STATISTICAL ANALYSIS PLAN

APL2-303

A Phase III, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

PROTOCOL IDENTIFIER: DERBY

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	07/23/2021	New Document
2.0	08/10/2021	• Changed the thresholds for censoring COVID-19 impacted data in the supplementary analyses for the primary and key secondary endpoints. • Added an additional covariance matrix to the MMRM models if the statistical modeling fails to converge with the first two covariance matrices • Fixed an error in the sample code and text for maximum reading speed calculation. • Fixed an error in Figure 2 with extraneous text boxes included. • Provided further details on the analysis of suspected, confirmed, and exudative AMD's.

APPROVAL SIGNATURES

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ABBREVIATIONS

ADA	Anti-drug Antibodies
ADY	Analysis Study Day
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BCVA/NL-BCVA	(Normal luminance) Best Corrected Visual Acuity
BLQ	Below the Limit of Quantification
BUN	Blood Urea Nitrogen
C3	Complement component 3
C_{max}	Maximum Observed Concentration
CMH	Cochran Mantel Haenszel
CNV	Choroidal Neovascularization
CRO	Contract Research Organization
cRORA	Complete retinal pigment epithelium and outer retinal atrophy
CSR	Clinical Study Report
DA	Disk Areas
DCFP	Digital Color Fundus Photography
DLS	Double-layer sign
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOM	Every Other Month
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FFA/FA	Fundus Fluorescein Angiography or Fluorescein Angiography
FRI	Functional Reading Independence
GA	Geographic Atrophy
IOP	Intra Ocular Pressure
iRORA	Incomplete retinal pigment epithelium and outer retinal atrophy
ITT	Intent-to-Treat
IVT	Intravitreal
kg	Kilogram
LOV	Last Observed Value
LL-BCVA	Low Luminance Best Corrected Visual Acuity
LLD	Low Luminance Deficit
LS	Least Square
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter

mmHg	Millimeter of Mercury
MMRM	Mixed effect Model for Repeated Measure
MNAR	Missing Not At Random
MNRead	Minnesota Reading Chart
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25 Item Version
NEI VFQ-39	National Eye Institute Visual Functioning Questionnaire 39 Item Version
NIR	Near Infrared Reflectance
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PDV	Protocol Deviation
PEG	Polyethylene glycol
PEOM	Pegcetacoplan Every-Other-Month
PK	Pharmacokinetics
PM	Pegcetacoplan Monthly
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD-OCT	Spectral Domain Optical Coherence Tomography
SEOM	Sham Every-Other-Month
SI	International System of Units
SM	Sham Monthly
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to Maximum Measured Concentration
µL	Micro liter
WBC	White Blood Cell
WHO	World Health Organization
WPM	Words per Minute

1. INTRODUCTION

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan (also known as APL-2) for geographic atrophy [GA] secondary to age-related macular degeneration (AMD). This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic data, supplementing what is described in the final study protocol, version 1.0, amendment 5, dated 12 August 2020.

The primary study analysis will be based on complete data from the first 12 months of the study and performed after all subjects have completed the Month 12 visit in the study or discontinued early, and all corresponding data have been entered into the database, reviewed, cleaned, and finalized as the Month 12 dataset. Analysis will include testing of hypotheses of the primary efficacy endpoint at Month 12. Key secondary, secondary, and exploratory endpoints will be evaluated based on data in the Month 12 datasets in a descriptive manner. An analysis of the safety data in the Month 12 dataset will also be performed.

The final study analysis will be based on data after all subjects have either completed the Month 24 visit in the study or discontinued the study early, and all data from the study are in the database and the database is reviewed, cleaned, and locked as the final dataset. Analysis will include testing of hypotheses of the key secondary endpoints at Month 24 as described in Section 6.3.1. A cumulative analysis of all data through the end of the study will be produced based on the final dataset.

See Section 3.5 for further details on analysis timing.

The analyses specified in this document supersede the analysis plan described in the study protocol (protocol version 1.0, amendment 5 dated 12 August 2020).

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of pegcetacoplan compared to sham in subjects with GA secondary to AMD assessed by change in the total area of GA lesions in the study eye from baseline as measured by Fundus Autofluorescence (FAF).

2.1.2. Key Secondary Objectives

The key secondary objectives are to evaluate the efficacy of pegcetacoplan compared to sham in subjects with GA secondary to AMD with respect to:

- Monocular maximum reading speed (study eye), as assessed by Minnesota Reading (MNRead) or Radner Reading Charts (in select countries)
- Functional Reading Independence (FRI) Index score (subject-level assessment)
- Normal luminance best-corrected visual acuity (NL-BCVA) score in the study eye

2.1.3. Secondary Objectives

To evaluate the efficacy of pegcetacoplan compared to sham in subjects with GA secondary to AMD with respect to:

- Low luminance best corrected visual acuity (LL-BCVA) score in the study eye
- Low luminance deficit (LLD) in the study eye
- Total area of GA lesion(s) in the study eye
- Monocular critical print size (study eye), as assessed by MNRead or Radner Reading Charts (in select countries)
- National Eye Institute Visual Functioning Questionnaire 25 Item Version (NEI VFQ-25) distance activity subscale score (in select countries)

To evaluate the pharmacokinetics (PK) of pegcetacoplan as assessed by systemic serum concentration of pegcetacoplan (in select sites).

2.1.4. Safety Objectives

To evaluate the safety and tolerability of pegcetacoplan compared to sham injection in subjects with GA secondary to AMD as indicated by:

- Incidence and severity of ocular and systemic treatment-emergent adverse events (TEAEs)
- Incidence of anti-drug antibodies (ADA) directed against pegcetacoplan peptide or polyethylene glycol (PEG)
- Incidence of new active choroidal neovascularization (CNV) in the study eye

2.1.5. Exploratory Objectives

- To evaluate the efficacy of pegcetacoplan compared to sham in subjects with GA secondary to AMD as indicated by:
    - NEI VFQ-25 composite score
    - NEI VFQ-25 near activity subscale score (in select countries)
    - Comparison between study eye and fellow eye of change in GA lesion size
    - To evaluate the binocular reading speed as assessed by MNRead or Radner Reading Charts (in select countries)
    - To evaluate the binocular critical print size as assessed by MNRead or Radner Reading Charts (in select countries)
    - To evaluate the relationship between genetic polymorphisms associated with AMD with GA progression and response to pegcetacoplan
- To evaluate the incidence of new onset of subclinical CNV in the study eye.
- To assess sensitivity and specificity of a digital reading speed application to detect disease progression / regression (optional, select sites)
- To assess sensitivity and specificity of a digital visual function application to detect disease progression / regression (optional, select sites)

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint is the change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.

2.2.2. Key Secondary Endpoints

The key secondary endpoints include:

- Change from baseline in uncorrected monocular maximum reading speed (study eye), at Month 24 as assessed by MNRead or Radner reading charts (in select countries).
- Change from baseline in mean FRI Index score (subject-level assessment) at Month 24
- Change from baseline in NL-BCVA score (study eye) at Month 24 as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

2.2.3. Secondary Endpoints

Other secondary endpoints include:

- Change from baseline in LL-BCVA score (study eye) over time as assessed by ETDRS chart.

- Change from baseline in the total area of GA lesion(s) in the study eye (in mm^2) as assessed by FAF over time other than Month 12.
- Change from baseline in monocular critical print size (study eye), as assessed by MNRead or Radner reading charts (in select countries) over time.
- Change from baseline in the NEI VFQ-25 distance activity subscale score (in select sites) (subject level assessment) over time.
- Systemic serum concentration of pegcetacoplan (selected sites) over time.

2.2.4. Exploratory Endpoints

- Additional NEI-VFQ endpoints including:
    - Change from baseline in the NEI VFQ-39 distance activity subscale score (in select sites) over time.
    - Change from baseline in NEI VFQ-25 composite score over time.
    - Change from baseline in NEI VFQ-39 composite score over time.
    - Change from baseline in NEI VFQ-25 near activity subscale score (in select countries) over time.
    - Change from baseline in NEI VFQ-39 near activity subscale score (in select countries) over time.
    - Change from baseline in NEI VFQ-25 driving subscale score (in select countries) over time as well as the number and percentage of subjects with worse driving outcomes for subjects who are currently driving at baseline.
- Difference between study eye and fellow eye in change in GA lesion size from baseline over time in subjects with bilateral GA.
- Change from baseline in binocular maximum reading speed as assessed by MNRead or Radner Reading Charts (in select countries) over time.
- Change from baseline in binocular critical print size as assessed by MNRead or Radner Reading Charts (in select countries) over time.
- Change from baseline in digital reading index (in select sites) over time as measured by the Spotlight instrument.
- Change from baseline in digital visual function (metamorphopsia) (in select sites) over time as measured by the Alleye instrument.
- Progression from incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) to complete retinal pigment epithelium and outer retinal atrophy (cRORA).
- Progression from large drusen to iRORA or cRORA.
- Other efficacy imaging endpoints including change in the distance of the atrophy junction to the fovea, and non-subfoveal atrophy to subfoveal atrophy conversion.

2.2.5. Safety Endpoints

- Incidence and severity of ocular and systemic treatment-emergent adverse events.
- Incidence of ADA directed against pegcetacoplan peptide or PEG.
- Incidence of new active CNV in the study eye.
- Incidence of new onset of subclinical CNV in the study eye.
- Incidence of subjects who lost letters based on NL-BCVA categories (≥15, ≥15 - <30, ≥30 ETDRS letters).
- Change/shift from baseline in clinical labs and incidence of abnormal lab values.
- Change from baseline in vital signs and incidence of abnormal vital sign results.
- Shift from baseline in ocular examination assessments including slit-lamp examination and indirect ophthalmoscopy.
- Change from baseline in Intra Ocular Pressure (IOP) and incidence of IOP above specified thresholds.
- Change/shift from baseline in ocular imaging assessments (including specular microscopy; select sites).

2.2.6. Exploratory Endpoints Closely Related to the Primary Efficacy Endpoint

- Change from baseline in square root of the total area of GA lesion(s) in the study eye (in mm) based on FAF over time.
- Percent change in total area of GA lesion(s) in the study eye (in mm^2) based on FAF over time.
- Percent change in square root of the total area of GA lesion(s) in the study eye (in mm) based on FAF over time.

2.2.7. Pharmacokinetic Endpoint

Serum pegcetacoplan concentrations will be determined from samples taken during the course of the study. Maximum serum concentration (C_{max}) will be determined from serum concentration data at Day 7 following pegcetacoplan treatment ($C_{Day\ 7}$).

2.2.8. Pharmacodynamics Endpoints

Change from baseline in serum complement profile (C3, CH50, AH50).

3. STUDY DESIGN

3.1. General Description

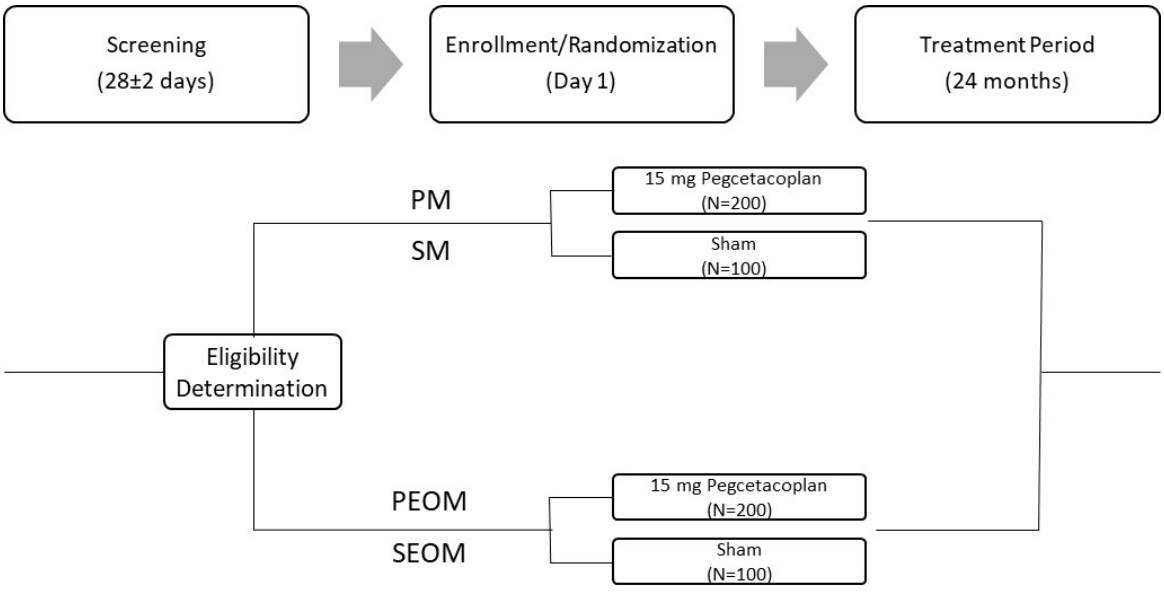
This is a Phase 3, multicenter, randomized, double-masked, sham-injection controlled study to assess the efficacy and safety of multiple intravitreal (IVT) injections of pegcetacoplan (also known as APL-2) in subjects with GA secondary to AMD.

The study will randomize approximately 600 subjects across approximately 100 multinational sites. Subjects will be screened within 28 days before receiving pegcetacoplan or Sham injection. Upon providing written informed consent and entry into the study, subjects will be assigned a screening number. Subjects who meet all inclusion and none of the exclusion criteria will return to the clinic for randomization and treatment on Visit 2 (Day 1). At this visit, subjects will be randomized 2:2:1:1 to receive pegcetacoplan Monthly (PM), pegcetacoplan Every-Other-Month (PEOM), Sham injection Monthly (SM) or Sham-injection Every-Other-Month (SEOM), respectively. Randomization will be stratified according to GA lesion area at screening (< 7.5 mm^2; ≥ 7.5 mm^2), and presence of CNV in the fellow eye.

The planned length of participation in the study for each subject is approximately 24 months (from the beginning of the screening period through Month 24 visit). After the COVID-19 pandemic started, Apellis added a rescreening procedure where the screening period was extended to up to 90 days (applicable only to subjects that fully qualified for the trial during a complete screening prior to March 30, 2020). The total length of participation in this study can be up to 27 months for subjects that were screened using this updated procedure. The schedules of assessments are presented in Appendices A, B, C, and D of Study Protocol Amendment 5, Version 1.0 dated 12 August 2020 and are also available in Appendix 1.

A study schematic diagram is shown in Figure 1.

Figure 1: Study Schema



PM= Pegcetacoplan Monthly; SM= Sham Monthly; PEOM= Pegcetacoplan Every-Other-Month; SEOM= Sham Every-Other-Month

3.2. Randomization

Subjects will be randomized 2:2:1:1 using a web-based randomization system to receive treatment with PM, PEOM, SM or SEOM, respectively.

The randomization scheme will be maintained by the Sponsor, or designee. Subject randomization will be stratified by GA lesion area at screening based on assessment from the reading center (< 7.5 mm^2; ≥ 7.5 mm^2) and presence of CNV in the fellow eye (yes; no).

3.3. Masking

This is a double-masked study. Designated masked study site staff (e.g., assistant(s), VA technicians, optical coherence tomography (OCT) technicians, photographers, technicians administering questionnaires, subjects, Reading Center personnel, the assigned evaluating physician(s), and the Sponsor) will be masked to treatment assignment. However, the treating physician and any associated support staff involved in performing the intravitreal or sham injections will be unmasked to study treatment. These individuals are only responsible for administering the study drug and are not involved in assessing adverse events. In addition, the unmasked individuals are not allowed to discuss treatment and/or subject outcomes with masked study staff, including the evaluating physician. The Principal Investigator must be masked to subjects' treatment assignment. To prevent bias in treatment assignment, eligible subjects will be randomized using a web-based randomization system. Processes and plans will be put in place to avoid unintentional unmasking during the study. All study roles will be clearly documented on the site delegation of authority log and once the roles have been designated and executed, these roles should not be switched during the conduct of the study. In unforeseen circumstances, a site can contact the Sponsor to switch a study staff member from the masked role to the unmasked role but not vice versa. Details on unmasking at the Month 12 reporting are in Section 3.5.

While the actual study treatment (pegcetacoplan vs. sham) is masked, the treatment frequency (monthly vs. every other month) for each individual subject is known.

3.4. Sample Size and Power Considerations

A total of approximately 600 subjects will be randomized in a 2:2:1:1 ratio to receive treatment with PM, PEOM, SM, or SEOM. The annual growth rate in GA lesion area is expected to have a mean of 1.47, 1.70 and 2.13 mm^2/year for PM, PEOM and Sham-Pooled (Sham) groups, respectively, as estimated from the results of a Phase 2 trial of pegcetacoplan. The standard deviation of the lesion growth is estimated to be 1.50 mm^2 based on the same Phase 2 trial data or 1.25 mm^2 based on natural history data (Holekamp N, 2019).

The power of the study for the primary endpoint is presented in Table 1 for sample size of 200 in each treatment arm. The approximation is calculated using PROC POWER ONEWAYANOVA, Statistical Analysis System (SAS) 9.4. The study power for the primary endpoint is likely larger when utilizing the longitudinal data to model the primary endpoint. The actual study power for the primary endpoint may also vary based on the distribution of the stratification factors (i.e., lesion area at screening, presence of CNV in fellow eye). Study power was not calculated for key secondary functional endpoints.

Table 1: Power to Detect a Difference among Three Groups with an Equal Size of 200 Subjects

Common Standard Deviation (mm^2)	Alpha (two-sided)	Power for a true mean of 1.47, 1.70, and 2.13 mm^2/year for PM, PEOM and Sham, respectively		
		PM vs Sham	PEOM vs Sham	Overall (Among 3 groups)
1.25	0.0495	> 99.9%	92.9%	99.9%
1.25	0.0248	99.9%	88.2%	99.7%
1.40	0.0495	99.7%	86.5%	99.3%
1.40	0.0248	99.3%	79.4%	98.6%
1.50	0.0495	99.2%	81.5%	98.4%
1.50	0.0248	98.4%	73.1%	97.0%

PM = pegcetacoplan Monthly, PEOM = pegcetacoplan Every-Other-Month; Sham = Sham Monthly + Sham Every-Other-Month

3.5. Analysis Timing and Unmasking

The analysis of data from the first 12 months of the study will be performed when all subjects have completed the Month 12 visit in the study or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized as the Month 12 dataset per the 12-Month Primary Analysis Data Cut Plan and the Programming Plan. At the time of the analysis of the Month 12 dataset, subjects who have not completed or discontinued from the study will still be followed by the sites as part of the second year.

At the time of the Month 12 reporting, Sponsor personnel who are analyzing, interpreting, and reporting data from the Month 12 dataset will be unmasked to treatment assignment. To maintain data integrity for the remainder of the study, sponsor and contract research organization (CRO) personnel responsible for continuing study oversight will remain masked as documented in the Study Masking Plan and the GA Internal Unmasking Plan.

Analyses will include formal hypothesis testing of the primary efficacy endpoint at Month 12. Key secondary, secondary, and exploratory endpoints will be evaluated based on the Month 12 dataset in a descriptive manner. An analysis of the safety data in the Month 12 dataset will also be performed.

The final study reporting will be based on data after all subjects have either completed the Month 24 visit in the study or discontinued the study early, and all data from the study are entered in the database and the database is reviewed, cleaned, and locked as the final dataset. Minor changes are expected from the Month 12 dataset (e.g. adverse event end dates for events ongoing in the Month 12 dataset), however, all subsequent differences in data prior to the Month 12 visit will be listed. Analysis of the final dataset will include testing of hypotheses of the key secondary endpoints at Month 24 as described in Section 6.3.1. A cumulative analysis of all data through the end of the study will be produced based on the final dataset.

Aggregate results of the Month 12 reporting may be reported before completion of the study. However, subjects, masked study site personnel, masked CRO personnel at Covance, Sponsor team members with study oversight responsibility, and central reading center personnel will remain masked to individual treatment assignments until after the study is completed

(after all subjects have either completed Month 24 or discontinued early from the study), the database is locked and the unmasking has been approved.

3.6. Definition of 12-Month Data in the Month 12 Dataset

All screening and post-baseline data with a clinical date (i.e., administration/assessment/ onset/start date) on or before the defined Month 12 data cutoff date will be included in the Month 12 Dataset. The 12-month data cutoff will include all data regardless of the type of study visit at which it was collected. This may include data collected at unscheduled visits or early termination visits if the visit date was on or before the 12-month data cutoff date. The Month 12 data cutoff is defined as:

- If the subject completed Month 12 (Visit 14) assessments, then the data cutoff will be the day that the Month 12 (Visit 14) assessments are completed, regardless of Study Day.
- If the subject did not complete the Month 12 (Visit 14) assessments (e.g. missed or early terminated) then Study Day 375 (Study Day 360 (target date) + 15) will be used as the Month 12 cutoff.

4. STATISTICAL ANALYSIS SETS

Two sham treatment arms (SM and SEOM) will be pooled into a single control (Sham) group for analyses.

4.1. Screened Set

The screened set consists of all subjects who provided written informed consent and are screened for participation in this study. This population will only be used for the purposes of describing the subject disposition and for listing the data.

4.2. Intent-to-Treat Set

The Intent-to-treat (ITT) set consists of all randomized subjects. Subjects will be analyzed in the treatment arm assigned at randomization.

