PEGCETACOPLAN (APL-2)

PROTOCOL APL2-304

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO COMPARE THE EFFICACY AND SAFETY OF INTRAVITREAL PEGCETACOPLAN THERAPY WITH SHAM INJECTIONS IN PATIENTS WITH GEOGRAPHIC ATROPHY (GA) SECONDARY TO AGE-RELATED MACULAR DEGENERATION (AMD)

US IND No.: 124784

EudraCT No.: 2018-001435-52

Phase: 3

Version: Amendment 5

Date: 12 August 2020

INVESTIGATOR AGREEMENT

Long Title:	A Phase 3, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal Pegcetacoplan Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)
Short Title:	Oaks
Protocol Number, Version, and Date:	APL2-304 / Amendment 5 / 12 August 2020
Study Phase:	Phase 3
Sponsor Name and Address:	Apellis Pharmaceuticals, Inc 100 5th Ave Waltham, MA 02451 USA
Investigational Test Article:	Pegcetacoplan intravitreal injection (also known as APL-2)
US IND Number:	124784
EudraCT Number:	2018-001435-52
Indication Studied:	Geographic atrophy secondary to age-related macular degeneration
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.

Principal Investigator:

Name: _____

Signature: _____

Date: _____/_____/_____ (DD/MMM/YYYY)

Pegcetacoplan
APL2-304 Protocol Amendment 5 12 August 2020

SPONSOR INFORMATION

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 5: Summary of Changes From the Previous Version

Amendment Date: 12 August 2020

Updates to the protocol implemented in this amendment are provided in the table below.

Description of change	Section(s) affected by change
Nonsubstantial changes that did not impact content of the document have been made for clarity.	Entire document
Updated company address	Investigator Agreement and Sponsor Information
Changed APL-2 to International Nonproprietary Name: pegcetacoplan, updated related abbreviations and protocol title	Entire document
Added the descriptor "maximum" when referencing reading speed	Synopsis, Section 5.1.2, Section 5.1.5, Section 12.7.2, Section 12.7.3
Removed the 6-month follow-up period and updated the study length from 30 months to 24 months and made it a 30- or 60-day follow-up period based on treatment group because that length of time is deemed sufficient to evaluate the safety of pegcetacoplan based on its half-life in the vitreous. Additionally, there is an option for subjects to enroll in a separate extension study (Study APL2-GA-305) during which longer-term safety and efficacy will be collected.	Synopsis, Section 8, Section 8.1.3.2.1, Section 11.8
Inclusion criterion 6c was updated from "Reliability test ratio must be ≤20%" to "Fixation losses must be ≤20%" on the basis of regulatory feedback provided to the microperimetry device manufacturer	Synopsis, Section 6.1.1
Updated the text regarding the sample size to both simplify and reduce redundancies	Synopsis, Section 12.5
Previous Section 4.1.3.1, Pharmacokinetics, moved to Section 4.1.3.2 to follow Section 4.1.3.1, Toxicology	Section 4.1.3.1, Section 4.1.3.2
Updated the formulation information	Section 4.1.2, Section 7.3.3.1
Revised number of injections for each treatment arm because the injections at Month 24 will no longer be administered	Section 7.3.1 (Table 1), Section 8
Updated the text regarding endophthalmitis for clarity	Section 7.5.3
Updated Study Schema	Section 8
Revised Study Procedures based on the removal of the Month 24 injection and the 6-month follow-up period	Section 8
Revised the language regarding genotyping samples to indicate that these samples will be collected only for subjects who consent to the analysis	Section 9.7
Updated the language within the Adverse Events definition section to be consistent with the new Apellis standard language	Section 11.1
Updated the language within the Recording Adverse Events section to be consistent with the new Apellis standard language	Section 11.2

