurrent events were handled implicitly within a mixed effects model for repeated measures (MMRM) analysis that assumes missing at random (MAR).

The proposed MMRM model included treatment (PM, PEOM, sham), presence of CNV in the fellow eye at baseline (Yes, No) and baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) as fixed effects, time (study month, categorical) as a factor, the time $\times$ treatment interaction term, and the baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) $\times$ time interaction term. A common unstructured covariance matrix was used to model the within-subject errors. From the model, the least square (LS) mean change from baseline to Month 12 was estimated for each of 3 groups as well as the comparisons of each treatment group against each other.

☐ Analysis of the DOP's Preferred Primary Efficacy Endpoint (Slope)

The analysis of mean rate of GA growth (Slope) was conducted using a linear mixed effects model assuming time as continuous and linear ("slope model"). The response variable is the GA lesion area. The model included treatment (PM, PEOM, sham), presence of choroidal neovascularization in the fellow eye at baseline (Yes, No), baseline GA lesion area ($<7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$) as fixed effects, time (study month, continuous assuming linearity), the time $\times$ treatment interaction term as well as the baseline GA lesion area $\times$ time interaction term.

A common unstructured covariance matrix was used to model the within-subject errors, the sandwich estimator was used to estimate the standard errors of the fixed effects parameters, and the degrees of freedom was partitioned into between-subject and within-subject portions. From the model, the mean rate of change (slope), standard error, and the estimated difference in slopes among the treatment groups along with the 2-sided 95% CIs and p-value is reported.

To allow for slope of lesion growth to differ between the different periods for each of the treatment groups, a second analysis using a piecewise linear mixed effect model assuming time as continuous and piecewise linear (“piecewise slope model”) was used. This analysis was conducted similar to the “slope model” except that a knot (s) at the Month 6/12 visits was added.

B. Sensitivity and Supplemental Analyses

□ Sensitivity Analysis for Missing Data

The Applicant conducted a control-based multiple imputation, and a tipping point analyses of the protocol defined primary as well as the DOP’s primary efficacy endpoints. For both analyses, intermittent missing data were first imputed using an MCMC approach to create a monotone missing data pattern. Multiple imputation was then carried out on the resultant monotone missing data as described below:

▪ Control-Based Imputation

In this analysis, for the active treatment arms, missing data due to reasons that are potentially related to study drug or lack of efficacy were imputed based on observed data from the pooled sham arm. Subjects who discontinued treatment or study due to reasons that are potentially related to study drug or lack of efficacy include:

- Subjects who discontinued due to ocular adverse event, adverse event related to treatment, or adverse event related to injection procedure.
- Subjects who withdrew consent due to lack of efficacy (specify field includes ‘Lack of efficacy’) or not otherwise specified as not related to efficacy (specified field includes “Not specified”).

For the active treatment arms, missing data due to reasons that are not related to study drug or lack of efficacy were imputed based on the observed data from their respective arm. All missing data in the pooled sham arm were imputed based on the observed values in the pooled sham arm.

▪ Tipping Point Analysis (Delta-adjusted Approach)

In this approach, missing data after the last assessment were explicitly imputed by multiple imputation assuming missing not at random (MNAR). For this analysis, first missing data in each arm was multiply imputed using observed data from each respective randomized arm. Then, for the active treatments, a shift parameter was added to the imputed values. The shift parameters were allocated to the missing data point(s) proportionally across timepoints. For example, for a shift parameter of 0.48 mm² at Month 12, incremental shifts of 0.08 mm² would apply to Month 2, Month 4, ... and Month 12, respectively [0.08 mm² x 6 visits = 0.48 mm²]. The range of the shift parameters will be from 0.06 mm² to 0.72 mm² by increments of 0.06 mm² for Month 12 and 0.09 mm² to 1.08 mm² by increments of 0.09 for Month 18 for the difference in the change of GA area from baseline between each pegcetacoplan arm (PM or PEOM) and sham arm.

□ Supplemental Analysis

▪ Post-hoc Analysis Adjusting for Baseline Characteristic

Per the Applicant, although randomization is intended to balance risk factors among treatment groups on average, chance imbalances may sometimes occur for any study, introducing random biases to the treatment effect estimate. To account for any major chance imbalances observed across treatment groups within each study, and to evaluate the impact of these imbalances on the treatment effect, the Applicant conducted post-hoc analyses adjusting for selected baseline characteristics. In this analysis, the Applicant first selected geographic region and 7 baseline disease characteristics for which they state is evidence of association with GA progression:

- study eye focality (multifocal/unifocal)
- study eye lesion location (subfoveal/nonsubfoveal)
- study eye lesion size (continuous)
- study eye pseudodrusen (present/absent)
- study eye low-luminance deficit (continuous)
- GA laterality (bilateral/study eye only)
- study eye number of intermediate/large drusen (>20/≤20)
- region (US/Latin America/ex-ROW)

To determine if there is imbalance across the three treatment arms with respect to these baseline characteristics, the three treatment arms within each study were compared using a chi-square test. Imbalance is assumed to have happened if the p-value associated with the treatment comparison with respect to a given characteristics is <0.2. With this approach, GA lesion focality (multifocal or unifocal) and number of intermediate/large drusen (>20/≤20 category) were identified to have major imbalances in study APL2-303. Similarly, in Study APL2-304, GA lesion location (with subfoveal involvement or without subfoveal involvement) was identified to have major imbalances between treatment groups. For the Phase 2 study (see Appendix for summary of this study), low-luminance deficit and intermediate/large drusen (>20/≤20 category) were identified to have major imbalances.

To estimate the treatment effects adjusted for the selected baseline characteristics with major imbalance, all identified baseline characteristics with major imbalance across the 3 studies [Studies APL2-304, APL2-303, and POT-CP121614 (See Appendix)] as well as the interaction terms between each baseline characteristic with major imbalance and the analysis visit were added to the primary analysis model (MMRM) for each study.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

The studies had three database locks. The first one, referred to as primary database lock, occurred after all subjects completed the Month 12 evaluation or exited the study early. The second database lock occurred after all subjects completed the 18 Month evaluation or exited the study early. The final database lock will take place after all subjects have completed the Month 24 evaluation or exited the study early. The patient disposition at the Month 12 and 18 database locks are included in this NDA submission and are summarized in this section.

As can be seen from Table 4 and Table 5, in both studies, the proportion of subjects who discontinued the study and/or treatment is slightly higher in the two dosing frequencies of pegcetacoplan compared to the sham arm. The main reason for study discontinuation was withdrawal by the patient. Subjects withdrew consent mainly due to reasons such as subjects' poor general health, study burden, and personal reasons. Treatment discontinuation due to concerns about treatment during the Month 12 to Month 18 period was not reported in Study APL2-304. In Study APL2-303, 3 subjects in the PM group and 1 subject in the SM group withdrew consent because of concerns about treatment through Month 18 (See Table 41 and Table 42).

In both studies, a numerically higher number of subjects in the two pegcetacoplan arms died. There were relatively few subjects who discontinued the study due to adverse events, and most of these subjects had non-ocular adverse events. There is noticeable increase in the number of subjects who discontinued the study from Month 12 to Month 18. For example, in the PM arm, 19 (9.2%) subjects in Study APL2-303 and 22 (10.3%) subjects in Study APL2-304 discontinued the study after Month 12 and prior to Month 18.

Table 4: Patient Disposition (Month 12: ITT)

	Study APL2-303			Study APL2-304		
	PM (N = 206)	PEOM (N = 208)	Sham pooled (N = 207)	PM (N = 213)	PEOM (N = 212)	Sham pooled (N = 212)
Randomized	206	208	207	213	212	212
Completed treatment	182 (88.3)	188 (90.4)	179 (86.5)	183 (85.9)	187 (88.2)	191 (90.1)
Withdrawn from treatment ¹	24 (11.7)	20 (9.6)	27 (13.0)	29 (13.6)	25 (11.8)	21 (9.9)
Adverse event (AE)	2 (0.5)	2 (1.0)	6 (2.9)	3 (1.4)	7 (3.3)	3 (1.4)
Ocular AE in study eye	0	1 (0.5)	2 (1.0)	0	3 (1.4)	1 (0.5)
Ocular AE in non-study eye	0	0	0	0	0	0
Non-ocular AE	2 (0.5)	1 (0.5)	4 (1.9)	3 (1.4)	4 (1.9)	2 (0.9)
Lost to follow-up	1 (0.5)	0	0	2 (0.9)	1 (0.5)	1 (0.5)
Physician's decision	1 (0.5)	0	0	0	0	0
Consent withdrawal	14 (6.8)	10 (4.8)	14 (6.8)	13 (6.1)	12 (5.7)	9 (4.2)
Death	5 (2.4)	2 (1.0)	2 (1.0)	7 (3.3)	3 (1.4)	3 (1.4)

Due to COVID impact ²	1 (0.5)	6 (2.9)	5 (2.4)	4 (1.9)	2 (0.9)	5 (2.4)
Other	0	1 (0.5)	0	0	0	0
Completed study	183 (88.8)	188 (90.4)	179 (86.5)	184 (86.4)	190 (89.6)	191 (90.1)
Withdrawn from study	23 (11.2)	20 (9.6)	28 (13.5)	29 (13.6)	22 (10.4)	21 (9.9)
Adverse event (AE)	1 (0.5)	2 (1.0)	5 (2.4)	3 (1.4)	4 (1.9)	2 (0.9)
Ocular AE in study eye	0	1 (0.5)	1 (0.5)	0	0	1 (0.5)
Ocular AE in non-study eye	0	0	0	0	0	0
Non-ocular AE	1 (0.5)	1 (0.5)	4 (1.9)	3 (1.4)	4 (1.9)	1 (0.5)
Lost to follow-up	1 (0.5)	0	0	2 (0.9)	1 (0.5)	1 (0.5)
Consent withdrawal	15 (7.3)	10 (4.8)	15 (7.2)	14 (6.6)	12 (5.7)	9 (4.2)
Physician's decision	0	0	0	0	0	0
Death	5 (2.4)	2 (1.0)	3 (1.4)	7 (3.3)	3 (1.4)	4 (1.9)
Due to COVID impact ²	1 (0.5)	6 (2.9)	5 (2.4)	3 (1.4)	2 (0.9)	5 (2.4)
Other	0	0	0	0	0	0

Source: Table 14.1.2.2.2 of the Applicant's response to IR submitted on July 22/2022. ¹Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study before Month 12. ²Any discontinuation due to COVID impact except for Adverse Event of COVID. Instances of Adverse Event of COVID are captured under the Adverse Event category.

Table 5: Patient Disposition (Month 18: ITT)

	Study APL2-303			Study APL2-304		
	PM (N = 206)	PEOM (N = 208)	Sham pooled (N = 207)	PM (N = 213)	PEOM (N = 212)	Sham pooled (N = 212)
Randomized	206	208	207	213	212	212
Completed treatment	163 (79.1)	175 (84.1)	172 (83.1)	161 (75.6)	175 (82.5)	172 (81.1)
Withdrawn from treatment	43 (20.9)	33 (15.9)	34 (16.4)	51 (23.9)	37 (17.5)	40 (18.9)
Adverse event (AE)	6 (2.9)	4 (1.9)	6 (2.9)	9 (4.2)	8 (3.8)	4 (1.9)
Ocular AE in study eye	2 (1.0)	1 (0.5)	2 (1.0)	3 (1.4)	4 (1.9)	1 (0.5)
Ocular AE in non-study eye	1 (0.5)	0	0	0	0	0
Non-ocular AE	3 (1.5)	3 (1.4)	4 (1.9)	6 (2.8)	4 (1.9)	3 (1.4)
Lost to follow-up	1 (0.5)	2 (1.0)	0	3 (1.4)	4 (1.9)	4 (1.9)
Physician's decision	3 (1.5)	0	0	0	1 (0.5)	1 (0.5)
Sponsor's decision	0	0	0	0	0	0
Consent withdrawal	24 (11.7)	14 (6.7)	17 (8.2)	21 (9.9)	14 (6.6)	14 (6.6)
Death	6 (2.9)	4 (1.9)	5 (2.4)	12 (5.6)	7 (3.3)	6 (2.8)
Due to COVID impact ²	3 (1.5)	9 (4.3)	6 (2.9)	6 (2.8)	3 (1.4)	11 (5.2)
Other	0	0	0	0	0	0
Completed study	167 (81.1)	176 (84.6)	172 (83.1)	165 (77.5)	179 (84.4)	172 (81.1)
Withdrawn from study	39 (18.9)	32 (15.4)	35 (16.9)	48 (22.5)	33 (15.6)	40 (18.9)
Adverse event (AE)	3 (1.5)	4 (1.9)	5 (2.4)	6 (2.8)	4 (1.9)	3 (1.4)
Ocular AE in study eye	0	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.5)
Ocular AE in non-study eye	1 (0.5)	0	0	0	0	0
Non-ocular AE	2 (1.0)	3 (1.4)	4 (1.9)	5 (2.3)	4 (1.9)	2 (0.9)
Lost to follow-up	1 (0.5)	2 (1.0)	0	3 (1.4)	4 (1.9)	4 (1.9)
Consent withdrawal	24 (11.7)	13 (6.3)	18 (8.7)	22 (10.3)	14 (6.6)	14 (6.6)
Physician's decision	2 (1.0)	0	0	0	1 (0.5)	1 (0.5)
Protocol Violation	0	0	0	0	0	0
Death	6 (2.9)	4 (1.9)	6 (2.9)	12 (5.6)	7 (3.3)	7 (3.3)
Because of COVID impact ²	3 (1.5)	9 (4.3)	6 (2.9)	5 (2.3)	3 (1.4)	11 (5.2)
Other	0	0	0	0	0	0

Source: Table 14.1.2.2.2 of the Applicant's response to IR submitted on July 22/2022. ¹Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study before Month 18. ²Any discontinuation due to COVID impact except for Adverse Event of COVID. Instances of Adverse Event of COVID are captured under the Adverse Event category.

Also note, in both studies, in addition to subject dropout, the extent of intermittent missing GA data is notable (Table 6 and Table 7). The Applicant stated that the main reason for the missed

intermittent GA data was due to subjects missing study visits because of the disruption caused by the COVID-19 pandemic.

- In Study APL2-303, over 22% of subjects randomized to the two pegcetacoplan arms (25.4% in the PM arm and 18.9% in the PEOM arm) had missing GA data at Month 12. This figure increased to 24% at Month 18 (26.4% in the PM arm and 22.4% in PEOM arm). A slightly different pattern is observed in the Sham arm. At Month 12, 24.1% of subjects in two sham arms (32.0% in SM arm and 16.3% in the SEOM) had missing GA data; and this has decreased to 22% by Month 18 (24.7% in SM and 19.4% in SEOM).
- In Study APL2-304, over 20% of subjects randomized to the two pegcetacoplan arms (21.5% in the PM arm and 19.5% in the PEOM arm) compared to 17% of subjects in two sham arms (21.9% in SM arm and 12.7% in the SEOM) had missing GA data at Month 12. At Month 18, missing data has increased to 24% in the two pegcetacoplan arms [PM (26.7%) and PEOM (21.5%)] and to 25% in the two sham arms [SM (29.5%) and SEOM (20.6%)].

Reviewer's remark: Per the Applicant, during the COVID-19 pandemic, although sites were encouraged to follow the full schedule of assessments (based on their treatment group assignment), a minimized schedule of assessment was implemented to reduce the pandemic exposure risk of subjects enrolled in the studies. This might partly explain the high rate of intermittent missing data. Note, in Study APL2-303, the first subject was enrolled (dosed) on 09/20/2018 and the last subject completed the Month 18 visit on 12/12/2021. Similarly, in Study APL2-304, the first subject was enrolled on 09/10/2018 and the last subject completed the Month 18 visit on 02/07/2022. These timeframes, especially for Study APL2-303, appear to coincide with the height of the COVID pandemic.

Table 6: Summary of GA Outcome Observed and Missing: APL2-303

Visit	GA Data in the Study Eye	Pegcetacoplan		Sham			Total (N=597) N (%)
		PM (N=201)	PEOM (N=201)	SM (N=97)	SEOM (N=95)	Pooled Sham (N=195)	
		N (%)	N (%)	N (%)	N (%)	N (%)	
Baseline	Available	201 (100.0)	201 (100.0)	97 (100.0)	98 (100.0)	195 (100.0)	597 (100.0)
	Missing	0	0	0	0	0	0
Month 2	Available	151 (75.1)	166 (82.6)	76 (78.4)	81 (82.7)	157 (80.5)	474 (79.4)
	Missing	50 (24.9)	35 (17.4)	21 (21.6)	17 (17.3)	38 (19.5)	123 (20.6)
Month 4	Available	167 (83.1)	159 (79.1)	78 (80.4)	75 (76.5)	153 (78.5)	479 (80.2)
	Missing	34 (16.9)	42 (20.9)	19 (19.6)	23 (23.5)	42 (21.5)	118 (19.8)
Month 6	Available	165 (82.1)	180 (89.6)	80 (82.5)	83 (84.7)	163 (83.6)	508 (85.1)
	Missing	36 (17.9)	21 (10.4)	17 (17.5)	15 (15.3)	32 (16.4)	89 (14.9)
Month 8	Available	155 (77.1)	155 (77.1)	70 (72.2)	81 (82.7)	151 (77.4)	461 (77.2)
	Missing	46 (22.9)	46 (22.9)	27 (27.8)	17 (17.3)	44 (22.6)	136 (22.8)
Month 10	Available	149 (74.1)	153 (76.1)	65 (67.0)	73 (74.5)	138 (70.8)	440 (73.7)
	Missing	52 (25.9)	48 (23.9)	32 (33.0)	25 (25.5)	57 (29.2)	157 (26.3)
Month 12	Available	150 (74.6)	163 (81.1)	66 (68.0)	82 (83.7)	148 (75.9)	461 (77.2)
	Missing	51 (25.4)	38 (18.9)	31 (32.0)	16 (16.3)	47 (24.1)	136 (22.8)
Month 14	Available	140 (69.7)	145 (72.1)	64 (66.0)	72 (73.5)	136 (69.7)	421 (70.5)
	Missing	61 (30.3)	56 (27.9)	33 (34.0)	26 (26.5)	59 (30.3)	176 (29.5)
Month 16	Available	142 (70.6)	149 (74.1)	66 (68.0)	78 (79.6)	144 (73.8)	435 (72.9)
	Missing	59 (29.4)	52 (25.9)	31 (32.0)	20 (20.4)	51 (26.2)	162 (27.1)
Month 18	Available	148 (73.6)	156 (77.6)	73 (75.3)	79 (80.6)	152 (77.9)	456 (76.4)

	Missing	53 (26.4)	45 (22.4)	24 (24.7)	19 (19.4)	43 (22.1)	141 (23.6)
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Source: Table 14.2.1.1.1.2 of the Applicant's response to information request (IR) submitted on July 21, 2022.

Table 7: Summary of GA Outcome Observed and Missing: APL2-304

Visit	GA Data in the Study Eye	Pegcetacoplan		Sham			Total (N=614) N (%)
		PM (N=202) N (%)	PEOM (N=205) N (%)	SM (N=105) N (%)	SEOM (N=102) N (%)	Pooled Sham (N=207) N (%)	
Baseline	Available	202 (100.0)	205 (100.0)	105 (100.0)	102 (100.0)	207 (100.0)	614 (100.0)
	Missing	0	0	0	0	0	0
Month 2	Available	173 (85.6)	176 (85.9)	83 (79.0)	91 (89.2)	174 (84.1)	523 (85.2)
	Missing	29 (14.4)	29 (14.1)	22 (21.0)	11 (10.8)	33 (15.9)	91 (14.8)
Month 4	Available	166 (82.2)	171 (83.4)	83 (79.0)	89 (87.3)	172 (83.1)	509 (82.9)
	Missing	36 (17.8)	34 (16.6)	22 (21.0)	13 (12.7)	35 (16.9)	105 (17.1)
Month 6	Available	166 (82.2)	176 (85.9)	88 (83.8)	89 (87.3)	177 (85.5)	519 (84.5)
	Missing	36 (17.8)	29 (14.1)	17 (16.2)	13 (12.7)	30 (14.5)	95 (15.5)
Month 8	Available	149 (73.8)	170 (82.9)	75 (71.4)	82 (80.4)	157 (75.8)	476 (77.5)
	Missing	53 (26.2)	35 (17.1)	30 (28.6)	20 (19.6)	50 (24.2)	138 (22.5)
Month 10	Available	135 (66.8)	160 (78.0)	66 (62.9)	70 (68.6)	136 (65.7)	431 (70.2)
	Missing	67 (33.2)	45 (22.0)	39 (37.1)	32 (31.4)	71 (34.3)	183 (29.8)
Month 12	Available	159 (78.7)	165 (80.5)	82 (78.1)	89 (87.3)	171 (82.6)	495 (80.6)
	Missing	43 (21.3)	40 (19.5)	23 (21.9)	13 (12.7)	36 (17.4)	119 (19.4)
Month 14	Available	132 (65.3)	156 (76.1)	70 (66.7)	82 (80.4)	152 (73.4)	440 (71.7)
	Missing	70 (34.7)	49 (23.9)	35 (33.3)	20 (19.6)	55 (26.6)	174 (28.3)
Month 16	Available	133 (65.8)	157 (76.6)	70 (66.7)	81 (79.4)	151 (72.9)	441 (71.8)
	Missing	69 (34.2)	48 (23.4)	35 (33.3)	21 (20.6)	56 (27.1)	173 (28.2)
Month 18	Available	148 (73.3)	161 (78.5)	74 (70.5)	81 (79.4)	155 (74.9)	464 (75.6)
	Missing	54 (26.7)	44 (21.5)	31 (29.5)	21 (20.6)	52 (25.1)	150 (24.4)

Source: Table 14.2.1.1.1.2 of the Applicant's response to information request (IR) submitted on July 21, 2022.

3.2.3.2 Demographic and Baseline Characteristics

Within each study, there were no significant baseline imbalances between the three arms in the demographics of age, gender, or race (Table 8). In all arms, there were more female participants than male participants, and most of the study participants were White and over 65 years of age (over 20% of subjects in both studies were over the age of 85 years). Black and Asian subjects appear to be severely under-represented, comprising of $\leq 1.5\%$ of the ITT subjects in both studies.