4.3. Modified Intent-to-Treat Set

The modified ITT (mITT) set consists of all randomized subjects who receive at least one injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye as assessed by FAF. Subjects will be analyzed in the treatment arm assigned at randomization.

4.4. Safety Set

The Safety set consists of all subjects randomized who receive at least one injection of pegcetacoplan or sham. Subjects will be analyzed according to the actual treatment received. In the case a subject received an incorrect injection of study medication than what they were randomized to, subjects will be presented under the corresponding pegcetacoplan arm if they received at least one injection of pegcetacoplan during the study and will only be presented under the corresponding sham arm if they did not receive any injections of pegcetacoplan. This population will be used for all safety analyses.

4.5. Per-Protocol Sets

The Per-Protocol (PP) sets will be identified separately for Month 12 and Month 24 analysis, respectively (i.e., Month 12 PP set and Month 24 PP set). The PP sets consist of all mITT subjects who have a valid GA lesion area assessment for either Month 10 or 12 (Month 12 PP set) or a valid GA lesion area assessment for at least one of Month 18, 20, 22, 24 (Month 24 PP set) and who follow the protocol without any major deviation(s) that could affect the primary efficacy data.

A valid GA lesion area assessment is defined as a non-missing measured GA lesion area assessment at a given timepoint where at least 75% of the expected injections over the course of participation ahead of the given timepoint have been received by the subject. For example:

- A valid GA lesion measurement at Month 10 in the Monthly arm would be a result available at Month 10 with no more than 2 missed injections prior to the Month 10 assessment (10 scheduled before Month 10, 2 missed = 80% compliance).

- A valid GA lesion measurement at Month 20 in the every other month (EOM) arm would be a result available at Month 20 with no more than 2 missing injections prior to the Month 20 assessment (10 scheduled before Month 20, 2 missed = 80% compliance).

Major protocol deviations (PDVs) that lead to exclusion from the Month 12 PP set and the Month 24 PP set are as follows:

(i) Violations of inclusion and/or exclusion criteria

A PDV with any of the following inclusion and/or exclusion criteria violations will be classified as a major PDV:

Inclusion Criterion #3: Clinical diagnosis of GA of the macula secondary to AMD as determined by the Investigator and confirmed by the Reading Center

Inclusion Criterion #4: The GA lesion must meet the criteria listed in the protocol as determined by the central Reading Center's assessment of FAF

- Total GA area must be ≥ 2.5 and ≤ 17.5 mm^2 (1 and 7 disk areas [DA] respectively).
- If GA is multifocal, at least one focal lesion must be ≥ 1.25 mm^2 (0.5 DA), with the overall aggregate area of GA as specified above in 4a.
- 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.
- Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (i.e., pattern = none) is exclusionary.

Exclusion Criterion #1: GA secondary to a condition other than AMD such as Stargardt disease, cone rod dystrophy or toxic maculopathies like plaquenil maculopathy in either eye.

Exclusion Criterion #3: Any history or active choroidal neovascularization (CNV), associated with AMD or any other cause, including any evidence of retinal pigment epithelium rips or evidence of neovascularization anywhere based on spectral domain optical coherence tomography (SD-OCT) imaging and/or fluorescein angiography as assessed by the Reading Center.

Exclusion Criterion #13: Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo.

(ii) Not receiving assigned treatment

Not receiving assigned treatment at more than 25% of the treatment visits over the analysis timeframe, either 12-month or 24-month, will be classified as a major PDV.

4.6. Pharmacokinetic Set

The PK set will include all subjects in the safety set who have at least one quantifiable post-dose concentration of pegcetacoplan (even with values below the limit of quantification (BLQ)).

4.7. Pharmacodynamic Set

The pharmacodynamic (PD) set will include all subjects in the safety set who have at least one quantifiable post-dose PD endpoint (C3, CH50, or AH50) evaluated.

4.8. Genotyping Set

The genotyping set consists of all ITT subjects who have at least one non-missing genotyping result for a single nucleotide polymorphism (SNP) associated with age-related macular degeneration from the genotype sequencing analysis.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The number of subjects screened, passed screening, screened failed, and the reasons for screen failure will be presented overall.

The number of subjects randomized and in each defined analysis set will be summarized by treatment group and overall for the ITT Set. In addition, the reasons for exclusion from the mITT and per-protocol populations will be summarized.

Subjects' disposition by region and country will also be provided for the ITT set. All summaries on subject disposition will be produced based on the Month 12 dataset for the Month 12 reporting and based on the final study dataset for the final reporting, as appropriate.

Overall summary of subjects' disposition includes:

- Number of subjects randomized
- Number of subjects completed treatment [through Month 12 or Month 24, as appropriate]
- Number of subjects discontinued from treatment and reason for discontinuation [prior to Month 12 or Month 24 as appropriate]
    - Subjects who discontinued from treatment without concurrent study discontinuation will be singled out [prior to Month 12 or Month 24 as appropriate]
- Number of subjects completed study [through Month 12 or Month 24, as appropriate]
- Number of subjects discontinued from study and reason for discontinuation [prior to Month 12 or Month 24 as appropriate]

A summary of the disposition through each study visit will also be presented by treatment group and overall for the ITT set.

In addition, to assess the impact of COVID-19 pandemic on disposition of subjects, the following summary will be provided for each study visit and by reason (COVID-19 vs. non-COVID-19) for the ITT set:

- Number of subjects discontinued from treatment
- Number of subjects discontinued from study

5.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be tabulated using descriptive statistics by treatment group and overall. Tables will be produced for the following analysis sets: ITT, Safety, mITT, Month 12 PP and Month 24 PP (as appropriate), PK, PD, and Genotyping. The following variables will be included in the tables:

The demographic data are:

- Age at screening (years) and in categories
  - < 65
  - 65-<75
  - 75-<85
  - ≥ 85
- Sex
- Race
- Ethnicity
- Geographic Region (United States vs. Rest of World)
- Country
- Weight (kg) at baseline
- Height (cm) at baseline
- Body Mass Index (kg/m^2)
- Tobacco use status (ever, never)

Baseline characteristics will be summarized for both study eye and fellow eye whenever applicable. Baseline characteristics include:

- Study eye laterality (OD, OS)
- Study eye status (better-seeing eye vs. worse-seeing eye, based on NL-BCVA – in the case of ties, study eye status will be classified as the better-seeing eye)
- GA lesion size (mm^2) (assessed by FAF)
- GA lesion size in categories, determined by reading center (as randomized status and actual status):
  - < 7.5 mm^2
  - ≥ 7.5 mm^2
- GA lesion size categories (approximately tertiles based on APL2-303/304 combined data*) – study eye only
- Square root GA lesion size (mm)

- GA lesion location (subfoveal involvement vs. non-subfoveal involvement) (assessed by FAF)
- GA focality (unifocal vs. multifocal) (assessed by FAF)
- Number of areas of atrophy (none, 1, 2-5, 6-10, 11-20, >20, cannot be determined) (assessed from FAF)
- Presence of double-layer sign (DLS) (assessed by SD-OCT)
- Central subfield thickness (CST) (assessed by SD-OCT)
- Presence of macular neovascularization (MNV) (i.e., subclinical CNV) (assessed by Optical Coherence Tomography Angiography (OCT-A))
- Presence of pseudodrusen (assessed by near-infrared reflectance imaging)
- Number of intermediate/large drusen (0-5, 6-10, 11-20, and >20) (assessed by color fundus photography)
- NL-BCVA in ETDRS letters
- NL-BCVA categories (≥70, ≥60 - <70, ≥35 - <60, <35 ETDRS letters)
- NL-BCVA (<60 vs. ≥60 ETDRS letters)
- LL-BCVA in ETDRS letters
- LL-BCVA categories (approximately tertiles based on APL2-303/304 combined data*) – study eye only
- IOP
- LLD in ETDRS letters
- LLD categories (<20 vs. ≥ 20 ETDRS letters)
- LLD categories (approximately tertiles based on the APL2-303/304 combined data*) – study eye only
- NL-BCVA (<60 vs. ≥60 ETDRS letters) and LLD (<20 vs. ≥ 20 ETDRS letters) combinations
- Advanced AMD (fellow eye with: GA only, GA with CNV, CNV only, neither GA nor CNV)
- GA laterality (bilateral GA vs. study eye GA Only)
- Presence of CNV in fellow eye (as randomized and actual status (based on medical history))
- Lens status:
    - Phakic
    - Pseudophakic
- Reading speed assessment method

- Monocular and binocular maximum reading speed and critical print size (without adjustment for reading inaccuracy)
- Monocular maximum reading speed categories (<60, 60-<160, ≥160 words per minute (wpm))
- Monocular maximum reading speed categories (approximately tertiles based on APL2-303/304 combined data*) – study eye only
- Mean FRI Index score
- FRI Level (1,2,3,4)
- NEI VFQ-25 distance activity subscale score
- NEI VFQ-25 near activity subscale score
- NEI VFQ-25 driving subscale score
- Number of subjects currently driving at baseline
- NEI VFQ-25 composite score
- C3 Complement level
- C3 Complement level categories (tertiles of C3)
- Dry AMD status (iRORA, large drusen) (at Month 24 reporting only)

*Approximately tertiles will be specified consistently across the APL2-303/304 studies to the nearest clinically relevant level.

Baseline will be defined as the last available pre-treatment value taken on or before the first dose date of study drug. In the case a subject did not receive study drug in the ITT population, the last assessment prior to study exit will be used as baseline.

Conversions for height and BMI are as follows:

- Height (m) = Height (cm) x 0.01
- Body mass index (kg/m^2) = Weight (kg) / [Height (m)]^2

Demographics and baseline characteristics will also be listed for the ITT set.

5.3. Medical ocular and non-ocular History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 23.1. Summaries will be presented by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages by treatment group and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

All ocular history will be summarized by SOC and PT with counts and percentages by treatment group and overall. The summaries will be produced separately for the study eye and the fellow eye. Any ocular condition associated with both eyes will be included in both summaries. Data listings of medical history and ocular history will be provided for the ITT set.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version WHO Drug Global B3-format March 2021. Non-ocular medications will be presented for the ITT set by anatomical therapeutic class (ATC) level 2 (therapeutic main group) and preferred term with counts and percentages by treatment group and overall. A subject who took more than one medication will be counted only once if these medications belong to the same extended ATC classification. In addition, prior and concomitant ocular medications used in study eye will be summarized. Similar summaries will be provided for the ocular medications used in the fellow eye. Any ophthalmological medications (ATC2 = 'Ophthalmologicals') that are not assigned to an eye will be presented under both eyes in the ocular medications tables and will not be presented in the non-ocular medications tables.

Prior medications will be defined as those medications taken prior to the administration of study drug on Day 1. Concomitant medications will be defined as those medications taken following the first administration of study drug on Day 1. Hence medications started before study dosing and continuing into the treatment period are considered as both prior and concomitant medications.

Separate tables will be provided for prior and concomitant medications, respectively. A data listing of prior and concomitant medications, for both ocular and non-ocular medications will be provided for the ITT set.

5.5. Concomitant Procedures

Concomitant procedures will be coded using MedDRA version 23.1. Non-ocular procedures will be presented for the ITT set by preferred term with counts and percentages by treatment group and overall. A subject who had more than one procedure will be counted only once in the summary. In addition, concomitant ocular procedures in study eye will be summarized. Similar summaries will be provided for the ocular procedures used in the fellow eye.

Concomitant procedures will be defined as those procedures taken following the first administration of study drug on Day 1.

A data listing of all procedures, for both non-ocular and ocular procedures will be provided for the ITT set.

5.6. Exposure to Investigational Product

Exposure to the investigational product will be summarized for the ITT, mITT, and Safety sets. All analyses will be repeated for the first 12 months at both the Month 12 and final reporting as well as the full 24 months for the final reporting.

For the analysis of exposure data for the first 12 months, exposure data prior to the Month 12 visit will be summarized (i.e., the Month 12 injection will not be included in the summaries). For analyses of the full 24 months, all data will be summarized.

Injections in the fellow eye will be considered in the calculation of the duration of treatment but will otherwise be considered as a missed injection in the study eye for all other measures of exposure.

The total number of injections and total number of missed injections received in each treatment group will be summarized by treatment group to support per-injection based TEAE rates.

The following categories for reason for missed injections will be summarized by treatment group using frequency counts and percentages based on the total number of missed injections: COVID-19 (with a breakdown of COVID-19 reasons as collected in the electronic case report form (eCRF)) vs. non-COVID-19 reasons (any reasons other than eCRF documented COVID-19 reasons). The total number of injections per subject will be summarized by treatment group both as a continuous summary and as a frequency and percent summary. In addition, the following categories of the total number of injections per subject will be summarized by treatment group using frequency counts and percentages:

- First 12 months summaries
    - Monthly: 1-3, 4-6, 7-9, 10-12
    - EOM: 1-2, 3-5, 5-6
- Full 24 months summaries
    - Monthly: 1-3, 4-6, 7-9, 10-12, 13-15, 16-18, 19-21, 22-24
    - EOM: 1-2, 3-5, 5-6, 7-8, 9-10, 11-12

The number of subjects who received at least 75% of the planned injections for the study period (first 12 months or full 24 months) will be presented. For the first 12 months, subjects will be considered to have received 75% of the planned injections if they received at least 9 (out of 12) injections for the Monthly group or 5 at least (out of 6) injections for the EOM group. For the full 24 months, subjects will be considered to have received 75% of the planned injections if they received at least 18 (out of 24) injections for the Monthly group or at least 9 (out of 12) injections for the EOM group.

The number of subjects missing at least one injection will be summarized by treatment group. The number of missed injections per subject as well as well as a breakdown of the number of missed injections per subject due to COVID-19 reasons and due to non-COVID-19 reasons will be summarized by frequency and counts. Additionally, for the missed injections due to COVID-19, the subjects will be summarized by their maximum drug holiday in the following categories:

- No Consecutive Injections (Subjects who are missing an injection due to COVID-19 but not at 2 injection visits in a row)
- 2 Consecutive Injections
- 3 Consecutive Injections
- 4 or More Consecutive Injections

The number of missed injections is defined as the scheduled injections missed up to completion or discontinuation of study treatment.

Additionally, the duration of treatment and compliance will be summarized by treatment group.

Duration of treatment will be defined as

- Monthly group: (date of last injection +30) – date of first injection +1
- EOM group: (date of last injection +60) – date of first injection +1

The duration of treatment will be truncated to a subject's early termination date, month 12 cutoff date, or study completion date as appropriate.

Compliance (%) is defined as the number of injections administered divided by the number of scheduled injections up to completion or discontinuation of study treatment × 100. Compliance will be summarized in the following groups: <75%, ≥75% to <100%, 100%, and >100%.

The number of subjects with scheduled IVT injection visits as well as the number of subjects receiving injections at each of the Months (1-24) will also be summarized by treatment group using frequency counts and percentages. For the EOM group, any injections given on the odd-numbered months will be presented as an unscheduled injection. In addition, to assess the impact of the COVID-19 pandemic on study drug exposure, the following summary will be provided by study visit:

- Number of missed IVT injection visits for study drug
- Number of missed IVT injection visits for study drug due to COVID-19 pandemic reasons
- Number of missed IVT injection visits for study drug due to non-COVID-19 pandemic reasons

Study drug administration will be listed by treatment group. In addition, a listing of total number of injections, duration of treatment, date and day of first and last dose and number of missed injections will be provided for the ITT set.

5.7. Protocol Deviations

Major and minor PDVs will be assessed by sponsor personnel following Protocol Deviation Management Plan.

A PDV is classified as major if there is the potential to significantly impact the completeness, accuracy, and/or reliability of the study data, or affect a subject's rights, safety, or well-being. All PDVs will be identified and finalized prior to the analysis of the first 12 months as well as the analysis of the full 24 month and documented.

In addition, a major PDV will be derived for any subjects who did not have a valid GA lesion area assessment for either Month 10 or 12 and who had not discontinued treatment prior to Month 12. The category for this deviation will be "Study Conduct/Procedures", the subcategory will be "Study Assessment", and the study specific category will be "No valid GA lesion area assessment for either Month 10 or Month 12".

PDVs will be presented for the ITT set by deviation category, subcategory, and study specific category with counts and percentages by treatment group and overall. In addition, similar summaries will be provided for major PDVs as well as for PDVs due to the COVID-19 pandemic.

All PDVs will be listed for the ITT set.

6. EFFICACY ANALYSES

Efficacy analysis including primary, key secondary, secondary, and exploratory analysis will be performed primarily using the mITT set, with subjects grouped according to the treatment assigned at randomization. Available data from all randomized subjects regardless of adherence to the protocol will be included in the efficacy analyses; this includes data from subjects who discontinued study drug early but continued with study assessments. All efficacy data will be listed for the ITT set.

Unless otherwise noted, hypothesis testing and estimation of treatment effects will be performed with a mixed effect model for repeated measure (MMRM) that includes data from all three treatment arms (PM, PEOM, and Sham). The Sham arm will represent the pool of the two sham treatment groups: SM and SEOM (i.e., the two sham arms will be pooled into a single "control" group). All hypothesis tests for efficacy endpoints will be two-sided.

Unless otherwise noted, analysis of efficacy endpoints (primary, key secondary, secondary, and exploratory) in the overall population will be adjusted for the following randomization stratification factors (actual status) and baseline covariates:

For primary efficacy endpoint

- Presence of CNV in the fellow eye (yes; no)
- Baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2)

For key secondary, secondary, and exploratory endpoints

- Presence of CNV in the fellow eye (yes; no)
- Baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2)
- Baseline value of the endpoint

Of note, the randomization stratification factors were assessed at the screening visit. In the event of a change in status in the GA lesion area between the screening visit and the baseline visit (i.e., GA lesion area < 7.5 mm^2 at screening to ≥ 7.5 mm^2) then the baseline status will be used.

If a statistical model is not directly specified and if necessary, data will be analyzed with the following approaches:

- For continuous endpoints, the MMRM analysis described for the primary endpoint in Section 6.2.2.
- For categorical or ordinal variables, a Cochran Mantel Haenszel (CMH) test with the baseline category status, presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as stratification factors.

6.1. Estimands

The primary scientific research question of this study is 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 principal.

The primary estimand in the study is defined through the following 5 attributes:

- **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.
- **Strategy for addressing intercurrent events:** See description of intercurrent events below.
- **Population-level summary:** Difference in mean change of GA lesion from baseline to Month 12 between pegcetacoplan and sham groups according to MMRM analysis.

The intercurrent events that will be considered are:

- Treatment discontinuation
- Lost to follow up
- Withdrawal from the study

The intercurrent events will be handled with a treatment policy strategy whereby any measured value will be used as is. Missing data resulting from these intercurrent events will be handled implicitly within the MMRM analysis that assumes missing at random.

The key secondary estimands will be defined and analyzed in the similar fashion as the primary estimand. The primary and key secondary estimands are summarized in Table 2.

Table 2: Estimands of Study

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The effect of pegcetacoplan compared to sham at Month 12 in impact on GA progression	**Main Analyses**			
		mITT	Change in the total area of GA lesions from baseline measured by FAF to Month 12	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change of GA lesion from baseline at Month 12 between pegcetacoplan and sham groups based on MMRM analysis
Key Secondary #1	The effects of pegcetacoplan compared to sham at Month 24 in impact on monocular maximum reading speed	mITT	Change in monocular maximum reading speed from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change in monocular maximum reading speed from baseline at Month 24 between pegcetacoplan and Sham groups based on MMRM analysis
Key Secondary #2	The effects of pegcetacoplan compared to Sham at Month 24 in impact on mean FRI Index score	mITT	Change in mean FRI Index score from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change in mean FRI Index score, from baseline at Month 24 between pegcetacoplan and sham groups based on MMRM analysis
Key Secondary #3	The effects of pegcetacoplan compared to Sham at Month 24 in impact on NL-BCVA score	mITT	Change in NL-BCVA score from baseline to Month 24	• Treatment policy strategy for subjects who discontinue treatment, are lost to follow-up, or withdraw from the study	Difference in mean change of NL-BCVA score from baseline at Month 24 between pegcetacoplan and sham groups based on MMRM analysis

6.2. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF.

The hypotheses of interest and Type I error management for analyses of the primary endpoint are specified below and take precedence over that specified in the study protocol.

For the primary efficacy endpoint, sensitivity analyses (Section 6.2.3), supplementary analyses (Section 6.2.4), and subgroup analyses (Section 6.2.5) will be performed.

All analyses of the first 12 months will be performed at the Month 12 reporting as well as repeated at the final reporting. Unless otherwise specified, at the time of the final reporting, all analyses will be repeated using the data for the full 24 months.

6.2.1. Type I Error Management

The null hypotheses for the primary efficacy endpoint are the following:

- H_{1a}: There is no difference between PM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set.
- H_{1b}: There is no difference between PEOM and Sham in mean change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on FAF for the mITT set.

For hypothesis testing of the primary efficacy endpoint, type I error will be controlled using a fixed sequencing approach by testing the two hypotheses (H_{1a} and H_{1b}) sequentially, beginning with H_{1b}. All hypothesis tests for the primary endpoint will be based on a two-sided alpha level of 0.05. The alpha will be adjusted in accordance with the protocol for the number of Data Monitoring Committee (DMC) unmasked reviews prior to the Month 12 analysis timepoint (i.e., 4 DMC unmasked reviews prior to Month 12: 2-sided alpha level = 0.0496). Testing for statistical significance proceeds to H_{1b} only if H_{1a} is statistically significant. The study will be considered positive if the first hypothesis (H_{1a}) is rejected.