Removed the section on Treatment and Follow-up of Adverse Events because the information contained within it is now included in other revised sections to align with new Apellis standard language	Section 11.3
Updated the language within the Reporting Adverse Events section to be consistent with the new Apellis standard language	Section 11.3
Updated the language within the Serious Adverse Events section to be consistent with the new Apellis standard language	Section 11.4
Removed the section on Unexpected Adverse Events or Unexpected Suspected Adverse Reactions because the information contained within it is now included in other revised sections to align with new Apellis standard language	previously Section 11.6
Updated the language within the Pregnancy section to be consistent with the new Apellis standard language	Section 11.6
Removed APL-2 investigator's brochure from references	Section 15
Updated Footnote G and M	Appendix A, Appendix B, Appendix C, Appendix D, and Appendix K
Deleted follow-up visits from Schedules of Activities	Appendix B and Appendix D, and Table B and Table D of Appendix K
Deleted pegcetacoplan and sham administration and postinjection assessment from Visit 20 of the Schedule of Activities for monthly and every-other-month treatment groups Month 13 to Month 24	Appendix B and Appendix D and Tables B and D of Appendix K

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2. SYNOPSIS

Study Title

A Phase 3, Multicenter, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal Pegcetacoplan Therapy With Sham Injections in Patients With Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Protocol Number, Version, and Date

APL2-304/ Amendment 5/ 12 August 2020

Investigational Product, Dose, and Route of Administration

- Pegcetacoplan (also known as APL-2)
- 15 mg/0.1 mL
- Intravitreal (IVT) Injection

Study Arms

Arm	Abbreviation	Randomization
Pegcetacoplan 15 mg/0.1 mL monthly for 24 months	PM	2
Pegcetacoplan 15 mg/0.1 mL every other month for 24 months	PEOM	2
Sham monthly for 24 months	SM	1
Sham every other month for 24 months	SEOM	1

Study Phase and Type

Phase 3, multicenter, randomized, double-masked, sham-injection controlled

Number of Subjects and Sites

- Approximately 600 subjects
- Approximately 100 sites

Objectives

Primary

To evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD assessed by change in the total area of GA lesions from baseline as measured by FAF.

Key Secondary

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

- Monocular maximum reading speed (study eye), as assessed by Minnesota Low-Vision Reading Test (MNREAD) or Radner Reading Charts (in select countries)
- Functional Reading Independence (FRI) index score
- Normal luminance best corrected visual acuity score (NL-BCVA) in the study eye

Secondary:

- To evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD with respect to:
    - Low luminance best corrected visual acuity score (LL-BCVA) 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)
    - Macular functional response as assessed by mesopic microperimetry

Safety:

- To evaluate the safety and tolerability of pegcetacoplan compared to sham injection in patients with GA secondary to AMD as indicated by:
    - Incidence and severity of ocular and systemic treatment-emergent adverse events
    - Incidence of anti-therapeutic antibodies directed against pegcetacoplan
    - Incidence of new active CNV in the study eye

Exploratory

- To evaluate the efficacy of pegcetacoplan compared to sham injection in patients 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 in change in GA lesion size
    - To evaluate the binocular maximum 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)

Inclusion Criteria

The study eye must meet all inclusion criteria. If both eyes meet the inclusion criteria, the eye with the worst visual acuity at the screening visit will be designated as the study eye. If both eyes have the same visual acuity, the right eye will be selected as the study eye.

Ocular-specific inclusion criteria apply to the **study eye** only, unless otherwise specified.

1. Age ≥60 years.
2. Normal Luminance best corrected visual acuity of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent).
3. Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
4. The GA lesion must meet the following criteria as determined by the central reading center's assessment of fundus autofluorescence (FAF) imaging at screening:
    a. Total GA area must be ≥2.5 and ≤17.5 mm^2 (1 and 7 disk areas [DA] respectively)
    b. If GA is multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 DA), with the overall aggregate area of GA as specified above in 4a.
    c. 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.
    d. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (ie, pattern = none) is exclusionary.[1]
5. Adequate clarity of ocular media, adequate pupillary dilation, and fixation to permit the collection of good quality images as determined by the investigator.
6. Meets the following criteria related to microperimetry:
    a. Able to detect fixation target.
    b. Total elapsed time to complete the 10-2 68-point exam is ≤30 minutes in duration.
    c. Fixation losses must be ≤20%.
    d. Subject is willing and able to undertake microperimetry assessment in the opinion of the investigator.
7. Female subjects must be:
    a. Women of non–childbearing potential (WONCBP), or
    b. Women of childbearing potential (WOCBP) with a negative serum pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and refrain from breastfeeding for the duration of the study.
8. Males with female partners of childbearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.
9. Willing and able to give informed consent and to comply with the study procedures and assessments.