Table 8: Baseline and Demographic Characteristics (mITT)

	Study APL2-303			Study APL2-304		
	PM N=201	PEOM N= 200	Sham pooled N=194	PM N=202	PEOM N=205	Sham pooled N=206
Age, years						
n	201	200	194	202	205	206
Mean (SD)	78.7 (6.91)	79.2 (7.07)	78.6 (7.29)	78.8 (7.24)	78.1 (7.74)	78.6 (7.26)
Min, Max	60, 93	61, 93	61, 96	61, 95	60, 100	60, 93
Age group, n (%)						
<65 years	5 (2.5)	6 (3.0)	8 (4.1)	5 (2.5)	9 (4.4)	9 (4.4)
≥ 65 -<75 years	46 (22.9)	51 (25.5)	49 (25.3)	52 (25.7)	50 (24.4)	45 (21.8)
≥ 75 - <86 years	110	95	90	97	99	109

	(54.7)	(47.5)	(46.4)	(48.0)	(48.3)	(52.9)
≥85 years	40 (19.9)	48 (24.0)	47 (24.2)	48 (23.8)	47 (22.9)	43 (20.9)
Sex						
Female, n (%)	118 (58.7)	120 (60.0)	122 (62.9)	125 (61.9)	117 (57.1)	133 (64.6)
Male, n (%)	83 (41.3)	80 (40.0)	72 (37.1)	77 (38.1)	88 (42.9)	73 (35.4)
Country						
US, n (%)	142 (70.6)	122 (61.0)	122 (62.9)	147 (72.8)	142 (69.3)	147 (71.4)
Rest of world, n (%)	59 (29.4)	78 (39.0)	72 (37.1)	55 (27.2)	63 (30.7)	59 (28.6)
Race						
White	187 (93.0)	185 (92.5)	187 (96.4)	185 (91.6)	189 (92.2)	187 (90.8)
Not reported	12 (6.0)	10 (5.0)	6 (3.1)	12 (5.9)	12 (5.9)	14 (6.8)
Asian	0	1 (0.5)	0	3 (1.5)	1 (0.5)	2 (1.0)
Unknown	0	1 (0.5)	0	0	1 (0.5)	3 (1.5)
Black or African American	1 (0.5)	1 (0.5)	0	2 (1.0)	0	0
Missing	1 (0.5)	1 (0.5)	1 (0.5)	0	2 (1.0)	0
American Indian or Alaska Native	0	0	0	0	0	0
Multiple	0	1 (0.5)	0	0	2 (1.0)	0
Study eye lesion size, mm ²						
n	201	200	194	202	205	206
Mean (SD)	8.3666 (4.184)	8.2198 (3.8779)	8.2617 (4.2600)	8.1779 (3.895)	8.2962 (3.904)	8.2048 (3.721)
Minimum, maximum	2.264, 17.832	2.439, 17.151	2.599, 17.490	2.489, 18.111	2.652, 17.706	2.587, 17.771
Study eye GA lesion location						
Subfoveal involvement, n (%)	129 (64.2)	119 (59.5)	121 (62.4)	116 (57.4)	131 (63.9)	146 (70.9)
Without subfoveal involvement, n (%)	72 (35.8)	81 (40.5)	73 (37.6)	86 (42.6)	74 (36.1)	60 (29.1)
Study eye GA focality (FAF)						
Unifocal, n (%)	54 (26.9)	53 (26.5)	66 (34.0)	59 (29.2)	62 (30.2)	68 (33.0)
Multifocal, n (%)	147 (73.1)	147 (73.5)	128 (66.0)	143 (70.8)	143 (69.8)	138 (67.0)
Study eye NL-BCVA score, ETDRS letters						
n	201	200	194	202	205	206
Mean (SD)	59.5 (17.40)	58.9 (15.97)	59.1 (16.85)	61.0 (15.30)	58.2 (17.03)	57.5 (16.57)
Minimum, maximum	24, 94	24, 93	23, 89	25, 86	24, 89	24, 87
Study eye LL-BCVA score, ETDRS letters						
n	200	199	191	202	205	206
Mean (SD)	32.1 (17.73)	33.0 (16.03)	33.7 (16.75)	34.0 (17.43)	32.3 (16.43)	32.7 (16.19)
Minimum, maximum	0, 73	0, 78	0, 73	0, 76	0, 72	0, 72
Study eye LLD, ETDRS letters						
n	200	199	191	202	205	206
Mean (SD)	27.5 (17.79)	25.9 (16.56)	25.6 (16.52)	26.9 (16.92)	25.9 (17.80)	24.9 (17.43)
Min, Max	-7, 77	-4, 73	-4, 71	-4, 66	-10, 76	-12, 71
Study eye number of intermediate or large drusen						
≤20, n (%)	123 (61.2)	122 (61.0)	96 (49.5)	108 (53.5)	101 (49.3)	102 (49.5)

>20, n (%)	78 (38.8)	78 (39.0)	98 (50.5)	93 (46.0)	104 (50.7)	103 (50.0)
GA laterality, n (%)						
Bilateral GA	164 (81.6)	160 (80.0)	149 (76.8)	167 (82.7)	174 (84.9)	165 (80.1)
Study eye GA only	37 (18.4)	40 (20.0)	45 (23.2)	35 (17.3)	31 (15.1)	41 (19.9)
Can't determine	NA	NA	NA	NA	NA	NA
Fellow eye lesion size, mm ²						
n	164	160	149	167	174	165
Mean (SD)	8.3053 (5.8533)	8.7382 (5.8234)	8.1401 (6.2022)	7.9042 (5.4671)	8.3894 (5.5955)	8.5792 (5.4305)
Minimum, maximum	0.213, 26.416	0.195, 35.857	0.172, 28.487	0.121, 25.227	0.040, 28.057	0.138, 26.026
NV in the fellow eye						
Present, n (%)	39 (19.4)	41 (20.5)	36 (18.6)	43 (21.3)	37 (18.0)	43 (20.9)
Absent, n (%)	162 (80.6)	159 (79.5)	158 (81.4)	159 (78.7)	168 (82.0)	163 (79.1)

Source: Adapted from Table 14 and 15 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Australia, Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

A. Primary Efficacy Analysis

- Analysis of Protocol Defined Primary Endpoint

Recall, that the protocol defined primary efficacy endpoint was the mean change from baseline in total GA area at Month 12; and evaluated in the mITT population for the primary analysis. The results are shown in Table 9. The treatment differences for this endpoint between each pegcetacoplan arm and the pooled sham are statistically significant in Study APL2-304 but not in Study APL2-303. Note, in both studies, the treatment differences for the mean change from baseline in total GA area at Month 18 between each pegcetacoplan arm and the pooled sham are nominally statistically significant (Table 9).

For Study APL2-303, the estimated mean change from baseline at Month 12 (SE) is 1.733 (0.079), 1.756 (0.074) and 1.964 (0.095) for the PM, PEOM and pooled sham arms, respectively. The estimated treatment difference (95% CI) between PM and pooled sham is -0.2301 (-0.470, 0.010). Similarly, the treatment difference (95% CI) between PEOM and pooled sham in this study is -0.2077 (-0.444, 0.029).

For Study APL2-304, the estimated mean change from baseline at Month 12 (SE) is 1.557 (0.083), 1.650 (0.081) and 1.968 (0.082) for the PM, PEOM and pooled sham arms, respectively. The estimated treatment differences (95% CI) between PM and pooled sham and between PEOM and pooled sham are -0.4113 (-0.639, -0.183), and -0.3181 (-0.542, -0.093), respectively (Table 9).

Table 9: Mean Change from Baseline in Total GA Area (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
	Study APL-303				
Month 12: Mean (SE) [1]	1.733 (0.079)	1.756 (0.074)	1.964 (0.095)	-0.2301 (-0.470, 0.010)	-0.2077 (-0.444, 0.029)
Month 18: Mean (SE) [2]	2.621 (0.1007)	2.633 (0.1032)	3.001 (0.1383)	-0.3800 (-0.713, -0.046)	-0.3677 (-0.706, -0.029)
	Study APL2-304				
	PM	PEOM	Sham Pooled	PM vs Sham Pooled	PEOM vs Sham Pooled
	Study APL2-304				
Month 12: Mean (SE) [1]	1.557 (0.083)	1.650 (0.081)	1.968 (0.082)	-0.4113 (-0.639, -0.183)	-0.3181 (-0.542, -0.093)
Month 18: Mean (SE) [2]	2.351 (0.1069)	2.516 (0.1088)	3.009 (0.1153)	-0.657 (-0.965, -0.350)	-0.492 (-0.802, -0.183)

[1] Source: Table 24 of the Applicant's study reports. SE: Standard Error

[2] Source: Table 2 of the Applicant's Post-Month 12 study reports. SE: Standard Error

❑ Analysis of DOP's Preferred Primary Endpoint

Recall, the Applicant has conducted two types of analyses of the mean rate of GA growth (Slope) at Month 12 and Month 18. The first analysis was conducted based on a linear mixed effects model in which time was included in the model as a continuous linear variable. The second analysis was conducted using a piecewise linear regression model to allow for potentially different slopes for each of the six-month intervals between baseline and Month 12/18.

The results of the analysis of this endpoint based on data collected through Month 12 mirrored the results observed for the protocol defined primary efficacy endpoint such that differences between each of the two dosing frequencies of pegcetacoplan against pooled sham in annual growth rates were nominally significant in Study APL2-304 but not in Study APL2-303 (Table 10). However, when a similar analysis is conducted based on data collected through Month 18, the treatment differences in Slope through Month 18 between each dosing frequency of pegcetacoplan and the pooled sham are statistically significant in favor of the two dosing frequencies in both studies (Table 10). The results of the piecewise regression provided similar conclusions as the linear model (Table 47--Table 48).

Table 10: Mean Rate of GA Growth (Slope; mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL-303				
Month 12: Slope (SE) [1]	1.762 (0.0762)	1.749 (0.0737)	1.959 (0.0905)	-0.197 (-0.430, 0.035)	-0.2101 (-0.439, 0.019)
Month 18: Slope (SE) [2]	2.644 (0.1013)	2.600 (0.1026)	3.001 (0.1361)	-0.356 (-0.689, -0.023)	-0.401 (-0.735, -0.067)
	Study APL2-304				
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL2-304				
Month 12: Slope (SE) [1]	1.560 (0.0802)	1.656 (0.0760)	1.968 (0.0797)	-0.407 (-0.629, -0.185)	-0.311 (-0.529, -0.094)
Month 18: Slope (SE) [2]	2.338 (0.110)	2.490 (0.1076)	2.970 (0.1144)	-0.632 (-0.943, -0.320)	-0.480 (-0.789, -0.171)

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

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

Reviewer's remark: For the DOP's primary efficacy endpoint, the efficacy results for the two dosing frequencies are mixed. In Study APL2-303, the PEOM arm appears to have slightly lower GA progression compared to the PM arm. Conversely, in Study APL2-304, the PM arm

performed better than PEOM. These findings should be taken into consideration when the to-be-marketed dose is determined.

B. Sensitivity and Supplemental Analyses

□ Sensitivity Analysis for Missing Data

Recall, the analyses of the protocol defined as well as the DOP's preferred primary efficacy endpoints were conducted assuming missing data due to any reason were missing at random (MAR). To evaluate the impact of deviation from this assumption, the Applicant conducted sensitivity analyses using a control-based imputation and a tipping point analysis. In addition, this reviewer conducted the analysis of the DOP's preferred primary efficacy endpoint employing a combination of multiple imputation and trimmed mean approaches. The results from these analyses are generally consistent with the results of the primary analyses (Table 11--Table 13).

Table 11: Sensitivity Analyses of Mean Change from Baseline in GA Area at Month 12 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Control-based [1]	1.7342 (0.08108)	1.7526 (0.07570)	1.9689 (0.09716)	-0.2347 (-0.4795, 0.0101)	-0.2163 (-0.4560, 0.0234)
Control-based [2]	1.7440 (0.08160)	1.7600 (0.07690)	1.9690 (0.09700)	-0.2250 (-0.4690, 0.0200)	-0.2090 (-0.4490, 0.0300)
Study APL2-304					
Control-based [1]	1.5592 (0.08358)	1.6536 (0.08122)	1.9673 (0.08263)	-0.4081 (-0.6365, -0.1797)	-0.3137 (-0.5379, -0.0895)
Control-based [2]	1.5790 (0.08310)	1.6660 (0.08140)	1.9660 (0.08240)	-0.3870 (-0.6140, -0.1600)	-0.3010 (-0.5250, -0.0770)

[1] Source: Table 14.2.1.2.1 of the study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.5.9 of the Applicant's study reports: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data in all arms was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

Table 12: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 12 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Control-based [1]	1.7597 (0.07753)	1.7457 (0.07610)	1.9658 (0.09258)	-0.2060 (-0.4420, 0.0300)	-0.2201 (-0.4551, 0.0149)
Control-based [2]	1.7684 (0.07711)	1.7540 (0.07537)	1.9736 (0.09236)	-0.2052 (-0.4391, 0.0287)	-0.2196 (-0.4530, 0.0138)
Control-based [3]	1.7841 (0.08022)	1.7689 (0.07715)	1.9654 (0.09165)	-0.1813 (-0.4191, 0.0565)	-0.1965 (-0.4304, 0.0375)
Trimmed Mean +MI [4-1]	1.7579 (0.07702)	1.7487 (0.07443)	1.9831 (0.0908)	-0.2251 (-0.4592, 0.0088)	-0.2344 (-0.4649, -0.00397)
Trimmed Mean +MI [4-2]	1.7547 (0.07682)	1.7482 (0.07428)	1.9720 (0.09057)	-0.2173 (-0.4506, 0.0159)	-0.2237 (-0.4536, 0.00601)
Study APL2-304					
Control-based [1]	1.5665	1.6542	1.9622	-0.3956	-0.3079

	(0.08138)	(0.07650)	(0.07982)	(-0.6185, -0.1727)	(-0.5254, -0.0905)
Control-based [2]	1.5833 (0.08059)	1.6684 (0.07721))	1.9668 (0.07979)	-0.3835 (-0.6056, -0.1614)	-0.2984 (-0.5153, -0.0816)
Control-based [3]	1.5948 (0.08054)	1.6776 (0.07736)	1.9601 (0.07972)	-0.3653 (-0.5863, -0.1443)	-0.2825 (-0.5020, -0.0630)
Trimmed Mean +MI [4-1]	1.5550 (0.08074)	1.6398 (0.07701)	1.9649 (0.07983)	-0.4098 (-0.6328, -0.1870)	-0.3251 (-0.5434, -0.1068)
Trimmed Mean +MI [4-2]	1.5654 (0.08076)	1.6522 (0.07686)	1.9668 (0.07948)	-0.4013 (-0.6238, -0.1790)	-0.3145 (-0.5322, -0.0968)

[1] Source: Table 14.2.1.2.5 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Missing data due to other reasons is imputed using observed data within the patient's treatment arm. In both cases, intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.2.1.2.6 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Table 14.2.1.2.7 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-1] Source: Reviewer's analysis: Subjects with missing data due to adverse event and lack of efficacy are excluded (trimmed). Missing data due to reasons other than lack of efficacy and adverse event in all arms was imputed using a multiple imputation approach.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, adverse event or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

Table 13: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 18 (mITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
	Study APL-303				
Control-based [1]	2.6252 (0.10057)	2.5895 (0.10516)	2.9805 (0.13547)	-0.3552 (-0.6867, -0.0238)	-0.3910 (-0.7287, -0.0532)
Control-based [2]	2.6593 (0.10568)	2.6193 (0.10655)	2.9823 (0.13502)	-0.3230 (-0.6569, 0.0108)	-0.3630 (-0.6993, -0.0267)
Control-based [3]	2.6505 (0.10488)	2.6167 (0.10758)	2.9607 (0.13314)	-0.3102 (-0.6412, 0.0209)	-0.3440 (-0.6780, -0.0100)
Trimmed Mean +MI [4-1]	2.6383 (0.10150)	2.5774 (0.10460)	3.0116 (0.13433)	-0.3733 (-0.7043, -0.0424)	-0.4342 (-0.7666, -0.1018)
Trimmed Mean +MI [4-2]	2.6288 (0.10058)	2.5852 (0.10415)	2.9955 (0.13375)	-0.3667 (-0.6957, -0.0377)	-0.4103 (-0.7411, -0.0794)
	Study APL2-304				
Control-based [1]	2.3336 (0.11005)	2.5101 (0.10753)	3.0232 (0.11479)	-0.6895 (-1.0037, -0.3753)	-0.5131 (-0.8209, -0.2053)
Control-based [2]	2.3966 (0.10799)	2.5418 (0.10693)	3.0399 (0.11382)	-0.6434 (-0.9474, -0.3394)	-0.4982 (-0.8014, -0.1949)
Control-based [3]	2.4103 (0.10964)	2.5517 (0.10766)	3.0323 (0.11452)	-0.6220 (-0.9285, -0.3155)	-0.4807 (-0.7877, -0.1736)
Trimmed Mean +MI [4-1]	2.3074 (0.10865)	2.4878 (0.10804)	3.0376 (0.11363)	-0.7302 (-1.0381, -0.4224)	-0.5499 (-0.8576, -0.2421)
Trimmed Mean +MI [4-2]	2.3210 (0.10860)	2.4991 (0.10749)	3.0406 (0.11320)	-0.7196 (-1.0268, -0.4124)	-0.5415 (-0.8481, -0.2349)

[1] Source: Table 14.2.1.2.5 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Table 14.2.1.2.6 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Table 14.2.1.2.7 of the Applicant's response to information request (IR) submitted 07/11/2022: Control based imputation based on sham control subjects was done on missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data, including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-1] Source: Reviewer's analysis: Subjects with missing data due to AE and lack of efficacy are excluded (trimmed). Missing data due to reasons other than lack of efficacy and adverse event in all arms was imputed using a multiple imputation approach.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, AE or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

Reviewer's remark:

[1]: In the first control-based analysis, intermittent missing data in both arms was first imputed using a multiple imputation approach based on observed data within each treatment arm to create a monotone missing data pattern. Then, a controlled-base imputation (using observed data from the pooled sham arm) is applied to impute the missing data in the active arm due to AE and lack of efficacy. Given that there is substantial intermittent missing data and that very few subjects had missing data due to AE and lack of efficacy, this analysis is expected to provide results that are similar to the primary efficacy analysis which implicitly imputed missing data.

[2]: The second control-based analysis followed the same steps as the first approach except that all missing data, regardless of reason for missingness, is imputed using the observed data from the pooled sham arm in the second step. However, here also, substantial intermittent missing data is imputed using observed data within each treatment arm.

[3]: In this analysis, all missing data in both arms regardless of the pattern (monotone or otherwise) is imputed using observed data from the pooled sham arm.

[4-1]: In this analysis, all observed data for subjects who discontinued the study due to AE or lack of efficacy in both arms were trimmed. Missing data due to all other reasons were imputed using the observed data within each treatment arm.

[4-2]: As noted in the disposition table, most subjects discontinued the study because they withdrew consent. Although the majority did so for reasons that appear to be unrelated to treatment, 3 subjects in the PM group and 1 subject in the SM group withdrew consent because of concerns about treatment through Month 18. Thus, in this analysis, all observed data for subjects who discontinued the study due to AE, lack of efficacy or who withdrew consent in both arms were trimmed. Missing data due to all other reasons were imputed using the observed data within each treatment arm.

Recall, the primary efficacy analysis was conducted based on the mITT population which excluded randomized and treated subjects with no-postbaseline GA measurements (Table 43--Table 45). To evaluate the impact of excluding subjects based on post randomization factors, up on request by this reviewer, the Applicant conducted the analysis of the GA growth rate in the ITT population (all randomized subjects). For subjects with no post-baseline GA data, the worst

observed outcome at each timepoint within the patient's treatment arm was imputed. The observed treatment differences in both studies are still numerically favorable to the two dosing frequencies of pegcetacoplan. However, the treatment difference between PM and pooled sham is not nominally significant in Study APL2-304 (Table 14).

Table 14: Sensitivity Analyses of Mean Rate of GA Growth (Slope): Baseline through Month 18 (ITT)

Approaches	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham pooled	PM vs Sham Pooled	PEOM vs Sham pooled
Study APL-303					
Worst Post-Baseline Outcome [1]	2.8879 (0.13413)	2.8368 (0.13173)	3.6399 (0.22657)	-0.7520 (-1.2684, -0.2356)	-0.8031 (-1.3165, -0.2896)
Study APL2-304					
Worst Post-Baseline Outcome [1]	2.7602 (0.17076)	2.7064 (0.13053)	3.1738 (0.13779)	-0.4136 (-0.8437, 0.0165)	-0.4673 (-0.8395, -0.0951)

[1] Source: Table 14.2.1.3.8.4 of the Applicant's response to information request (IR) submitted 07/11/2022: Patients that were treated but have no post-baseline assessments in scheduled visit window have all assessments imputed based on the worst observed change at each timepoint within the patient's treatment arm.

Reviewer's remark: Note, per the Applicant, the analysis on the ITT population based on the worst outcome imputation provided more favorable treatment effect in Study APL2-303 because one sham subject had a very rapid GA lesion area growth. Conversely, the worst outcome in the PM arm of APL2-304 was from a subject who had a very rapid GA growth in comparison to the rest of the population. Because this subject's outcome is used to impute missed GA data for all subjects in the PM arm with no post-baseline GA, the estimated treatment effect in this study is very conservative.

❑ **Tipping Point Analysis Results**

A tipping point analysis was first conducted by applying a set of shifting parameters to imputed data for subjects in the pegcetacoplan arms who discontinued the study due to adverse events or lack of efficacy. However, because most subjects discontinued the studies due to withdrawal of consent, a second tipping point analysis, where imputed data for subjects who withdrew consent for reasons that are assumed to be related to the efficacy or safety of the drug or injection (in addition to those reported due to lack of efficacy or adverse event) were also shifted, is conducted.

Recall, the treatment difference in the mean change from baseline at Month 12 was not statistically significant in Study APL2-303. However, the treatment differences in the mean change from baseline at Month 18 and the rate of GA growth (Slope through Month 18) were all statistically significant in both studies. For the latter, the tipping point, the shift that led to the treatment difference to no longer be statistically significant, was not reached for either of the two pegcetacoplan arms in both studies (Table 27--Table 36).

❑ **Analysis Without Pooling the Sham Arms**

Although there was no notable difference between the two sham arms with respect to pre-treatment baseline and demographic characteristics, some differences, including differences in missed visits, missing GA data, study discontinuation rates (including discontinuation due to adverse events) and adverse event rates are observed. For example:

- The proportion of subjects who discontinued the study due to adverse events was 8.2% in SM and 2.4% in SEOM.
- In Study APL2-303, the proportion of subjects with missing GA data at Month 12 was 32% in SM and 16.3% in SEOM. The corresponding figures at Month 18 were 24.7% vs 19.4%. Similarly, in APL2-304, the rates were 21.9% vs 12.7% at Month 12 and 29.5% vs 20.6% at Month 18.
- The proportion of subjects who died during the 18 month was 4.8% in SM and 1.4% in SEOM.

In response to the reviewer's information request to provide possible explanation on the observed discrepancy between the two sham arms, the Applicant stated that although the two studies were double masked to treatment assignment, treatment frequency (monthly [SM] vs every-other month [SEOM]) was known to investigators and subjects since enrollment into the study.

Per the Applicant, during the COVID-19 pandemic, sites were encouraged to follow the full schedule of assessments (based on their treatment group assignment). However, to reduce the pandemic exposure risk of subjects enrolled in the studies, a minimized schedule of assessment was followed. This included a less frequent number of assessments that did not require subjects in the SEOM treatment group to be seen for visits with no injection procedure (e.g., Month 1, Month 3). Per the Applicant, it is possible that the differences observed between SM and SEOM arms in missing visits, missing GA data, adverse event rates, and study discontinuation rates were driven by prior knowledge of the injection procedure visit, as well as the minimized assessment schedules implemented in the SEOM arm during the COVID-19 pandemic, thus leading to better compliance. Conversely, the greater treatment burden in the SM arm may have led to relatively lower compliance.

To evaluate the impact on the efficacy results of the observed differences between the two sham arms, the analyses of the protocol defined, and the DOP's preferred endpoints has been conducted without pooling the sham arms. Per this analysis, there is a notable difference in GA growth rate between the two sham arms; the SM arm had a slower GA growth rate compared to the SEOM arm. Consequently, while the treatment differences between the PEOM and SEOM are nominally statistically significant in both studies, the treatment differences between PM and SM arms were nominally significant in Study APL2-304 only. Detailed summaries of the results are provided below.

▪ Analysis of the Protocol Defined Endpoint

The Applicant conducted the analysis of the mean change from baseline at Month 12/18 comparing each dosing frequency to the corresponding sham arm (PM vs. SM and PEOM vs SEOM). In Study APL2-303, while there was only a slight difference in the observed mean change from baseline at Month 12/18 between PM and PEOM arms, there was noticeable

difference between the two sham arms. The SEOM arm had higher mean change from baseline (worse) than the corresponding figure in the SM arm. Consequently, the difference between PM and SM is not nominally significant.

However, the difference between PEOM and SEOM is nominally significant. Recall, the treatment differences between each of the two pegcetacoplan arms against the pooled sham arm were not significant in this study. Similarly, in Study APL2-304, the SEOM arm had a higher mean change from baseline compared to the SM arm. However, in line with the pooled analysis, in Study APL2-304, there was a nominally significance difference between each of the two pegcetacoplan arms against the corresponding sham arm (Table 15).

Table 15: Mean Change from Baseline in Total GA Area: Without Pooling Sham (mITT)

	LS mean (SE)				Difference (95% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Parameters	Study APL2-303					
Month 12 [1]: Mean Change (SE)	1.7345 (0.07922)	1.7570 (0.07445)	1.8547 (0.13397)	2.0632 (0.13583)	-0.1202 (-0.4213, 0.1809)	-0.3062 (-0.6105, -0.0020)
Month 18 [2]: Mean Change (SE)	2.6218 (0.10078)	2.6337 (0.10320)	2.7712 (0.18978)	3.2140 (0.1970)	-0.1494 (-0.5678, 0.2689)	-0.5803 (-1.0177, -0.1428)
	Study APL2-304					
Month 12 [1]: Mean Change (SE)	1.5575 (0.08349)	1.6509 (0.08115)	1.8523 (0.09549)	2.0806 (0.13082)	-0.2948 (-0.5422, -0.0473)	-0.4298 (-0.7291, -0.1304)
Month 18 [2]: Mean Change (SE)	2.3512 (0.10694)	2.5168 (0.10879)	2.8540 (0.13340)	3.1579 (0.18516)	-0.5028 (-0.8375, -0.1680)	-0.6411 (-1.0601, -0.2221)

[1]: Source: Table 31 of the Applicant's study reports.