6.2.2. Main Analysis of Primary Efficacy Endpoint

The primary endpoint will be analyzed in the mITT population with subjects grouped according to the treatment assigned at randomization.

A MMRM model will be used to analyze the primary endpoint. The analysis model will include treatment (PM, PEOM, sham), presence of choroidal neovascularization in the fellow eye at baseline (Yes, No) and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects, time (study month, categorical) as a factor, the time × treatment interaction term, and the baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) × time interaction term. The least square [LS] mean change from baseline to Month 12 will be estimated from the model for each of three arms as well as the comparisons of each of the three arms to each other. For other time points of interest, LS mean change from baseline will be estimated and compared between treatments. For each estimated LS mean, the corresponding 95% CI will be presented based on the model. For the comparison of the LSmeans, the corresponding 95% CI and the 2-sided P-value along with the percentage difference (difference in LS means between the arms/the comparison group LS mean) will be

presented. A common unstructured covariance matrix will be used to model the within-subject errors, the sandwich estimator (Diggle, Liang, and Zeger 1994) will be used to estimate the standard errors of the fixed effects parameters, and the degrees of freedom will be partitioned into between-subject and within-subject portions. If there are convergence problems with the model, then a heterogeneous autoregressive (1) covariance matrix will be used. If convergence problems still exist, an autoregressive (1) covariance matrix will be used. The LS mean of the change from baseline in the total area of GA lesion(s) ± the standard error will be plotted over time by treatment group.

The observed values for the total area of GA lesion(s) will be summarized by treatment group and visit for both the study and the fellow eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data by visit.

The mean change from baseline in the total area of GA lesion (s) in the study eye ± the standard error will be plotted over time by treatment group.

All GA lesion (s) size data will be listed for the ITT set.

6.2.3. Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis results. Analyses will be performed for the overall population based on the outcome of the primary analyses including all subjects in the mITT set.

6.2.3.1. Missing Data Analyses Based on Multiple Imputation

The following sensitivity analysis based on multiple imputation will be performed, as appropriate, using the same statistical approach as the one used in the primary analysis:

- Subjects with treatment discontinuation or study withdrawal assessed as potentially related to study drug or lack of efficacy will have missing data after the discontinuation or withdrawal imputed via a control-based imputation based on the sham control subjects. This will be based on the mITT set.
    - Subjects who discontinue the treatment or study due to reasons that are potentially related to study drug or lack of efficacy include
        - Subjects who discontinue due to ocular adverse event, adverse event related to treatment, or adverse event related to injection procedure
        - Subjects who withdraw consent due to lack of efficacy (specify field includes ‘Lack of efficacy’) or not otherwise specified as not related to efficacy (specify field includes “Not specified”)
- Subjects with a monotone missing data pattern due to treatment discontinuation or study withdrawal will have missing data after the last assessment explicitly imputed by multiple imputation using a tipping point analysis method assuming missing not at random (MNAR). This will be based on the mITT set.

Imputation for the non-monotone missing pattern (i.e., arbitrary missing pattern) will be performed prior to the multiple imputation for the monotone missing pattern (i.e., where a missing GA area measurement at a visit for a subject implies that GA area measurements at all subsequent visits for that subject are missing).

For the nonmonotone missing pattern, missing value(s) between two visits with measured GA area will be imputed using the monotone data MCMC method, which was first proposed by Li (1988) and Liu (1993) described the algorithm. Multiple imputation will then be carried out for monotone missing pattern.

The two imputation methods will be implemented in SAS using the three standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step. Details are illustrated with SAS codes in Section 1.2.2.

- The missing data are filled in 1000 times to generate 1000 complete datasets.
- The 1000 complete datasets are analyzed by using the same approach as for the analysis for the primary objective.
- The results from the 1000 complete datasets are combined for the inference.

Methods used in the imputation step are described below.

- Pattern Mixture Model Method (a copy-reference approach): The pattern mixture model method will be implemented.
    - Subjects with monotone missing data in the pooled sham arm will have missing data imputed based on the observed values in the pooled sham arm.
    - For the active treatment arms, subjects with monotone missing data who discontinued treatment or withdrew from the study due to reasons that are potentially related to study drug or lack of efficacy will have missing data imputed based on the pooled sham arm.
    - For the active treatment arms, subjects with monotone missing data who did not discontinue treatment or withdraw from the study due to reasons that are potentially related to study drug or lack of efficacy will have missing data imputed based on the observed values in the corresponding treatment arm.
- Tipping Point Analysis Method (a delta-adjusted approach): The tipping point analysis method will be implemented for each active treatment arm under the MNAR assumption by searching for a tipping point that reverses the conclusion regarding positive treatment effect. For the pooled sham arm, subjects will have missing data imputed based on the observed values in the pooled sham arm. For the active treatments, subjects with monotone missing data without treatment discontinuation or early withdrawal will have missing data imputed based on the observed values in the corresponding treatment arm. For the active treatment arms, subjects with monotone missing data due to treatment discontinuation or early withdrawal will have the missing data imputed based on the available values (observed values plus values imputed for non-monotone missing data) in the same treatment arm with a shift parameter added to the imputed values. Multiple imputation will be implemented on the differences between two consecutive visits, with the shift parameter allocated to

the missing data point(s) proportionally across timepoints. (e.g., For a shift parameter of 0.48 mm^2 at Month 12, incremental shifts of 0.08 mm^2 would apply to Month 2, Month 4, … and Month 12, respectively. 0.08 mm^2 x 6 visits = 0.48 mm^2) The range of the shift parameters will be from 0.06 mm^2 to 0.72 mm^2 by increments of 0.06 mm^2 for Month 12 and 0.12 mm^2 to 1.44 mm^2 for Month 24 for the difference in the change of GA area from baseline between each pegcetacoplan arm (PM or PEOM) and Sham arm. The precision of the tipping point will be at two decimal points. A tipping point may not exist within reasonable clinical assumptions.

For each analysis, the number and percent of subjects without monotone missing data, the number of subjects with monotone missing data and a breakdown of reasons will be reported. The reasons will include monotone missing without treatment discontinuation or early withdrawal, monotone missing due to treatment discontinuation or early withdrawal due to reasons that are potentially related to study drug or lack of efficacy, and monotone missing due to treatment discontinuation or early withdrawal not due to reasons that are potentially related to study drug or lack of efficacy.

6.2.3.2. Other Sensitivity Analyses

The primary endpoint will also be analyzed without pooling the two sham arms (SM and SEOM). The comparison for pegcetacoplan and sham injection within each dose schedule (i.e., PM vs SM and PEOM vs SEOM, respectively) will be conducted using the MMRM analyses described in Section 6.2.2.

The primary endpoint will also be summarized excluding GA total area assessments with an indeterminate boundary. The summary and presentation of the observed values for the total area of GA lesion(s) by treatment group and visit described in Section 6.2.2 will be repeated. The summary and presentation of the analysis results for all timepoints described in Section 6.2.2 will be repeated.

6.2.4. Supplemental Analyses of the Primary Efficacy Endpoint

6.2.4.1. COVID-19 Adjusted Estimand

Despite the occurrence of the COVID-19 pandemic, the scientific question of interest in this study remains unchanged. The primary scientific research question of this study is to assess the effect of pegcetacoplan compared with that of sham at Month 12 on GA lesion progression under-real life conditions without COVID-19 pandemic impact.

To manage the increase in missed/not received injections due to COVID-19 pandemic (as collected on the eCRF), i.e., undertreatment with an expected relevant impact on efficacy, the hypothetical strategy will be used whereby assessments after the intercurrent event (relevant undertreatment) occurs will be set to missing/censored in the analysis. The threshold for missed/not received injections due to the COVID-19 pandemic is missing a pre-specified number of scheduled injections prior to the analysis timepoint of interest. For the Monthly schedule group, this is missing 2 or more injections and for the EOM schedule group, this is missing 1 or more injections prior to the Month 12 visit attributable due to the COVID-19 pandemic.

In terms of the underlying cause of the excessive missing/not received injections and subsequent missing data, it is assumed that the missingness resulting from censoring occurs at random because of the ongoing pandemic and not because of the subjects' unobserved outcome, so

missing data resulting from this intercurrent event in the primary analysis model will be handled implicitly in the MMRM analysis.

The number of subjects with any censoring included in the model, the number of subjects with any censoring not included in the model, and the number of assessments censored by visit will be presented for each treatment group.

All summaries and presentations of the observed values for the total area of GA lesion(s) in the study eye by treatment group and visit described in Section 6.2.2 will be repeated for the COVID-19 adjusted estimand. All summaries and presentations of the analysis results for all timepoints described in Section 6.2.2 will be repeated for the COVID-19 adjusted estimand. The same plots as for the primary endpoint analysis will be presented.

In addition, a supplemental analysis will also be performed where the threshold for missed/not received injections will be restricted to external events attributable to COVID-19. These events are defined based on the COVID-19 collection form and include COVID-19 diagnosis, COVID-19 Suspected, Site Closure, Travel Ban, Shelter in Place, City Lockdown, and Other. Except for the plots, the analyses described above will be repeated for the threshold based only on these external events attributable to COVID-19.

6.2.4.2. Per Protocol Set

The main analysis described in Section 6.2.2 will be repeated using the Month 12 PP set to investigate the impact of changing the population in the estimand. Any GA lesion area assessments that are deemed not valid according to what is described in Section 4.5 will be set to missing in this analysis. The summary and presentation of the observed values for the total area of GA lesion(s) by treatment group and visit described in Section 6.2.2 will be repeated. The summary and presentation of the analysis results for all timepoints described in Section 6.2.2 will be repeated.

6.2.4.3. Rate of Change Analyses

The mean rate of change in GA area (i.e., slope) will be compared between each pegcetacoplan arm and the pooled sham arm by use of linear mixed effects model assuming time as continuous and linear ("slope model"). The analysis model will include treatment (PM, PEOM, sham), presence of choroidal neovascularization in the fellow eye at baseline (Yes, No), baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects, time (study month, continuous assuming linearity), the time × treatment interaction term as well as the baseline GA lesion area × time interaction term. The response variable will be the GA lesion area. A common unstructured covariance matrix will be used to model the within-subject errors, the sandwich estimator will be used to estimate the standard errors of the fixed effects parameters, and the degrees of freedom will be partitioned into between-subject and within-subject portions. If there are convergence problems with the model, then a heterogeneous autoregressive (1) covariance matrix will be used. If convergence problems still exist, an autoregressive (1) covariance matrix will be used. The mean rate of change (slope), standard error, and confidence interval will be estimated for the baseline to Month 12 as well as the baseline to Month 6 and Month 6 to Month 12 periods for each treatment group. In addition, the estimated difference in slopes among the treatment groups along with the 95% CIs and p-value will be reported. The slopes and 95% CIs will be converted to an annualized rate of growth for each period and each treatment group.

The observed values for the total area of GA lesion(s) will be summarized by treatment group and visit for the baseline to Month 6 and Month 6 to Month 12 time periods. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline to Month 6 and change from Month 6 to Month 12 data. In addition, the annualized rate of growth for each time period will also be presented.

The mean rate of change in GA area will be compared between each pegcetacoplan arm and the pooled sham arm by use of a piecewise linear mixed effect model assuming time as continuous and piecewise linear ("piecewise slope model"). The analysis to be performed will be similar to what is described above in the "slope model" except that a knot at the Month 6 visit will be added which allows for the slope of lesion growth to differ between the two periods for each of the treatment groups. The same presentation as for the "slope model" will be prepared except for the Baseline to Month 12 slope. Additionally, an investigation of the impact of changing the knot to Month 2, 4, 8, 10 will be explored if necessary.

6.2.5. Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses will be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. Analyses will be performed for the primary efficacy endpoint (change from baseline in total area of GA lesion(s) in the study eye at Month 12) for each of the following subgroups (as appropriate per actual subgroup sample size, levels with low sample size may be pooled to allow for an analysis to be conducted):

- Age Group (<75 years, 75 to <85 years, ≥85 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, unknown)
  - Note: If most subjects (e.g., >90%) are of a single race, this analysis will not be conducted.
- Geographic Region (United States vs Rest of World)
- Subgroups indicative of disease severity at baseline
  - Study eye baseline GA lesion size (<7.5 mm^2; ≥7.5 mm^2)
  - Study eye baseline GA lesion size categories (approximately tertiles based on APL2-303/304 combined data*)
  - Study eye baseline NL-BCVA categories (≥70, ≥60 - <70, ≥35 - <60, <35 ETDRS letters)
  - Study eye baseline NL-BCVA categories (<60 vs. ≥60 ETDRS letters)
  - Study eye baseline LL-BCVA categories (approximately tertiles based on APL2-303/304 combined data*)
  - Study eye baseline monocular maximum reading speed categories (approximately tertiles based on APL2-303/304 combined data*)
  - Baseline FRI Level (1,2,3,4)

- Subgroups associated with GA progression
  - Study eye baseline GA focality (multifocal, unifocal)
  - Study eye baseline GA lesion location (subfoveal involvement, without subfoveal involvement)
  - Baseline GA laterality (bilateral GA (with or without CNV in fellow eye) vs. Study eye GA Only)
  - Baseline CNV in fellow eye (Fellow eye CNV vs. No fellow eye CNV)
  - Study eye baseline LLD categories (<20 vs. ≥ 20 ETDRS letters)
  - Study eye baseline LLD categories (approximately tertiles based on the APL2-303/304 combined data*)
  - Study eye baseline NL-BCVA (<60 vs. ≥60 ETDRS letters) and LLD (<20 vs. ≥ 20 ETDRS letters) combinations

*Approximately tertiles will be specified consistently across the APL2-303/304 studies to the nearest clinically relevant level.

For the primary efficacy endpoint, the approach described in the Section 6.2.2 will be used for each subgroup analysis based on the data subset for the subject subgroup of interest. Baseline covariates included in the main analysis but no longer relevant given the subgroup of interest will be excluded from the model. The estimated treatment effects (PM vs. Sham; PEOM vs. Sham) and corresponding 95% CIs and p-values from the models will be displayed graphically for each pegcetacoplan treatment arm and each level of the subgroups specified (e.g., via forest plots).

6.2.6. Full 24 Month Analyses

In general, the same analysis approach for the changes from baseline GA lesion size for the final reporting of the full 24 months will be repeated as described in Sections 6.2.2, 6.2.3, 6.2.4, 6.2.5. Key differences include:

- The definition of excessive missed/not received injection in the supplementary estimand will be defined based on the Month 24 period. The threshold for missed/not received injections due to the COVID-19 pandemic is missing 4 or more injections for the Monthly schedule group and 2 or more injections for the EOM schedule group prior to the Month 24 visit attributable due to the COVID-19 pandemic.
- The Month 12 PP set will be replaced with the Month 24 PP set for the supplementary analysis.

6.2.7. Exploratory Endpoints Closely Related to the Primary Efficacy Endpoint

Analyses of the following endpoints closely related to the primary efficacy endpoint, will be performed for the mITT set to provide supplemental information.

6.2.7.1. Change in Square Root of GA Area

For each subject and timepoint, the square root of GA area will be calculated. The change from baseline in square root of GA area will be analyzed using the same methodology as described for the primary endpoint analysis in Section 6.2.2, except that change from baseline in the square root of GA area will be the response variable. This analysis will be conducted both for the first 12 months summaries as well as the full 24 months summaries.

6.2.7.2. Percent Change in GA Area and Square Root of GA Area

For each subject and timepoint, the percent change in GA area will be defined as the change from baseline in GA area (mm^2) divided by the GA area (mm^2) at baseline and the percent change in square root of GA area will be defined as the change from baseline in GA area (mm) divided by the GA area (mm) at baseline. The percent change in GA area from baseline and percent change in square root of GA area will be analyzed using the same methodology as described for the primary endpoint analysis in Section 6.2.2, except that percent change from baseline will be the response variable. This analysis will be conducted both for the first 12 months summaries as well as the full 24 months summaries.

6.3. Analyses of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are listed in Section 2.2.2. At the Month 12 reporting, all key secondary efficacy endpoints will be evaluated based on data from baseline to Month 12 (see Section 3.5). For the Month 12 analyses, post-baseline visits, up to and including Month 12, will be included and nominal p-values will be presented. At the time of the final study analysis, all key secondary efficacy endpoints will be evaluated based on data from baseline to Month 24, and formal statistical testing for key secondary endpoints will be performed as described in Section 6.3.1. Unless otherwise specified, all secondary efficacy endpoints will be analyzed for the mITT set.

6.3.1. Type I Error Management

The planned submission of pegcetacoplan in GA consists of 2 studies of very similar design (APL2-303 and APL2-304), each with multiple endpoints. It is planned to control the type I error rate for the primary endpoint hypotheses testing at the level of the individual studies (as described in Section 6.2.1), and at a level of the submission as a whole for the key secondary endpoints hypotheses testing based on pooling APL2-303 and APL2-304. Figure 2 presents the overall hypotheses testing strategy for the APL2-303 and APL2-304 studies.

The primary endpoint hypotheses in the PM vs. Sham and PEOM vs. Sham will be tested in a hierarchical order within a study. If both hypothesis tests for the primary endpoint in both studies are statistically significant, then hypotheses testing will be performed for the key secondary endpoints within the pooled APL2-303/APL2-304 data for hypotheses H_{2a} – H_{4b} and within the APL2-304 study for H_{5a} and H_{5b} at the presented α level. The key secondary efficacy endpoints hypotheses that will be tested in the pooled APL2-303/APL2-304 studies are below:

- H_{2a} There is no difference between PM and Sham regarding mean change from baseline in monocular maximum reading speed (study eye), as assessed by MNRead or Radner Reading Charts at Month 24.

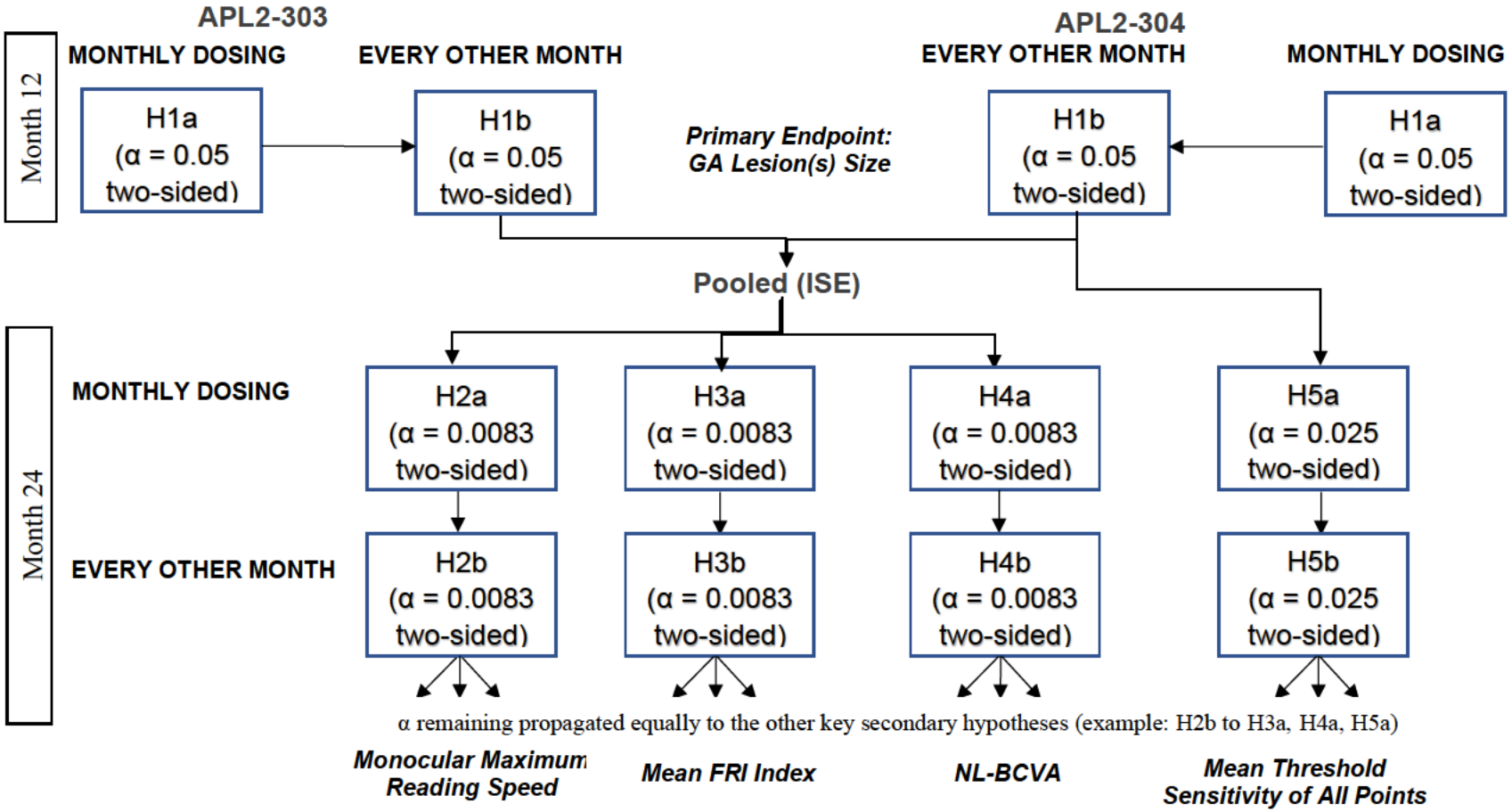
- H_{2b}: There is no difference between PEOM and Sham regarding mean change from baseline in monocular maximum reading speed (study eye), as assessed by MNRead or Radner Reading Charts at Month 24.
- H_{3a}: There is no difference between PM and Sham regarding mean change from baseline in mean FRI Index score at Month 24.
- H_{3b}: There is no difference between PEOM and Sham regarding mean change from baseline in mean FRI Index score at Month 24.
- H_{4a}: There is no difference between PM and Sham regarding mean change from baseline in NL-BCVA score at Month 24 (study eye) as assessed by ETDRS chart.
- H_{4b}: There is no difference between PEOM and Sham regarding mean change from baseline in NL-BCVA score at Month 24 (study eye) as assessed by ETDRS chart.