Exclusion Criteria

Ocular specific exclusion criteria apply to the **study eye** only, unless otherwise specified.

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.

2. Spherical equivalent of the refractive error demonstrating > 6 diopters of myopia or an axial length >26 mm.
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 SD-OCT imaging and/or fluorescein angiography as assessed by the reading center.
4. Presence of an active ocular disease that in the opinion of the investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (eg, clinically significant epiretinal membrane [ERM], full thickness macular hole or uncontrolled glaucoma/ocular hypertension). Benign conditions in the opinion of the investigator such as peripheral retina dystrophy are not exclusionary.
5. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.
6. History of laser therapy in the macular region.
7. Aphakia or absence of the posterior capsule. Note: YAG laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not exclusionary.
8. Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention during the study period or, in the opinion of the investigator, could compromise visual function during the study period.
9. Any contraindication to IVT injection including current ocular or periocular infection.
10. History of prior intravitreal injection.
11. Unable to perform microperimetry reliably in the opinion of the investigator.
12. Prior participation in another interventional clinical study for intravitreal therapies in either eye (including subjects receiving sham).
13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo.
14. Participation in any systemic experimental treatment or any other systemic investigational new drug within 6 weeks or 5 half-lives of the active ingredient (whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.
15. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the 24-month treatment period unlikely, or would make the subject an unsafe study candidate.
16. Any screening laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the investigator is clinically significant and not suitable for study participation.
17. Known hypersensitivity to fluorescein sodium for injection or hypersensitivity to pegcetacoplan or any of the excipients in pegcetacoplan solution.

Study Design

This is a 24-month, Phase 3, multicenter, randomized, double-masked, sham-injection controlled study to assess the efficacy and safety of multiple IVT injections of pegcetacoplan in subjects with GA secondary to AMD.

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 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, pegcetacoplan every other month, sham injection monthly, or sham injection every other month, 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.

All subjects will be assessed monthly during the first 12 months regardless of treatment regimen. From Month 12 to Month 24, subjects will follow the outlined visit schedule (Appendix A to Appendix D) based on treatment assignment (ie, subjects in the monthly groups will be assessed monthly while subjects in the every-other-month [EOM] groups will be assessed every other month). The last visit in the study will be at Month 24, approximately 30 days (monthly treatment group) or 60 days (EOM treatment group) after the last visit at which investigational product is administered. At the end of the 24-month study period, subjects will have the option to enroll into a separate open-label study.

Subjects who discontinue study treatment can continue participation in the study and should be encouraged to return to the clinical site for as many follow-up visits as they can (with the exception of pegcetacoplan/sham administration). Subjects who wish to fully withdraw from the study before Month 24, should be encouraged to complete the early termination visit.

Endpoints and statistical analysis:

Endpoints

Primary Efficacy Endpoint

- Change from baseline to Month 12 in total area of GA lesion(s) in the study eye (in mm^2) based on fundus autofluorescence (FAF).

Key Secondary Efficacy Endpoints

- Change from baseline in monocular maximum reading speed (study eye), as assessed by MNREAD or Radner Reading Charts at Month 24 (in select countries)
- Change from baseline in Functional Reading Independence (FRI) index score, at Month 24.
- Change from baseline in normal luminance best corrected visual acuity score (NL-BCVA) at Month 24 as assessed by ETDRS chart.

Secondary Efficacy Endpoints

- Change from baseline in low luminance best corrected visual acuity score (LL-BCVA) at Month 12 and Month 24 as assessed by ETDRS chart.
- Change from baseline in low luminance deficit (LLD) at Month 12 and Month 24.
- Change from baseline at each planned assessment in the total area of GA lesion(s) in the study eye (in mm^2) as assessed by FAF.
- Change from baseline in monocular critical print size (study eye), as assessed by MNREAD or Radner Reading Charts, at Month 12 and Month 24 (in select countries).
- Change from baseline in the National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ-25) distance activity subscale score at Month 12 and Month 24 (in select sites).
- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response.

- Change in macular sensitivity as assessed by mesopic microperimetry for the evaluation of the macular functional response.