[2]: Source: Table 14.2.1.2.3 of the Applicant's study reports.

▪ Analysis of the DOP's Preferred Endpoint (Slope)

The Applicant has also conducted the analysis of the slope endpoint without pooling the two sham arms. The observed results are consistent with the results observed for the protocol defined primary efficacy endpoint (Table 16).

Table 16: Mean Rate of GA Growth (Slope): Without Pooling Sham (mITT)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
	Study APL2-303					
Month 12: Slope (SE) [1]	1.7623 (0.07622)	1.7494 (0.07371)	1.8425 (0.12061)	2.0725 (0.13330)	-0.0802 (-0.3604, 0.2000)	-0.3232 (-0.6223, -0.0240)
Month 18: Slope (SE) [2]	2.6449 (0.10131)	2.5999 (0.10266)	2.7896 (0.18219)	3.2032 (0.19896)	-0.1447 (-0.5533, 0.2639)	-0.6033 (-1.0424, -0.1642)
	Study APL2-304					
Month 12: Slope (SE) [1]	1.5607 (0.08031)	1.6569 (0.07607)	1.8706 (0.09596)	2.0644 (0.12614)	-0.3099 (-0.5548, -0.0649)	-0.4075 (-0.6974, -0.1177)
Month 18: Slope (SE) [2]	2.3383 (0.11021)	2.4905 (0.10766)	2.7900 (0.12891)	3.1444 (0.18548)	-0.4517 (-0.7832, -0.1203)	-0.6539 (-1.0744, -0.2334)

[1] Source: Table 4.2.1.3.8.8 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 4.2.1.3.8.8 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model with time included in the model as a linear continuous variable and GA data through Month 18 included.

This reviewer conducted sensitivity analyses of the treatment comparisons with respect to the mean rate of GA growth through Month 18 without pooling the sham arms (Table 17). The results from the sensitivity analyses are generally consistent with the results summarized in Table 16.

Table 17: Sensitivity Analysis: Mean Rate of GA Growth: Month 18 (Slope): Without Pooling (mITT)

Approaches	LS mean (SE)				Difference (95% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Study APL2-303						
Control-based [1]	2.6486 (0.10157)	2.5842 (0.10399)	2.7791 (0.18639)	3.2242 (0.19789)	-0.1305 (-0.5498, 0.2887)	-0.6399 (-1.0778, -0.2020)
Control-based [2]	2.6637 (0.10623)	2.6301 (0.10797)	2.7781 (0.18195)	3.2063 (0.19455)	-0.1144 (-0.5242, 0.2954)	-0.5762 (-1.0120, -0.1403)
Control-based [3]	2.6661 (0.10710)	2.6328 (0.10848)	2.7654 (0.17945)	3.1958 (0.19264)	-0.0993 (-0.5064, 0.3078)	-0.5630 (-0.9955, -0.1306)
Trimmed Mean +MI [4-2]	2.6551 (0.10215)	2.5785 (0.10279)	2.8003 (0.17986)	3.2484 (0.19225)	-0.1452 (-0.5510, 0.2606)	-0.6699 (-1.0956, -0.2443)
Study APL2-304						
Control-based [1]	2.3186 (0.10674)	2.5084 (0.10820)	2.8578 (0.14330)	3.1426 (0.18582)	-0.5392 (-0.8863, -0.1921)	-0.6342 (-1.0565, -0.2118)
Control-based [2]	2.3795 (0.10931)	2.5307 (0.11059)	2.8699 (0.14048)	3.1355 (0.18401)	-0.4904 (-0.8333, -0.1475)	-0.6048 (-1.0235, -0.1861)
Control-based [3]	2.3997 (0.11107)	2.5457 (0.11209)	2.8568 (0.13769)	3.1470 (0.18507)	-0.4571 (-0.7933, -0.1210)	-0.6013 (-1.0217, -0.1809)
Trimmed Mean +MI [4-2]	2.3108 (0.10684)	2.5003 (0.10820)	2.8863 (0.14158)	3.1646 (0.18173)	-0.5755 (-0.9163, -0.2347)	-0.6643 (-1.0795, -0.2492)

[1] Source: Reviewer's analysis: Control based imputation based on frequency-matched sham control subjects (i.e., missing PM data imputed using observed SM data and missing PEOM data imputed using observed data from the SEOM arm) was done for missing data for subjects on active treatment after discontinuation or withdrawal if the reason for treatment discontinuation or study withdrawal was assessed as potentially related to study drug or lack of efficacy. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[2] Source: Reviewer's analysis: Control based imputation based on frequency-matched sham control subjects (i.e., missing PM data imputed using observed SM data and missing PEOM data imputed using observed data from the SEOM arm) was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. Intermittent missing data was first imputed using observed data within each treatment arm to create a monotone missing data pattern.

[3] Source: Reviewer's analysis: Control based imputation based on frequency-matched sham control subjects (i.e., missing PM data imputed using observed SM data and missing PEOM data imputed using observed data from the SEOM arm) was done for missing data for subjects on active treatment after discontinuation or withdrawal for any reason. All missing data, including intermittent missing data was imputed using observed data from the pooled sham arm.

[4-2] Source: Reviewer's analysis: Subjects with missing data due to withdrawal of consent, AE or lack of efficacy are excluded (trimmed). Missing data due to other reasons in all arms was imputed using a multiple imputation approach.

□ Analyses Adjusting for Baseline Imbalances Observed Post-hoc

The Applicant conducted post-hoc analyses of the protocol defined as well as the DOP's preferred primary efficacy endpoints adjusting for selected baseline characteristics (prognostics factors) for which they state were major chance imbalances among the treatment arms. In both studies, the results from these analyses show that there is nominally significant difference between each of the two dosing frequencies of pegcetacoplan against the pooled sham with respect to both the protocol defined as well as the DOP's preferred primary efficacy endpoints (Table 18 and Table 19).

Table 18: Mean Change from Baseline in Total GA Area: Adjusted (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL-303					
Month 12: Mean change (SE) [1]	1.7060 (0.07448)	1.7256 (0.07120)	2.0195 (0.08969)	-0.3135 (-0.5385, -0.0885)	-0.2940 (-0.5189, -0.0691)
Month 18: Mean change (SE) [2]	2.5845 (0.09670)	2.5788 (0.09515)	3.0722 (0.12921)	-0.4877 (-0.8024, -0.1729)	-0.4934 (-0.8098, -0.1770)
Study APL2-304					
Month 12: Mean change (SE) [1]	1.5095 (0.07922)	1.6645 (0.07511)	2.0098 (0.07772)	-0.5003 (-0.7195, -0.2811)	-0.3453 (-0.5535, -0.1372)
Month 18: Mean change (SE) [2]	2.2695 (0.10307)	2.5321 (0.09845)	3.0692 (0.10742)	-0.7997 (-1.0949, -0.5045)	-0.5371 (-0.8183, -0.2560)

[1] Source: Table 25 of the Applicant's study reports.

[2] Source: Table 14.2.1.1.2.1 of the Applicant's study reports.

Table 19: Mean Rate of GA Growth (Slope): Adjusted (mITT)

Parameters	Treatments			Difference (95.1% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL-303					
Month 12: Slope (SE) [1]	1.7431 (0.07123)	1.7276 (0.06993)	2.0160 (0.08307)	-0.2729 (-0.4879, -0.0578)	-0.2884 (-0.5026, -0.0741)
Month 18: Slope (SE) [2]	2.6113 (0.09594)	2.5656 (0.09532)	3.0924 (0.12587)	-0.4811 (-0.7921, -0.1702)	-0.5269 (-0.8379, -0.2158)
Study APL2-304					
Month 12: Slope (SE) [1]	1.5100 (0.07683)	1.6682 (0.06977)	2.0026 (0.07523)	-0.4925 (-0.7062, -0.2788)	-0.3343 (-0.5344, -0.1343)
Month 18: Slope (SE) [2]	2.2698 (0.10615)	2.5179 (0.09771)	3.0335 (0.10724)	-0.7637 (-1.0627, -0.4647)	-0.5156 (-0.7971, -0.2342)

[1] Source: Table 28 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 14.2.1.3.8.1 of the Applicant's study reports. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 18 included.

Per the Applicant, the individual sham groups are half the size of the pooled sham group and are more subject to chance differences. As an example, the Applicant pointed out that, in Study APL2-304, examination of the baseline characteristics revealed an imbalance between SM and SEOM arms on the baseline lesion location where a greater percentage of subjects in the SEOM group (35.3%) had a lesion without subfoveal involvement at baseline than in the SM group (22.9%).

The Applicant also conducted the analyses of both the protocol defined and the DOP's preferred endpoints adjusting for selected baseline characteristics and without pooling the sham arms (Table 20).

Table 20: Mean Rate of GA Growth (Slope): Adjusted: Without Pooling Sham (mITT)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)	
	PM	PEOM	SM	SEOM	PM vs SM	PEOM vs SEOM
Study APL2-303						
Month 12: Slope (SE) [1]	1.7408 (0.07122)	1.7256 (0.06985)	1.8814 (0.10530)	2.1431 (0.12494)	-0.1406 (-0.3922, 0.1110)	-0.4175 (-0.6986, -0.1363)
Month 18: Slope (SE) [2]	2.6104 (0.09602)	2.5654 (0.09523)	2.8591 (0.16137)	3.3172 (0.18669)	-0.2487 (-0.6187, 0.1212)	-0.7518 (-1.1630, -0.3407)
Study APL2-304						
Month 12:	1.5108	1.6688	1.9625	2.0424	-0.4517	-0.3736

Slope (SE) [1]	(0.07677)	(0.06981)	(0.09101)	(0.11723)	(-0.6851, -0.2183)	(-0.6426, -0.1046)
Month 18:	2.2700	2.5176	2.9349	3.1269	-0.6649	-0.6093
Slope (SE) [2]	(0.10608)	(0.09777)	(0.12171)	(0.17120)	(-0.9804, -0.3493)	(-0.9960, -0.2225)

[1] Source: Table 4.2.1.3.8.9 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 12 included.

[2] Source: Table 4.2.1.3.8.9 of the Applicant's response to information request (IR) submitted on 13/09/2022. The analysis is conducted using a linear mixed effects model adjusting for selected prognostic factors and with time included in the model as a linear continuous variable and GA data through Month 18 included.

❑ Identifying Potential Factors That Led to Difference in Magnitude of Treatment Effects Between PM Arms Across the Two Studies

Per the study results, the estimated mean change from baseline at Month 12 in the pooled sham arm is similar in the two studies. However, the magnitude of the observed treatment effect for the PM arm in Study APL2-303 is 50% lower than the magnitude observed in Study APL2-304. Although there does not appear to be noticeable difference in the demographic characteristics of age, sex and ethnicity among subjects randomized to the PM arms across the two studies, there were some notable differences in baseline disease characteristics between subjects randomized to the PM arms across the two studies. Note, some of these characteristics were identified by the Applicant as potentially having effect on GA progression. These include foveal involvement, number of intermediate or large drusen >20, and whether GA was multi or unifocal. For example, compared to subjects in the PM arm in Study APL2-304, there were more subjects in the PM arm of study APL2-303 with multifocal GA lesion at baseline (73.1% vs 70.8%), more subjects with GA lesion at baseline with subfoveal involvement (64.2% vs. 57.4%) and fewer subjects with number of intermediate or large drusen at baseline of more than 20 units (28.8% vs. 46%).

As can be seen from the subgroup analyses, subjects with the baseline characteristics identified above are shown to have faster GA progressions. For example, in Study APL2-303, the mean change from baseline in GA area at Month 18 for sham randomized subjects with intermediate or large drusen at baseline of > 20 units was 2.5145 mm². The corresponding figure for sham randomized subjects with intermediate or large drusen at baseline of < 20 units was 3.573 mm² (faster GA growth). Therefore, the difference in GA progression across the PM arms of the two studies could be partly attributed to the difference in the number of subjects enrolled in the two studies with these disease characteristics at baseline.

Also note, based on the results of the piecewise linear regression, the Applicant showed that the observed higher GA rate of progression in Study APL2-303 compared to Study APL2-304 was mostly driven by the higher progression observed in the Month 0 to 6 period. As time progressed, the difference between the PM arms across the two studies has reduced (Table 21).

Note, in addition to the chance imbalances in some baseline disease characteristics, there were some notable differences in treatment compliances between the two studies. For example, among subjects in the mITT population randomized to the PM arm in Study APL2-303, 16% have missed at least 5 of the 18 injections compared to 10% in the corresponding arm in Study APL2-304. The proportion of subjects who received all planned injections was also slightly lower for subjects randomized to the PM arm of Study APL2-304 (31.3%) compared to the

corresponding arm in Study APL2-303 (33.7%). The difference in drug exposure might have also contributed to the discrepancy in the efficacy outcomes (See Section 3.3.1 for detailed drug exposure summary).

Table 21: Percentage Difference in Slope PM vs. Sham Pooled from a Piecewise Linear Regression

	APL2-304	APL2-303	Magnitude of APL2-303 Treatment Effect Relative to APL2-304 (%)
Estimates for Baseline to Month 6			
Unadjusted, PM vs. Sham Pooled	-22.8	-5.6	24.6
Covariate-Adjusted, PM vs. Sham Pooled	-27.0	-9.7	35.9
Estimates for Month 6 to Month 12			
Unadjusted, PM vs. Sham Pooled	-19.2	-17.3	90.1
Covariate-Adjusted, PM vs. Sham Pooled	-22.2	-20.4	91.9
Estimates for Month 12 to Month 18			
Unadjusted, PM vs. Sham Pooled	-22.0	-14.2	64.5
Covariate-Adjusted, PM vs. Sham Pooled	-26.3	-17.0	64.6
Estimates for Month 18 to Month 24 (available data as included in NDA)			
Unadjusted, PM vs. Sham Pooled	-30.0	-24.7	82.3
Covariate-Adjusted, PM vs. Sham Pooled	-32.1	-26.0	81.0

Source: Table 2 of the Applicant's response to information request (IR) submitted on 13/09/2022. Unadjusted and covariate adjusted refers to results with or without adjusting for baseline characteristics with major imbalance.

C. Analysis of Secondary Efficacy Endpoints

A. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of the two studies are changes from baseline at Month 24 in monocular maximum reading speed, FRI index score, and NL-BCVA score. In the current NDA submission, the results of these endpoints were not included.

B. Other Secondary Efficacy Endpoints

This section presents the results of three additional secondary efficacy endpoints evaluated in the two studies. For each endpoint, the analysis was conducted using a similar MMRM that was used for the protocol defined primary efficacy endpoint based on all observed data on the mITT population. From each model, the least squares mean change from baseline for each treatment arm, the differences between treatment arms and the associated 2-sided 95% confidence intervals are provided. Per the Applicant, no clinically meaningful changes were observed in all the three endpoints. Detailed results for each endpoint are provided below.

▪ Low-Luminance Best-Corrected Visual Acuity (LL-BCVA)

The estimated mean change from baseline in LL-BCVA score in letters read were negative in all the three arms. This implies that subjects in all arms had a decline in the number of letters read from baseline at Month 12. Per the Applicant, these results are consistent with the visual function changes expected at Month 12 in subjects with GA.

In study APL2-303, the estimated mean change from baseline in LL-BCVA score at Month 12 were [PM (−1.933), PEOM (−0.182), and sham pooled (−0.706) groups]. The treatment differences between PM and the pooled sham and the PEOM and the pooled sham and the corresponding 95% confidence intervals are −1.228 (−3.505, 1.050) and 0.524 (−1.847, 2.894), respectively. In study APL2-304, the estimated mean change from baseline in LL-BCVA score at Month 12 were [PM (−2.369), PEOM (−2.847), and sham pooled (−2.391) groups]. The treatment differences between PM and the pooled sham and the PEOM and the pooled sham and the corresponding 95% confidence intervals are 0.022 (−2.018, 2.061) and −0.456 (−2.543, 1.630), respectively.

Table 22: Mean Change from Baseline in LL-BCVA Score at Month 12 (mITT)

Study	LS mean (SE)			Difference (95% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	−1.933 (0.7452)	−0.182 (0.7954)	−0.706 (0.9013)	−1.228 (−3.505, 1.050)	0.524 (−1.847, 2.894)
Study APL2-304	−2.369 (0.7006)	−2.847 (0.7331)	−2.391 (0.8127)	0.022 (−2.018 to 2.061)	−0.456 (−2.543 to 1.630)

Source: Table 46 (APL2-303) and Table 45 (APL2-304) of the Applicant's study reports.

▪ **Monocular Critical Print Size (MCPS)**

Per the Applicant, critical print size is calculated as the smallest print size which supports reading speed at 80% of the maximum reading speed, with no adjustment for reading inaccuracy. For reference, a print size of 1.0 logMAR is equivalent to 24-point font, as is used in large print books. The reported results show that in both studies, there were minor changes from baseline at Month 12 in all the three arms.

In study APL2-303, the estimated mean change from baseline in MCPS at Month 12 were [PM (0.018), PEOM (0.019), and sham pooled (0.037) groups]. The treatment differences between PM and the pooled sham and the between PEOM and the pooled sham, and the corresponding 95% confidence intervals are −0.018 (−0.084, 0.048) and −0.017 (−0.080, 0.046), respectively.

In study APL2-304, the estimated mean change from baseline in MCPS at Month 12 were [PM (0.021), PEOM (0.060), and sham pooled (0.050) groups]. The treatment differences between PM and the pooled sham and the between PEOM and the pooled sham, and the corresponding 95% confidence intervals are −0.029 (−0.085, 0.027) and 0.010 (−0.044, 0.063), respectively.

Table 23: Mean Change from Baseline in MCPS at Month 12 (mITT)

Study	LS mean (SE)			Difference (95% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	0.018 (0.0253)	0.019 (0.0216)	0.037 (0.0283)	−0.018 (−0.084, 0.048)	−0.017 (−0.080, 0.046)
Study APL2-304	0.021 (0.0217)	0.060 (0.0206)	0.050 (0.0230)	−0.029 (−0.085, 0.027)	0.010 (−0.044, 0.063)

Source: Table 47 (APL2-303) and Table 46 (APL2-304) of the Applicant's study reports.

❑ NEI VFQ-25 Distance Activity Subscale Score

In study APL2-303, the estimated mean change from baseline in NEI VFQ-25 at Month 12 were [PM (−0.928), PEOM (−2.761), and sham pooled (−2.807) groups]. The treatment differences between PM and the pooled sham and between PEOM and the pooled sham, and the corresponding 95% confidence intervals are 1.879 (−2.501, 6.260) and 0.046 (−4.173, 4.265), respectively. In study APL2-304, the estimated mean change from baseline in NEI VFQ-25 at Month 12 were [PM (−5.631), PEOM (−6.907), and sham pooled (−6.751) groups]. The treatment differences between PM and the pooled sham and between PEOM and the pooled sham and the corresponding 95% confidence intervals are 1.120 (−2.685, 4.924) and −0.157 (−3.981, 3.668), respectively.

Table 24: Mean Change from Baseline in NEI VFQ-25 at Month 12 (mITT)

Study	LS mean (SE)			Difference (95% Confidence Interval)	
	PM	PEOM	Sham Pooled	PM vs Sham pooled	PEOM vs Sham pooled
Study APL2-303	−0.928 (1.6782)	−2.761 (1.6245)	−2.807 (1.7766)	1.879 (−2.501, 6.260)	0.046 (−4.173, 4.265)
Study APL2-304	−5.631 (1.6238)	−6.907 (1.6614)	−6.751 (1.2588)	1.120 (−2.685, 4.924)	−0.157 (−3.981, 3.668)

Source: Table 48 (APL2-303) and Table 47 (APL2-304) of the Applicant's study reports.

3.3 Evaluation of Safety

This section presents treatment exposure and descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), using MedDRA 20.1 dictionary derived term, from Study APL2-303 and Study APL2-304. These summaries are provided for the safety analysis population, which is defined in the SAPs as all randomized patients who receive at least 1 dose of study medication. The safety analysis population is comprised of 620 subjects in Study APL2-303 [PM (206); PEOM (208); Pooled sham (206: 102 SM and 104 SEOM)], and 636 subjects in Study APL2-304 [PM (213); PEOM (212); Pooled sham (211: 105 SM and 106 SEOM subjects)].

3.3.1 Extent of Treatment Exposure

Per the study protocol, during the first 12/18 months, subjects randomized to the monthly dosing frequencies (PM and SM) were to receive up to 12/18 injections, whereas those randomized to every other month dosing frequency (PEOM and SEOM) were to receive up to 6/9 injections. In both studies, the percentage of subjects who received the maximum number of planned injections during the first 12/18 months was relatively low. This appears to be more pronounced in the monthly injections raising the issue of treatment compliance. Per the Applicant, the main reason for missed injections was the disruption caused by the COVID-19 pandemic. Detailed exposure summary is provided below.

▪ Month 12 cut-off

In Study APL2-303, the percentage of subjects who received the maximum allowed number of injections was (PM: 40.8%), (PEOM: 60.5%), (SM: 35.1%), and (SEOM: 66%). The

corresponding figures in Study APL2-304 were (PM: 40.1%), (PEOM: 67.3%), (SM: 39.4%), and (SEOM: 57.8%). In Study APL2-303, the Mean (SD) number of injections was 10.2 (2.24), 5.3 (1.05), 10.0 (2.54), and 5.4 (0.97) for the PM, PEOM, SM and SEOM groups, respectively. The corresponding figures in Study APL2-304 were 10.2 (2.31), 5.4 (1.12), 10.1 (2.55), and 5.3 (0.92) for the PM, PEOM, SM and SEOM groups, respectively.

▪ **Month 18 cut-off**

In Study APL2-303, the percentage of subjects who received the maximum allowed number of injections (did not miss any injection) was (PM: 31.3%), (PEOM: 51.7%), (SM: 30.9%), and (SEOM: 57.1%). The corresponding figures in Study APL2-304 were (PM: 33.7%), (PEOM: 60.0%), (SM: 32.4%), and (SEOM: 52%).

In Study APL2-303, the [Mean (SD), min, max] number of injections of was [14.7 (4.03), 1, 18], [7.7 (1.87), 1, 10], [14.6 (4.29), 2, 18] and [7.8 (1.8), 1, 9] for the PM, PEOM, SM and SEOM groups, respectively. In Study APL2-304, the [Mean (SD), min, max] number of injections was [14.8 (4.08), 2, 18], [7.9 (1.97), 1, 9], [14.4 (4.58), 0, 18], [7.9 (1.59), 2, 9] for the PM, PEOM, SM and SEOM groups, respectively.

3.3.2 Adverse Events

The overall adverse event summary for the pooled data up to Month 18 is presented in Table 25. By Month 18, a higher percentage of subjects in the two pegcetacoplan arms reported at least one ocular adverse event compared to the sham arms (58% in PM, 51% in PEOM, 42% in SM and 41% in SEOM). Note, although the proportion of subjects who reported at least one adverse event does not appear to be significantly higher in the two pegcetacoplan arms compared to sham, the number of reported adverse events per subject was significantly higher in the two pegcetacoplan arms compared to the sham arm. For example, a total of 2030 adverse events were reported by subjects randomized to the PM arms compared to 1627 by subjects randomized in the two sham arms combined.

The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms (PM; PEOM) were: vitreous floaters (8.5%; 6.4%), Neovascular age-related macular degeneration (8.4%; 5.5%), conjunctival haemorrhage (7.6%; 6.9%), and eye pain (6.4%; 5.2%). The incidence rate of these adverse events in the sham arms (SM; SEOM) were vitreous floaters (1.0%;1.0%), Neovascular age-related macular degeneration (1.9%; 1.9%), conjunctival haemorrhage (2.4%; 3.8%), and eye pain (5.8%; 6.2%).