Hypothesis tests will be conducted in the order indicated by the arrows in Figure 2 and will continue as long as all preceding hypotheses are rejected at a given α level. If both the PM vs. Sham and the PEOM vs. Sham comparisons are statistically significant for a given key secondary endpoint, then the α will be allocated equally to the other key secondary hypotheses. At the study-level, the type I error rate (one-sided) is controlled at 0.025 for the primary endpoint hypotheses. In the submission, the type I error rate (one-sided) is controlled at 0.000625 (0.025^2) for the primary endpoint hypotheses and at 0.025 for the key secondary endpoint hypotheses. All hypothesis tests will be adjusted for the number of DMC unmasked reviews prior to the Month 12 analysis.

Type I error will be controlled by the testing procedure via the graphical methods approach (Bretz 2009). All confidence intervals and p-values will be presented without adjustments.

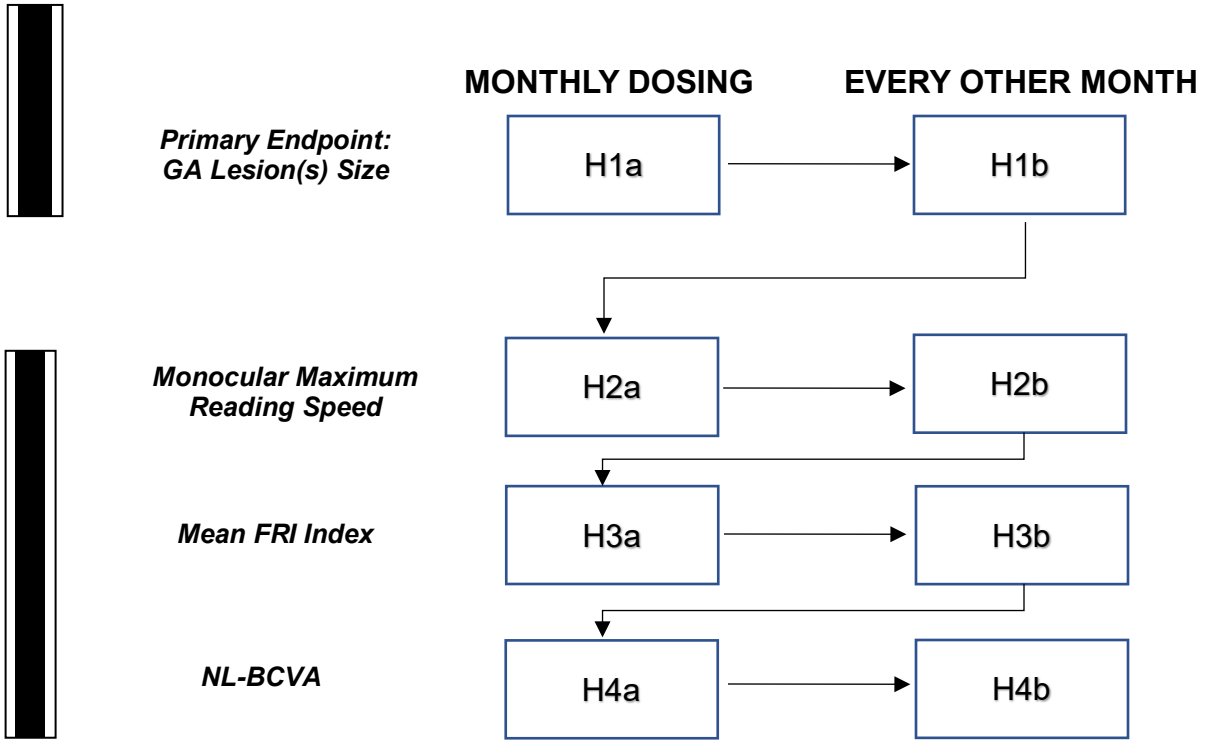
If at least one of the hypothesis tests for the primary endpoint in the APL2-304 study is not statistically significant but both hypothesis tests for the primary endpoint in the APL2-303 study are statistically significant, then any hypothesis testing for the key secondary endpoints will not be rejected at the submission level. Within the APL2-303 study, hypotheses testing for the key secondary endpoints will be tested as shown in Figure 3 and type I error will be controlled using a fixed sequencing approach. All hypotheses tests will be adjusted for the number of DMC unmasked reviews prior to the Month 12 analysis. All confidence intervals and p-values will be presented without adjustments.

Figure 2: APL2-303 and APL2-304 Hypothesis Testing and Type I Error Control



Endpoint data are compared to sham injections in hypotheses testing. Hypotheses can only be tested in sequential order as indicated by arrows. Sequential testing will continue as long as all preceding hypotheses can successfully be rejected at the given alpha level. At the study-level, the Type I error rate (one-sided) is controlled at 0.025 for the primary endpoint hypotheses. In the submission, the Type-I error rate (one-sided) is controlled at 0.000625 (0.025^2) for the primary endpoint hypotheses and at 0.025 for the key secondary endpoints.

Figure 3: APL2-303 Hypothesis Testing and Type I Error Control If There is No α Remaining in APL2-304 to Allow Pooling Secondary Functional Endpoints



Endpoint data are compared to sham injections in hypotheses testing. Hypotheses can only be tested in sequential order as indicated by arrows. Sequential testing will continue as long as all preceding hypotheses can successfully be rejected at the given alpha level. This testing tree will only be used when APL2-304 cannot pass α from the primary endpoint testing to the pooled secondary functional endpoint testing.

6.3.2. Main Analyses of Key Secondary Efficacy Endpoints

6.3.2.1. Monocular Maximum Reading Speed

Maximum reading speed will be calculated per MNRead or Radner user manuals, with no adjustment for reading inaccuracy. An additional step to cap resulting reading speed values at a maximum of 300 words per minute will be implemented. Values above 300 words per minute exceed values reported in the literature for adults with no vision impairment for MNRead (Calabrese et al. 2016) or Radner (Radner et al. 2002; Radner and Diendorfer 2014) assessments. Maximum reading speed will be calculated as the mean of the three highest nonzero reading speeds (or two, or one value, as available) (Baskaran et al. 2019; Patel et al. 2011), except when all words per minute are calculated as 0: then the maximum reading speed will be calculated as 0.

Monocular maximum reading speed in the study eye will be summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment (PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline monocular maximum reading speed as well as the chart type (MNRead or Radner) as covariates, time (in months) as a factor; the time × treatment interaction term as well as the baseline monocular maximum reading speed × time interaction term.

The observed values for the monocular maximum reading speed will be summarized by treatment group and visit for both the study and the fellow eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the monocular maximum reading speed of the study eye ± the standard error as well as the LS mean of the change from baseline in the monocular maximum reading speed of the study eye ± the standard error will be plotted over time by treatment group.

In addition, the categorical changes (improvements of ≥ 20 to <40, ≥ 40 to <60, ≥ 60 and minimal/no change (-20 to 20), worsening of ≥ 20 to <40, ≥ 40 to <60, ≥ 60) for the study eye will be summarized by treatment group and visit.

The shift from baseline in the monocular maximum reading speed for the study eye categories over time will be presented by treatment group for the following categories:

- < 40 wpm
- 40 to < 80 wpm
- 80 to <160 wpm
- ≥ 160 wpm

All monocular maximum reading speed data will be listed for the ITT set.

6.3.2.2. Mean FRI Index Score

The mean FRI Index score will be calculated per the scoring algorithm in the FRI Index user's manual.

The mean FRI Index score will be summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment

(PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline mean FRI Index score and baseline study eye status (Better-seeing Eye vs. Worse-seeing Eye) as covariates, time (in months) as a factor; the time × treatment interaction term as well as the baseline mean FRI Index score × time interaction term.

The observed values for the mean FRI Index score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the mean FRI Index score ± the standard error as well as the LS mean of the change from baseline in the mean FRI Index score ± the standard error will be plotted over time by treatment group.

In addition, the mean FRI Index score will be converted to the FRI Level variable, as per the user manual, ranging from 1 (Unable to do) to 4 (Totally independent). The categorical changes from baseline (improvements (an increase in FRI level), minimal/no change (no change in FRI level), and worsening (decrease in FRI level)) will be summarized by treatment group and visit.
The shift from baseline in the FRI level over time will be presented by treatment group.

All FRI data will be listed for the ITT set.

6.3.2.3. NL-BCVA Score

The mean NL-BCVA score for the study eye will be summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment (PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline NL-BCVA score as a covariate, time (in months) as a factor; the time × treatment interaction term as well as the baseline NL-BCVA score × time interaction term. Note, for the second year, only timepoints that were measured for all three treatment groups will be included in the model.

The observed values for the NL-BCVA will be summarized by treatment group and visit for both the study and the fellow eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the NL-BCVA score for the study eye ± the standard error as well as the LS mean of the change from baseline in the NL-BCVA score for the study eye ± the standard error will be plotted over time by treatment group.

In addition, the categorical changes (improvements of ≥15, ≥10 to <15, ≥5 to <10, and minimal/no change (-4 to 4), worsening of ≥5 to <10, and ≥10 to <15 and ≥15) for the study eye will be summarized by treatment group and visit.

The shift from baseline in the NL-BCVA of the study eye categories (≥70, ≥60 - <70, ≥35 - <60, ≥20 - <35, <20 ETDRS letters over time will be presented by treatment group and visit. The above-mentioned ETDRS letter thresholds are based on WHO definitions for vision impairment and blindness. WHO criteria were implemented in an attempt to capture the progressive nature of

Geographic Atrophy and the ultimate treatment goal of avoiding successive vision impairment and blindness through application of active treatment (Pegcetacoplan vs. Sham).[1]

The average NL-BCVA score over the last 3 months for each reporting period (Month 10 - Month 12 for the Month 12 reporting; Month 22 - Month 24 for the Month 24 reporting) will be calculated for each subject who has at least one NL-BCVA assessment in these windows. The observed values for the NL-BCVA and changes from baseline will be summarized by treatment group for the study eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

All NL-BCVA data will be listed for the ITT set.

6.3.3. Sensitivity Analyses of Key Secondary Efficacy Endpoints

The missing data analyses based on imputation described in Section 6.2.3.1 will be repeated for the key secondary efficacy endpoints at the time of the final study analysis for the full 24 months only. The key secondary endpoints will also be analyzed without pooling the two sham arms (SM and SEOM) for the full 24 months only.

In addition, to assess the potential effect of different assessment tools, the main analysis of monocular maximum reading speed will be repeated by reading chart type. Maximum reading speed with adjustment for reading inaccuracy will also be analyzed, only in the study eye, for the first 12 months as well as the full 24 months.

6.3.4. Supplementary Analyses of Key Secondary Efficacy Endpoints

The supplementary analyses described for the primary endpoint in Section 6.2.4.1 and Section 6.2.4.2 will also be performed for the key secondary endpoints for the first 12 months as well as the full 24 months.

6.3.5. Subgroup Analyses of Key Secondary Efficacy Endpoints

The subgroup analyses of the key secondary endpoints will be performed for the full 24 months. Select subgroup analyses of the key secondary endpoints may be performed at Month 12, if necessary, to support regulatory filings. The subgroups evaluated for key secondary endpoints will be the same as evaluated for the primary efficacy endpoint (see Section 6.2.5).

In addition, the following subgroup analyses will be performed:

<u>Monocular Maximum Reading Speed</u>

- Study eye baseline monocular maximum reading speed (<60, 60-<160, ≥160 wpm)

<u>Mean FRI Index score</u>

- Baseline Study Eye Status (Better-seeing Eye vs. Worse-seeing Eye)

For each endpoint, a MMRM similar to that specified for the main analysis of the key secondary endpoints (Section 6.3.2) will be used for each subgroup analysis based on the data subset for the subject subgroup of interest. Baseline covariates included in the main analysis but no longer

[1] approximated from 6/18; see https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1103667651

relevant given the subgroup of interest will be excluded from the model. The estimated treatment effects (PM vs. Sham or PEOM vs. Sham) and corresponding 95% CIs and p-values from the models will be displayed graphically for each pegcetacoplan arm and each level of the subgroups specified (e.g., via forest plots).

6.4. Analyses of Other Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 2.2.3. At the time of the Month 12 reporting, all secondary efficacy endpoints will be evaluated based on data from baseline to Month 12 (see Section 3.5). For the Month 12 analyses, post-baseline visits, up to and including Month 12, will be included. At the time of the final study analysis, all secondary efficacy endpoints will be evaluated based on data from baseline to Month 24. For the Month 24 analyses, post-baseline visits, up to and including Month 24, will be included.

Unless otherwise specified, all secondary efficacy endpoints will be analyzed for the mITT set.

6.4.1. Low Luminance Best-Corrected Visual Acuity (LL-BCVA)

LL-BCVA of the study eye will be summarized and analyzed in the similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment (PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline LL-BCVA score as a covariate, time (in months) as a factor; the time × treatment interaction term as well as the baseline LL-BCVA score × time interaction term. Note, for the second year, only timepoints that were measured for all three treatment groups will be included in the model.

The observed values for the LL-BCVA will be summarized by treatment group and visit for both the study and the fellow eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The mean change from baseline in the LL-BCVA score in the study eye ± the standard error as well as the LS mean of the change from baseline in the LL-BCVA score in the study eye ± the standard error will be plotted over time by treatment group.

The categorical changes (improvements of ≥15, ≥10 to <15, ≥5 to <10, and minimal/no change

(-4 to 4), worsening of ≥5 to <10, and ≥10 to <15 and ≥15) for the study eye will be summarized by treatment group and visit.

Additionally, the average LL-BCVA score over the last 3 months for each reporting period (Month 10 - Month 12 for the Month 12 reporting; Month 22 - Month 24 for the Month 24 reporting) will be calculated for each subject who has at least one LL-BCVA assessment in these windows. The observed values for the LL-BCVA and changes from baseline will be summarized by treatment group for the study eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The same subgroup analyses as described for NL-BCVA in Section 6.3.5 will also be repeated for LL-BCVA for the full 24 months.

All LL-BCVA data will be listed for the ITT set. In addition, the low luminance deficit will be calculated as the difference between NL-BCVA and LL-BCVA and listed for the ITT set.

6.4.2. Total Area of GA lesion(s) at Each Planned Assessment

The change from baseline at each planned assessment (other than Month 12 and Month 24) in the total area of GA lesion(s) in the study eye, as assessed by FAF, will be estimated from the MMRM analyses described in Section 6.2.2.

6.4.3. Monocular Critical Print Size

Critical print size will be calculated as the smallest print size which support reading speed at 80% of the maximum reading speed, without adjustment for reading inaccuracy (Baskaran et al. 2019).

Monocular critical print size of the study eye will be summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment (PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline monocular critical print size as well as the chart type (MNRead or Radner) as covariates, time (in months) as a factor; the time × treatment interaction term as well as the baseline monocular critical print size × time interaction term.

The observed values for the monocular critical print size will be summarized by treatment group and visit for both the study and the fellow eye. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

To assess the potential effect of different assessment tools, the analysis of monocular critical print size will be repeated by chart type.

All monocular critical print size data will be listed for the ITT set.

6.4.4. NEI VFQ-25 Distance Activity Subscale Score

NEI VFQ-25 distance activity subscale score will be calculated per the scoring algorithms in user's manual.

NEI VFQ-25 distance activity subscale score will be summarized and analyzed in a similar fashion as the primary efficacy endpoint using MMRM described in Section 6.2.2. The model will include treatment (PM, PEOM, Sham), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as fixed effects; baseline NEI VFQ-25 distance activity subscale score and baseline study eye status (Better-seeing Eye vs. Worse-seeing Eye) as covariates, time (in months) as a factor; as well as the time × treatment interaction term as well as the baseline NEI VFQ-25 distance activity subscale score × time interaction term.

The observed values for the NEI VFQ-25 distance activity subscale score will be summarized by treatment group and visit. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

The categorical changes (improvements of >5 units and minimal/no change (-5 to 5), worsening of a decrease of >5 units) will be summarized by treatment group and visit.

In addition, the shift from baseline in NEI VFQ-25 distance activity subscale score categories (>80, >65 - ≤80, >50 - ≤65, ≥35 - ≤50, <35) will be summarized by treatment group and visit.

All NEI VFQ-25 data will be listed for the ITT set.

6.5. Multiplicity Adjustment

No hypothesis testing of the (non-key) secondary endpoints will be performed. Control of Type I error for (non-key) secondary endpoints is not applicable.

6.6. Analyses of Exploratory Endpoints

The exploratory efficacy endpoints are listed in Section 2.2.4. At the time of Month 12 reporting, all exploratory efficacy endpoints will be evaluated based on data from baseline to Month 12 (see Section 3.5). For the Month 12 analyses, post-baseline visits, up to and including Month 12, will be included. At the time of the final study analysis, all exploratory efficacy endpoints will be evaluated based on data from baseline to Month 24. For the Month 24 analyses, post-baseline visits, up to and including Month 24, will be included.

Unless otherwise specified, all exploratory efficacy endpoints will be analyzed for the mITT set.

6.6.1. NEI VFQ-25 and NEI VFQ-39 Additional Analyses

Descriptive summary statistics for baseline, absolute values and change from baseline data will be provided by treatment group and visit for the following NEI VFQ-25 and NEI VFQ-39 scores:

- NEI VFQ-39 distance activity subscale
- NEI VFQ-25 composite score
- NEI VFQ-39 composite score
- NEI VFQ-25 near activity subscale score
- NEI VFQ-39 near activity subscale score
- NEI VFQ-25 driving subscale score (for subjects who are currently driving at baseline)

The shift from baseline in NEI VFQ score categories (>80, >65 - ≤80, >50 - ≤65, ≥35 - ≤50, <35) will be summarized by treatment group and visit for the scores described above.

In addition, the categorical changes (improvements of >5 units and minimal/no change (-5 to 5), worsening of a decrease of >5 units) will be summarized by treatment group and visit for the following NEI VFQ-25 Scores: Composite and Near Activity.

For the NEI VFQ-25 Driving subscale score, the number and percentage of subjects with a worsening driving outcome compared to baseline will be summarized by treatment group and visit. Each visit will display the number of patients who were driving at baseline with at least one of the worsening driving outcomes. The categories to determine worsening driving outcomes are: conversion to no longer currently driving, increase in difficulty driving in familiar places in daytime, increase in difficult driving at night or stopped doing this due to vision, increase in difficulty driving in difficult conditions or stopped doing this due to vision.

All NEI VFQ-25 data will be listed for the ITT set.

6.6.2. Binocular Maximum Reading Speed and Critical Print Size

Descriptive summary statistics for baseline, absolute values and change from baseline data will be provided by treatment group and visit for the binocular maximum reading speed and critical print size with no adjustment for reading inaccuracy. All binocular maximum reading speed and critical print size data will be listed for the ITT set.

Categorical changes over time and categorical shifts from baseline will be presented, as will be done for the monocular reading speed.

6.6.3. GA Lesion (s) Study Eye to Fellow Eye Comparisons

Descriptive summary statistics will be provided by treatment and visit for the change from baseline in total area of GA Lesion(s) for the study eye as well as for the fellow eye in subjects with bilateral GA with fellow eyes that satisfy the following characteristics at baseline:

- Absence of CNV in the medical history
- Baseline GA lesion size between 2.5 and 17.5 mm^2
- Presence of any pattern of hyperautofluorescence in the junctional zone of GA
- GA not confluent with any peripapillary atrophy

The change from baseline in total area of GA Lesion(s) ± the standard error in the study eye as well as the fellow eye will be plotted over time by treatment group for the subjects with bilateral GA with fellow eyes that satisfy the above characteristics.

6.6.4. Digital Reading Index and Visual Function Application

The digital reading index will only be analyzed at the Month 24 reporting while the digital visual functional application will be analyzed at both the Month 12 and Month 24 reporting.

Descriptive summary statistics for baseline, absolute values, and change from baseline data to Month 12 and Month 24 will be provided by treatment group for digital reading index.