In addition, a slightly higher proportion of subjects in the PM pegcetacoplan arm reported at least one serious adverse event compared to the PEOM as well as the sham arms (28% in PM, 21% in PEOM, 25% in SM and 19% in SEOM). The proportion of subjects who died during the 18 month was 4.8% in PM, 2.6% in PEOM, 4.8% in SM and 1.4% in SEOM. The proportion of subjects who discontinued the study due to adverse events was 7.2% in PM, 4.8% in PEOM, 8.2% in SM and 2.4% in SEOM. Note, most of the adverse events that led to treatment discontinuation were non-ocular in nature. Also note, the differences in the observed

incidence rates in the two pegcetacoplan arms suggest that more frequent injection leads to increased adverse events.

❑ Adverse Events of Special Interest

The Applicant provided summaries of adverse events of special interest, namely, endophthalmitis, intraocular inflammations and exudative AMD. Per the study results, no subject reported endophthalmitis. The percentage of subjects with intraocular inflammations was 3.3% in the PM arm, 0.7% in the PEOM arm and none in the sham arms.

A higher percentage of subjects in the pegcetacoplan pooled group (7.9%) than in the sham pooled group (2.9%) had an exudative AMD adverse event in the study eye. Subjects in the PM (9.5%) group had a higher incidence of exudative AMD adverse events in the study eye than in the PEOM (6.2%) group. Per the Applicant, most of the adverse events of special interest were mild to moderate and did not lead to study or treatment discontinuation.

Table 25: Overall Summary of Adverse Events (Up to Month 18)

	PM (N=419)	PEOM (N=420)	Pegcetacoplan pooled (N = 839)	SM (N=207)	SEOM (N=210)	Sham pooled (N=417)	Total (N=1256)
All AE	355 (84.7)	348 (82.9)	703 (83.8)	161 (77.8)	172 (81.9)	333 (79.9)	1036 (82.5)
Ocular AE	244 (58.2)	213 (50.7)	457 (54.5)	87 (42.0)	85 (40.5)	172 (41.2)	629 (50.1)
All Serious AE	116 (27.7)	89 (21.2)	205 (24.4)	52 (25.1)	39 (18.6)	91 (21.8)	296 (23.6)
Ocular	9 (2.1)	4 (1.0)	13 (1.5)	1 (0.5)	1 (0.5)	2 (0.5)	15 (1.2)
Death	20 (4.8)	11 (2.6)	31 (3.7)	10 (4.8)	3 (1.4)	13 (3.1)	44 (3.5)
AEs leading to treatment discontinuation	35 (8.4)	23 (5.5)	58 (6.9)	17 (8.2)	5 (2.4)	22 (5.3)	80 (6.4)
AEs leading to study discontinuation	30 (7.2)	20 (4.8)	50 (6.0)	17 (8.2)	5 (2.4)	22 (5.3)	72 (5.7)

Source: Adapted from Table 14 of the Clinical summary of safety. AE: Adverse event.

Table 26: Summary of Ocular Adverse Events in the Study Eye (Up to Month 18)

	PM (N=419) n (%)	PEOM (N=420)	Pegcetacopl an pooled (N=839) n (%)	SM (N=207) n (%)	SEOM (N = 210) n (%)	Sham pooled (N=417) n (%)	Total (N = 1256) n (%)
At least one ocular AE in the study eye	244 (58.2)	213 (50.7)	457 (54.5)	87 (42.0)	85 (40.5)	172 (41.2)	629 (50.1)
Eye disorders	238 (56.8)	203 (48.3)	441 (52.6)	83 (40.1)	78 (37.1)	161 (38.6)	602 (47.9)
Vitreous floaters	35 (8.4)	27 (6.4)	62 (7.4)	2 (1.0)	2 (1.0)	4 (1.0)	66 (5.3)
Conjunctival haemorrhage	32 (7.6)	29 (6.9)	61 (7.3)	5 (2.4)	8 (3.8)	13 (3.1)	74 (5.9)
Neovascular age-related macular degeneration	35 (8.4)	23 (5.5)	58 (6.9)	4 (1.9)	4 (1.9)	8 (1.9)	66 (5.3)
Eye pain	27 (6.4)	22 (5.2)	49 (5.8)	12 (5.8)	13 (6.2)	25 (6.0)	74 (5.9)
Visual acuity reduced	24 (5.7)	21 (5.0)	45 (5.4)	12 (5.8)	12 (5.7)	24 (5.8)	69 (5.5)
Vitreous detachment	13 (3.1)	23 (5.5)	36 (4.3)	4 (1.9)	6 (2.9)	10 (2.4)	46 (3.7)
Dry eye	19 (4.5)	16 (3.8)	35 (4.2)	6 (2.9)	7 (3.3)	13 (3.1)	48 (3.8)
Retinal haemorrhage	16 (3.8)	15 (3.6)	31 (3.7)	4 (1.9)	4 (1.9)	8 (1.9)	39 (3.1)
Cataract	14 (3.3)	12 (2.9)	26 (3.1)	1 (0.5)	7 (3.3)	8 (1.9)	34 (2.7)
Punctate keratitis	17 (4.1)	8 (1.9)	25 (3.0)	1 (0.5)	1 (0.5)	2 (0.5)	27 (2.1)
Eye irritation	15 (3.6)	10 (2.4)	25 (3.0)	10 (4.8)	10 (4.8)	20 (4.8)	45 (3.6)
Posterior capsule opacification	14 (3.3)	11 (2.6)	25 (3.0)	5 (2.4)	3 (1.4)	8 (1.9)	33 (2.6)

Foreign body sensation in eyes	13 (3.1)	10 (2.4)	23 (2.7)	4 (1.9)	3 (1.4)	7 (1.7)	30 (2.4)
Low luminance BCVA decreased	12 (2.9)	10 (2.4)	22 (2.6)	7 (3.4)	4 (1.9)	11 (2.6)	33 (2.6)
Vision blurred	11 (2.6)	10 (2.4)	21 (2.5)	7 (3.4)	9 (4.3)	16 (3.8)	37 (2.9)
Blepharitis	7 (1.7)	13 (3.1)	20 (2.4)	3 (1.4)	4 (1.9)	7 (1.7)	27 (2.1)
Ocular hypertension	10 (2.4)	9 (2.1)	19 (2.3)	0	0	0	19 (1.5)
Visual impairment	9 (2.1)	9 (2.1)	18 (2.1)	3 (1.4)	4 (1.9)	7 (1.7)	25 (2.0)
Ocular hyperaemia	9 (2.1)	5 (1.2)	14 (1.7)	6 (2.9)	1 (0.5)	7 (1.7)	21 (1.7)
Lacrimation increased	6 (1.4)	6 (1.4)	12 (1.4)	5 (2.4)	3 (1.4)	8 (1.9)	20 (1.6)

Source: Adapted from Table 18 of the Clinical summary of safety. BCVA: best-corrected visual acuity.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses for each individual study are presented in Figure 4--Figure 11. The subgroup analyses are conducted using the same methodology used for the analysis of the primary efficacy endpoint. The subgroup results are generally consistent with the Applicant's primary efficacy analysis results.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In this review, issues related to missing data and pooling of the two the sham arms in the evaluation of efficacy were encountered. First, the amount of missing data, i.e., subjects who did not have efficacy measurements reported at the primary analysis time points, i.e., Month12/18, is relatively very high. Specifically, approximately 20-22% of subjects randomized to the two pegcetacoplan arms (with more subjects in the PM arm) had missing GA data at Month 12. This figure increased to 24% at Month 18.

Second, the protocol defined as well as the DOP's primary efficacy endpoints were conducted by comparing each pegcetacoplan arm to the pooled sham arm. However, notable differences between the SM and SEOM arms in missing visits, missing GA data, adverse event rates, and study discontinuation rates were observed. Besides, subjects randomized to the SEOM arm had a faster GA progression compared to those in SM arm. Therefore, the observed favorable differences between the two pegcetacoplan arms and the pooled sham arm might be mostly driven by the observed faster GA growth rate in the SEOM arm.

5.2 Collective Evidence

The Applicant's analyses of the protocol defined primary efficacy endpoint provided statistically significant (Study APL2-304) and numerically favorable (Study APL2-303) results for the two pegcetacoplan arms. The analyses of the DOP's preferred primary efficacy endpoint evaluated using data through Month 18 provided statistically significant results in favor of the two pegcetacoplan arms in both studies. The analyses of the protocol defined as well as DOP's primary efficacy endpoints under different missing data handling methods are generally consistent with the primary analysis findings, providing credence to the results of the primary efficacy analyses. Treatment comparisons with respect to secondary efficacy endpoints did not

result in any meaningful differences between the two pegcetacoplan arms and the pooled sham arm.

The incidence of adverse events was higher in the two pegcetacoplan arms especially in the PM arm, compared to the pooled sham. The most frequently reported ocular adverse events in subjects randomized to the two pegcetacoplan arms were vitreous floaters, Neovascular age-related macular degeneration, conjunctival hemorrhage, and eye pain. Also note, a higher incidence of adverse events of special interest, namely, intraocular inflammations and exudative AMD, were reported in the two pegcetacoplan arms compared to the pooled sham.

In both studies, approximately only one third of the subjects randomized to the monthly injection group (PM) received the maximum allowed number of injections during the 18-month period. This raises potential treatment compliance issues in the real world, and the potential for underestimation of incidence of adverse events with a full treatment regimen.

5.3 Conclusions and Recommendation

Overall, the results of the Applicant's and the reviewer's analyses in this review provide evidence to support the efficacy of pegcetacoplan for the treatment of GA secondary to AMD. It is noted that for the DOP's primary efficacy endpoint, the efficacy results for the two dosing frequencies are mixed. In Study APL2-303, the PEOM arm appears to have resulted in slightly slower GA progression compared to the PM arm. Conversely, in Study APL2-304, the PM arm performed better than PEOM. Safety wise, incidence of adverse events, including adverse events of special interest (intraocular inflammations and exudative AMD), were higher in the two pegcetacoplan arms; with more adverse events reported for the PM arm than the PEOM arm.

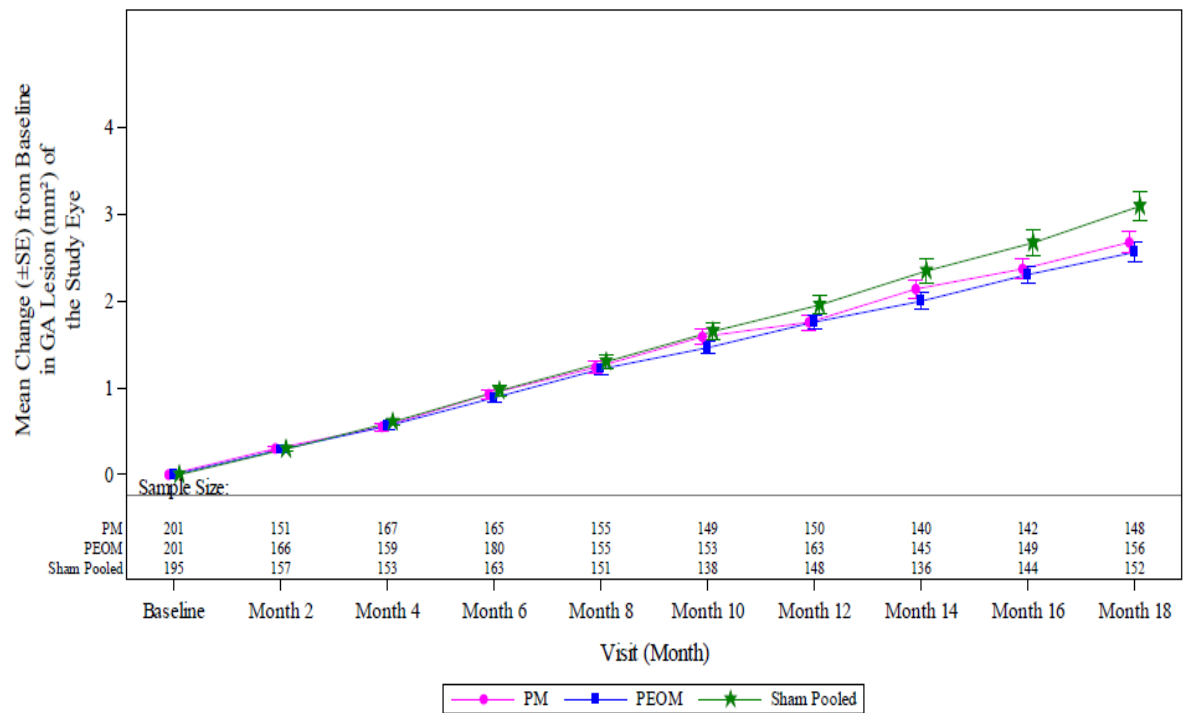
Therefore, the final determination for the approval of this drug, and the selection of the to be marketed dosing frequency should be made based on the totality of evidence, taking the absence of alternative treatment for this indication and the potential safety issues into account.

5.4 Labeling Recommendations

(b) (4)

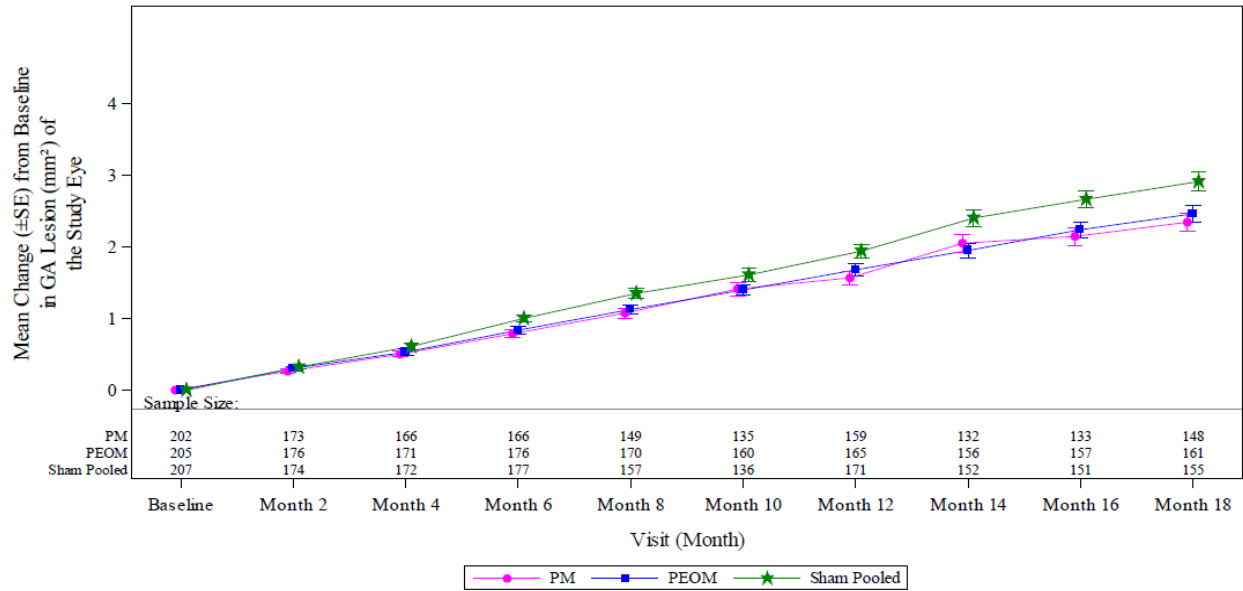
6 Appendix A: Selected Efficacy and Safety Summaries (APL2-303 and APL2-304)

Figure 2: Plot of Mean Change from Baseline Total GA Area (Study APL2-303)



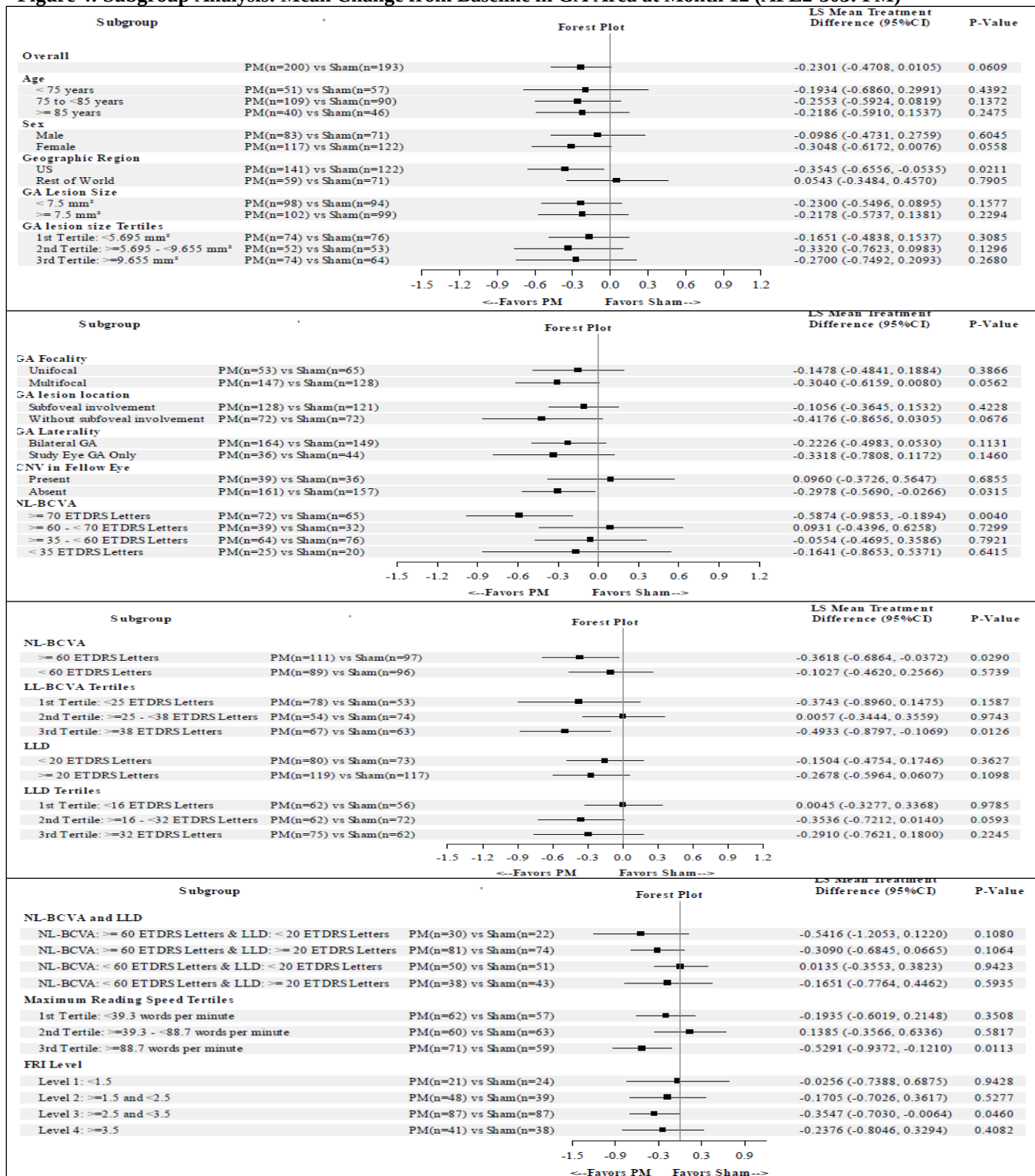
Source: Figure 14.2.1.1.1 of the Applicant’s Study report

Figure 3: Plot of Mean Change from Baseline Total GA Area (Study APL2-304)



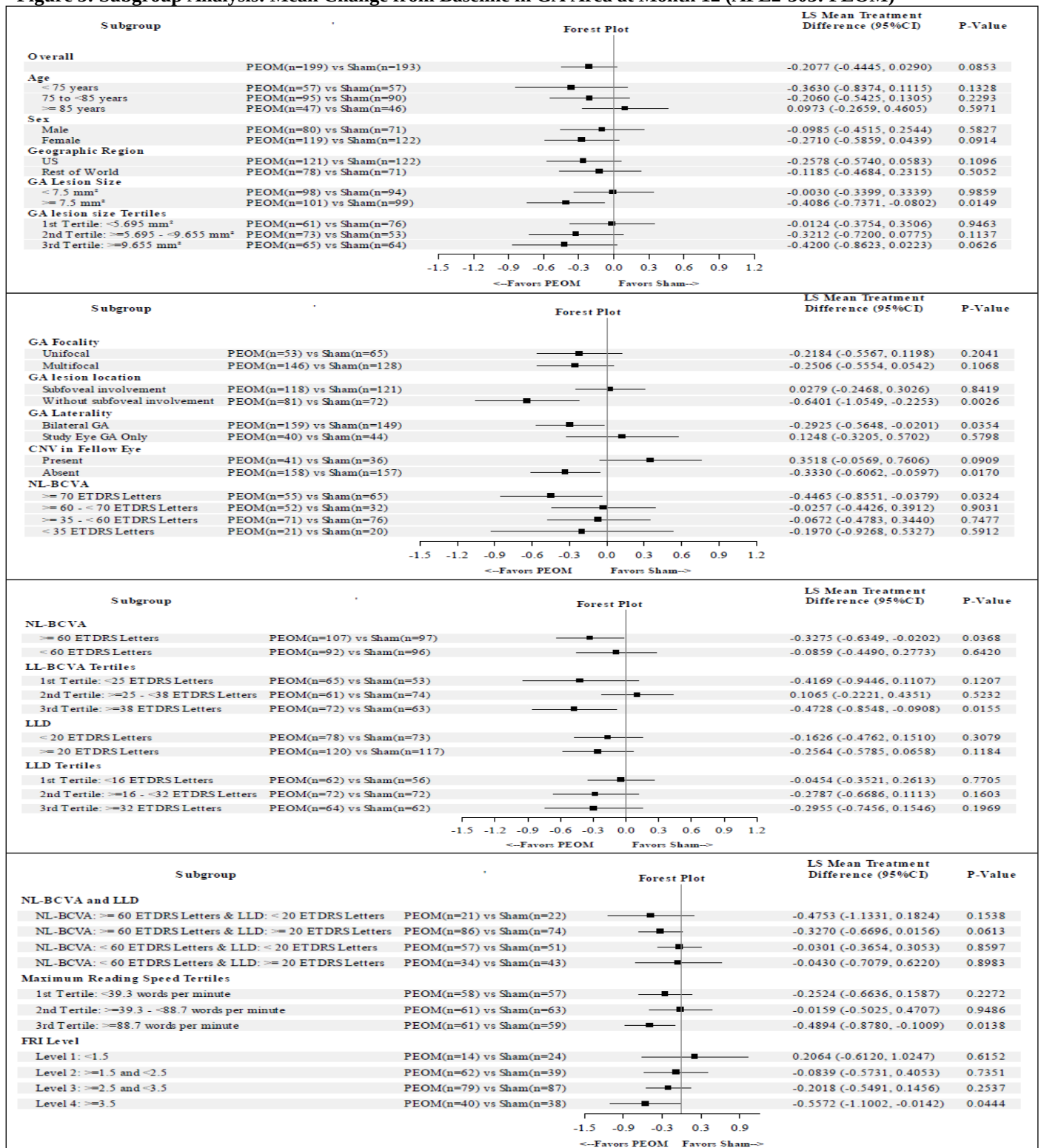
Source: Figure 14.2.1.1.1 of the Applicant’s study report

Figure 4: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-303; PM)



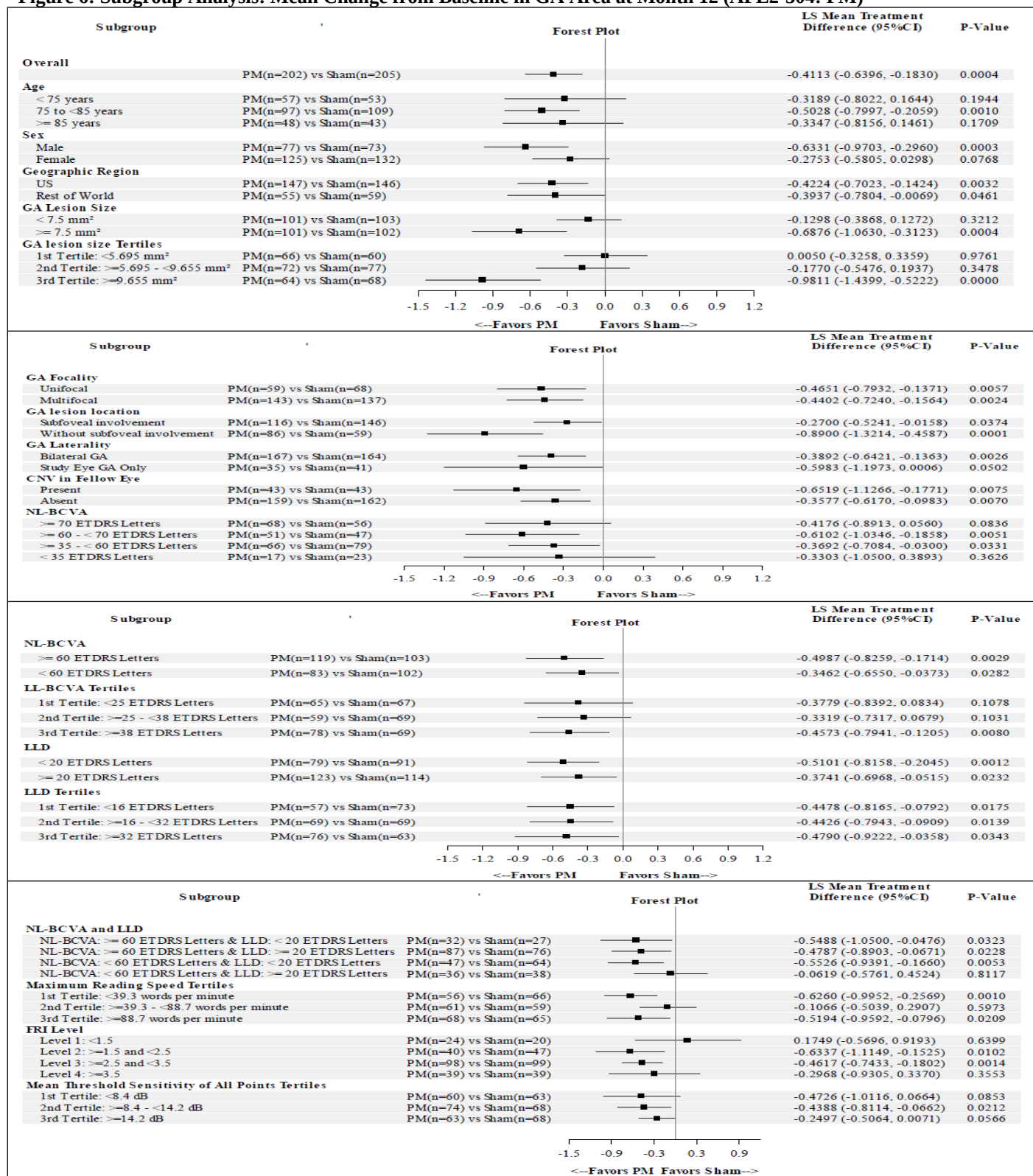
Source: Figure 6 of the Applicant's study report.