Additionally, the average digital reading index score over the last 3 months for each reporting period (Month 10 - Month 12 for the Month 12 reporting; Month 22 - Month 24 for the Month 24 reporting) will be calculated for each subject who has at least one digital reading index assessment in these windows. The observed values for the digital reading index and changes from baseline will be summarized by treatment group. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

Descriptive summary statistics for baseline, absolute values and change from baseline data to Month 12 and Month 24 will be provided by treatment group for digital visual function.

Additionally, the average digital visual function score over the last 3 months for each reporting period (Month 10 - Month 12 for the Month 12 reporting; Month 22 - Month 24 for the Month 24 reporting) will be calculated for each subject who has at least one digital visual function assessment in these windows. The observed values for the digital visual function and changes from baseline will be summarized by treatment group. Summaries will present the descriptive statistics for baseline, absolute values and change from baseline data.

6.6.5. Genetic Polymorphisms

The genetic polymorphisms data will be analyzed and reported in a separate report and briefly summarized in the clinical study report (CSR). The genetic polymorphisms data will be listed for the genotyping set.

6.6.6. Dry AMD Analysis

Biomarkers of early and intermediate stage of AMD outside the GA area will also be evaluated in this study. The number and percentage of subjects with at least one lesion (up to 5) area in the study eye classified as iRORA will be summarized at baseline by treatment group in the mITT set. The number and percentage of subjects with a progression from iRORA to cRORA based on SD-OCT in the study eye will be summarized over time by treatment group. A CMH test with the number of baseline iRORA lesions (0, 1, 2, 3, 4, ≥ 5), presence of CNV in the fellow eye (yes or no), and baseline GA lesion area (< 7.5 mm^2 or ≥ 7.5 mm^2) as the stratification factors will be presented for each post-baseline visit. If necessary due to sparse cells, an unadjusted analysis may be performed. In addition, the percentage of baseline lesions with a progression will also be presented over time by treatment group.

The above summary and analysis will also be repeated in those subjects with at least one lesion in the study eye classified as large drusen at baseline and whether these progressed to iRORA or cRORA in the study eye. Large drusen is defined as a drusen that is greater than or equal to 40 microns in height on SD-OCT.

This analysis will not be conducted at the Month 12 reporting and will only be conducted for the final study reporting.

All dry AMD data will be listed for the ITT set.

6.6.7. Analyses of Other Ophthalmology Efficacy Imaging Data

In addition to the GA lesion(s) size data from the FAF, analysis of additional efficacy parameters will be performed from this imaging instrument for the mITT set. The following summaries will be performed separately by study eye and by fellow eye and will be presented by treatment group.

- Descriptive summary statistics for baseline, absolute values and change from baseline data for the distance of GA lesion from atrophy junction to the fovea in study eyes with non-subfoveal involvement of the GA lesion at baseline (assessed from FAF). For the fellow eye, this will be presented for fellow-eyes with non-subfoveal involvement of the GA lesion at baseline. Non-subfoveal involvement is defined as distance of the atrophy junction to the fovea > 0.
- Conversion from non-subfoveal involvement to subfoveal involvement of the GA lesion at each visit (assessed from FAF). This will include only study eyes with non-subfoveal involvement for GA lesions at baseline. For the fellow eye, this should be presented for fellow eyes with non-subfoveal involvement at baseline. This will be presented as a cumulative incidence at each scheduled visit.

All FAF data will be listed for the ITT set.

7. SAFETY ANALYSES

Safety analyses will be performed using the Safety set. Safety variables include adverse events (AEs), deaths, clinical laboratory results, vital signs, incidence of ADA against pegcetacoplan, ocular assessments (e.g., NL-BCVA, IOP and ophthalmic examinations), and ocular imaging.

At the time of the Month 12 reporting, safety summaries will be produced based on the complete Month 12 data. At the time of the final study reporting, safety summaries will be produced based on cumulative data.

For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable. Last Observed Value (LOV) will be defined as the last valid assessment obtained after baseline. The LOV will be presented for the Month 12 reporting as well as the final study reporting.

All safety analyses will be conducted according to the actual treatment the subject received. Unless otherwise specified, all safety summaries will be performed on the Safety set.

7.1. Adverse Events

AEs will be coded using the MedDRA version 23.1 and summarized separately for those occurred in the study eye, those in the fellow eye, and the non-ocular events.

An AE will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product but increases in severity on or after the date of the first dose of investigational product.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with:

- Any TEAEs
- TEAEs related to study drug (evaluated by the investigator as definitely related, possibly related)
- TEAEs related to study drug injection procedure
- All TEAEs by maximum severity
- Serious TEAEs
- Serious TEAEs related to study drug (evaluated by the investigator as definitely related, possibly related)
- Serious TEAEs related to study drug injection procedure
- Serious TEAEs by maximum severity
- TEAEs leading to interruption of study treatment
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to study discontinuation
- TEAEs leading to death

This overall summary will also include the total number of TEAEs reported. This overall summary will also be summarized separately for those occurred in the study eye, those in the fellow eye, and the non-ocular events.

The number and percentage of subjects reporting TEAEs in each treatment group and overall will be tabulated by SOC and PT for all of the categories in the list above. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

Endophthalmitis and intraocular inflammation ocular TEAEs will be presented by PT for study eye and fellow eye.

Endophthalmitis and intraocular inflammation ocular TEAEs in the study eye will also be presented on a per-injection basis (i.e., number of events/total number of injections given).

All SOC and PT summaries will be ordered alphabetically by SOC and within SOC, by descending order of the total number of subjects in the PM, PEOM, and Sham groups combined.

Non-ocular AEs, ocular AEs in the study eye, and ocular AEs in the fellow eye will be listed separately. This presentation will be repeated for serious AEs. Additionally, separate listings for deaths, AEs leading to discontinuation of study, AEs leading to discontinuation of study drug, and AEs due to COVID-19 will also be generated.

7.1.1. TEAEs of New Onset Exudative AMD

For subjects who experience a TEAE of "Choroidal neovascularization" or "Neovascular AMD" ("Exudative AMD TEAE"), the following summaries will be performed:

- The overall summary table described in Section 7.1 will be repeated replacing "TEAEs" with "Exudative AMD TEAEs". This will be reported for the study eye.
- The incidence of Exudative AMD TEAEs in the study eye will be presented by treatment group and overall. In addition, the analysis will be repeated by fellow eye CNV status at baseline and study eye DLS on SD-OCT at baseline. A similar analysis will be repeated for the Exudative AMD TEAEs in the fellow eye with an additional analysis by fellow eye DLS on SD-OCT at baseline. Subjects with a medical history of CNV in the corresponding eye will be excluded from the analysis.
- The incidence and rate per 100 subject-years of Exudative AMD TEAEs in the study and fellow eye as well as a summary (for study and fellow eye) and Kaplan Meier plot for the time to development of Exudative AMD TEAEs in the study eye will be presented by treatment group and overall. Subjects with a medical history of CNV in the corresponding eye will be excluded from the analysis.
- In addition, the characteristics of the Exudative AMD TEAEs in the study eye will be presented at baseline, study visit preceding exudation, study visit at exudation and at Month 12 (or Month 24 if the final analysis) for characteristics based on SD-OCT and baseline, study visit at exudation and at Month 12 (or Month 24 if the final analysis) for characteristics based on Fluorescein Angiography (FA). The following characteristics will be presented by treatment group and overall:

- Presence of cystoid spaces on SD-OCT
- Central (center point) retinal thickness on SD-OCT
- Central subfield thickness on SD-OCT
- Presence of CNV on FA.
- CNV type on FA
- Presence of subretinal fluid on SD-OCT

- A summary of concomitant anti-VEGF therapy for new exudative AMD in the study eye will be provided by treatment group and overall. This summary will include the total number of subjects that received any anti-VEGF for new exudative AMD as well as the average number of injections per month post exudative AMD. There will also be a breakdown by preferred term of ranibizumab or aflibercept and the average number of injections per month for each term. Subjects will be presented by the number of injections received for that medication.
- BCVA scores at the baseline visit, study visit preceding exudation, the study visit at the exudation, and at Month 12 (or Month 24 if the final analysis) will be presented for all subjects with an Exudative AMD TEAE in the study eye by treatment group and overall. In addition, the change in BCVA scores from baseline, the visit prior to the exudation, and the exudation visit will be presented where appropriate.

A listing of Exudative AMD TEAEs and baseline characteristics including fellow eye CNV status, study eye double layer sign and study eye MNV presence, a listing of the characteristics of the new Exudative AMD TEAEs, anti-VEGF exposure, and the BCVA values for subjects with the new Exudative AMD TEAEs will be provided.

7.2. Clinical Laboratory Data

All laboratory parameters collected at each center's local laboratory will be normalized by converting values in original units to values in SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization.

Observed and change from baseline clinical laboratory data (hematology, chemistry and urinalysis) will be summarized by treatment group and protocol specified time points for the following clinical laboratory variables.

Hematology	Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell count (WBC)– total and differential.
Biochemistry	Aspartate transaminase, alanine transaminase, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), bilirubin (total, direct and indirect), creatinine, creatine kinase, glucose, and albumin.
Urinalysis	Glucose, specific gravity, blood, ketones, protein, bilirubin, pH, urobilinogen, leukocyte esterase, and nitrite.

Clinical laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 3. The number and percentage of subjects with baseline and/or post-baseline PCS values will be tabulated by treatment group and overall.
The percentages will be calculated relative to the number of subjects with available values for

each lab parameter in each treatment group at the analysis visit. The numerator is the total number of subjects with at least 1 PCS value at the analysis visit. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline values.

Table 3: Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/L	<25 g/L	
Alanine Aminotransferase (ALT)	U/L		≥3*ULN
Alkaline Phosphatase (ALP)	U/L		≥3*ULN
Aspartate Aminotransferase (AST)	U/L		≥3*ULN
Bilirubin, Direct	umol/L		>1.5*ULN
Bilirubin, Total	umol/L		>1.5*ULN
Bicarbonate	mmol/L	<LLN	
Blood Urea nitrogen	mmol/L		>2.5*ULN
Chloride	mmol/L	<90 mmol/L	>115mmol/L
Creatinine	umol/L		≥178.8 umol/L
Creatine kinases	U/L		≥3*ULN
Glucose	mmol/L	<3.05 mmol/L	≥8.88 mmol/L
Potassium	mmol/L	<3.5 mmol/L	>5.5 mmol/L
Sodium	mmol/L	<130 mmol/L	>150 mmol/L
Hematology			
Hemoglobin	g/L	<0.9*LLN	
Hematocrit	%	<0.9*LLN	
Platelet Count	10^9/L	<LLN	
Urinalysis			
Specific Gravity		<0.9*LLN	>1.1*ULN
pH		<LLN	
Protein			>2+
Glucose			>1+
Blood			>2+

LLN: Lower limit of normal value provided by the laboratory
ULN: Upper limit of normal value provided by the laboratory

Descriptive statistics will be used for continuous data and frequency counts and percentages for categorical data. A shift table from baseline, by treatment group and protocol specified time points, of normal, abnormal low, and abnormal high records will also be summarized for hematology and chemistry data with marginal totals using frequency counts and percentages.

All laboratory data will be listed for the safety set.

7.3. Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, respiratory rate, temperature and pulse rate) and their changes from baseline at each post-baseline visit will be presented by treatment group and overall.

Vital sign values will be considered PCS if they meet both the observed value criteria and the change from baseline criteria listed in Table 4. The number and percentage of subjects with PCS baseline and/or post-baseline values will be tabulated by treatment group and overall. The percentages will be calculated relative to the number of subjects with values for each vital sign parameter in each treatment group at the analysis visit. The numerator is the total number of subjects with at least 1 PCS vital sign value at the analysis visit. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥180	Increase of ≥20
	Low	≤90	Decrease of ≥20
Diastolic blood pressure (mmHg)	High	≥105	Increase of ≥15
	Low	≤50	Decrease of ≥15
Pulse rate (beats per minute)	High	≥120	Increase of ≥15
	Low	≤50	Decrease of ≥15

[a] A post-baseline value is considered as a PCS value if its meets both criteria for observed value and change from baseline.

All vital signs data will be listed for the safety set.

7.4. Physical Examination Findings

Any relevant findings from the baseline physical examination are to be reported on the medical history. Any relevant findings from the post-baseline physical examination are to be reported as AE's. No separate physical examination findings were collected to summarize.

7.5. Complete Ophthalmic Exam

Results of the ocular assessments will be summarized by shift tables showing the shift from baseline in the individual slit-lamp examination and indirect ophthalmoscopy endpoint. These will be provided by treatment group, overall and visit for study eye and fellow eye. The visits to be presented are Month 12, Month 24, and LOV.

Any relevant findings from the post-baseline ophthalmic examination are to be reported as AEs.

The change from baseline in chronic (first measurement of the day) IOP will be summarized over time by treatment group. In addition, the incidence of IOP above specified thresholds (i.e., >21 mmHg at pre-injection/chronic (first measurement of the day); >30 mmHg post injection) will be summarized by treatment group and overall, protocol specified timepoint (at Month 12 and Month 24 readout, respectively) and over the whole study.

The mean change from baseline in the chronic IOP ± the standard error will be plotted over time by treatment group.

Details of the ocular assessments will be provided in listings for the safety set and for IOP, the ITT set.

7.6. NL-BCVA

The number and percentage of subjects who lost letters compared with baseline at each visit based on NL-BCVA in the study and fellow eye will be presented. The three categories are >=15, ≥15- < 30 and ≥30 ETDRS letters.

7.7. Other Ophthalmology Imaging Assessments

Unless otherwise stated, ocular imaging data collected will be listed by treatment group and overall for the Safety set. The summary will be performed separately by study eye and by fellow eye. The ophthalmology imaging assessments performed in this study include the following:

- Digital Color Fundus Photographs (DCFP)
    - Shift from baseline in the presence/absence of hemorrhage at each visit
- FA
    - The following analyses will be performed in all study eyes and in non-study eyes without a history of CNV at baseline (in medical history) in the corresponding eye.
        - Incidence of new CNV. This will be summarized as the cumulative number of CNV events by each visit and the cumulative incidence by that visit based on Kaplan Meier methods.
        - Incidence of new CNV by type (classic, occult, classic & occult, disciform scar) at first emergence will be summarized at each visit for the cumulative number of events.
        - Total CNV size (diameter) at first emergence will be summarized at each visit for the cumulative number of events.
- SD-OCT
    - Descriptive statistics on central subfield thickness at each visit
    - Plot of the mean change from baseline in central subfield thickness in the study eye ± the standard error over time by treatment group.
    - Descriptive statistics on central (center point) retinal thickness at each visit
    - Shift from baseline in the presence/absence of subretinal fluid at each visit
    - Shift from baseline in the presence/absence of cystoid spaces at each visit
- Specular Microscopy

  - Endothelial Cell Count is assessed using specular microscopy, and the change from baseline in cell density (cells/mm^2) as well as the change from baseline in average cell-size will be summarized with descriptive statistics.

- OCT-A
  - Incidence of subclinical CNV (referred to as MNV in the datasets) determined by OCT-A in eyes without previous CNV reported in the medical history or as an adverse event in the corresponding eye at each visit.

In addition, the following summary of suspected and reading-center confirmed CNV cases will be presented by treatment group. This will be presented separately for the study eye only.

- The number and percentage of subjects with an Exudative AMD TEAE on or before Month 12 (or Month 24 if the final analysis)
- The number and percentage of subjects with at least one suspected new onset CNV case submitted to the reading center by the Investigator post-baseline through Month 12 (or Month 24 if the final analysis)
- The number and percentage of subjects with a reading-center confirmed new onset CNV case (out of the suspected CNV cases submitted by the Investigator) post-baseline through Month 12 (or Month 24 if the final analysis). Reading-center confirmed CNV case is identified as either:
  - Presence of CNV on FA (Type = classic, occult, classic & occult, disciform scar) OR
  - Presence of CNV thickness on SD-OCT
- The number and percentage of subjects with a reading-center confirmed new onset CNV case (out of the suspected CNV cases submitted by the Investigator) post-baseline through Month 12 (or Month 24 if the final analysis) and also reported as an Exudative AMD TEAE.
- The number and percentage of subjects with a reading-center confirmed new onset CNV case (out of the suspected CNV cases submitted by the Investigator) post-baseline through Month 12 (or Month 24 if the final analysis) without an Exudative AMD TEAE ever reported.
- The number and percentage of subjects with at least one suspected CNV case, confirmed by the reading-center but previously reported as an Exudative AMD TEAE.
- The number and percentage of subjects with at least one suspected CNV case, not confirmed by the reading-center but still reported as an Exudative AMD TEAE.
- The number and percentage of subjects with a reading-center finding of presence of new-onset CNV (defined in the same way as a confirmed new onset CNV case) without any other submission to the reading center of a suspected case post-baseline through Month 12 (or Month 24 if the final analysis) and also reported as an Exudative AMD TEAE on or before Month 12 (or Month 24 if the final analysis)

- The number and percentage of subjects with a reading-center finding of presence of new-onset CNV (defined in the same way as a confirmed new onset CNV case) without any other submission to the reading center of a suspected case post-baseline through Month 12 (or Month 24 if the final analysis) and no report of an Exudative AMD TEAE.
- The number and percentage of subjects with Exudative AMD TEAE and without a suspected case submitted to the reading center as well as without a reading center finding of new-onset CNV (defined in the same way as a confirmed new onset CNV case).

7.8. Immunogenicity

Immunogenicity data will be listed separately for anti-pegcetacoplan peptide antibody and anti-PEG antibody results. The number and percentage of samples confirmed positive for ADA response will be summarized by treatment groups (i.e., PM, PEOM, and Sham). The number and percentage of subjects with treatment-emergent and treatment-boosted responses will be presented by treatment group. Treatment emergent response is defined as a confirmed positive antibody result postdose after a negative antibody result reported at baseline. Treatment-boosted response is defined as a ≥4-fold increase in titer from the baseline level.

7.9. Death

Subject deaths and primary cause of death will be summarized.

7.10. Other Safety Data

Urine pregnancy test will be provided in a listing.

8. PHARMACOKINETICS ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic set.

Pegcetacoplan concentrations reported as BLQ will be taken as zero for linear plots, and equal to the lower limit of quantification (LLOQ) for semi-logarithmic plots. For the computation of descriptive statistics, BLQ will be taken as zero, except for the calculation of the geometric mean where the LLOQ will be used.

Pegcetacoplan concentrations will be summarized by pegcetacoplan treatment group (i.e., PM and PEOM) at each scheduled time point using descriptive statistics ((including at least Mean, SD, CV, Median, Min, Max, Geometric Mean/%CV).

Linear and log-linear individual concentration profile plots against time will be produced for each pegcetacoplan treatment group. The actual sampling time will be used on the x-axis.

Linear and log-linear median (± standard error) concentration profile plots against time will be produced by treatment group. The nominal sampling time will be used on the x-axis.

Linear and log-linear mean (± standard error) concentration profile plots against time will be produced for each pegcetacoplan treatment group (i.e., PM and PEOM), with nominal sampling time on the x-axis.

The number of subjects with values BLQ will be tabulated.

A listing of serum concentration data will be presented by treatment arm. The actual time, deviation and percent deviation from nominal time will also be listed.

The C_{max} values are obtained from serum samples collected at Day 7 following pegcetacoplan treatment ($C_{Day\ 7}$) and will be listed and summarized as part of the concentration data. The results will be listed and summarized using descriptive statistics. No additional presentations are required for other pharmacokinetic parameters.

Population pharmacokinetic and exposure-response modelling of the safety and efficacy data may be performed using a separate Population Pharmacokinetic/Pharmacodynamic Analysis Plan.

9. PHARMACODYNAMIC ANALYSES

The PD parameters (CH50, AH50, and C3) will be evaluated based on the Pharmacodynamic set. Absolute values, changes from baseline and percentage changes from baseline for the PD parameters will be summarized by treatment group at each protocol specified time point using descriptive statistics.

For each PD parameter, the individual absolute values and individual changes from baseline will be presented graphically for each treatment group. Actual sampling times will be used for the graphical presentation of individual data. If a baseline PD value is zero, then the percentage change from baseline will not be calculated. For the PD plots, a BLQ value will be set equal to LLOQ.

The mean absolute values, mean changes from baseline and mean percentage changes from baseline will also be presented graphically by treatment group. Nominal sampling times will be used for the mean plots.

Individual PD parameters will be listed together with changes from baseline and percentage changes from baseline by treatment group.

10. OTHER ANALYSES

No other analyses are planned for this study.

11. INTERIM ANALYSIS

No formal interim analyses are planned for this study.

To support regulatory submissions, data cuts of the Month 12 – Month 24 data of the study may be taken prior to the final database lock and summarized prior to the final study reporting. The analysis of this data will not be used to modify the pre-planned analyses of this study.

12. DATA MONITORING COMMITTEE

An external, independent DMC reviews unmasked data across the conduct of the study approximately every 6 months. A charter for the DMC as well as a DMC statistical analysis plan was prepared separately.

13. DATA HANDLING CONVENTIONS

13.1. General Data Reporting Conventions

Continuous variables will be summarized using the number of non-missing observations (n), mean, SD, median, quartile 1, quartile 3, minimum, and maximum. Geometric mean and CV will be included for PK parameters, where appropriate. Categorical variables will be summarized using frequencies and percentages. Unless stated otherwise, for all percentages, the number of subjects in the analysis population for the treatment group will be the denominator.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer.