Figure 5: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-303; PEOM)



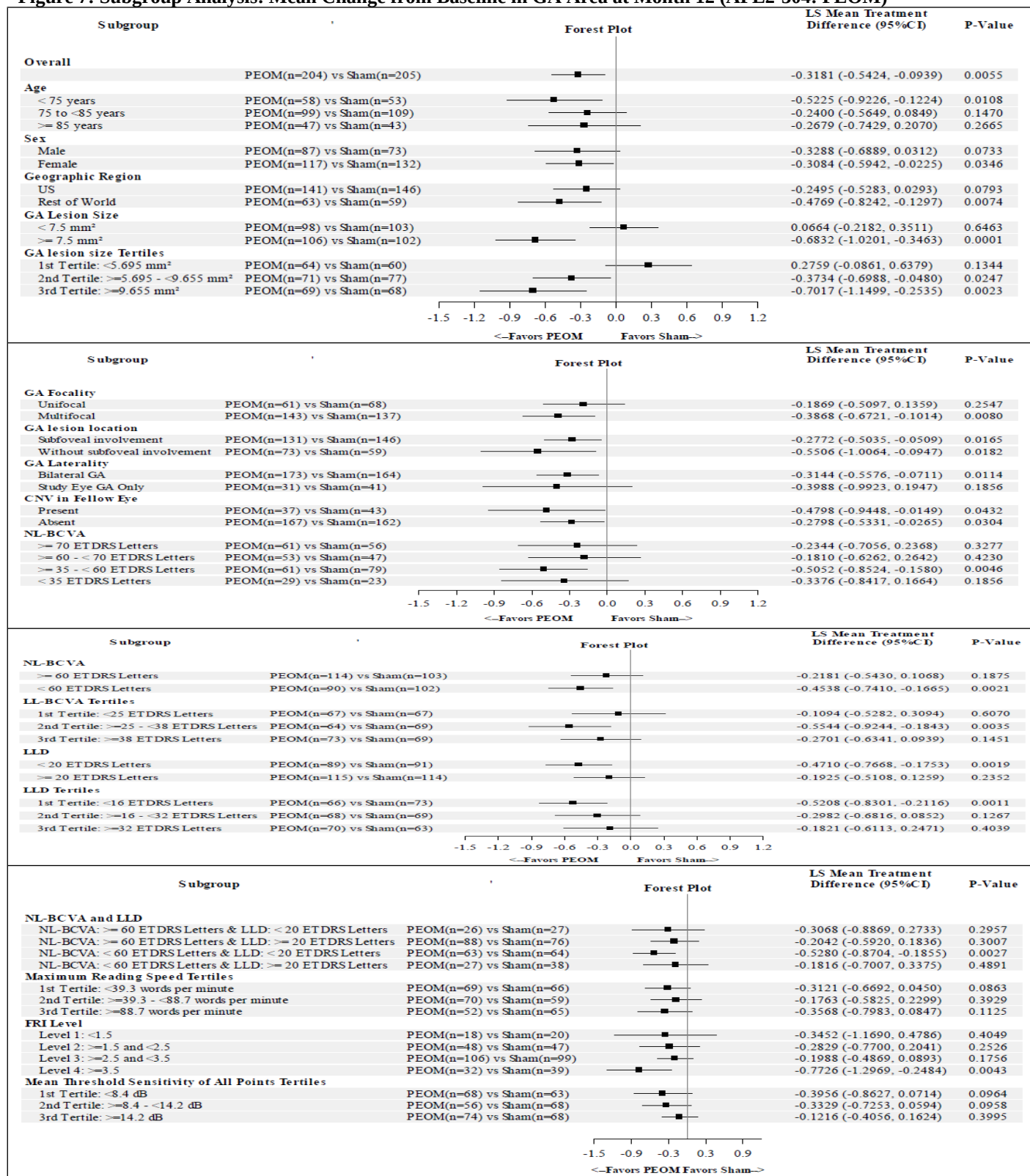
Source: Figure 7 of the Applicant's study report.

Figure 6: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-304: PM)



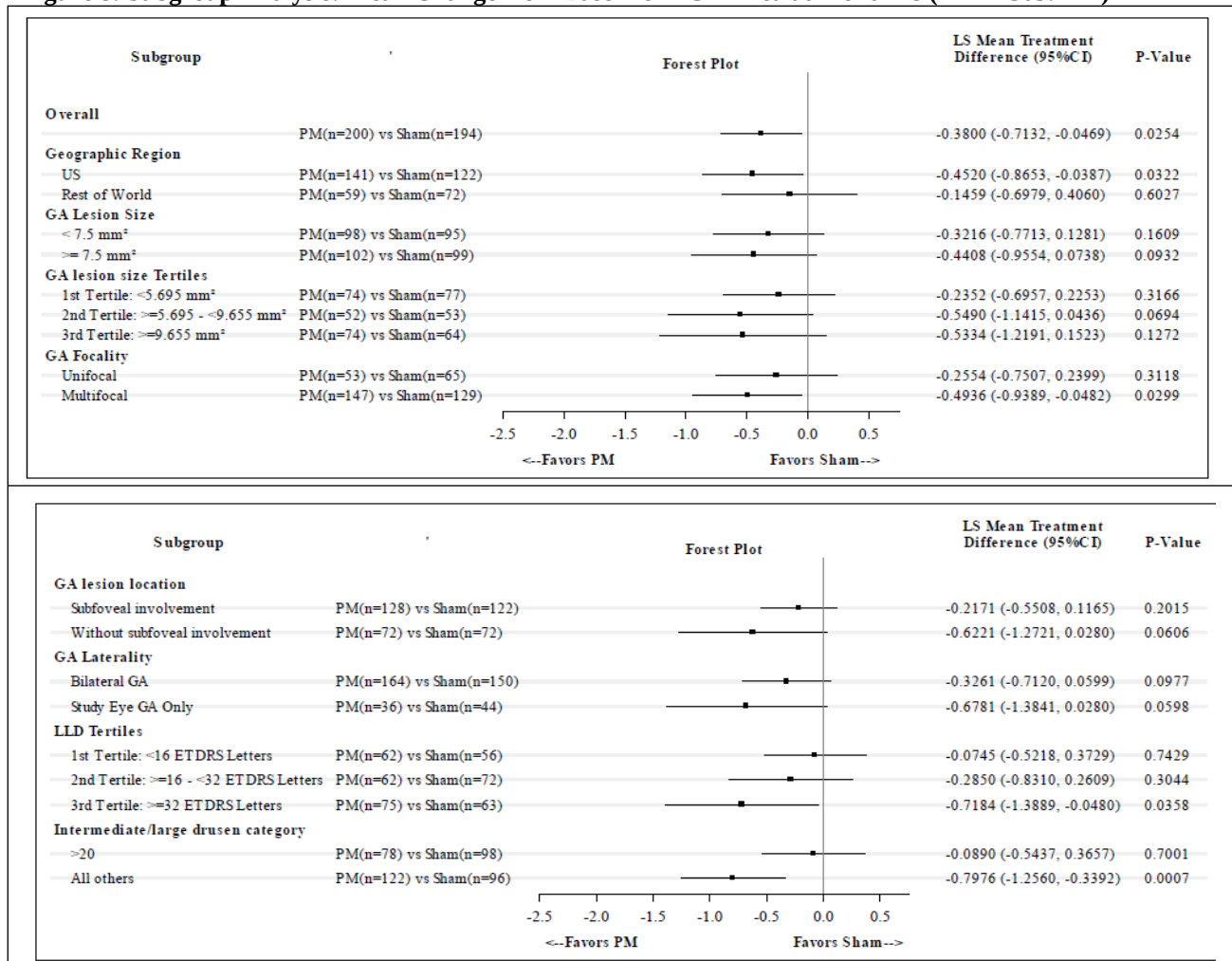
Source: Figure 6 of the Applicant's study report.

Figure 7: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (APL2-304: PEOM)



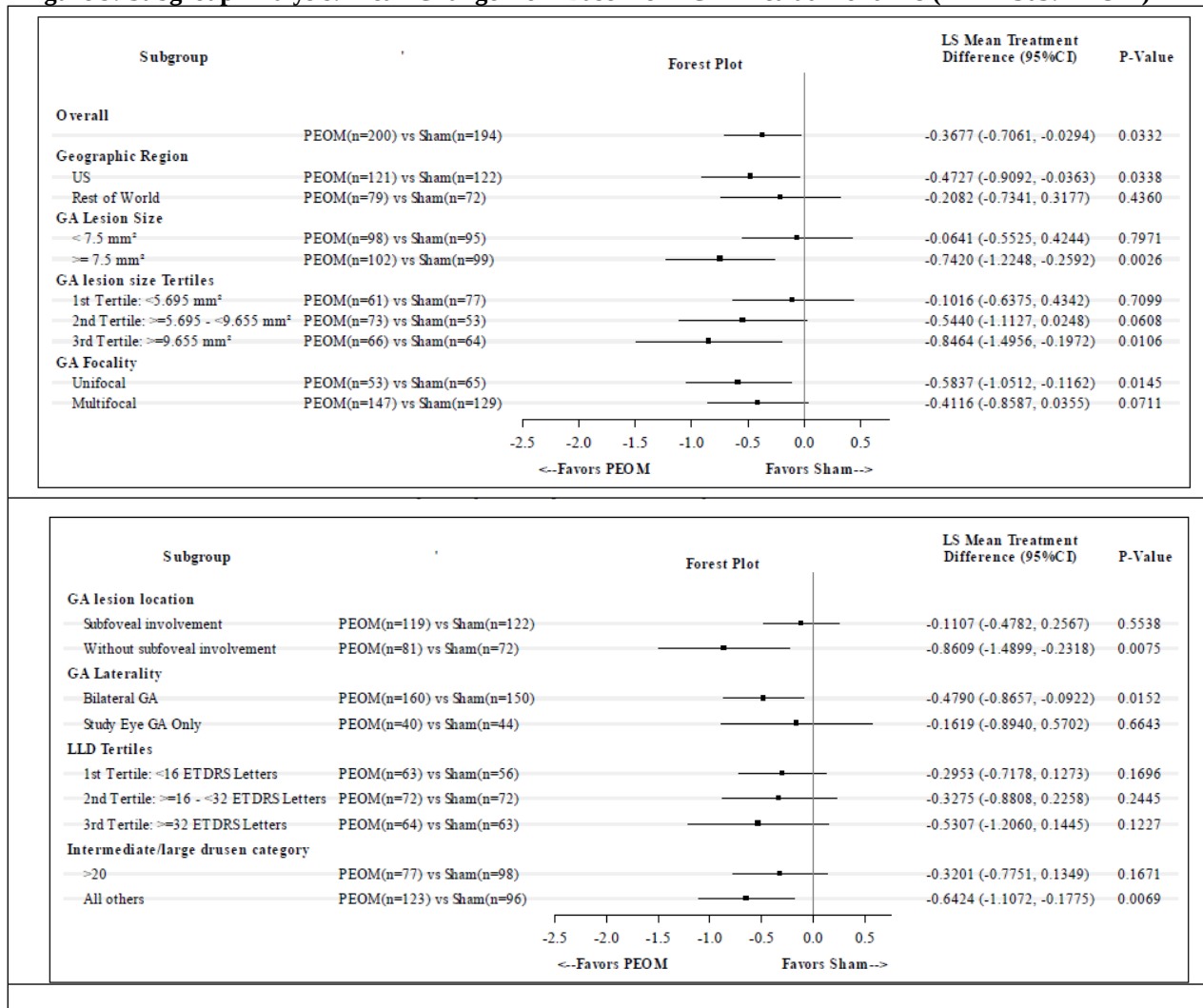
Source: Figure 7 of the Applicant's study report.

Figure 8: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-303: PM)



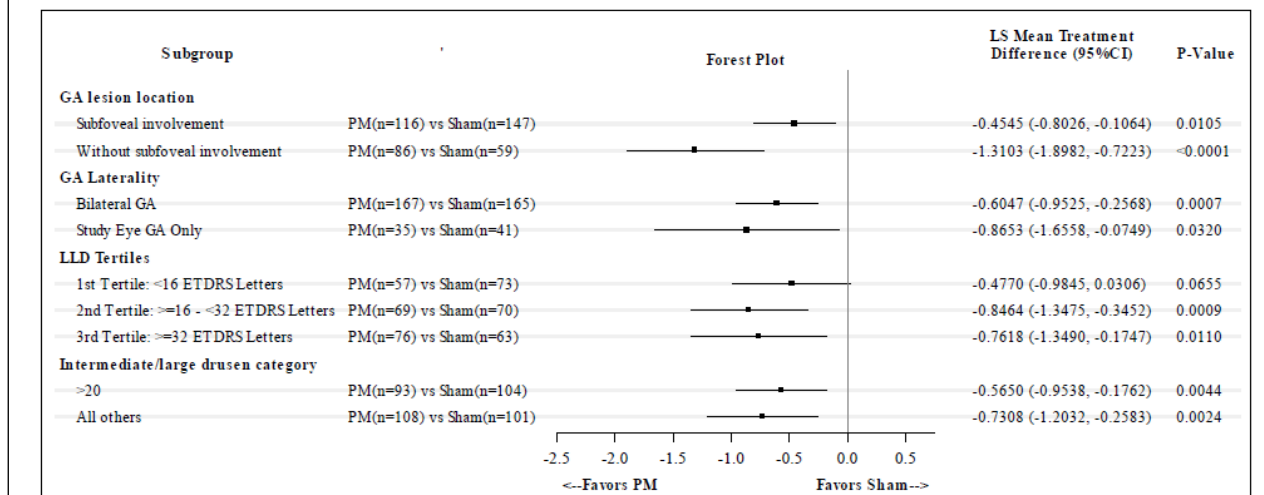
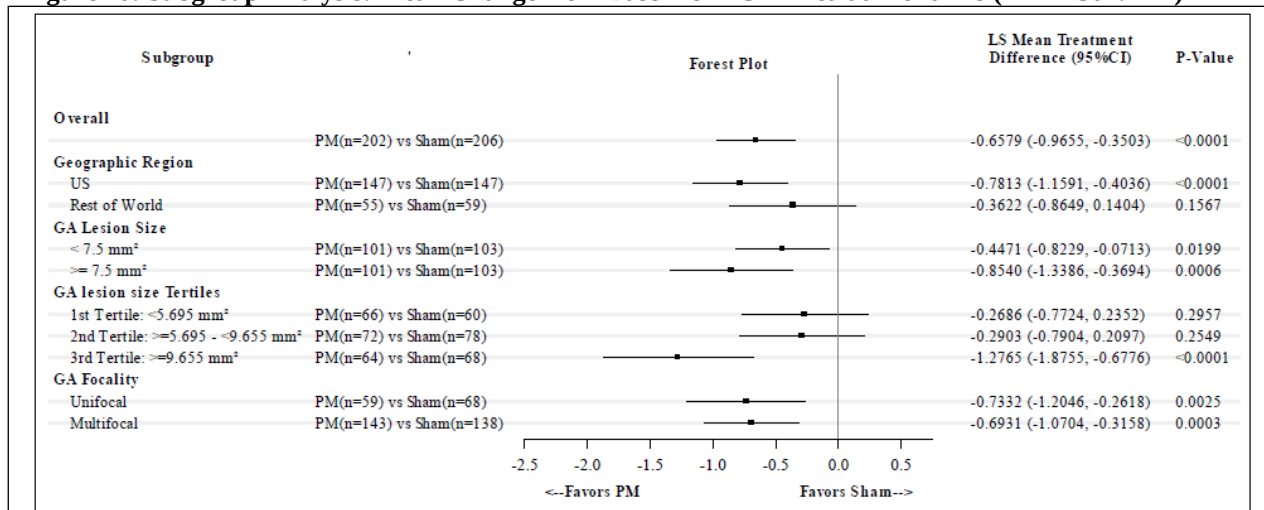
Source: Figure 14.2.1.4.1 of the Applicant's study report.

Figure 9: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-303: PEOM)



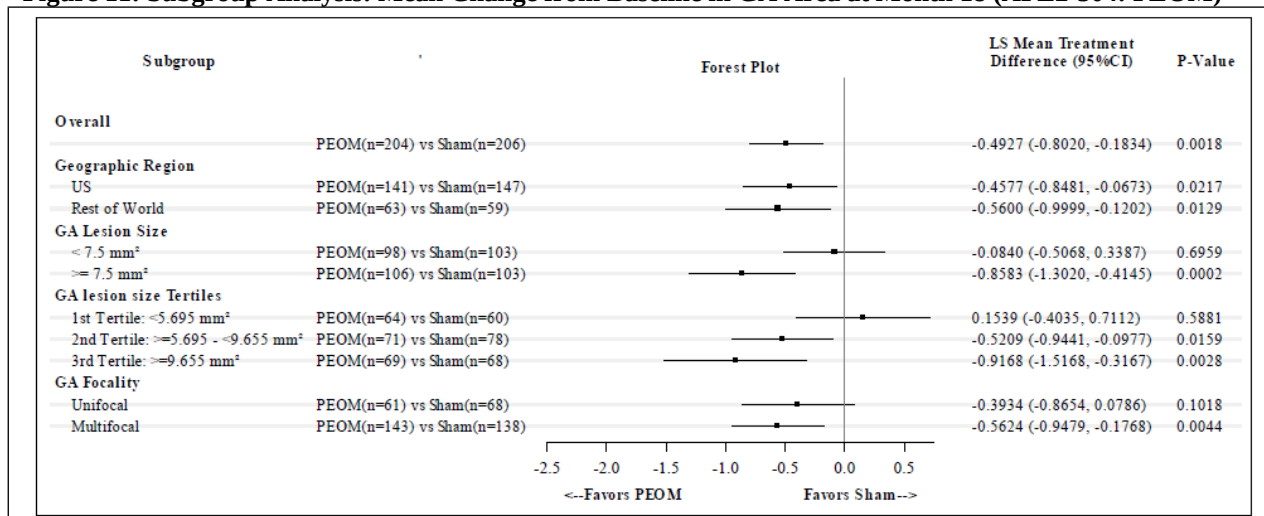
Source: Figure 14.2.1.4.1 of the Applicant's study report.

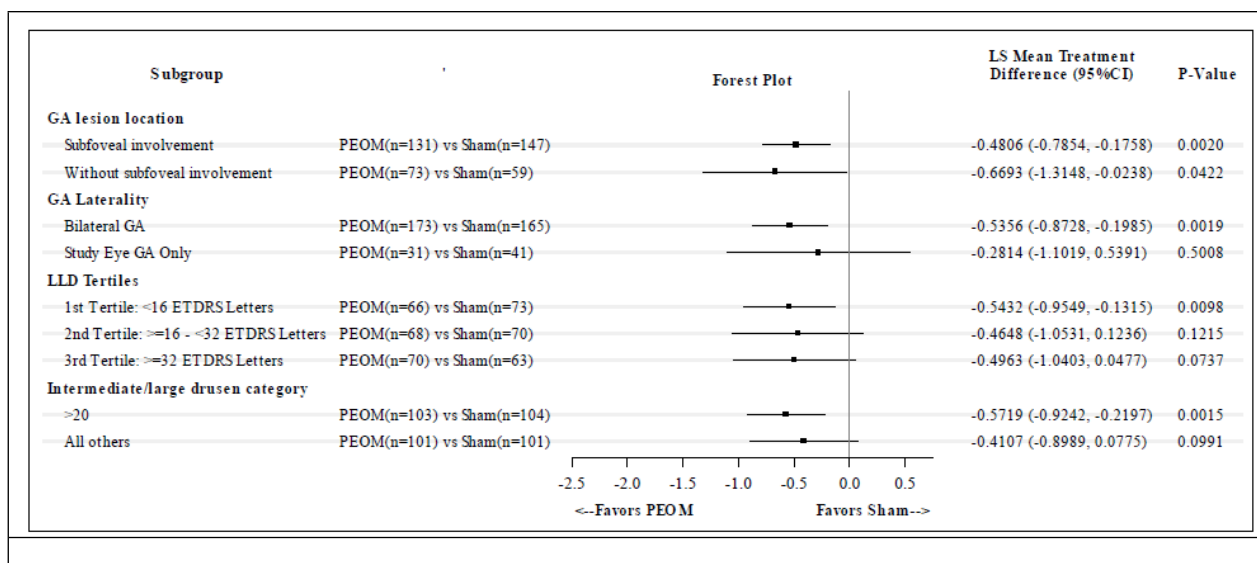
Figure 10: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-304: PM)



Source: Figure 14.2.1.4.1 of the Applicant's study report.

Figure 11: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (APL2-304: PEOM)





Source: Figure 14.2.1.4.1 of the Applicant's study report.

Table 27: Tipping Point Analyses of Mean Change from Baseline at Month 12 (APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2292	(-0.4682, 0.0097)	0.0601
	0.12	-0.2281	(-0.4669, 0.0106)	0.0611
	0.18	-0.2268	(-0.4649, 0.0113)	0.0620
	0.24	-0.2230	(-0.4624, 0.0164)	0.0679
	0.30	-0.2209	(-0.4600, 0.0182)	0.0702
	0.36	-0.2173	(-0.4563, 0.0217)	0.0748
	0.42	-0.2143	(-0.4531, 0.0245)	0.0786
	0.48	-0.2127	(-0.4515, 0.0260)	0.0808
	0.54	-0.2069	(-0.4458, 0.0321)	0.0898
	0.60	-0.2081	(-0.4478, 0.0316)	0.0888
	0.66	-0.2042	(-0.4435, 0.0351)	0.0944
	0.72	-0.2006	(-0.4394, 0.0383)	0.0998
PEOM vs Sham Pooled	0.06	-0.2129	(-0.4460, 0.0203)	0.0735
	0.12	-0.2109	(-0.4445, 0.0227)	0.0768
	0.18	-0.2104	(-0.4443, 0.0234)	0.0778
	0.24	-0.2073	(-0.4415, 0.0268)	0.0827
	0.30	-0.2041	(-0.4380, 0.0298)	0.0872
	0.36	-0.2010	(-0.4346, 0.0325)	0.0916
	0.42	-0.1992	(-0.4329, 0.0344)	0.0946
	0.48	-0.1980	(-0.4327, 0.0367)	0.0983
	0.54	-0.1931	(-0.4275, 0.0414)	0.1065
	0.60	-0.1921	(-0.4274, 0.0431)	0.1094
	0.66	-0.1911	(-0.4261, 0.0438)	0.1109
	0.72	-0.1867	(-0.4207, 0.0474)	0.1180

Source: Table 14.2.1.2.2 of the Applicant's study report. The shift parameters were applied to imputed data due to AE or Lack of efficacy.

Table 28: Tipping Point Analyses of Mean Change from Baseline at Month 12 [2] (APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2276	(-0.4661, 0.0110)	0.0615
	0.12	-0.2335	(-0.4744, 0.0074)	0.0575
	0.18	-0.2293	(-0.4688, 0.0102)	0.0606
	0.24	-0.2306	(-0.4698, 0.0087)	0.0589
	0.30	-0.2320	(-0.4704, 0.0065)	0.0565
	0.36	-0.2314	(-0.4715, 0.0087)	0.0589
	0.42	-0.2242	(-0.4635, 0.0151)	0.0663
	0.48	-0.2263	(-0.4667, 0.0141)	0.0650
	0.54	-0.2295	(-0.4686, 0.0096)	0.0599
	0.60	-0.2256	(-0.4632, 0.0120)	0.0628
	0.66	-0.2202	(-0.4595, 0.0190)	0.0712
PEOM vs Sham Pooled	0.06	-0.2121	(-0.4452, 0.0209)	0.0745
	0.12	-0.2140	(-0.4477, 0.0197)	0.0727
	0.18	-0.2142	(-0.4496, 0.0213)	0.0746
	0.24	-0.2123	(-0.4453, 0.0206)	0.0740
	0.30	-0.2089	(-0.4431, 0.0253)	0.0804
	0.36	-0.2084	(-0.4422, 0.0254)	0.0807
	0.42	-0.2088	(-0.4415, 0.0239)	0.0786
	0.48	-0.2081	(-0.4430, 0.0268)	0.0826
	0.54	-0.2076	(-0.4431, 0.0279)	0.0840
	0.60	-0.2060	(-0.4397, 0.0277)	0.0840
	0.66	-0.2027	(-0.4373, 0.0319)	0.0903
	0.72	-0.2026	(-0.4366, 0.0314)	0.0897

Source: Table 14.2.1.2.1 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 29: Tipping Point Analyses of Rate of GA Growth (Slope: Month 12: APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.2078	(-0.4388, 0.0232)	0.0779
	0.12	-0.2131	(-0.4457, 0.0196)	0.0726
	0.18	-0.2097	(-0.4433, 0.0239)	0.0785
	0.24	-0.2118	(-0.4429, 0.0193)	0.0724
	0.30	-0.2137	(-0.4455, 0.0181)	0.0708
	0.36	-0.2138	(-0.4469, 0.0192)	0.0721
	0.42	-0.2065	(-0.4391, 0.0261)	0.0819
	0.48	-0.2090	(-0.4414, 0.0234)	0.0780
	0.54	-0.2085	(-0.4406, 0.0237)	0.0784
	0.60	-0.2077	(-0.4389, 0.0236)	0.0784
	0.66	-0.2040	(-0.4376, 0.0296)	0.0869
	0.72	-0.2035	(-0.4362, 0.0292)	0.0865
PEOM vs Sham Pooled	0.06	-0.2216	(-0.4491, 0.0060)	0.0563
	0.12	-0.2243	(-0.4534, 0.0049)	0.0551
	0.18	-0.2235	(-0.4539, 0.0069)	0.0573
	0.24	-0.2227	(-0.4504, 0.0050)	0.0552
	0.30	-0.2193	(-0.4489, 0.0102)	0.0611
	0.42	-0.2193	(-0.4483, 0.0098)	0.0606
	0.48	-0.2199	(-0.4493, 0.0094)	0.0602
	0.54	-0.2173	(-0.4476, 0.0130)	0.0644
	0.60	-0.2171	(-0.4462, 0.0121)	0.0634

	0.66	-0.2147	(-0.4451, 0.0157)	0.0677
	0.72	-0.2135	(-0.4429, 0.0159)	0.0681

Source: Table 14.2.1.3.15 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 30: Tipping Point Analyses of Mean Change from Baseline at Month 12 (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4084	(-0.6376, -0.1792)	0.0005
	0.12	-0.4044	(-0.6332, -0.1757)	0.0005
	0.18	-0.4036	(-0.6319, -0.1754)	0.0005
	0.24	-0.3970	(-0.6255, -0.1685)	0.0007
	0.30	-0.3942	(-0.6229, -0.1654)	0.0007
	0.36	-0.3885	(-0.6173, -0.1598)	0.0009
	0.42	-0.3865	(-0.6151, -0.1579)	0.0009
	0.48	-0.3841	(-0.6127, -0.1555)	0.0010
	0.54	-0.3790	(-0.6079, -0.1501)	0.0012
	0.60	-0.3752	(-0.6041, -0.1463)	0.0013
	0.66	-0.3718	(-0.6012, -0.1424)	0.0015
PEOM vs Sham Pooled	0.72	-0.3672	(-0.5964, -0.1380)	0.0017
	0.06	-0.3140	(-0.5386, -0.0894)	0.0061
	0.12	-0.3113	(-0.5363, -0.0864)	0.0067
	0.18	-0.3091	(-0.5343, -0.0839)	0.0072
	0.24	-0.3071	(-0.5317, -0.0826)	0.0073
	0.30	-0.3046	(-0.5295, -0.0797)	0.0079
	0.36	-0.3005	(-0.5253, -0.0756)	0.0088
	0.42	-0.2995	(-0.5244, -0.0745)	0.0091
	0.48	-0.2971	(-0.5224, -0.0718)	0.0097
	0.54	-0.2957	(-0.5207, -0.0706)	0.0100
	0.60	-0.2922	(-0.5174, -0.0671)	0.0110
	0.66	-0.2906	(-0.5159, -0.0652)	0.0115
	0.72	-0.2878	(-0.5132, -0.0624)	0.0123

Source: Table 14.2.1.2.2 of the Applicant's study report. The shift parameters were applied to imputed data due to AE or Lack of efficacy.

Table 31: Tipping Point Analyses of Mean Change from Baseline at Month 12 [2] (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4173	(-0.6476, -0.1870)	0.0004
	0.12	-0.4142	(-0.6426, -0.1859)	0.0004
	0.18	-0.4101	(-0.6387, -0.1814)	0.0004
	0.24	-0.4131	(-0.6407, -0.1855)	0.0004
	0.30	-0.4057	(-0.6343, -0.1771)	0.0005
	0.36	-0.4062	(-0.6344, -0.1781)	0.0005
	0.42	-0.4025	(-0.6319, -0.1732)	0.0006
	0.48	-0.4004	(-0.6294, -0.1713)	0.0006
	0.54	-0.4052	(-0.6348, -0.1755)	0.0005
	0.60	-0.4054	(-0.6366, -0.1742)	0.0006
	0.66	-0.4011	(-0.6281, -0.1741)	0.0005
PEOM vs Sham Pooled	0.72	-0.4037	(-0.6323, -0.1750)	0.0005
	0.06	-0.3226	(-0.5444, -0.1008)	0.0044
	0.12	-0.3154	(-0.5396, -0.0913)	0.0058
	0.18	-0.3112	(-0.5354, -0.0869)	0.0065
	0.24	-0.3154	(-0.5398, -0.0909)	0.0059
	0.30	-0.3115	(-0.5364, -0.0866)	0.0066
	0.36	-0.3128	(-0.5385, -0.0871)	0.0066
	0.42	-0.3066	(-0.5320, -0.0812)	0.0077
	0.48	-0.3044	(-0.5292, -0.0795)	0.0080

	0.54	-0.3111	(-0.5364, -0.0858)	0.0068
	0.60	-0.3089	(-0.5344, -0.0835)	0.0072
	0.66	-0.3070	(-0.5329, -0.0811)	0.0077
	0.72	-0.3059	(-0.5305, -0.0813)	0.0076

Source: Table 14.2.1.2.1 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 32: Tipping Point Analyses of Rate of GA Growth (Slope: Month 12: APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.06	-0.4095	(-0.6344, -0.1847)	0.0004
	0.12	-0.4076	(-0.6319, -0.1834)	0.0004
	0.18	-0.4058	(-0.6285, -0.1830)	0.0004
	0.24	-0.4078	(-0.6282, -0.1874)	0.0003
	0.30	-0.4005	(-0.6240, -0.1770)	0.0004
	0.36	-0.4019	(-0.6260, -0.1777)	0.0004
	0.42	-0.3963	(-0.6199, -0.1727)	0.0005
	0.48	-0.3953	(-0.6185, -0.1721)	0.0005
	0.54	-0.3998	(-0.6228, -0.1769)	0.0004
	0.60	-0.3999	(-0.6259, -0.1738)	0.0005
	0.66	-0.3977	(-0.6207, -0.1747)	0.0005
PEOM vs Sham Pooled	0.72	-0.3972	(-0.6218, -0.1725)	0.0005
	0.06	-0.3179	(-0.5330, -0.1028)	0.0038
	0.12	-0.3123	(-0.5299, -0.0947)	0.0049
	0.18	-0.3112	(-0.5292, -0.0932)	0.0051
	0.24	-0.3129	(-0.5296, -0.0962)	0.0047
	0.30	-0.3097	(-0.5272, -0.0922)	0.0053
	0.36	-0.3110	(-0.5294, -0.0927)	0.0052
	0.42	-0.3057	(-0.5238, -0.0877)	0.0060
	0.48	-0.3031	(-0.5202, -0.0861)	0.0062
	0.54	-0.3090	(-0.5268, -0.0913)	0.0054
	0.60	-0.3085	(-0.5267, -0.0902)	0.0056
	0.66	-0.3071	(-0.5261, -0.0881)	0.0060
	0.72	-0.3040	(-0.5221, -0.0859)	0.0063

Source: Table 14.2.1.3.15 of the response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 33: Tipping Point Analyses of Mean Change from Baseline at Month 18 (APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.3851	(-0.7213, -0.0488)	0.0248
	0.18	-0.3684	(-0.7017, -0.0350)	0.0303
	0.27	-0.3801	(-0.7144, -0.0457)	0.0259
	0.36	-0.3734	(-0.7083, -0.0386)	0.0288
	0.45	-0.3673	(-0.6972, -0.0374)	0.0291
	0.54	-0.3622	(-0.6931, -0.0314)	0.0319
	0.63	-0.3546	(-0.6901, -0.0191)	0.0383
	0.72	-0.3634	(-0.6986, -0.0282)	0.0336
	0.81	-0.3553	(-0.6861, -0.0244)	0.0353
	0.90	-0.3499	(-0.6829, -0.0170)	0.0394
	0.99	-0.3484	(-0.6817, -0.0151)	0.0405
PEOM vs Sham Pooled	1.08	-0.3372	(-0.6711, -0.0033)	0.0477
	0.09	-0.3828	(-0.7200, -0.0455)	0.0261
	0.18	-0.3691	(-0.7029, -0.0353)	0.0302
	0.27	-0.3762	(-0.7101, -0.0422)	0.0273
	0.36	-0.3715	(-0.7060, -0.0370)	0.0295

	0.45	-0.3701	(-0.7003, -0.0400)	0.0280
	0.54	-0.3639	(-0.6976, -0.0303)	0.0325
	0.63	-0.3615	(-0.6977, -0.0252)	0.0351
	0.72	-0.3664	(-0.6990, -0.0339)	0.0308
	0.81	-0.3589	(-0.6917, -0.0262)	0.0345
	0.90	-0.3522	(-0.6861, -0.0183)	0.0387
	0.99	-0.3479	(-0.6817, -0.0141)	0.0411
	1.08	-0.3473	(-0.6819, -0.0126)	0.0420

Source: Table 14.2.1.2.2 of the Response to the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 34: Tipping Point Analyses of Rate of GA Growth (Slope: Month 18 [2]; APL2-303)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.3735	(-0.7037, -0.0432)	0.0267
	0.18	-0.3560	(-0.6856, -0.0265)	0.0342
	0.27	-0.3673	(-0.6950, -0.0395)	0.0281
	0.36	-0.3589	(-0.6884, -0.0293)	0.0328
	0.45	-0.3537	(-0.6791, -0.0283)	0.0331
	0.54	-0.3483	(-0.6749, -0.0218)	0.0366
	0.63	-0.3426	(-0.6731, -0.0120)	0.0422
	0.72	-0.3507	(-0.6812, -0.0201)	0.0376
	0.81	-0.3436	(-0.6706, -0.0166)	0.0395
	0.90	-0.3380	(-0.6661, -0.0099)	0.0435
	0.99	-0.3366	(-0.6643, -0.0089)	0.0441
PEOM vs Sham Pooled	1.08	-0.3250	(-0.6549, 0.0049)	0.0535
	0.09	-0.4147	(-0.7479, -0.0816)	0.0147
	0.18	-0.4009	(-0.7328, -0.0690)	0.0179
	0.27	-0.4068	(-0.7378, -0.0759)	0.0160
	0.36	-0.4008	(-0.7328, -0.0688)	0.0180
	0.45	-0.3989	(-0.7262, -0.0716)	0.0169
	0.54	-0.3952	(-0.7250, -0.0654)	0.0188
	0.63	-0.3915	(-0.7243, -0.0586)	0.0212
	0.72	-0.3986	(-0.7279, -0.0693)	0.0177
	0.81	-0.3913	(-0.7204, -0.0623)	0.0198
	0.90	-0.3859	(-0.7166, -0.0553)	0.0222
	0.99	-0.3791	(-0.7095, -0.0488)	0.0245
	1.08	-0.3789	(-0.7116, -0.0463)	0.0256

Source: Table 14.2.1.3.15 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 35: Tipping Point Analyses of Mean Change from Baseline at Month 18 (APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.6569	(-0.9635, -0.3502)	<0.0001
	0.18	-0.6539	(-0.9609, -0.3469)	<0.0001
	0.27	-0.6511	(-0.9610, -0.3413)	<0.0001
	0.36	-0.6541	(-0.9612, -0.3469)	<0.0001
	0.45	-0.6521	(-0.9618, -0.3425)	<0.0001
	0.54	-0.6514	(-0.9578, -0.3449)	<0.0001
	0.63	-0.6536	(-0.9606, -0.3465)	<0.0001
	0.72	-0.6418	(-0.9520, -0.3316)	<0.0001
	0.81	-0.6368	(-0.9425, -0.3312)	<0.0001
	0.90	-0.6371	(-0.9458, -0.3284)	<0.0001
	0.99	-0.6405	(-0.9522, -0.3288)	<0.0001
	1.08	-0.6311	(-0.9388, -0.3234)	<0.0001

PEOM vs Sham Pooled	0.09	-0.4923	(-0.8014, -0.1833)	0.0018
	0.18	-0.4870	(-0.7955, -0.1786)	0.0020
	0.27	-0.4916	(-0.8014, -0.1818)	0.0019
	0.36	-0.4882	(-0.7953, -0.1811)	0.0018
	0.45	-0.4812	(-0.7907, -0.1717)	0.0023
	0.54	-0.4815	(-0.7908, -0.1721)	0.0023
	0.63	-0.4855	(-0.7927, -0.1783)	0.0020
	0.72	-0.4755	(-0.7817, -0.1693)	0.0023
	0.81	-0.4718	(-0.7792, -0.1644)	0.0026
	0.90	-0.4699	(-0.7772, -0.1626)	0.0027
	0.99	-0.4681	(-0.7754, -0.1609)	0.0028
	1.08	-0.4659	(-0.7753, -0.1565)	0.0032

Source: Table 14.2.1.2.2 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE.

Table 36: Tipping Point Analyses of Rate of GA Growth (Slope: Month 18 [2]; APL2-304)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
PM vs Sham Pooled	0.09	-0.7115	(-1.0132, -0.4098)	<0.0001
	0.18	-0.7080	(-1.0094, -0.4067)	<0.0001
	0.27	-0.7068	(-1.0171, -0.3965)	<0.0001
	0.36	-0.7086	(-1.0118, -0.4055)	<0.0001
	0.45	-0.7047	(-1.0118, -0.3977)	<0.0001
	0.54	-0.7054	(-1.0090, -0.4018)	<0.0001
	0.63	-0.7057	(-1.0105, -0.4010)	<0.0001
	0.72	-0.6957	(-1.0044, -0.3869)	<0.0001
	0.81	-0.6901	(-0.9935, -0.3866)	<0.0001
	0.90	-0.6881	(-0.9953, -0.3808)	<0.0001
	0.99	-0.6963	(-1.0073, -0.3853)	<0.0001
PEOM vs Sham Pooled	1.08	-0.6835	(-0.9855, -0.3814)	<0.0001
	0.09	-0.5354	(-0.8396, -0.2311)	0.0006
	0.18	-0.5317	(-0.8361, -0.2272)	0.0006
	0.27	-0.5341	(-0.8418, -0.2264)	0.0007
	0.36	-0.5305	(-0.8338, -0.2272)	0.0006
	0.45	-0.5233	(-0.8289, -0.2176)	0.0008
	0.54	-0.5250	(-0.8303, -0.2196)	0.0008
	0.63	-0.5282	(-0.8318, -0.2247)	0.0006
	0.72	-0.5173	(-0.8187, -0.2159)	0.0008
	0.81	-0.5143	(-0.8188, -0.2098)	0.0009
	0.90	-0.5130	(-0.8165, -0.2094)	0.0009
	0.99	-0.5122	(-0.8155, -0.2089)	0.0009
	1.08	-0.5095	(-0.8150, -0.2039)	0.0011

Source: Table 14.2.1.3.15 of the IR submitted on 09/13/2022. The shift parameters were applied to imputed data reported due to AE, Lack of efficacy or consent withdrawal related to lack of efficacy or AE (study burden, concerns about treatment, concerns about procedures).

Table 37: Patient Disposition Without Pooling Sham (Month 12: Study APL2-303: ITT)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacopla n pooled (N = 425) n (%)	SM (N = 106) n (%)	SEOM (N = 106) n (%)	Sham pooled (N = 212) n (%)	Total (N = 637) n (%)
Randomized, n	206	208	414	102	105	207	621
Completed treatment through Month 12, n (%)	182 (88.3)	188 (90.4)	370 (89.4)	89 (87.3)	90 (85.7)	179 (86.5)	549 (88.4)
Continued in the study to Month 12 after treatment discontinuation, n (%)	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Completed study through Month 12, n	183 (88.8)	188 (90.4)	371 (89.6)	89 (87.3)	90 (85.7)	179 (86.5)	550 (88.6)

(%)							
Discontinued from treatment through Month 12 ^a , n (%)	24 (11.7)	20 (9.6)	44 (10.6)	13 (12.7)	14 (13.3)	27 (13.0)	71 (11.4)
Primary reason for discontinuation from treatment prior to Month 12							
Adverse event	1 (0.5)	4 (1.9)	5 (1.2)	5 (4.9)	1 (1.0)	6 (2.9)	11 (1.8)
Lost to follow-up	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	15 (7.3)	9 (4.3)	24 (5.8)	6 (5.9)	8 (7.6)	14 (6.8)	38 (6.1)
Pregnancy	0	0	0	0	0	0	0
Death ^b	5 (2.4)	0	5 (1.2)	0	2 (1.9)	2 (1.0)	7 (1.1)
Because of COVID-19 impact ^c	1 (0.5)	6 (2.9)	7 (1.7)	2 (2.0)	3 (2.9)	5 (2.4)	12 (1.9)
Other ^d	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Completed study through Month 12, n (%)	184 (86.4)	190 (89.6)	374 (88.0)	95 (89.6)	96 (90.6)	191 (90.1)	565 (88.7)
Discontinued from study through Month 12, n (%)	29 (13.6)	22 (10.4)	51 (12.0)	11 (10.4)	10 (9.4)	21 (9.9)	72 (11.3)
Primary reason for discontinuation from study prior to Month 12, n (%)							
Adverse event	1 (0.5)	4 (1.9)	5 (1.2)	4 (3.9)	1 (1.0)	5 (2.4)	10 (1.6)
Lost to follow-up	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	15 (7.3)	10 (4.8)	25 (6.0)	6 (5.9)	9 (8.6)	15 (7.2)	40 (6.4)
Pregnancy	0	0	0	0	0	0	0
Death ^b	5 (2.4)	0	5 (1.2)	1 (1.0)	2 (1.9)	3 (1.4)	8 (1.3)
Due to COVID-19 impact ^c	1 (0.5)	6 (2.9)	7 (1.7)	2 (2.0)	3 (2.9)	5 (2.4)	12 (1.9)
Other	0	0	0	0	0	0	0

Source: Table 12 of the Applicant's study report.

a Includes reasons for subjects who discontinued from treatment only and those who discontinued from treatment and study.

b Two subjects in the PEOM group (Subject (b) (6) and Subject (b) (6)) were incorrectly reported as having discontinued because of an AE. These have been corrected in the APL2-303 CSR erratum to death as the reason for discontinuation.

c Any discontinuation due to COVID-19 impact except for adverse event of COVID-19. Instances of adverse event of COVID-19 were captured under the adverse event category.

d Subject (b) (6) (PEOM group) was incorrectly reported as discontinuing treatment because of 'other.' This has been corrected in the APL2-303 CSR erratum to reflect that the subject withdrew consent and should not have been reported as discontinuing treatment for other reasons.

Table 38: Patient Disposition Without Pooling Sham (Month 12: Study APL2-304: ITT)

	PM (N = 213) n (%)	PEOM (N = 212) n (%)	Pegcetacopla n pooled (N = 425) n (%)	SM (N = 106) n (%)	SEOM (N = 106) n (%)	Sham pooled (N = 212) n (%)	Total (N = 637) n (%)
Randomized, n	213	212	425	106	106	212	637
Completed treatment through Month 12, n (%)	183 (85.9)	188 (88.7)	371 (87.3)	95 (89.6)	96 (90.6)	191 (90.1)	562 (88.2)
Discontinued from treatment prior to Month 12, n (%)	29 (13.6)	24 (11.3)	53 (12.5)	11 (10.4)	10 (9.4)	21 (9.9)	74 (11.6)
Continued in the study to Month 12 after treatment discontinuation, n (%)	1 (0.5)	2 (0.9)	3 (0.7)	0	0	0	3 (0.5)
Not treated, n (%)	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Primary reason for discontinuation from treatment prior to Month 12 ^a							
Adverse event	3 (1.4)	7 (3.3)	10 (2.4)	1 (0.9)	1 (0.9)	2 (0.9)	12 (1.9)

Lost to follow-up	2 (0.9)	1 (0.5)	3 (0.7)	0	1 (0.9)	1 (0.5)	4 (0.6)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	13 (6.1)	11 (5.2)	24 (5.6)	5 (4.7)	4 (3.8)	9 (4.2)	33 (5.2)
Pregnancy	0	0	0	0	0	0	0
Death	7 (3.3)	3 (1.4)	10 (2.4)	4 (3.8)	0	4 (1.9)	14 (2.2)
Because of COVID impact ^b	4 (1.9)	2 (0.9)	6 (1.4)	1 (0.9)	4 (3.8)	5 (2.4)	11 (1.7)
Other	0	0	0	0	0	0	0
Completed study through Month 12, n (%)	184 (86.4)	190 (89.6)	374 (88.0)	95 (89.6)	96 (90.6)	191 (90.1)	565 (88.7)
Discontinued from study prior to Month 12, n (%)	29 (13.6)	22 (10.4)	51 (12.0)	11 (10.4)	10 (9.4)	21 (9.9)	72 (11.3)
Primary reason for discontinuation from study prior to Month 12, n (%)							
Adverse event	3 (1.4)	5 (2.4)	8 (1.9)	1 (0.9)	1 (0.9)	2 (0.9)	10 (1.6)
Lost to follow-up	2 (0.9)	1 (0.5)	3 (0.7)	0	1 (0.9)	1 (0.5)	4 (0.6)
Noncompliance with study drug	0	0	0	0	0	0	0
Physician's decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Consent withdrawal	14 (6.6)	11 (5.2)	25 (5.9)	5 (4.7)	4 (3.8)	9 (4.2)	34 (5.3)
Pregnancy	0	0	0	0	0	0	0
Death	7 (3.3)	3 (1.4)	10 (2.4)	4 (3.8)	0	4 (1.9)	14 (2.2)
Because of COVID impact ^b	3 (1.4)	2 (0.9)	5 (1.2)	1 (0.9)	4 (3.8)	5 (2.4)	10 (1.6)
Other	0	0	0	0	0	0	0

Source: Table 12 of the Applicant's study reports. a Includes reasons for patients who discontinued from treatment only and those who discontinued from treatment and study. b Any discontinuation because of COVID impact except for adverse event of COVID. Instances of adverse event of COVID are captured under the adverse event category.