13.2. Definition of Baseline

Unless stated otherwise, baseline will be defined as the last available pre-treatment value taken on or before the first dose date of study drug, and will be used for summary of baseline characteristics, as well as for all change-from-baseline analyses of efficacy and safety endpoints.

13.3. Definition of Relative Study Days

Unless otherwise noted, relative study days (Rel Days) of an evaluation are defined as number of days relative to the first dose date of study drug which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc.

If evaluation date is on or after first dose date, then relative study days are calculated as

Evaluation date - first dose date of study drug + 1.

If evaluation date is before first dose date, then relative study days are calculated as

Evaluation date - first dose date of study drug

Relative study days take negative values if evaluation date occurs prior to first dose date and take positive values if evaluation date occurs on or after first dose date of study drug.

13.4. Definition of Visit Windows

All assessments occurring on or before the first date of dosing (Analysis Study Day (ADY) ≤ 1) will be assigned to the Baseline analysis visit window.

Unless otherwise specified, the actual scheduled nominal post-baseline visit will be used for over time summaries. Post-baseline unscheduled visits and early termination visits will be mapped to a scheduled visit and will only be used in the analysis if the nominal scheduled visit result is missing, Table 5 and Table 6 presents the analysis visit window mapping for unscheduled and early term visits. In the case that multiple unscheduled or early termination visits are in the same analysis window, the one closest to the target date will be used. In the event that windowed visit is mapped to an illogical sequence of visits when considering nearby scheduled visits

(i.e., windowed visit is higher than the subsequent visit or lower than the preceding visit), the windowed visit will be set to the logical scheduled visit.

Table 5: Post-Baseline Analysis Visit Window for Unscheduled and Early Termination Visits: Monthly Regimen

Analysis Visit	Target Study Day	Analysis Window (days)
Day 7	7	2 to 15
Month 1	30	16 to 45
Month 2	60	46 to 75
Month 3	90	76 to 105
Month 4	120	106 to 135
Month 5	150	136 to 165
Month 6	180	166 to 195
Month 7	210	196 to 225
Month 8	240	226 to 255
Month 9	270	256 to 285
Month 10	300	286 to 315
Month 11	330	316 to 345
Month 12	360	346 to 375
Month 13	390	376 to 405
Month 14	420	406 to 435
Month 15	450	436 to 465
Month 16	480	466 to 495
Month 17	510	496 to 525
Month 18	540	526 to 555
Month 19	570	556 to 585
Month 20	600	586 to 615
Month 21	630	616 to 645
Month 22	660	646 to 675
Month 23	690	676 to 705
Month 24	720	706 to EOS

Table 6: Post-Baseline Analysis Visit Window for Unscheduled and Early Termination Visits: Every Other Month Regimen

Analysis Visit	Target Study Day	Analysis Window (days)
Day 7	7	2 to 15
Month 1	30	16 to 45
Month 2	60	46 to 75
Month 3	90	76 to 105
Month 4	120	106 to 135
Month 5	150	136 to 165
Month 6	180	166 to 195
Month 7	210	196 to 225
Month 8	240	226 to 255
Month 9	270	256 to 285
Month 10	300	286 to 315
Month 11	330	316 to 345
Month 12	360	346 to 375
Month 14	420	376 to 450
Month 16	480	451 to 510
Month 18	540	511 to 570
Month 20	600	571 to 630
Month 22	660	631 to 690
Month 24	720	690 to EOS

13.5. Derived Efficacy Endpoints

13.5.1. GA Lesion Size

For all independent ophthalmic assessments (performed by DARC laboratory), which includes GA lesion size, if assessments by only two independent readers are available, then the median of the 2 readings will be used in the calculation of summary statistics. If assessments by three independent readers are available, then the median of the three readings will be used for the summary calculations.

In the case that the GA lesion size has an indeterminate boundary noted, then the lesion size for this indeterminate boundary will be used in all analyses of GA lesion size unless otherwise noted in the case that primary lesions size assessment for an individual reader is missing.

13.5.2. MNRead Reading Chart

13.5.2.1. Reading Speed

13.5.2.1.1. Without adjustment for reading inaccuracy

Any print size with “Not Done” will have the associated wpm marked as 0.

Reading speed (wpm) = 600 / (reading time in seconds)

If reading speed >300 wpm, reading speed = 300.

13.5.2.1.2. With adjustment for reading inaccuracy

Any print size with "Not Done" will have the associated wpm marked as 0.

Reading speed (wpm) = 60 (10 – errors) / (reading time in seconds)

If reading speed >300 wpm, reading speed = 300.

If 10 or more errors were made in a sentence (implying wpm<0), then the reading speed for that sentence can be assumed to be zero (wpm).

13.5.2.2. Maximum reading speed

Maximum reading speed will be calculated as the mean of the three highest nonzero reading speeds (or 2 or 1 if that is all that exists). For subjects having all wpm values = 0, the maximum reading speed will be set to 0, and for those same visits the critical print size will be set to missing. Reading speed will equal 0 wpm at each print size for which (time=0) or Not Done (indicating no words in the sentence could not be read or sentence was not attempted due to vision) is checked for that print size.

13.5.2.3. Critical Print Size

Critical print size will be calculated as the smallest print size which support reading speed at 80% of the maximum reading speed. If all wpm at all print sizes = 0 at a visit then that visit's critical print size will be missing. Print size will be adjusted for viewing distance as follows:

- MNRead Charts:
    - For all viewing distances:
        - Print size = Print size + correction, where correction=log10 [40 / (viewing distance in cm)], rounded to two decimal places

Note: the CRFs for the MNRead charts have print sizes pre-filled for a 40 cm viewing distance, while the Radner charts have print sizes pre-filled for a 32 cm viewing distance.

13.5.2.4. Reading acuity

Reading acuity will be calculated at each visit as: 1.4 – (# sentences read x 0.1) + (# of words read incorrectly x 0.01). This variable will not be included in the CSR.

13.5.3. Radner Reading Chart

13.5.3.1. Reading Speed

13.5.3.1.1. Without adjustment for reading inaccuracy

Reading Speed (wpm) = 14 / (time in seconds) x 60 = 840 / (time in seconds)

If reading speed >300 wpm, reading speed = 300.

13.5.3.1.2. With adjustment for reading inaccuracy

Reading Speed (wpm) = (14 – errors)/ (time in seconds) x 60

If 14 or more errors were made in a sentence (implying wpm<0), then the reading speed for that sentence can be assumed to be zero (wpm).

If reading speed >300 wpm, reading speed = 300.

13.5.3.2. Maximum Reading Speed

Maximum reading speed will be calculated as the mean of the three highest nonzero reading speeds (or 2 or 1 if that is all that exists). For subjects having all wpm values = 0, the maximum reading speed will be set to 0, and for those same visits the critical print size will be set to missing. Reading speed will equal 0 wpm at each print size for which (time=0) or Not Done (indicating no words in the sentence could not be read or sentence was not attempted due to vision) is checked for that print size.

13.5.3.3. Critical Print Size

Critical print size will be calculated as the smallest print size which support reading speed at 80% of the maximum reading speed. If all wmp at all print sizes = 0 at a visit then that visit's critical print size will be missing. Print size needs to be adjusted for viewing distance as follows:

- Radner Charts:
    - For viewing distance of 32 cm
        - No correction is needed.
    - For viewing distance of other than 32 cm:
        - Print size= Print size – 0.1 + correction, where correction=log10 [40 / (viewing distance in cm)], rounded to two decimal places

Note: the CRFs for the MNRead charts have print sizes pre-filled for a 40 cm viewing distance, while the Radner charts have print sizes pre-filled for a 32 cm viewing distance.

13.5.3.4. Reading Acuity

Reading acuity will be calculated at each visit as: 1.4 – (# sentences read x 0.1) + (# of words read incorrectly x 0.01). This variable will not be included in the CSR.

13.5.4. Mean FRI Index Score and FRI Level

Follow Section 4.3.2 of FRI Index User Manual (Version 1.4).

SAS code for scoring FRI Index and FRI Level is available in Appendix C of FRI Index Under Manual (Version 1.4).

13.5.5. NL-BCVA and LL-BCVA

13.5.5.1. BCVA Letter Score

- If the 4-meter score is >19 letters read correctly, the visual acuity score is the sum of total letters correctly read at 4 meters plus the addition of 30.
- If the 4-meter score is ≤19 letters read correctly, the visual acuity score is the sum of total letters read correctly at 4 meters and total letters read correctly at the 1-meter distance.

- If no letters are read correctly at either the 4-meter distance or the 1-meter distance, the visual acuity score is 0.

13.5.5.2. Conversion of BCVA Letter Score to Snellen Equivalent

Conversions between letter, logMAR, and Snellen visual acuity scores are available in Beck et al. (2003) and Holladay et al. (2004). Letter scores are converted to logMAR equivalents using the formula logMAR = 1.7 – (.02)(letter score). With this conversion, a 5-letter difference in visual acuity is equivalent to a difference of 0.1 logMAR and to one Snellen line. Conversion from logMAR to Snellen can be done after rounding logMAR values to one decimal place following Table 1 in Holladay et al. (2004).

13.5.6. Low Luminance Deficit

LLD = NL-BCVA - LL-BCVA

13.5.7. NEI VFQ-25 scores

Scoring VFQ-25 with or without optional item is a two-step process:

- First, original numeric values from the survey are re-coded following the scoring rules outlined in Table 2 of user's manual. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format, scores represent the achieved percentage of the total possible score, e.g., a score of 50 represents 50% of the highest possible score.
- In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores, Table 3 of user's manual indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the sub-scale that the respondent answered.

13.5.7.1. NEI VFQ-25 Distance Activity Subscale Score

Average of items 8, 9, and 14

13.5.7.2. NEI VFQ-25 Near Activity Subscale Score

Average of items 5, 6, and 7

13.5.7.3. NEI VFQ-25 Driving Subscale Score

For subjects who are currently driving at baseline only. Average of items 15c, 16, 16a

13.5.7.4. NEI VFQ-25 Composite Scores

To calculate an overall composite score for the VFQ-25, simply average the vision-targeted sub-scale scores, excluding the general health rating question.

13.5.8. NEI VFQ-39 Scores

For subjects responded to additional questions A1-A13, VFQ-39 subscale scores can be calculated using Table 4 of user's manual.

13.5.8.1. NEI VFQ-39 Distance Activity Subscale Score

Average of items 8, 9, 14, A6, A7, and A8

13.5.8.2. NEI VFQ-39 Near Activity Subscale Score

Average of items 5, 6, 7, A3, A4, and A5

13.5.8.3. NEI VFQ-39 Composite score

Calculated by simply averaging the vision related subscales, excluding the general health rating question.

13.6. Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end-of-study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

13.7. Handling of Missing, Unused, and Spurious Data

13.7.1. Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety set, all efforts should be made to obtain the date from the investigator.

13.7.2. Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

If either the start or stop date of medication is missing, the worst or most conservative case will be considered when assigning medications to categories. So, for a missing start date (where stop date is after date of first dose or missing) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the last study date.

13.7.2.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

13.7.2.1.1. Missing Day and Month

If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.

If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

13.7.2.1.2. Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.7.2.1.3. Missing Day Only

If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.

If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.

If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

13.7.2.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

13.7.2.2.1. Missing Day and Month

If the year of the incomplete stop date is the same as the year as of the last study date, then the day and month of the date of the last study date will be assigned to the missing fields.

If the year of the incomplete stop date is before the year of the last study date, then 31 December will be assigned to the missing fields.

If the year of the incomplete stop date is after the year of the last study date, then 01 January will be assigned to the missing fields.

13.7.2.2.2. Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedure.

13.7.2.2.3. Missing Day Only

If the month and year of the incomplete stop date are the same as the month and year of the last study date, then the day of the last study date will be assigned to the missing day

If either the year is before the year of the last study date or if both years are the same but the month is before the month of the last study date, then the last day of the month will be assigned to the missing day

If either the year is after the year of the last study date or if both years are the same but the month is after the month of the last study date, then the first day of the month will be assigned to the missing day.

13.7.3. Missing Date Information for Adverse Events

Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. So, for a missing start date (where stop date is after first dosing date or missing) the date will be imputed as the first dose date; for a missing stop date the date will be imputed as the last study date. If a partial date is recorded, the following convention will be used to assign the AE.

13.7.3.1. Incomplete Start Date

If a start date is missing the day information and month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing the month and the year is the same as first dose date then use first dose date, else January will be used for the start month.

If AE end date is earlier than treatment start date (i.e., could be inferred by any combination of year/month/day), then any missing part of AE start date will be imputed based on the AE end date.

13.7.3.2. Incomplete Stop Date

If a stop date is missing the day information and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the month and year is the same as last study date then use last study date, else December will be used for the stop month.

13.7.4. Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

13.7.5. Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" to the investigational product will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

13.7.6. Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis (e.g., a character string is reported for a numerical variable), the appropriately determined coded value will be used in the statistical analysis, several examples are shown in Table 7 for an illustration purpose. The actual values as reported in the database will be presented in data listings.

Table 7: Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: Bilirubin, Total/Direct	<1.7	0.85
	<2	1
Urinalysis: Specific Gravity	≤1.005	0.5025
	>1.030	1.030
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0
Urinalysis: Protein	≥500	500
Other: FSH	<0.2	0.1

14. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following changes were made to the analyses specified in the protocol:

- The mITT set, which includes subjects with a baseline and at least one post-baseline GA lesion assessment, replaced the ITT set as the main efficacy population to be aligned with the primary analysis methodology.
- The change in GA lesion(s) size at Month 24 between PM and Sham was to be the third hypothesis tested in the hypotheses testing strategy as specified in the protocol. This was removed from the hypotheses testing strategy in the SAP.
- The hypotheses testing strategy and α allocation for the key secondary endpoints was not precisely specified within the protocol and has been clarified to follow the hypotheses testing procedure and α allocation as described in Section 6.3.1.
- Several new exploratory endpoints not specified in the protocol were added.
    - NEI-VFQ-39 distance activity, composite, near activity subscale score
    - NEI-VFQ-25 driving subscale score
    - Progression from iRORA to cRORA
    - Progression from large drusen to iRORA or cRORA
    - Change in the distance of the atrophy junction to the fovea and without subfoveal atrophy to subfoveal atrophy conversion
- No pre-specified analysis will be performed on the secondary endpoint of change from baseline in LLD over time. This data will only be listed.
- No formal interim analyses are planned for this study: however, analyses of interim data from Months 12 to 24 that may support regulatory submissions may be conducted.
- The pharmacokinetic endpoints of AUC, C_{max}, and T_{max} were specified in the protocol; however, since only trough concentrations were collected throughout the study it is only possible to assess C_{max}. C_{max} should occur at Day 7 following pegcetacoplan treatment. Therefore, the concentration on Day 7 will be used ($C_{Day\ 7}$) as the observed C_{max} values.
- Other minor editorial changes were made to provide clarity.

16. REFERENCES

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17. APPENDIX

APPENDIX 1. SCHEDULE OF ACTIVITIES

Table 8: Visit Schedule - Monthly Group- Screening, Day 1 through Month 12

	Screening	Treatment														Early Term[A]
Visit #	**1**	**2**	**2A**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Day	**–28 to –1**	**1**	**7**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	
Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Month	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Window (+ or – days)	**2**	**0**	**1**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Informed Consent/Assign Screening Number	x															
Demographic Data	x															
Inclusion/Exclusion Criteria [B]	x	x														
Medical/Surgical/Ocular History [C]	x															
Blood Draw—Safety Labs [D,E,F]	x	x			x				x						x	x
Urine Sample Collection [D, E,F]	x	x			x				x						x	x
Urine Pregnancy Test [D,E,F]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D, S]		x	x	x					x						x	x
Blood Draw—Genotyping (if applicable) [D]					x											
Blood Draw—Anti-Pegcetacoplan Ab [D]		x		x	x				x						x	x
Blood Draw for Clinical Repository (if applicable)[D,G]					x				x						x	x
Vital Signs [H]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [I]	x														x	x
BCVA [J]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
LL-BCVA [J]		x		x	x	x	x	x	x	x	x	x	x	x	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]		x							x						x	x
Slitlamp Examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

Table 8: Visit Schedule - Monthly Group- Screening, Day 1 through Month 12

	Screening	Treatment														Early Term[A]
Visit #	1	2	2A	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	7	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	1	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	1	8	8	8	8	8	8	8	8	8	8	8	8	
Endothelial Cell Count[S]		x							x						x	x
NEI VFQ-25 [L]		x							x						x	x
FRI [L]		x							x						x	x
Home-Based Digital Applications [L,M S]		x		x	x	x			x						x	
Dilated Indirect Ophthalmoscopy	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
IOP Measurement	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [N]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [N]	x	x			SE		SE		x		SE		SE		x	x
NIR [N]	x	x			SE		SE		x		SE		SE		x	x
DCFP [N]	x														x	x
FFA [N]	x														x	x
OCT-A[R S]		x[R]							x[R]						x[R]	x
Study Eye Determination	x															
Randomization		x														
Pegcetacoplan administration or Sham Injection[T]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Postinjection Assessment [O]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Follow-Up Call [P]		x		x	x	x										
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open-label study.

B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.

C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.

D. Obtain prior to fluorescein angiography and before study drug administration.

E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.

F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.

G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at each of the specified visits.

H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.

I. Height and weight should be collected at screening.

J. Perform assessments prior to dilating the eyes.

K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.

L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.

M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.

N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (select sites) images must be collected and sent to the reading center for analysis.

O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.

P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 3) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.

Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.

R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.

S. At select sites only.

T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP.

Table 9: Visit Schedule - Monthly Group- Month 13 to Month 24

	Treatment												Early Term [A]
Visit #	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Informed Consent/Assign Screening Number													
Demographic Data													
Inclusion/Exclusion Criteria [B]													
Medical/Surgical/Ocular History [C]													
Blood Draw—Safety Labs [D,E,F]						x						x	x
Urine Sample Collection [D,E,F]						x						x	x
Urine Pregnancy Test [D,E,F]	x	x	x	x	x	x	x	x	x	x	x	x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50)[D,S]												x	x
Blood Draw—Genotyping (if applicable) [D]													
Blood Draw—Anti-Pegcetacoplan Ab [D]		x				x						x	x
Blood Draw for Clinical Repository (if applicable) [D,G]												x	x
Vital Signs [H]	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [I]												x	x
BCVA [J]	x	x	x	x	x	x	x	x	x	x	x	x	x
LL-BCVA [I]	x	x	x	x	x	x	x	x	x	x	x	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]						x						x	x
Slitlamp Examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Endothelial Cell Count[S]												X	X
NEI VFQ-25 [L]						x						x	x
FRI [L]						x						x	x
Dilated Indirect Ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
Home-Based Digital Applications [L,M,S]						x						x	

Table 9: Visit Schedule - Monthly Group- Month 13 to Month 24

	Treatment												
Visit #	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**Early Term [A]**
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
IOP Measurement	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [N]	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [N]		SE		SE		x		SE		SE		x	x
NIR [N]		SE		SE		x		SE		SE		x	x
DCFP [N]												x	x
FFA [N]												x	x
OCT-A[R,S]						x[R]						x[R]	x
Study Eye Determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]	x	x	x	x	x	x	x	x	x	x	x		
Postinjection Assessment [O]	x	x	x	x	x	x	x	x	x	x	x		
Follow-Up Call [P]													
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open-label study.

B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.

C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.
D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
I. Height and weight should be measured at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (selected sites) images should be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be $\leq$30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is $\leq$30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 $\pm$ 2 days after each study treatment visit (through Month 3) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP.

Table 10: Visit Schedule - Every-Other-Month Group Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	**1**	**2**	**2A**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Day	**–28 to –1**	**1**	**7**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	
Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Month	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Window (+ or – days)	**2**	**0**	**1**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Informed Consent/Assign Screening Number	x															
Demographic Data	x															
Inclusion/Exclusion Criteria [B]	x	x														
Medical/Surgical/Ocular History [C]	x															
Blood Draw—Safety Labs [D,E,F]	x	x			x				x						x	x
Urine Sample Collection [D,E,F]	x	x			x				x						x	x
Urine Pregnancy Test [D,E,F]		x			x		x		x		x		x		x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D,S]		x	x	x					x						x	x
Blood Draw—Genotyping (if applicable) [D]					x											
Blood Draw- Anti-Pegcetacoplan Ab [D]		x		x	x				x						x	x
Blood Draw for Clinical Repository (if applicable) [D,G]					x				x						x	x
Vital Signs [H]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination [I]	x														x	x
BCVA [J]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
LL-BCVA [J]		x		x	x	x	x	x	x	x	x	x	x	x	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]		x							x						x	x
Slitlamp Examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Endothelial Cell Count[S]		x							x						x	x
NEI VFQ-25 [L]		x							x						x	x
FRI [L]		x							x						x	x
Home-Based Digital Applications [L,M,S]		x		x	x	x			x						x	
Dilated Indirect Ophthalmoscopy	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
IOP Measurement	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

Table 10: Visit Schedule - Every-Other-Month Group Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	1	2	2A	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	7	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	1	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	1	8	8	8	8	8	8	8	8	8	8	8	8	
SD-OCT [N]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [N]	x	x			SE		SE		x		SE		SE		x	x
NIR [N]	x	x			SE		SE		x		SE		SE		x	x
DCFP [N]	x														x	x
FFA [N]	x														x	x
OCT-A[R, S]		x[R]							x[R]						x[R]	x
Study Eye Determination	x															
Randomization		x														
Pegcetacoplan administration or Sham Injection[T]		x			x		x		x		x		x		x	x
Postinjection Assessment [O]		x			x		x		x		x		x		x	x
Follow-Up Call [P]		x			x		x									
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed At Month 24, all subjects should be offered entry into an open-label study.