Table 39: Baseline and Demographic Characteristics Without Pooling Sham (Study APL-303)

	PM (N = 202)	PEOM (N=205)	Pegcetacoplan pooled (N = 407)	SM (N = 104)	SEOM (N = 102)	Sham pooled (N = 206)	Total (N = 613)
Sex, n (%)							
Female	118 (58.7)	120 (60.0)	238 (59.4)	61 (62.9)	61 (62.9)	122 (62.9)	360 (60.5)
Male	83 (41.3)	80 (40.0)	163 (40.6)	36 (37.1)	36 (37.1)	72 (37.1)	235 (39.5)
Age, years							
Mean (SD)	78.7 (6.91)	79.2 (7.07)	78.9 (6.99)	79.0 (7.35)	78.2 (7.25)	78.6 (7.29)	78.8 (7.08)
Minimum, maximum	60, 93	61, 93	60, 93	61, 94	61, 96	61, 96	60, 96
Age group, n (%)							
<65 years	5 (2.5)	6 (3.0)	11 (2.7)	3 (3.1)	5 (5.2)	8 (4.1)	19 (3.2)
≥65-<75 years	46 (22.9)	51 (25.5)	97 (24.2)	26 (26.8)	23 (23.7)	49 (25.3)	146 (24.5)
≥75-<85 years	110 (54.7)	95 (47.5)	205 (51.1)	40 (41.2)	50 (51.5)	90 (46.4)	295 (49.6)
≥85 years	40 (19.9)	48 (24.0)	88 (21.9)	28 (28.9)	19 (19.6)	47 (24.2)	135 (22.7)
Geographic region, n (%)							
US	142 (70.6)	122 (61.0)	264 (65.8)	63 (64.9)	59 (60.8)	122 (62.9)	386 (64.9)
ROW	59 (29.4)	78 (39.0)	137 (34.2)	34 (35.1)	38 (39.2)	72 (37.1)	209 (35.1)
Country, n(%)							
US	142 (70.6)	122 (61.0)	264 (65.8)	63 (64.9)	59 (60.8)	122 (62.9)	386 (64.9)

Argentina	18 (9.0)	21 (10.5)	39 (9.7)	10 (10.3)	8 (8.2)	18 (9.3)	57 (9.6)
Brazil	9 (4.5)	13 (6.5)	22 (5.5)	2 (2.1)	8 (8.2)	10 (5.2)	32 (5.4)
France	12 (6.0)	13 (6.5)	25 (6.2)	3 (3.1)	4 (4.1)	7 (3.6)	32 (5.4)
Germany	3 (1.5)	4 (2.0)	7 (1.7)	5 (5.2)	5 (5.2)	10 (5.2)	17 (2.9)
UK	4 (2.0)	6 (3.0)	10 (2.5)	3 (3.1)	3 (3.1)	6 (3.1)	16 (2.7)
Poland	2 (1.0)	7 (3.5)	9 (2.2)	2 (2.1)	3 (3.1)	5 (2.6)	14 (2.4)
Czech Republic	2 (1.0)	7 (3.5)	9 (2.2)	1 (1.0)	3 (3.1)	4 (2.1)	13 (2.2)
Australia	3 (1.5)	1 (0.5)	4 (1.0)	1 (1.0)	3 (3.1)	4 (2.1)	8 (1.3)
Canada	2 (1.0)	1 (0.5)	3 (0.7)	4 (4.1)	0	4 (2.1)	7 (1.2)
Israel	0	4 (2.0)	4 (1.0)	2 (2.1)	0	2 (1.0)	6 (1.0)
Italy	2 (1.0)	1 (0.5)	3 (0.7)	0	0	0	3 (0.5)
Spain	1 (0.5)	0	1 (0.2)	1 (1.0)	1 (1.0)	2 (1.0)	3 (0.5)
New Zealand	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Race, n (%)							
White	187 (93.0)	185 (92.5)	372 (92.8)	94 (96.9)	93 (95.9)	187 (96.4)	559 (93.9)
Not Reported	12 (6.0)	10 (5.0)	22 (5.5)	3 (3.1)	3 (3.1)	6 (3.1)	28 (4.7)
Missing	1 (0.5)	1 (0.5)	2 (0.5)	0	1 (1.0)	1 (0.5)	3 (0.5)
Black or African American	1 (0.5)	1 (0.5)	2 (0.5)	0	0	0	2 (0.3)
Asian	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Multiple	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Unknown	0	1 (0.5)	1 (0.2)	0	0	0	1 (0.2)
Ethnicity, n (%)							
Hispanic or Latino	32 (15.9)	34 (17.0)	66 (16.5)	13 (13.4)	16 (16.5)	29 (14.9)	95 (16.0)
Not Hispanic or Latino	158 (78.6)	151 (75.5)	309 (77.1)	82 (84.5)	77 (79.4)	159 (82.0)	468 (78.7)
Not reported ^a	10 (5.0)	11 (5.5)	21 (5.2)	2 (2.1)	4 (4.1)	6 (3.1)	27 (4.5)
Unknown	0	3 (1.5)	3 (0.7)	0	0	0	3 (0.5)
Missing	1 (0.5)	1 (0.5)	2 (0.5)	0	0	0	2 (0.3)
Tobacco use history, n (%)							
Ever	103 (51.2)	100 (50.0)	203 (50.6)	43 (44.3)	43 (44.3)	86 (44.3)	289 (48.6)
Never	98 (48.8)	100 (50.0)	198 (49.4)	54 (55.7)	54 (55.7)	108 (55.7)	306 (51.4)

Source: Table 14 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Australia, Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

Table 40: Baseline and Demographic Characteristics Without Pooling Sham (Study APL-304)

	PM (N = 202)	PEOM (N=205)	Pegcetacopla n pooled (N = 407)	SM (N = 104)	SEOM (N = 102)	Sham pooled (N = 206)	Total (N = 613)
Sex, n (%)							
Female	125 (61.9)	117 (57.1)	242 (59.5)	64 (61.5)	69 (67.6)	133 (64.6)	375 (61.2)
Male	77 (38.1)	88 (42.9)	165 (40.5)	40 (38.5)	33 (32.4)	73 (35.4)	238 (38.8)
Age, years							
Mean (SD)	78.8 (7.24)	78.1 (7.74)	78.4 (7.49)	78.4 (7.38)	78.8 (7.18)	78.6 (7.26)	78.5 (7.41)
Minimum, maximum	61, 95	60, 100	60, 100	60, 93	63, 92	60, 93	60, 100

Age group, n (%)							
<65 years	5 (2.5)	9 (4.4)	14 (3.4)	6 (5.8)	3 (2.9)	9 (4.4)	23 (3.8)
≥65-<75 years	52 (25.7)	50 (24.4)	102 (25.1)	23 (22.1)	22 (21.6)	45 (21.8)	147 (24.0)
≥75-<85 years	97 (48.0)	99 (48.3)	196 (48.2)	54 (51.9)	55 (53.9)	109 (52.9)	305 (49.8)
≥85 years	48 (23.8)	47 (22.9)	95 (23.3)	21 (20.2)	22 (21.6)	43 (20.9)	138 (22.5)
Geographic region, n (%)							
US	147 (72.8)	142 (69.3)	289 (71.0)	73 (70.2)	74 (72.5)	147 (71.4)	436 (71.1)
Rest of world	55 (27.2)	63 (30.7)	118 (29.0)	31 (29.8)	28 (27.5)	59 (28.6)	177 (28.9)
Country, n(%)							
US	147 (72.8)	142 (69.3)	289 (71.0)	73 (70.2)	74 (72.5)	147 (71.4)	436 (71.1)
France	12 (5.9)	14 (6.8)	26 (6.4)	5 (4.8)	10 (9.8)	15 (7.3)	41 (6.7)
Australia	9 (4.5)	14 (6.8)	23 (5.7)	6 (5.8)	4 (3.9)	10 (4.9)	33 (5.4)
Germany	7 (3.5)	8 (3.9)	15 (3.7)	6 (5.8)	5 (4.9)	11 (5.3)	26 (4.2)
Czech Republic	9 (4.5)	7 (3.4)	16 (3.9)	3 (2.9)	2 (2.0)	5 (2.4)	21 (3.4)
Poland	5 (2.5)	5 (2.4)	10 (2.5)	5 (4.8)	4 (3.9)	9 (4.4)	19 (3.1)
Italy	3 (1.5)	3 (1.5)	6 (1.5)	2 (1.9)	1 (1.0)	3 (1.5)	9 (1.5)
UK	1 (0.5)	4 (2.0)	5 (1.2)	3 (2.9)	1 (1.0)	4 (1.9)	9 (1.5)
Israel	3 (1.5)	2 (1.0)	5 (1.2)	1 (1.0)	0	1 (0.5)	6 (1.0)
Netherlands	3 (1.5)	1 (0.5)	4 (1.0)	0	0	0	4 (0.7)
New Zealand	1 (0.5)	2 (1.0)	3 (0.7)	0	1 (1.0)	1 (0.5)	4 (0.7)
Spain	1 (0.5)	3 (1.5)	4 (1.0)	0	0	0	4 (0.7)
Brazil	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Race, n (%)							
Asian	3 (1.5)	1 (0.5)	4 (1.0)	0	2 (2.0)	2 (1.0)	6 (1.0)
Black or African	2 (1.0)	0	2 (0.5)	0	0	0	2 (0.3)
White	185 (91.6)	189 (92.2)	374 (91.9)	96 (92.3)	91 (89.2)	187 (90.8)	561 (91.5)
Unknown	0	1 (0.5)	1 (0.2)	3 (2.9)	0	3 (1.5)	4 (0.7)
Not reported	12 (5.9)	12 (5.9)	24 (5.9)	5 (4.8)	9 (8.8)	14 (6.8)	38 (6.2)
Missing	0	2 (1.0)	2 (0.5)	0	0	0	2 (0.3)
Ethnicity, n (%)							
Hispanic or Latino	4 (2.0)	7 (3.4)	11 (2.7)	4 (3.8)	0	4 (1.9)	15 (2.4)
Not Hispanic or Latino	184 (91.1)	186 (90.7)	370 (90.9)	93 (89.4)	94 (92.2)	187 (90.8)	557 (90.9)
Not reported	14 (6.9)	12 (5.9)	26 (6.4)	7 (6.7)	8 (7.8)	15 (7.3)	41 (6.7)
Unknown	0	0	0	0	0	0	0
Tobacco use history, n (%)							
Ever	108 (53.5)	95 (46.3)	203 (49.9)	54 (51.9)	49 (48.0)	103 (50.0)	306 (49.9)
Never	94 (46.5)	110 (53.7)	204 (50.1)	50 (48.1)	53 (52.0)	103 (50.0)	307 (50.1)

Source: Table 14 of the Applicant's study reports. Because some countries do not allow the collection of race and ethnicity, there is a category of 'Not Reported' to account for this. Rest of world includes Brazil, Czech Republic, France, Germany, Italy, Israel, Netherlands, New Zealand, Poland, Spain, and UK.

Table 41: Breakdown of Subjects Who Withdrew Consent (Study APL-303)

	Baseline up to Month 12					Baseline up to Month 18					Post-Month 12 up to Month 18				
	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207	PM N=206	PEOM N=208	SM N=102	SEOM N=105	Sham pooled N=207
Reason for consent withdrawal															
All reasons	14 (6.8%)	10 (4.8%)	6 (5.9%)	8 (7.6%)	14 (6.8%)	24 (11.7%)	14 (6.7%)	6 (5.9%)	11 (10.5%)	17 (8.2%)	10 (4.9%)	4 (1.9%)	0	3 (2.9%)	3 (1.4%)
Poor general health	4	1	0	2	2	5	2	0	2	2	1	1	0	0	0
Travel to site too difficult or moved away	1	2	2	2	4	4	3	2	3	5	3	1	0	1	1
Study burden	2	3	1	2	3	5	4	1	2	3	3	1	0	0	0
Personal reasons	2	2	0	1	1	3	2	0	1	1	1	0	0	0	0
Concerns about study procedures	0	1	1	1	2	0	1	1	2	3	0	0	0	1	1
Concerns about treatment	2	0	1	0	1	3	0	1	0	1	1	0	0	0	0
Reason not specified	3	1	1	0	1	4	2	1	1	2	1	1	0	1	1

Abbreviations: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.
Source: Table 5; Study APL-303 Table 14.1.2.2.2.

Table 42: Breakdown of Subjects Who Withdrew Consent (Study APL-304)

	Baseline up to Month 12					Baseline up to Month 18					Post-Month 12 up to Month 18				
	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212	PM N=213	PEOM N=212	SM N=106	SEOM N=106	Sham pooled N=212
Reason for consent withdrawal															
Any reason	13 (6.1%)	12 (5.7%)	5 (4.7%)	4 (3.8%)	9 (4.2%)	21 (9.9%)	14 (6.6%)	8 (7.5%)	6 (5.7%)	14 (6.6%)	8 (3.8%)	2 (0.9%)	3 (2.8%)	2 (1.9%)	5 (2.4%)
Study burden	4	2	1	1	2	7	2	2	2	4	3	0	1	1	2
Poor general health	2	3	1	1	2	4	3	2	2	4	2	0	1	1	2
Concerns about treatment	3	2	0	0	0	3	2	0	0	0	0	0	0	0	0
Travel to site too difficult or moved away	1	1	1	1	2	2	1	2	1	3	1	0	1	0	1
Personal reasons	1	0	1	1	2	1	0	1	1	2	0	0	0	0	0
Missed too many visits (COVID-19 pandemic)	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0
Reason not specified	2	4	1	0	1	3	6	1	0	1	1	2	0	0	0

Abbreviations: PEOM = pegcetacoplan every other month; PM = pegcetacoplan monthly; SEOM = sham every other month; SM = sham monthly.
Source: Table 4; Study APL-304 Table 14.1.2.2.2.

Table 43: Number of Subjects Included in the Analyses Populations (APL2-303)

Populations	PM	PEOM	Pegcetacoplan Pooled	SM	SEOM	Sham Pooled	Total
	(N=206)	(N=208)	(N=414)	(N=102)	(N=105)	(N=207)	(N=621)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intent-to-treat (ITT)	206 (100)	208 (100)	414 (100)	102 (100)	105 (100)	207 (100)	621 (100)
Modified ITT	201 (97.6)	200 (96.2)	401 (96.9)	97 (95.1)	97 (92.4)	194 (93.7)	595 (95.8)
Excluded from mITT	5 (2.4)	8 (3.8)	13 (3.1)	5 (4.9)	8 (7.6)	13 (6.3)	26 (4.2)
No post-baseline value of GA lesion area in the study eye	5 (2.4)	8 (3.8)	13 (3.1)	5 (4.9)	7 (6.7)	12 (5.8)	25 (4.0)
No injection of pegcetacoplan or Sham	0	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)
Per protocol (PP) set	155 (75.2)	163 (78.4)	318 (76.8)	71 (69.6)	80 (76.2)	151 (72.9)	469 (75.5)
Safety Set	206 (100)	208 (100)	414 (100)	102 (100)	104 (99.0)	206 (99.5)	620 (99.8)

Source: Table 14.1.2.1 of the Applicant's study report.

Table 44: Number of Subjects Included in the Analyses Populations (APL2-304)

Populations	PM	PEOM	Pegcetacoplan Pooled	SM	SEOM	Sham Pooled	Total
	(N=213)	(N=212)	(N=425)	(N=106)	(N=106)	(N=212)	(N=637)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Intent-to-treat (ITT)	213 (100)	212 (100)	425 (100)	106 (100)	106 (100)	212 (100)	637 (100)
Modified ITT (mITT)	202 (94.8)	205 (96.7)	407 (95.8)	104 (98.1)	102 (96.2)	206 (97.2)	613 (96.2)
Excluded from mITT	11 (5.2)	7 (3.3)	18 (4.2)	2 (1.9)	4 (3.8)	6 (2.8)	24 (3.8)
No post-baseline value of GA lesion area in the study eye	10 (4.7)	7 (3.3)	17 (4.0)	2 (1.9)	4 (3.8)	6 (2.8)	23 (3.6)
No injection of pegcetacoplan or Sham	1 (0.5)	0	1 (0.2)	0	0	0	1 (0.2)
Per protocol (PP) set	51 (23.9)	35 (16.5)	86 (20.2)	25 (23.6)	23 (21.7)	48 (22.6)	134 (21.0)
Safety Set	213 (100)	212 (100)	425 (100)	105 (99.1)	106 (100)	211 (99.5)	636 (99.8)

Source: Table 14.1.2.1 of the Applicant's study report.

Table 45: Summary of Specific Reasons for Exclusion from the mITT

	APL2-303			APL2-304		
	PM	PEOM	Sham pooled	PM	PEOM	Sham pooled
Intent-to-treat set	N=206	N=208	N=207	N = 213	N = 212	N = 212
Exclusion from mITT set, n (%)	5 (2.4)	8 (3.8)	13 (6.3)	11 (5.2)	7 (3.3)	6 (2.8)
Reason for no postbaseline GA area assessment						
Withdrew consent	3	2	6	4	2	2
Lost to follow-up	0	0	0	2	1	1
COVID impact leading to missed visits or discontinuation	1	3	4	2	1	2
Death	1	0	0	1	2	0
AE leading to discontinuation	0	2	2	1	1	0
GA area could not be measured	0	1	0	0	0	1

Source: Table 3 of the Applicant's response to IR submitted on 07/11/2022.

Table 46: Applicant's Analyses of Mean rate of GA growth (Slope at Month 12; Piecewise linear model)

	Study APL2-304			Study APL2-303			Study POT-CP121614		
	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 206)	PM (N = 201)	PEOM (N = 200)	Sham pooled (N = 194)	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
Number of subjects included in the model	202	204	205	200	199	193	84	78	80
Estimates for baseline to Month 6									
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7728 (0.04559)	0.8208 (0.04350)	0.9794 (0.04619)	0.8989 (0.04775)	0.8849 (0.04489)	0.9468 (0.04800)	0.8281 (0.10292)	0.9852 (0.10466)	0.9850 (0.10167)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6833-0.8624	0.7354-0.9062	0.8887-1.0701	0.8051-0.9926	0.7967-0.9730	0.8525-1.0411	0.6253 - 1.0309	0.7790- 1.1915	0.7846 - 1.1854
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.2065 (-0.3339 to -0.0792)	-0.1586 (-0.2838 to -0.0333)	NA	-0.0479 (-0.1812 to 0.0853)	-0.0619 (-0.1910 to -0.0672)	NA	-0.1569 (-0.4420 to 0.1282)	0.0002 (-0.2874 to -0.2878)	NA
Percentage difference in slope of GA lesion area	-21.1%	-16.2%	NA	-5.1%	-6.5%	NA	-15.9%	0.0%	NA

growth vs sham pooled group									
P value vs sham pooled group	.0015	.0132	NA	.4801	.3468	NA	.2793	.9990	NA
Estimates for Month 6 to Month 12									
Slope (SE) of GA lesion area growth (mm ² /6 months)	0.7924 (0.05685)	0.8393 (0.05403)	0.9913 (0.04909)	0.8538 (0.05116)	0.8611 (0.05047)	1.0292 (0.05967)	0.5656 (0.09824)	0.7221 (0.10437)	1.0764 (0.09767)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6807-0.9041	0.7331-0.9454	0.8949-1.0877	0.7533-0.9543	0.7620-0.9602	0.9120-1.1463	0.3718-0.7594	0.5162-0.9280	0.8837-1.2691
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1989 (-0.3463 to -0.0515)	-0.1520 (-0.2955 to -0.0086)	NA	-0.1754 (-0.3299 to -0.0209)	-0.1681 (-0.3217 to -0.0145)	NA	-0.5108 (-0.7841 to -0.2376)	-0.3543 (-0.6363 to -0.0723)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-20.1%	-15.3%	NA	-17.0%	-16.3%	NA	-47.5%	-32.9%	NA
P value vs sham pooled group	.0083	.0379	NA	.0262	.0320	NA	.0003	.0141	NA
Estimates for baseline to Month 12									
Average slope (SE) of GA lesion area growth, mm ² /12 months	1.5652 (0.08236)	1.6601 (0.07785)	1.9707 (0.07965)	1.7527 (0.07606)	1.7460 (0.07420)	1.9760 (0.09260)	1.3937 (0.16305)	1.7074 (0.16950)	2.0614 (0.16228)
95% CI of slope of GA lesion area growth, mm ² /12 months	1.4035-1.7270	1.5072-1.8130	1.8142-2.1271	1.6033-1.9021	1.6002-1.8917	1.7941-2.1578	1.0723-1.7152	1.3733-2.0415	1.7415-2.3814
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /12 months	-0.4054 (-0.6304 to -0.1805)	-0.3106 (-0.5299 to -0.0913)	NA	-0.2233 (-0.4588 to 0.0122)	-0.2300 (-0.4630 to -0.0030)	NA	-0.6677 (-1.1213 to -0.2142)	-0.3541 (-0.8167 to 0.1085)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-20.6%	-15.8%	NA	-11.3%	-11.6%	NA	-32.4%	-17.2%	NA
P value vs sham pooled group	.0004	.0056	NA	.0631	.0530	NA	.0041	.1328	NA

Source: Table 10 of the Applicants Clinical efficacy summary. This model includes knots at Month 6.

Table 47: Mean rate of GA growth (Slope at Month 18; Piecewise linear model: APL2-303)

	PM (N = 201)	PEOM (N = 201)	Sham pooled (N = 195)
Number of subjects included in the model	200	200	194
Estimates for baseline to Month 6			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.9059 (0.04709)	0.8814 (0.04689)	0.9599 (0.04998)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.8136-0.9982	0.7895-0.9734	0.8619-1.0579
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.0540 (-0.1889 to 0.0809)	-0.0785 (-0.2129 to 0.0560)	NA
Percentage difference in slope of GA lesion	-5.6%	-8.2%	NA

area growth vs sham pooled group			
<i>P</i> value vs sham pooled group	.4324	.2526	NA
Annual GA lesion area growth rate	1.8118	1.7629	1.9198
95% CI of annual GA lesion area growth rate	1.6271-1.9964	1.5790-1.9467	1.7238-2.1158
Estimates for Month 6 to Month 12			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8364 (0.05058)	0.8470 (0.05102)	1.0106 (0.06118)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7373-0.9356	0.7469-0.9470	0.8906-1.1305
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1741 (-0.3298 to -0.0184)	-0.1636 (-0.3200 to -0.0072)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-17.2%	-16.2%	NA
<i>P</i> value vs sham pooled group	.0284	.0404	NA
Annual GA lesion area growth rate	1.6728	1.6939	2.0211
95% CI of annual GA lesion area growth rate	1.4745-1.8712	1.4939-1.8940	1.7813-2.2610
Estimates for Month 12 to Month 18			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8975 (0.05097)	0.8673 (0.05188)	1.0555 (0.05835)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7976-0.9975	0.7656-0.9690	0.9411-1.1699
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1579 (-0.3100 to -0.0058)	-0.1881 (-0.3415 to -0.0348)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-15.0%	-17.8%	NA
<i>P</i> value vs sham pooled group	.0418	.0162	NA
Annual GA lesion area growth rate	1.7951	1.7347	2.1109
95% CI of annual GA lesion area growth rate	1.5952-1.9949	1.5312-1.9381	1.8821-2.3397
Estimates for baseline to Month 18			
Average slope (SE) of GA lesion area growth, mm ² /18 months	2.6398 (0.09993)	2.5957 (0.10283)	3.0259 (0.13892)
95% CI of slope of GA lesion area growth, mm ² /18 months	2.4439-2.8358	2.3941-2.7973	2.7536-3.2983
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /18 months	-0.3861 (-0.7217 to -0.0505)	-0.4302 (-0.7691 to -0.0912)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-12.8%	-14.2%	NA
<i>P</i> value vs sham pooled group	.0242	.0129	NA

Source: Table 4 of the Applicants Post 12-month Study report. Annual Growth Rate was calculated as the slope for time period multiplied by 2. Model includes treatment + baseline GA lesion area (< 7.5 mm² or ≥7.5 mm²) + time (continuous) + time spline at month 6 (continuous) + time spline at month 12 (continuous) + presence of CNV in the fellow eye (yes or no) + time (continuous) x treatment + time spline at month 6 (continuous) x treatment + time spline at month 12 (continuous) + baseline GA lesion area x time (continuous) + baseline GA lesion area x time spline at month 6 (continuous) + baseline GA lesion area x time spline at month 12 (continuous). A heterogeneous autoregressive covariance matrix is used to model the within-subject errors.

Table 48: Mean rate of GA growth (Slope at Month 18; Piecewise linear model: APL2-304)

	PM (N = 202)	PEOM (N = 205)	Sham pooled (N = 207)
Number of subjects included in the model	202	204	206
Estimates for baseline to Month 6			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7607 (0.04630)	0.8221 (0.04344)	0.9839 (0.04670)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6699-0.8515	0.7369-0.9072	0.8923-1.0754
Difference (95% CI) in slope of GA lesion area growth (vs sham pooled), mm ² /6 months	-0.2232 (-0.3521 to -0.0943)	-0.1618 (-0.2875 to -0.0361)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-22.7%	-16.4%	NA
P value vs sham pooled group	.0007	.0116	NA
Annual GA lesion area growth rate	1.5214	1.6442	1.9677
Estimates for Month 6 to Month 12			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.7865 (0.05997)	0.8167 (0.05683)	0.9710 (0.05164)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.6689-0.9040	0.7053-0.9281	0.8698-1.0723
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.1846 (-0.3396 to -0.0295)	-0.1543 (-0.3051 to -0.0036)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-19.0%	-15.9%	NA
P value vs sham pooled group	.0197	.0448	NA
Annual GA lesion area growth rate	1.5729	1.6334	1.9420
95% CI of annual GA lesion area growth rate	1.3378-1.8080	1.4105-1.8562	1.7395-2.1445
Estimates for Month 12 to Month 18			
Slope (SE) of GA lesion area growth, mm ² /6 months	0.8039 (0.05075)	0.8600 (0.05035)	1.0257 (0.05423)
95% CI of slope of GA lesion area growth, mm ² /6 months	0.7044-0.9034	0.7613-0.9588	0.9194-1.1321
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /6 months	-0.2218 (-0.3674 to -0.0763)	-0.1657 (-0.3109 to -0.0205)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-21.6%	-16.2%	NA
P value vs sham pooled group	.0028	.0253	NA
Annual GA lesion area growth rate	1.6078	1.7201	2.0515
95% CI of annual GA lesion area growth rate	1.4088-1.8068	1.5227-1.9175	1.8389-2.2641
Estimates for baseline to Month 18			

Average slope (SE) of GA lesion area growth, mm ² /182 months	2.3510 (0.10991)	2.4988 (0.10878)	2.9806 (0.11508)
95% CI of slope of GA lesion area growth, mm ² /18 months	2.1356-2.5665	2.2855-2.7121	2.7550-3.2062
Difference (95% CI) in slope of GA lesion area growth vs sham pooled group, mm ² /18 months	-0.6296 (-0.9414 to -0.3177)	-0.4818 (-0.7928 to -0.1708)	NA
Percentage difference in slope of GA lesion area growth vs sham pooled group	-21.1%	-16.2%	NA
P value vs sham pooled group	<.0001	.0024	NA

Source: Table 4 of the Applicants Post 12-month Study report. Annual Growth Rate was calculated as the slope for time period multiplied by 2. Model includes treatment + baseline GA lesion area (< 7.5 mm² or ≥ 7.5 mm²) + time (continuous) + time spline at month 6 (continuous) + time spline at month 12 (continuous) + presence of CNV in the fellow eye (yes or no) + time (continuous) x treatment + time spline at month 6 (continuous) x treatment + time spline at month 12 (continuous) x treatment + baseline GA lesion area x time (continuous) + baseline GA lesion area x time spline at month 6 (continuous) + baseline GA lesion area x time spline at month 12 (continuous). A heterogeneous autoregressive covariance matrix is used to model the within-subject errors.

7. Appendix B: Summary of Additional Study: POT-CP12164

In addition to the two pivotal studies, the Applicant conducted and presented the results from a Phase 2, prospective, multicenter, randomized, single-masked, sham injection study. The primary objective of this study was to assess the safety, tolerability, and evidence of activity of pegcetacoplan in patients with GA secondary to AMD. This section presents the results of this study.

Executive Summary

This was a Phase 2, multicenter, randomized, single-masked, sham-controlled study. In this study, a total of 246 subjects were randomized in an approximately 2:2:1:1 ratio to receive pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham injection monthly (SM), or sham injection every other month (SEOM), respectively. Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

The primary efficacy endpoint for this study was defined as the annual growth rate of GA area in the study eye as measured by the mean change from baseline in square root area of GA lesion at Month 12. Per the study results, there was a statistically significant difference in the annual rate of growth in square root GA area in favor of both dosing frequencies compared to the sham group ([PM vs Sham, P=0.008]; [PEOM vs Sham; P=0.0630]); Table 49).

Table 49: Annual Growth Rate in CFB Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.025)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean	0.20 to 0.30	0.23 to 0.33	0.30 to 0.40
Difference in LS mean (95% CI) versus sham pooled group, mm	-0.10 (-0.16 to -0.03)	-0.07 (-0.14 to 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA
P value versus sham pooled group	.008	.063	NA
Difference in LS mean (95% CI) versus PEOM group	-0.03 (-0.10 to 0.04)	NA	NA
P value versus PEOM group	.444	NA	NA

Source: Table 19 of the Applicant's study reports.

Regarding safety, the incidence of ocular adverse events was higher in the two pegcetacoplan arms compared to the Sham arm. The percentage of subjects with ocular adverse events was 58.2% in the PM group, 50.7% in the PEOM group, 42.0% in SM group, and 40.5% in the SEOM group (41.2% for the Pooled sham group). The most frequently reported ocular adverse events in the PM group were vitreous floaters (8.4%), neovascular age-related macular degeneration (8.4%) and conjunctival haemorrhage (7.6%). The corresponding figures in the

PEOM group were vitreous floaters (6.4%), neovascular age-related macular degeneration (5.5%) and conjunctival haemorrhage (6.9%). The incidence of these events in the pooled sham group was vitreous floaters (1.0%), neovascular age-related macular degeneration (1.9%) and conjunctival haemorrhage (3.1%).

Reviewer's remark: In Study POT-CP121614, the subject, and assessors (i.e., photographer[s] and visual acuity technicians) were masked to the specific treatment being administered. However, the investigators and study site personnel not performing assessments of efficacy variables were unmasked to treatment assignment. Regarding efficacy, the square root of GA area was used; and treatment comparisons were conducted at a 10% level of significance. Note, the Division informed the Applicant that this study could be considered as an adequate and well-controlled study.

(b) (4)

❑ Study Design and Endpoints

▪ Study Design

Study POT-CP121614 was prospective, multicenter, randomized, single-masked, sham-injection controlled study. This study was designed to evaluate the safety, tolerability, and evidence of activity of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD. To be eligible for these studies, patients had to meet the following ocular inclusion criteria for the study eye:

- Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
- The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
 - o Total GA area must be ≥ 2.5 and ≤ 17.5 mm² (1 and 7 disk areas respectively).
 - o If GA is multifocal, at least 1 focal lesion must be ≥ 1.25 mm² (0.5 disk areas).
 - o The entire GA lesion must be completely visualized on the macula centered image.
 - o Presence of any pattern of hyper autofluorescence in the junctional zone of GA.

▪ Randomization and Treatment

In this study, 246 subjects were randomized in a 2:2:1:1 randomization ratio to the four study treatments:

- Pegcetacoplan monthly (PM): Pegcetacoplan 15 mg/0.1 mL monthly for 24 months.

- Pegcetacoplan every other month (PEOM): Pegcetacoplan 15 mg/0.1 mL every other month for 24 months.
- Sham monthly (SM): Sham injection monthly for 24 months.
- Sham every other month (SEOM): Sham injection every other month for 24 months.

Note, for efficacy analysis, subjects in the two sham arms were pooled, i.e., the primary treatment comparisons involved the comparison of each dosing frequency of pegcetacoplan against the pooled sham.

▪ Efficacy Endpoints

The protocol defined primary efficacy endpoint was annual growth rate of GA area in the study eye as measured by the mean change from baseline in square root area of GA lesion at Month 12 based on fundus autofluorescence photographs (FAF).

❑ Statistical Methods

In this study, all statistical tests were 2-sided at the 0.1 level of significance. There were no adjustments for multiple comparisons.

Analysis Populations

The studies defined the following analysis populations:

- The intent-to-treat (ITT): The ITT set includes all randomized subjects who received at least 1 injection of study medication. Each subject was included in their randomized treatment group even if they received the wrong study medication.
- The modified ITT (mITT): The mITT includes all randomized all subjects who received at least 1 injection of study medication and who had at least 1 visit at or after Month 2 where primary efficacy data were collected; Month 2 was the first visit on-treatment where lesion area was measured.
- The per-protocol (PP): The PP set includes all subjects in the mITT population who did not violate any inclusion or exclusion criteria and did not deviate from the protocol in a way that could influence their efficacy assessment. Subjects were excluded if they:
 - Received less than 75% of their expected injections prior to Month 12
 - For subjects receiving monthly injections: less than 9 injections
 - For subjects receiving EOM injections: less than 4 injections
 - Received the incorrect study medication at any time point throughout the study.

Analysis Methods

▪ Primary Analyses

The primary efficacy analysis was conducted using a mixed effects model for repeated measures (MMRM). The model included the fixed effects of treatment (3 groups: PM, PEOM and Sham), baseline square root area for GA lesion, visit (2, 6 and 12 months), treatment by visit interaction, visit by baseline interaction and treatment by baseline interaction. An unstructured covariance structure was used to model the within subject error.

▪ Sensitivity and Supplemental Analyses

Per the Applicant, the robustness of the primary analysis was evaluated by repeating the primary analysis with the PP population. In addition, the following sensitivity analyses were conducted using the mITT population:

- A MMRM analysis including only data which is within a specific time period of the last injection. In this analysis, month 6 data were to be included if a subject was dosed on or after Month 4, and Month 12 were to be included if a subject was dosed on or after Month 8. All Month 2 data was included, as the criteria to be included in the mITT population requires a subject to have had at least one dose of study medication.
- An analysis using the last observed carried forward (LOCF) method for handling missing data. In this analysis, all available Month 12 data was included, and missing data was replaced using LOCF method. An analysis of Covariance (ANCOVA) model was fitted for the Month 12 change from baseline in square root area for GA lesion, that includes baseline as a covariate and treatment (3 groups: PM, PEOM and Sham).
- Completer analysis i.e., observed data for those subjects who complete the treatment period (for subjects receiving monthly injections this will be 12 injections and for subjects receiving EOM injections this will be 6 injections) and have their Month 12 assessment. The analysis model was the same as for the primary analysis.

❑ Patient Disposition and Demographic and Baseline Characteristics

▪ Patient Disposition

As can be seen, the proportion of subjects who discontinued the study and/or treatment is higher in the two dosing frequencies of pegcetacoplan compared to the sham arm. The main reason for study discontinuation was adverse event. Note, almost four times more subjects in the PM arm compared to the pooled sham arm discontinued the study due to adverse event. Two subjects each in PEOM and pooled sham arms died (Table 50).

Table 50: Patient Disposition (POT-CP121614: ITT)

	PM (N = 86)	PEOM	Sham pooled (N = 81)	Total

Category Subcategory	n (%)	(N = 79) n (%)	n (%)	(N = 246) n (%)
Randomized	86	79	81	246
Completed treatment	52 (60.5)	60 (75.9)	69 (85.2)	181 (73.6)
Completed study	65 (75.6)	64 (81.0)	69 (85.2)	198 (80.5)
Withdrawn from treatment	34 (39.5)	19 (24.1)	12 (14.8)	65 (26.4)
Withdrawn from study	21 (24.4)	15 (19.0)	12 (14.8)	48 (19.5)
Primary reason for withdrawal from treatment				
Adverse Event	17 (19.8)	5 (6.3)	4 (4.9)	26 (10.6)
Investigator's decision	5 (5.8)	1 (1.3)	0	6 (2.4)
Sponsor's decision	1 (1.2)	0	1 (1.2)	2 (0.8)
Subject request	6 (7.0)	5 (6.3)	3 (3.7)	14 (5.7)
Death	0	2 (2.5)	2 (2.5)	4 (1.6)
Other	5 (5.8)	6 (7.6)	2 (2.5)	13 (5.3)
Primary reason for withdrawal from study				
Adverse Event	6 (7.0)	3 (3.8)	4 (4.9)	13 (5.3)
Withdrawal by subject	9 (10.5)	9 (11.4)	3 (3.7)	21 (8.5)
Investigator's decision	2 (2.3)	0	0	2 (0.8)
Lost to follow-up	1 (1.2)	1 (1.3)	0	2 (0.8)
Death	2 (2.3)	2 (2.5)	4 (4.9)	8 (3.3)
Other	1 (1.2)	0	1 (1.2)	2 (0.8)

Source: Table 7 of the Applicant's Study report.

▪ **Baseline and Demographic Characteristics**

There were no significant baseline imbalances between the three arms in the demographics of age, gender, or race. In all arms, there were more female participants than male participants; and most of the study participants were White and over the age of 65 years. Black and Asian subjects appear to be severely under-represented, comprising of only 1.2% each in the ITT subjects (Table 51).

Table 51: Baseline and Demographic Characteristics (POT-CP121614: ITT)

	PM (N = 86) n (%)	PEOM (N = 79) n (%)	Sham pooled (N = 81) n (%)	Total (N = 246) n (%)
Sex				
Female	55 (64.0)	50 (63.3)	49 (60.5)	154 (62.6)
Male	31 (36.0)	29 (36.7)	32 (39.5)	92 (37.4)
Age, years				
Mean (SD)	79.6 (7.51)	81.0 (7.55)	78.4 (7.43)	79.7 (7.54)
Minimum, maximum	63, 95	60, 97	60, 96	60, 97
<65 years	2 (2.3)	1 (1.3)	3 (3.7)	6 (2.4)
≥65-<75 years	21 (24.4)	14 (17.7)	21 (25.9)	56 (22.8)
≥75-<85 years	38 (44.2)	37 (46.8)	40 (49.4)	115 (46.7)
≥85 years	25 (29.1)	27 (34.2)	17 (21.0)	69 (28.0)

Country				
Australia	12 (14.0)	11 (13.9)	12 (14.8)	35 (14.2)
New Zealand	3 (3.5)	3 (3.8)	4 (4.9)	10 (4.1)
US	71 (82.6)	65 (82.3)	65 (80.2)	201 (81.7)
Race				
Asian	1 (1.2)	0	0	1 (0.4)
Black or African American	1 (1.2)	1 (1.3)	0	2 (0.8)
White	84 (97.7)	76 (96.2)	81 (100.0)	241 (98.0)
Other	0	2 (2.5)	0	2 (0.8)
Ethnicity				
Hispanic or Latino	2 (2.3)	1 (1.3)	2 (2.5)	5 (2.0)
Not Hispanic or Latino	81 (94.2)	76 (96.2)	77 (95.1)	234 (95.1)
Not reported	2 (2.3)	0	0	2 (0.8)
Unknown	1 (1.2)	2 (2.5)	2 (2.5)	5 (2.0)

Source: Table 10 of the Applicant's Study report.

❑ **Results And Conclusions**

▪ **Primary Efficacy Analysis Results**

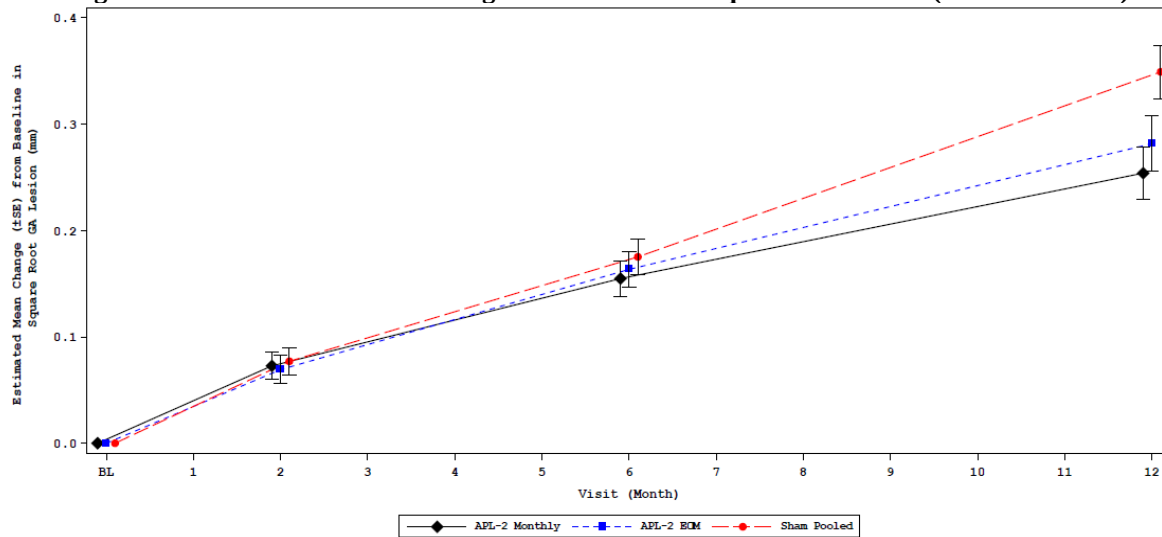
The Applicant reports that there was a statistically significant difference in the annual rate of growth in square root GA area in favor of both dosing frequencies compared to the sham group ([PM vs Sham, P=0.008]; (PEOM vs Sham; P=0.0630)];Table 52).

Table 52: Change from Baseline in Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.025)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean	0.20 to 0.30	0.23 to 0.33	0.30 to 0.40
Difference in LS mean (95% CI) versus sham pooled group, mm	-0.10 (-0.16 to -0.03)	-0.07 (-0.14 to 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA
P value versus sham pooled group	.008	.063	NA
Difference in LS mean (95% CI) versus PEOM group	-0.03 (-0.10 to 0.04)	NA	NA
P value versus PEOM group	.444	NA	NA

Source: Table 19 of the study reports.

Figure 12: Mean Plot of Mean Change from Baseline in Square Root of GA (POT-CP121614)



Source: Figure 1 of the study report.

■ Sensitivity Analysis Results

Recall, the Applicant conducted sensitivity analyses to evaluate the robustness of the primary efficacy analysis results. The results of the sensitivity analyses are generally consistent with the primary efficacy analysis results.

Table 53: Change from Baseline in Square Root GA (POT-CP121614: Per Protocol)

Statistic	PM (N = 66)	PEOM (N = 71)	Sham pooled (N = 73)
n included in the model	66	71	73
LS mean (SE), mm	0.26 (0.027)	0.28 (0.027)	0.35 (0.025)
95% CI of LS mean, mm	0.21, 0.31	0.22, 0.33	0.30, 0.40
Difference (95% CI) in LS mean from sham pooled group, mm	-0.09 (-0.16, -0.02)	-0.07 (-0.15, 0)	NA
Percentage difference in LS mean from sham pooled group	-26%	-20%	NA

Source: Table 21 of the Applicant's study report.

Table 54: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.25 (0.026)	0.28 (0.026)	0.35 (0.025)
95% CI of LS mean, mm	0.20, 0.30	0.23, 0.33	0.30, 0.40
Difference (95% CI) in LS mean from sham pooled group, mm	-0.10 (-0.17, -0.03)	-0.07 (-0.14, 0)	NA
Percentage difference in LS mean from sham pooled group	-29%	-20%	NA

Source: Table 22 of the Applicant's study report.

Table 55: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT: LOCF)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	84	78	80
LS mean (SE), mm	0.34 (0.032)	0.36 (0.033)	0.45 (0.033)
95% CI of LS mean, mm	0.28, 0.40	0.29, 0.42	0.39, 0.51
Difference (95% CI) in LS mean from sham pooled group, mm	-0.11 (-0.20, -0.02)	-0.09 (-0.19, 0)	NA
Percentage difference in LS mean from sham pooled group	-24%	-20%	NA

Source: Table 23 of the Applicant's study report. LOCF: Last observation carried forward.

Table 56: Sensitivity Analysis: Change from Baseline in Square Root GA (POT-CP121614: mITT: CC)

Statistic	PM (N = 84)	PEOM (N = 78)	Sham pooled (N = 80)
n included in the model	49	54	64
LS mean (SE), mm	0.25 (0.031)	0.28 (0.029)	0.36 (0.027)
95% CI of LS mean, mm	0.19, 0.31	0.22, 0.34	0.30, 0.41
Difference (95% CI) in LS mean from sham pooled group, mm	-0.10 (-0.18, -0.02)	-0.08 (-0.16, 0)	NA
Percentage difference in LS mean from sham pooled group	-28%	-22%	NA

Source: Table 24 of the Applicant's study report. CC: Complete cases.

☐ **Safety Summary**

☐ **Extent of Treatment Exposure**

The mean numbers of injections in the sham-treated groups (11.6 injections in the SM group and 6.6 injections in the SEOM group) were higher than in their pegcetacoplan-treated counterparts (10.5 injections in the PM group and 6.2 injections in the PEOM group). The proportion of subjects who received all planned injection was 45.3% in the PM group and 70.9% in the PEOM group. The corresponding figures in the sham arms were 61.0% (SM) and 80.0% (SEOM), respectively.

Table 57: Summary of Drug Exposure (POT-CP121614: ITT)

Statistic	PM (N = 86)	PEOM (N = 79)	SM (N = 41)	SEOM (N = 40)
n	86	79	41	40
Mean (SD) number of injections	10.5 (3.51)	6.2 (1.58)	11.6 (2.67)	6.6 (1.25)
Median number of injections	12.0	7.0	13.0	7.0
Minimum, maximum number of injections	1, 13	1, 8	2, 13	1, 8
Number (%) of subjects who received all planned injections	39 (45.3)	56 (70.9)	25 (61.0)	32 (80.0)

Source: Table 48 of the Applicant's study report

▪ **Adverse Events**

The incidence of ocular adverse events was higher in the two pegcetacoplan arms compared to the sham arm. The percentage of subjects with ocular adverse events was 58.2% in the PM group, 50.7% in the PEOM group, 42.0% in SM group, and 40.5% in the SEOM group (41.2% for the Pooled sham group;). The most frequently reported ocular adverse events in the PM group were vitreous floaters (8.4%), neovascular age-related macular degeneration (8.4%) and conjunctival haemorrhage (7.6%). The corresponding figures in the PEOM group were vitreous floaters (6.4%), neovascular age-related macular degeneration (5.5%) and conjunctival haemorrhage (6.9%). The incidence of these events in the pooled sham group was vitreous floaters (1.0%), neovascular age-related macular degeneration (1.9%) and conjunctival haemorrhage (3.1%;).

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/s/

ABEL T ESHETE
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