B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.

C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.

D. Obtain prior to fluorescein angiography and before study drug administration.

E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.

F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
I. Height and weight should be measured at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital application will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (select sites) images should be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 4) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP.

Table 11: Visit Schedule - Every-Other-Month Group Month 13 to Month 24

	Treatment												Early Term [A]
Visit #		**15**		**16**		**17**		**18**		**19**		**20**	
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)		**16**		**16**		**16**		**16**		**16**		**16**	
Informed Consent/Assign Screening Number													
Demographic Data													
Inclusion/Exclusion Criteria [B]													
Medical/Surgical/Ocular History [C]													
Blood Draw—Safety Labs [D,E,F]						x						x	x
Urine Sample Collection [D, E,F]						x						x	x
Urine Pregnancy Test [D,E,F]		x		x		x		x		x		x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D,S]												x	x
Blood Draw—Anti-Pegcetacoplan Ab [D]		x				x						x	x
Blood Draw for Clinical Repository (if applicable) [D,G]												x	x
Vital Signs [H]		x		x		x		x		x		x	x
Physical Examination [I]												x	x
BCVA [J]		x		x		x		x		x		x	x
LL-BCVA [J]		x		x		x		x		x		x	x
MNREAD or Radner Reading Charts (select countries) [J,K]						x						x	x
Slitlamp Examination		x		x		x		x		x		x	x
Endothelial Cell Count[S]												x	x
NEI VFQ-25 [L]						x						x	x
FRI [L]						x						x	x
Home-Based Digital Applications (optional, select sites) [L,M,S]						x						x	
Dilated Indirect Ophthalmoscopy		x		x		x		x		x		x	x

Table 11: Visit Schedule - Every-Other-Month Group Month 13 to Month 24

	Treatment												Early Term [A]
Visit #		**15**		**16**		**17**		**18**		**19**		**20**	
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)		**16**		**16**		**16**		**16**		**16**		**16**	
IOP Measurement		x		x		x		x		x		x	x
SD-OCT [N]		x		x		x		x		x		x	x
FAF [N]		SE		SE		x		SE		SE		x	x
NIR[N]		SE		SE		x		SE		SE		x	x
DCFP [N]												x	x
FFA [N]												x	x
OCT-A[R,S]						x[R]						x[R]	x
Study Eye Determination													
Pegcetacoplan administration or Sham Injection[T]		x		x		x		x		x			
Postinjection Assessment [O]		x		x		x		x		x			
Follow-Up Call [P]													
Concomitant Medication/Concomitant Ocular Procedures [Q]		x		x		x		x		x		x	x
Adverse Events		x		x		x		x		x		x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. . All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open-label study.

B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.

C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.

D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
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M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (select sites) images should be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given in order to lower IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes the gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 4) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the investigator determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP.

1.1 Protocol Changes to be followed during COVID-19 Restrictions

OVERVIEW

In response to the COVID-19 crisis, to ensure the safety of study subjects and Investigative Sites as well as proper conduct of the study, TEMPORARY changes to the protocol have been implemented. These changes should be followed only during COVID-19 restrictions and include extended IP administration windows, changes to masking rules, rescreening instructions, and a revised schedule of assessments.

Where feasible, sites could continue to follow the full schedule of assessments (based on their treatment group assignment).

EXTENDED IP ADMINISTRATION WINDOWS

In order to allow more flexibility to sites and subjects, and to potentially mitigate missed IP administration, an extended IP administration window can be followed. The extended window can ONLY be used in situations related to COVID-19 restrictions and after medical monitor approval. Footnote "T" of each COVID-19 assessment table below reflects these extended IP options.

Per protocol, the IP administration window is as follows:

- Monthly treatment group: +/– 8 days for the entire study duration
- EOM treatment group: +/– 8 days for the first study year and +/- 16 days for the second study year

During COVID-19 restrictions, the IP administration window can be extended to the following:

- Monthly treatment group: –8 days to +15 days. Note, interval for consecutive injections must be at least 14 days.
- EOM treatment group: –8 days to +30 days for the first study year and –16 days to +30 days for the second study year.

MASKING RULES

Due to current COVID-19 restrictions, clinical sites might encounter difficulties maintaining appropriate clinic staffing to satisfy the approved masking rules for the APL2-303 (Derby) study. Based on this, and in an attempt to minimize the amount of missed data and IP administrations, Apellis is implementing a temporary adjustment to the study masking rules.

This temporary change must be approved by the Apellis Medical Director **prior to** implementation and must be documented via a temporary and modified delegation of authority Log. Each masked assessment performed by an unmasked staff and vice versa (even with Apellis approval and following the below guidelines) should be documented.

The principal investigator (PI) is responsible for the overall oversight of the study site data and s/he will not be allowed to switch into an unmasked role. Every masked individual that performs IP administration and/or postinjection assessment (all unmasked assessment) as a temporary measure, will **permanently** be considered an unmasked individual and will not be able to perform masked assessments once these exemptions are lifted.

RESCREENING PROCEDURE

Prior to the implementation of these temporary changes, sites continuing to screen patients have been encouraged to complete the screening and baseline assessments in their entirety. However, if a subject was deemed a screen failure for not being able to meet the original screening window (Day –28 to Day –1 [+/- 2 days]) due to COVID-19 related restrictions, a rescreening visit is allowed and should be followed according to the 2 scenarios below.

Subjects Who Completed Screening and Were Considered Eligible by Reading Center and Investigator

Subjects who were screened prior to 30 March 2020 and completed all screening assessments (as described in the Schedule of Assessments Table 8 [every month treatment group] and Table 10 [every other month [EOM] treatment group]) and considered eligible by the reading center and investigator and are able to return to the clinic within 90 days of initial screening, will receive a new subject ID number and undergo an *abbreviated screening*, prior to randomization, that includes the following assessments:

- Informed consent/assign new screening number
- Normal luminance best corrected visual acuity assessment
- Slitlamp examination
- Dilated indirect ophthalmoscopy
- IOP measurement
- SD-OCT*
- Concomitant medication/concomitant ocular procedures collection
- AE collection

*SD-OCT images collected at this visit will not be used by the reading center to determine eligibility but should be used by the investigator to detect any potential new exclusion criterion.

If the investigator deems it necessary, additional assessments can be performed if there is a concern that the subject might now meet an exclusion criterion that was not the case during the original screening (eg, FFA to exclude the presence of CNV).

Subjects With Incomplete Screening Assessment

Subjects that signed the informed consent but were not able to complete all screening assessments due to COVID-19-related restrictions are not eligible for the abbreviated screening. These subjects can be rescreened but must follow the standard screening schedule of assessment (as described in the Schedule of Assessments Table 8 [every month treatment group] and Table 10 [EOM treatment group]). These subjects will also receive a new screening ID number.

MINIMUM SCHEDULE OF ASSESSMENT

Schedule of Assessments

Where feasible, sites could continue to follow the full schedule of assessments (based on their treatment group assignment). The minimum assessment tables, only to be followed during this COVID-19 effort and if determined necessary to use based on the investigator's clinical judgment, are provided below to reduce the time required for each study visit. Subjects in the EOM treatment group do not need to be seen for the non-IP administration visits. Assessments not performed (even those that have been removed in the minimum assessment table) should be documented.

Subjects that are not able to come into the clinic for a study visit due to COVID-19-related restrictions, including visits for the EOM group that do not include IP administration, should be contacted via the phone for the collection of AEs (including SAEs) and concomitant medications. **All SAEs are still required to be reported to Apellis within 24 hours of site awareness, even if reported via phone call**. All communications via phone call should also be documented in the source documents and in the respective CRF page. In addition, these subjects should be instructed to self-monitor their vision at home and report any changes in vision or their overall health via phone call. The site must inform the Sponsor of any subjects lost to follow-up.

It is critical that local, country, and regional governance regarding COVID-19 is followed along with your best clinical judgment when managing this situation. All visits or assessments missed as a result of COVID-19 will be captured in the case report forms.

Table 12 (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	**1**	**2**	**2A**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Day	**–28 to –1**	**1**	**7**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	
Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Month	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Window (+ or – days)	**2**	**0**	**1**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Informed Consent/Assign Screening Number	x															
Demographic Data	x															
Inclusion/Exclusion Criteria [B]	x	x														
Medical/Surgical/Ocular History [C]	x															
Blood Draw—Safety Labs [D,E,F]	x	x			⁎				⁎						x	x
Urine Sample Collection [D, E,F]	x	x			⁎				⁎						x	x
Urine Pregnancy Test [D,E,F]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D, S]		x	x	x					x						x	x
Blood Draw—Genotyping (if applicable) [D]					⁎											
Blood Draw- Anti-Pegcetacoplan Ab [D]		x		⁎	⁎				⁎						x	x
Blood Draw for Clinical Repository (if applicable)[D,G]					⁎				⁎						⁎	⁎
Vital Signs [H]	x	x		⁎	⁎	⁎	⁎	⁎	x	⁎	⁎	⁎	⁎	⁎	x	x
Physical Examination [I]	x														x	x
BCVA [J]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
LL-BCVA [J]		x		⁎	⁎	⁎	⁎	⁎	x	⁎	⁎	⁎	⁎	⁎	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]		x							⁎						x	x
Slitlamp Examination	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Endothelial Cell Count[S]		x							x						x	x
NEI VFQ-25 [L]		x							⁎						x	x
FRI [L]		x							⁎						x	x

Table 12 (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	**1**	**2**	**2A**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Day	**–28 to –1**	**1**	**7**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	
Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Month	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Window (+ or – days)	**2**	**0**	**1**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Home-Based Digital Applications [L,M,S]		x		~~x~~	~~x~~	~~x~~			~~x~~						x	
Dilated Indirect Ophthalmoscopy	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
IOP Measurement	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [N]	x	x		~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [N]	x	x			~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [N]	x	x			~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
DCFP [N]	x														x	x
FFA [N]	x														x	x
OCT-A[R,S]		x[R]							~~x~~[R]						x[R]	x
Study Eye Determination	x															
Randomization		x														
Pegcetacoplan administration or Sham Injection[T]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Postinjection Assessment [O]		x		x	x	x	x	x	x	x	x	x	x	x	x	
Follow-Up Call [P]		x		x	x	x										
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	~~x~~	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	~~x~~	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open-label study.
B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.
C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.
D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
I. Height and weight should be collected at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (select sites) images must be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 3) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP. **During the COVID-19 pandemic, the following flexibility is allowed for IP administration: –8 days to +15 days after medical monitor approval. Note, interval for consecutive injections must be at least 14 days.**

Table 13 (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Month 13 to Month 24

	Treatment												
Visit #	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**Early Term [A]**
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Informed Consent/Assign Screening Number													
Demographic Data													
Inclusion/Exclusion Criteria [B]													
Medical/Surgical/Ocular History [C]													
Blood Draw—Safety Labs [D,E,F]						✱						x	x
Urine Sample Collection [D,E,F]						✱						x	x
Urine Pregnancy Test [D,E,F]	x	x	x	x	x	x	x	x	x	x	x	x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D,S]												x	x
Blood Draw—Genotyping (if applicable) [D]													
Blood Draw—Anti-Pegcetacoplan Ab [D]		✱				✱						x	x
Blood Draw for Clinical Repository (if applicable)[D,G]												✱	✱
Vital Signs [H]	✱	✱	✱	✱	✱	x	✱	✱	✱	✱	✱	x	x
Physical Examination [I]												x	x
BCVA [J]	x	x	x	x	x	x	x	x	x	x	x	x	x
LL-BCVA [I]	✱	✱	✱	✱	✱	x	✱	✱	✱	✱	✱	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]						✱						x	x
Slitlamp Examination	x	x	x	x	x	x	x	x	x	x	x	x	x
Endothelial Cell Count[S]												x	x
NEI VFQ-25 [L]						✱						x	x
FRI [L]						✱						x	x
Dilated Indirect Ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
Home-Based Digital Applications [L,M,S]						✱						✱	

Table 13 (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Month 13 to Month 24

	Treatment												
Visit #	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**Early Term [A]**
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
IOP Measurement	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [N]	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [N]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [N]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
DCFP [N]												x	x
FFA [N]												x	x
OCT-A [R,S]						~~x~~ [R]						x [R]	x
Study Eye Determination													
Randomization													
Pegcetacoplan administration or Sham Injection [T]	x	x	x	x	x	x	x	x	x	x	x		
Postinjection Assessment [O]	x	x	x	x	x	x	x	x	x	x	x		
Follow-Up Call [P]													
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, then the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open-label study.
B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.
C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.
D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
I. Height and weight should be measured at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (selected sites) images should be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 3) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of pegcetacoplan or sham can be done on separate days from the assessment visit if both days fall within the visit window. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is preinjection IOP. During the COVID-19 pandemic, the following flexibility is allowed for IP administration: –8 days to +15 days after medical monitor approval. Note, interval for consecutive injections must be at least 14 days.

Table 14 (TRACKED): COVID-19 VISIT SCHEDULE—Every-Other-Month Group—Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	1	2	2A	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	7	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	1	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	1	8	8	8	8	8	8	8	8	8	8	8	8	
Informed Consent/Assign Screening Number	x															
Demographic Data	x															
Inclusion/Exclusion Criteria [B]	x	x														
Medical/Surgical/Ocular History [C]	x															
Blood Draw—Safety Labs [D,E,F]	x	x			*				*						x	x
Urine Sample Collection [D,E,F]	x	x			*				*						x	x
Urine Pregnancy Test [D,E,F]		x			x		x		x		x		x		x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D,S]		x	x	x					x						x	x
Blood Draw—Genotyping (if applicable) [D]					*											
Blood Draw- Anti-Pegcetacoplan Ab [D]		x		*	*				*						x	x
Blood Draw for Clinical Repository (if applicable) [D,G]					*				*						*	x
Vital Signs [H]	x	x		*	*	*	*	*	x	*	*	*	*	*	x	x
Physical Examination [I]	x														x	x
BCVA [J]	x	x		*	x	*	x	*	x	*	x	*	x	*	x	x
LL-BCVA [J]		x		*	*	*	*	*	x	*	*	*	*	*	x	x
MNREAD or Radner Reading Charts (select countries) [J,K]		x							*						x	x
Slitlamp Examination	x	x		*	x	*	x	*	x	*	x	*	x	*	x	x
Endothelial Cell Count[S]		x							x						x	x
NEI VFQ-25 [L]		x							*						x	x
FRI [L]		x							*						x	x
Home-Based Digital Applications [L,M,S]		x		*	*	*			*						x	

Table 14 (TRACKED): COVID-19 VISIT SCHEDULE—Every-Other-Month Group—Screening, Day 1 Through Month 12

	Screening	Treatment														Early Term[A]
Visit #	**1**	**2**	**2A**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Day	**–28 to –1**	**1**	**7**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	
Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Month	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Window (+ or – days)	**2**	**0**	**1**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	
Dilated Indirect Ophthalmoscopy	x	x		~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	x
IOP Measurement	x	x		~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	x
SD-OCT [N]	x	x		~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [N]	x	x			~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [N]	x	x			~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
DCFP [N]	x														x	x
FFA [N]	x														x	x
OCT-A[R, S]		x[R]							~~x~~[R]						x[R]	x
Study Eye Determination	x															
Randomization		x														
Pegcetacoplan administration or Sham Injection[T]		x			x		x		x		x		x		x	
Postinjection Assessment [O]		x			x		x		x		x		x		x	
Follow-Up Call [P]		x			x		x									
Concomitant Medication/Concomitant Ocular Procedures [Q]	x	x	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	x
Adverse Events	x	x	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	~~x~~	x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date with the exception of Visit 2a which should be based on the Day 1 dose date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, the visit should be considered the early termination visit and all early termination procedures should be performed At Month 24, all subjects should be offered entry into an open-label study.
B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.
C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should also be recorded. Any history of tobacco use should be recorded.
D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected each of the specified visits.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken predose.
I. Height and weight should be measured at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital application will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (select sites) images should be collected and sent to the reading center for analysis.
O. Post- injection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given to lower the IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 4) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the physician determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is the preinjection IOP. <u>During the COVID-19 pandemic, the following flexibility is allowed for IP administration: –8 days to +30 days after medical monitor approval.</u>

Table 15 (TRACKED): COVID-19 VISIT SCHEDULE—Every-Other-Month Group—Month 13 to Month 24

	Treatment												Early Term [A]
Visit #		**15**		**16**		**17**		**18**		**19**		**20**	
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)		**16**		**16**		**16**		**16**		**16**		**16**	
Informed Consent/Assign Screening Number													
Demographic Data													
Inclusion/Exclusion Criteria [B]													
Medical/Surgical/Ocular History [C]													
Blood Draw—Safety Labs [D,E,F]						*						x	x
Urine Sample Collection [D, E,F]						*						x	x
Urine Pregnancy Test [D,E,F]		x		x		x		x		x		x	
Blood Draw—PK and Complement Profile (C3, CH50, AH50) [D,S]												x	x
Blood Draw—Anti-Pegcetacoplan Ab [D]		*				*						x	x
Blood Draw—Genotyping (if applicable) [D]													
Blood Draw for Clinical Repository (if applicable) [D,G]												*	*
Vital Signs [H]		*		*		x		*		*		x	x
Physical Examination [I]												x	x
BCVA [J]		x		x		x		x		x		x	x
LL-BCVA [J]		*		*		x		*		*		x	x
MNREAD or Radner Reading Charts (select countries) [J,K]						*						x	x
Slitlamp Examination		x		x		x		x		x		x	x
Endothelial Cell Count [S]												x	x
NEI VFQ-25 [L]						*						x	x
FRI [L]						*						x	x
Home-Based Digital Applications [L,M,S]						*						*	

Table 15 (TRACKED): COVID-19 VISIT SCHEDULE—Every-Other-Month Group—Month 13 to Month 24

	Treatment												Early Term [A]
Visit #		**15**		**16**		**17**		**18**		**19**		**20**	
Day	**390**	**420**	**450**	**480**	**510**	**540**	**570**	**600**	**630**	**660**	**690**	**720**	
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	
Window (+ or – days)		**16**		**16**		**16**		**16**		**16**		**16**	
Dilated Indirect Ophthalmoscopy		x		x		x		x		x		x	x
IOP Measurement		x		x		x		x		x		x	x
SD-OCT [N]		~~x~~		~~x~~		x		~~x~~		~~x~~		x	x
FAF [N]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [N]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
DCFP [N]												x	x
FFA [N]												x	x
OCT-A [R,S]						~~x~~[R]						x[R]	x
Study Eye Determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]		x		x		x		x		x			
Postinjection Assessment [O]		x		x		x		x		x			
Follow-Up Call [P]													
Concomitant Medication/Concomitant Ocular Procedures [Q]		x		x		x		x		x		x	x
Adverse Events		x		x		x		x		x		x	x

Abbreviations: AH50 = alternative pathway of complement functional test; BCVA = best corrected visual acuity; CH50 = classical pathway of complement functional test; CNV = choroidal neovascularization; DCFP = digital color fundus photography; eCRF = electronic case report form; FAF = fundus autofluorescence; FFA = fundus fluorescein angiography; FRI = Functional Reading Independence Index; IOP = intraocular pressure; LL-BCVA = low luminance best corrected visual acuity; MNREAD = Minnesota Low-Vision Reading Test; NEI VFG-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; NIR = near infrared reflectance; OCT-A = optical coherence tomography angiography; PK = pharmacokinetics; SD-OCT = spectral domain optical coherence tomography; SE = study eye; Term = termination; VEGF = vascular endothelial growth factor.

Note: All ocular assessments are to be performed for both eyes unless annotated with 'SE' (study eye) in the above schedule. All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit date.

A. For subjects that discontinue the study early, the early termination assessments should be performed after a minimum of 30 days have passed from the last dosing visit. If a subject reports for a scheduled visit and decides to terminate early prior to dosing, then the visit should be considered the early termination visit and all early termination procedures should be performed. At Month 24, all subjects should be offered entry into an open label study.
B. At Day 1 (Visit 2), confirm subject eligibility through reviewing the inclusion/exclusion criteria and receive confirmation of eligibility from the reading center.
C. Significant medical/surgical history from the previous 5 years. Anti-VEGF treatments (fellow eye) and invasive ocular procedures performed within the past 5 years and while on study should be recorded. Any history of tobacco use should be recorded.
D. Obtain prior to fluorescein angiography and before study drug administration.
E. At screening, serum pregnancy should be performed for women of childbearing potential. If positive, subject is not eligible to continue in the study.
F. Beginning at Day 1, perform the urine pregnancy test for women of childbearing potential at each treatment visit. If positive, perform a serum pregnancy test. If serum test is positive, study drug should not be administered and an early term visit should be completed.
G. Only subjects that sign the separate consent for the clinical repository and genotyping will have these samples collected. A 14-mL whole-blood sample will be collected at the specified time points.
H. Blood pressure, respiratory rate, heart rate, and temperature. On dosing days, vital signs should be taken pre- dose.
I. Height and weight should be measured at screening.
J. Perform assessments prior to dilating the eyes.
K. In select countries, the MNREAD or Radner Reading Charts should be done during the study visit, prior to dilating the eyes. It should be performed monocularly first, then binocularly.
L. To be administered by the masked site staff prior to any other assessments performed on that day. In-clinic assessments on the digital application should be completed after completion of all functional tests and quality of life measures prior to dilating the eyes.
M. At select sites, and for those subjects who decide to participate, the digital applications will be completed on an electronic device and will consist of assessments for visual function and reading speed. Subjects will receive training at Day 1 on the use of the digital applications and the electronic device and will perform the tests using the application in the clinic at Month 1, Month 2, Month 3, Month 6, Month 12, Month 18, and Month 24. Beginning at Day 1, subjects will complete the functional assessments weekly at home. Subjects should be instructed to complete the assessments on the same day each week and at approximately the same time of day each week, if possible.
N. FAF and SD-OCT images, near infrared reflectance, fluorescein angiograms, and fundus photographs will be performed for the study eye only on days where 'SE' is specified and for both eyes at all other visits as specified in the above schedule and will be sent to the reading center for evaluation (consult the reading center manual for specifics on image capture, processing, and transmission). Images should be captured prior to dosing on dosing days. If a subject misses a study visit or images cannot be obtained at a specific visit, study staff should make every effort to obtain images at the next scheduled visit. If new active CNV is suspected, SD-OCT, FFA, and OCT-A (selected sites) images should be collected and sent to the reading center for analysis.
O. Postinjection assessments should be performed within 5 minutes after dosing by the unmasked physician or study staff and should include a gross assessment of vision (finger-counting, hand motion, then light perception when applicable). If subject passes gross vision test, the subject may leave the site. If subject fails gross vision test, the tonometry should be performed. IOP should be ≤30 mm Hg in order for the subject to leave the site. If necessary, antiglaucomatous medication can be given in order to lower IOP. If IOP is >30 mm Hg, assessments will continue every approximately 30 minutes from the previous measurement until the subject passes the gross vision test and IOP is ≤30 mm Hg. Note: if the study eye is treated with a ranibizumab or aflibercept injection during the same visit as the study treatment (pegcetacoplan or sham), the treatment with ranibizumab or aflibercept must be performed first. The pre- and post- anti-VEGF IOP values must be measured and recorded on the eCRF.
P. Starting at Day 1, study subjects will be contacted by study site staff within 4 ± 2 days after each study treatment visit (through Month 4) to collect any information on any safety concerns, decrease in vision, eye pain, unusual ocular events, or any new ocular symptoms in the study eye. If the investigator determines that there are any safety concerns, a follow-up visit should be scheduled as soon as possible.
Q. Record concomitant medications (ie, prescription and over-the-counter medications) used by the patient within 30 days of screening and throughout the subject's participation in the study.
R. In addition to the time points indicated on the study schedule, OCT-A should be performed at the time of any suspected new active CNV. If new active CNV is confirmed in the study eye, OCT-A should be repeated every 2 months for the study eye.
S. At select sites only.
T. Administration of pegcetacoplan or sham can be done on separate days from the assessment visit if both days fall within the visit window. Administration of study treatment (pegcetacoplan or sham) can be done on a separate day from the assessment visit if both days fall within the visit window. If this occurs on the randomization visit, then the administration of pegcetacoplan or sham should be done within 3 days of randomization and after approval from the medical monitor. When study treatment administration is on a day other than a study visit, then the only assessment that must be done on the day of study treatment administration is preinjection IOP. <u>During the COVID-19 pandemic, the following flexibility is allowed for IP administration: –16 days to +30 days after medical monitor approval.</u>

1.2 Sample of SAS Code

```
* The SAS codes in this section are shown as examples
* Some modifications (such as variables used in the model statement)
* may require further changes to reflect the methods specified in the
* SAP and analysis data structure
* e.g., change trtan to trtpn to reflect analysis w/ the ITT set;
```

1.2.1. Mixed Effect Model for Repeated Measure

```
*-----------------------------------------------------
* Read Analysis data
*-----------------------------------------------------
* In this example, repeated measures are available at
* avisitn = 0.5 (baseline), 2 (Month 2),
*   6 (Month 6), and 12 (Month 12)
*-----------------------------------------------------;

data ga;
 set adam.adga;
 if paramcd = 'SEGAORG' and
 avisitn in (0.5, 2, 6, 12) and
 ANL01FL = 'Y';

  * trtan (actual treatment[number])
  * 1 = APL-2 Monthly
  * 2 = APL-2 Every Other Month
  * 3 = pooled Sham group;
 if trtan in (4,5) then trtan = 3;

 * trt01 are trt02 are used in multiple imputation
 * trt01 = 1 if Sham group
 * trt02 = 1 if APL2 Monthly group
 * trt01 = trt02 = 0 for APL2 EOM group;
 if trtan = 3 then trt01= 1; else trt01 = 0;
  if trtan = 1 then trt02= 1; else trt02 = 0;

 * avisitc will be used in PROC TRANSPOSE;
 if avisitn = 0.5 then avisitc = '00'; * Baseline;
 if avisitn = 2 then avisitc = '02'; * Month 2;
 if avisitn = 6 then avisitc = '06'; * Month 6;
 if avisitn = 12 then avisitc = '12'; * Month 12;
run;

*******************************;
*** MAIN ANALYSIS using MMRM ***;
*******************************;

proc mixed data=ga method=reml covtest empirical;
  where avisitn NE 0.5; * exclude rows for baseline;
  * cnv (CNV in the fellow eye)
  * 0 = No
  * 1 = Yes;
  *base cat (baseline lesion size (<7.5 vs. ≥ 7.5);
  class trtan cnv avisitn usubjid base_cat;
  model chg = trtan cnv base_cat avisitn trtan*avisitn base_cat*avisitn
  /cl;
```

```
 repeated avisitn / subject=usubjid type=un r;
 lsmeans trtan*avisitn/pdiff cl e alpha=.05;
 ods output diffs= diff1 LSMeans= LSMean1;
run;
```

1.2.2. Multiple Imputation

```
*******************************;
*** RESHAPE DATA FOR PROC MI ***;
*******************************;

proc sort data= ga;
 by usubjid cnv trta trtan trt01 trt02 param paramcd base base_cat avisitc;
run;

proc transpose data= ga out= ga_t(drop= _NAME_ _LABEL_) prefix=V;
 by usubjid cnv trta trtan trt01 trt02 param paramcd base base_cat;
 id avisitc;
 var aval;
run;

* Examine the missing patterns of the data;
proc mi data=ga_t nimpute=0;
 var cnv trtan v00 -- v12;
 ods output missPattern=pattern;
run;

***************************************;
*** MCMC (impute nonmonotone missing) ***;
***************************************;

* Below statements invoke MCMC procedure and specify IMPUTE=MONOTONE
 to turn the arbitrary missing patterns to monotone missing patterns
 under missing at random (MAR) assumption;

proc mi data=ga t out=ga t mono seed= 12135541 nimpute=1000;
 mcmc chain=multiple impute= monotone displayinit
     initial=em(itprint);
 var cnv trt01 trt02 v00 -- v12;
run;

* Examine the missing patterns of the data;
proc mi data=ga_t_mono nimpute=0;
 var cnv trt01 trt02 v00 -- v12;
 ods output missPattern=pattern;
run;

*****************************************************************;
*** Control-based pattern imputation(impute monotone missing) ***;
*****************************************************************;
data ga t mono2;
      set ga t mono;
      **Identify the subjects in the active groups we want to keep
  imputed as MAR;
      **DSCREASN is just an example;
      if trtan in (1,2) and DCSREASN = 1 then mar = 1;
      else mar = 0;
```

```
      run;

**First impute general MAR based on regression method for all subjects to get
the true MAR;
proc mi data=ga t_mono2 out=ga_step1 nimpute=1 seed=1284054;
 by  Imputation_;
 class trtan;
 monotone reg(v00 -- v12/details);
 var cnv trtan v00 -- v12;
run;

**Identify and keep the data from the subjects in the active group that
should remain as a MAR;
data ga step2;
      set ga step1;
      if Mar = 1;
      run;

**Update the dataset and keep the MAR imputed data for the subjects in the
active group that should remain as a MAR, all others remain to be imputed
with control based imputation;
data ga_t_mono3;
      update ga t mono2 ga step2;
      by  Imputation_ subjid;
      run;

**Fill out the remaining missing where missing data should be imputed based
on the controls;
proc mi data=ga t_mono3 out=ga_t_cbp nimpute=1 seed=1284054;
 by  imputation_;
 class trtan;
 var cnv v00 -- v12;
 monotone reg(/details);
 mnar model(v02 -- v12 / modelobs= (trtan='3'));
run;

**General control based (all monotone missing);
proc mi data=ga_t_mono out=ga_t_cbp2 nimpute=1 seed=1284054;
 by  imputation_;
 class trtan;
 var cnv v00 -- v12;
 monotone reg(/details);
 mnar model(v02 -- v12 / modelobs= (trtan='3'));
run;

*****************************************************************;
*** Delta-Adjusted Pattern Imputation (impute monotone missing) ***;
*****************************************************************;
**First identify the subjects in the active treatment groups that we want to
apply the shift parameter if they have monotone missing data;
data ga t mono2;
      set ga_t_mono;

      **This is just an example of a reason that we do not want to
  apply the shift parameter. The actual reasons are in the text;
      if DCSREAS1 = "Death" then flag = 1;
      else flag = 0;
```

```
      if trtan in (1,2) and flag = 0 then adjustthis = 1;
      else adjustthis = 0;
      run;

proc mi data=ga t_mono2 out=ga_t_tip6 nimpute=1 seed=9484353;
 by _imputation_;
 class trtan adjustthis;
 var cnv trtan v00 -- v12;
 monotone reg(/details);
 mnar adjust(v02 / shift=0.12 adjustobs=(adjustthis = '1' ))
  adjust(v06 / shift=0.12 adjustobs=(adjustthis = '1' ))
  adjust(v12 / shift=0.12 adjustobs=(adjustthis = '1' ));
run;

*****************************************************;
*** SAS macro to run MIANALYZE on outputs from MMRM *;
*****************************************************;

%macro mi_results(in, lsm, dif);

* After imputation, the data sets are in the wide format in which
 different variables (V00--V12) represent the outcome measured at
 different occasions. Before analyzing using PROC MIXED,
 the data sets need to be converted into long format in which one
 variable represents all outcome with different values of AVISITN
 differentiating different occasions;

proc transpose data= &in
    out= ga mi (rename= ( NAME  = AVISITN COL1 = AVAL));
 by _imputation_ usubjid trta trtan trt01 trt02 param paramcd base base_cat;
 var V00 -- V12;
run;

data ga mi;
 set ga mi;
 label AVISITN = 'AVISITN';
  chg = aval - base;
  * baseline record is not used in MMRM;
 if AVISITN = 'V00' then delete;
run;

proc sort; by _imputation_; run;

proc mixed data=ga_mi method=reml empirical;
 by _imputation_;
 class trtan cnv avisitn usubjid base_cat;
 model chg=trtan cnv base cat avisitn trtan*avisitn base_cat*avisitn / cl;
 repeated avisitn / subject=usubjid type=UN;
 lsmeans trtan*avisitn / pdiff cl alpha=.05;
 ods output diffs= diffs lsmeans= lsmeans;
run;

* In the final step, the analysis results obtained from PROC MIXED
  procedure are combined into a single estimation with standard error
  using PROC MIANALYZE;
```

```
proc sort data=lsmeans;
 by avisitn trtan _imputation_;
run;
proc mianalyze parms=lsmeans;
 by avisitn trtan;
 modeleffects trtan*avisitn;
 ods output ParameterEstimates=&lsm;
run;

proc sort data=diffs (where= (_trtan= 3 and (avisitn = _avisitn)));
 by avisitn trtan _trtan _imputation_;
run;

proc mianalyze parms=diffs;
 by avisitn trtan  trtan;
 modeleffects trtan*avisitn;
 ods output ParameterEstimates=&dif;
run;

proc sql; *** LSMEANS using Multiple Imputation;
  select Parm as Effect, AVISITN, TRTAN, Estimate, StdErr, DF,
    tValue, Probt, LCLMean as L95, UCLMean as U95
 from &lsm;

  select Parm as Effect, AVISITN, TRTAN, _TRTAN, Estimate, StdErr, DF,
    tValue, Probt, LCLMean as L95, UCLMean as U95
 from &dif;
quit;
%mend;

%mi_results(in= ga_t_mcmc, lsm= lsm_mcmc, dif=dif_mcmc);
%mi_results(in= ga_t_reg, lsm= lsm_reg, dif=dif_reg );
%mi_results(in= ga_t_cbp, lsm= lsm_cbp, dif=dif_cbp );
%mi_results(in= ga_t_tip6, lsm= lsm_tip6, dif=dif_tip6);
```

1.2.3. Rate of Change Models

```
*******************************;
*** Rate of Change analyses ***;

* In this example, repeated measures are available at
* avisitn = 0 (baseline), 2 (Month 2), 4 (Month 4)
*   6 (Month 6), 8 (Month 8), 10 (Month 10) and 12 (Month 12)
*
* AVAL is the actual GA lesion measurement at the corresponding visit * for
the study eye from ADGA.
* SGALESAT is the GA lesion size (categorical) at baseline
* FCNVAT is the fellow eye CNV status at baseline
* TR01PG2N is the pooled treatment group (1 = PM, 2 = PEOM, 3 = Sham)
* T is equivalent to AVISITN
*
* The data is read in from ADGA
*******************************;


proc mixed data=ga method=reml covtest empirical;
```

```
      class subjid TR01PG2N FCNVAT SGALESAT t;
      model aval = SGALESAT TR01PG2N avisitn TR01PG2N * avisitn
            SGALESAT*avisitn FCNVAT/cl solution;
      repeated t /type=un sub=subjid r ;

      **Month 6;
      estimate 'PM Month 0 to 6 slope' TR01PG2N*avisitn 6 0 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'PEOM Month 0 to 6 slope' TR01PG2N*avisitn 0 6 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'Sham Month 0 to 6 slope' TR01PG2N*avisitn 0 0 6
            avisitn 6 SGALESAT*avisitn 3 3 /cl;

      estimate 'Month 0 to Month 6 Difference in slope PM - Sham'
            TR01PG2N*avisitn 6 0 -6 /cl;
      estimate 'Month 0 to Month 6 Difference in slope PEOM - Sham'
            TR01PG2N*avisitn 0 6 -6 /cl;
      estimate 'Month 0 to Month 6 Difference in slope PM - PEOM'
            TR01PG2N*avisitn 6 -6 0 /cl;

      **Month 12;
      estimate 'PM Month 6 to 12 slope' TR01PG2N*avisitn 6 0 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'PEOM Month 6 to 12 slope' TR01PG2N*avisitn 0 6 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'Sham Month 6 to 12 slope' TR01PG2N*avisitn 0 0 6
            avisitn 6 SGALESAT*avisitn 3 3 /cl;

      estimate 'Month 6 to 12 Difference in slope PM - Sham'
            TR01PG2N*avisitn 6 0 -6 /cl;
      estimate 'Month 6 to 12 Difference in slope PEOM - Sham'
            TR01PG2N*avisitn 0 6 -6 /cl;
      estimate 'Month 6 to 12 Difference in slope PM - PEOM'
            TR01PG2N*avisitn 6 -6 0 /cl;

      ods output diffs= diff2 LSMeans= LSMean2 CovParms = COV2
            estimates = estimates2;

      **Month 0 to 12;
      estimate 'PM Month 0 to 12 slope' TR01PG2N*avisitn 12 0 0
            avisitn 12 SGALESAT*avisitn 6 6 /cl;
      estimate 'PEOM Month 0 to 12 slope' TR01PG2N*avisitn 0 12 0
            avisitn 12 SGALESAT*avisitn 6 6 /cl;
      estimate 'Sham Month 0 to 12 slope' TR01PG2N*avisitn 0 0 12
            avisitn 12 SGALESAT*avisitn 6 6 /cl;

      estimate 'Month 0 to Month 12 Difference in slope PM - Sham'
            TR01PG2N*avisitn 12 0 -12 /cl;
      estimate 'Month 0 to Month 12 Difference in slope PEOM - Sham'
            TR01PG2N*avisitn 0 12 -12 /cl;
      estimate 'Month 0 to Month 12 Difference in slope PM - PEOM'
            TR01PG2N*avisitn 12 -12 0 /cl;

run;
```

```
* For the piecewise model, a knot at Month 6 is added to the dataset and
included in the model to allow for different slopes for the two 6 month
periods;

data ga2;
      set ga;

      k = 6;
      if avisitn <= k then avisitnspl1 = 0;
      if avisitn > k then avisitnspl1 = avisitn - k;
run;

proc mixed data=ga2 method=reml covtest empirical;
      class subjid TR01PG2N FCNVAT SGALESAT t;
      model aval = SGALESAT TR01PG2N avisitn avisitnspl1 TR01PG2N *
            avisitn TR01PG2N*avisitnspl1 SGALESAT*avisitn
            SGALESAT*avisitnspl1 FCNVAT/cl ;
      repeated t /type=un sub=subjid r ;

      **Month 6;
      estimate 'PM Month 0 to 6 slope' TR01PG2N*avisitn 6 0 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'PEOM Month 0 to 6 slope' TR01PG2N*avisitn 0 6 0
            avisitn 6 SGALESAT*avisitn 3 3 /cl;
      estimate 'Sham Month 0 to 6 slope' TR01PG2N*avisitn 0 0 6
            avisitn 6 SGALESAT*avisitn 3 3 /cl;

      estimate 'Month 0 to Month 6 Difference in slope PM - Sham'
            TR01PG2N*avisitn 6 0 -6 /cl;
      estimate 'Month 0 to Month 6 Difference in slope PEOM - Sham'
            TR01PG2N*avisitn 0 6 -6 /cl;
      estimate 'Month 0 to Month 6 Difference in slope PM - PEOM'
            TR01PG2N*avisitn 6 -6 0 /cl;

      **Month 12;
      estimate 'PM Month 6 to 12 slope' TR01PG2N*avisitn 6 0 0
            avisitn 6 SGALESAT*avisitn 3 3 TR01PG2N*avisitnspl1 6 0 0
            avisitnspl1 6 SGALESAT*avisitnspl1 3 3 /cl;
      estimate 'PEOM Month 6 to 12 slope' TR01PG2N*avisitn 0 6 0
            avisitn 6 SGALESAT*avisitn 3 3 TR01PG2N*avisitnspl1 0 6 0
            avisitnspl1 6 SGALESAT*avisitnspl1 3 3 /cl;
      estimate 'Sham Month 6 to 12 slope' TR01PG2N*avisitn 0 0 6
            avisitn 6 SGALESAT*avisitn 3 3 TR01PG2N*avisitnspl1 0 0 6
            avisitnspl1 6 SGALESAT*avisitnspl1 3 3 /cl;

      estimate 'Month 6 to 12 Difference in slope PM - Sham'
            TR01PG2N*avisitn 6 0 -6 TR01PG2N*avisitnspl1 6 0 -6/cl;
      estimate 'Month 6 to 12 Difference in slope PEOM - Sham'
            TR01PG2N*avisitn 0 6 -6 TR01PG2N*avisitnspl1 0 6 -6/cl;
      estimate 'Month 6 to 12 Difference in slope PM - PEOM'
            TR01PG2N*avisitn 6 -6 0 TR01PG2N*avisitnspl1 6 -6 0/cl;

      ods output diffs= diff2 LSMeans= LSMean2 CovParms = COV2
            estimates = estimates2;
run;
```

1.2.4. Sample Code for Maximum Reading Speed and Critical Print Size

Please see below regarding the uncorrected and corrected reading speed calculation, and Critical Print Size: Flag = 1 MNREAD , 2 = Radner .

```
if flag = 1 then do;
   if (time  = 0 or notdone = 1) then urs = 0;
   /** "Not Done" indicates the print size was not attempted due to vision or
that the sentence was attempted but could not be read **/
   else if time > 0 then urs = 600/time;
   if urs > 300 then urs = 300;
    /** Calculate Corrected Reading Speed **/
   if (time = 0 or numerr >= 10) or (notdone = 1) then crs = 0;
   else if numerr >=0 and time > 0 then crs = 60*(10-numerr)/time;
   else if (numerr = 0 or time = 0) then crs = urs;
   if crs > 300 then crs = 300;
  end;
  if flag = 2 then do;
   if (time  = 0 or notdone = 1) then urs = 0;
   else if time > 0 then urs =  840/time;
   if urs > 300 then urs = 300;
   if (time = 0 or numerr >= 14) or (notdone = 1) then crs = 0;
   else if numerr >=0 and time  > 0 then crs = 60*(14-numerr)/time;
   else if (numerr = 0 or time = 0) then crs = urs;
   if crs > 300 then crs = 300;
end;

Critical Print Size:
if flag = 1 and n(aval,dist) =2 and dist ne 40 then aval = aval +
round(log10(40/dist),.01); /** Apply correction for viewing distance ne 40
**/
if flag = 2 and n(aval,dist) =2 and dist not in (32 40) then aval = aval -
0.1 + round(log10(40/dist),.01);
```