Exploratory Endpoints

- Change from baseline in NEI VFQ-25 composite score at Month 12 and Month 24.
- Change from baseline in NEI VFQ-25 near activity subscale score at Month 12 and Month 24 (in select countries).
- Comparison between study eye and fellow eye in change in GA lesion size from baseline to Month 12 and Month 24.
- Binocular maximum reading speed as assessed by MNREAD or Radner Reading Charts over time (in select countries).
- Binocular critical print size as assessed by MNREAD or Radner Reading Charts over time (in select countries).
- Relationship between genetic polymorphisms associated with AMD with GA progression and response to pegcetacoplan.
- Incidence of new onset of subclinical CNV in the study eye.
- Assess sensitivity and specificity of a digital reading speed application to detect disease progression / regression (optional, select sites).
- Assess sensitivity and specificity of a digital visual function application to detect disease progression / regression (optional, select sites).

Safety Endpoints

- Incidence and severity of ocular and systemic treatment-emergent adverse events.
- Incidence of anti-therapeutic antibodies directed against pegcetacoplan.
- Incidence of new active CNV in the study eye.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Month 12 in the total area of GA lesion(s) in eyes injected with pegcetacoplan, either monthly (PM) or every-other month (PEOM), or sham injections. GA lesion area (mm^2) as measured by a quantified central reading center based on FAF images. The primary analysis will be the comparison of pegcetacoplan, either monthly (PM) or every-other month (PEOM) versus the combined 2 sham arms (the 2 sham arms will be combined into a single 'control' group).

The null and alternative hypotheses for the primary efficacy analysis are:

H_0: $\mu_S = \mu_{PM}$ vs H_A: $\mu_S \neq \mu_{PM}$, and

H_0: $\mu_S = \mu_{PEOM}$ vs H_A: $\mu_S \neq \mu_{PEOM}$

Note: here μ indicates each group's respective mean change from baseline to Month 12 in GA lesion area for the comparison of the primary endpoint.

A mixed effect model for longitudinal data will be used to analyze the change from baseline in GA lesion area. The model will include treatment, and presence of CNV in the fellow eye as fixed effects; baseline GA lesion area (at screening), time (in months) as a factor; as well as the time × treatment interaction term. All available data up to 12

months will be included in the model for the primary analysis. The mean change from baseline to 12 months will be estimated from the model (ie, least square [LS] mean) and compared between each of the pegcetacoplan arms to the sham control. For other time point of interest, LS mean change from baseline will be estimated and compared between treatments. Unstructured variance covariance will be used,

For the analysis of final study data, a similar model including data up to 24 months will be used and LS means at time points of interest will be estimated and compared between treatment.

This study is expected to have an approximately 5 DMC data reviews. Allocating an alpha level of 0.0001 for each DMC data review, the alpha level remains for the efficacy analysis at 0.0495 to maintain an overall study alpha of 0.05.

The hypothesis testing strategy for the primary and secondary efficacy endpoints will be based on the Gate-keeping multiple testing procedures controlling for the study wide type I error strongly at 2-sided 0.0495 as follows:

Step 1. The mean GA lesion growth at 12 months will be compared between the PM group and the Control at the α level of 0.0495. If the null hypotheses of no difference between groups in this step is rejected, the testing proceeds to **Step 2** and **Step 3**. If it's not rejected, the testing procedure stops at this step.

Step 2. The mean GA lesion growth at 12 months will be compared between the PEOM group and the Control at the **α1** level. If the null hypotheses of no difference between groups in this step is rejected, the **α1** level will be passed down to **Step 3**. The actual value of **α1** will be specified in the SAP and it will be defined to ensure an adequate power of at least 80% for the comparison in this step.

Step 3. The mean GA lesion growth at 24 months will be compared between the PM group and the Control at the α level of **0.0495** if the null hypotheses are rejected at both **Step 1** and **Step 2**; or at the α level of **(0.0495 – α1)** if **Step 2** testing does not reject the null hypothesis. If the null hypothesis at this step is rejected, the α level used at this step will be passed down to the next step of testing. If it's not rejected, the testing procedure stops at this step.

Step 4. The prioritization and alpha allocation for the remaining secondary endpoints will be specified in the SAP.

The following sensitivity and supportive analyses will be performed to evaluate the robustness of the results from the primary analysis method:

- Analyses will be repeated using the mITT and per-protocol sets
- Primary and secondary endpoints will also be summarized with no pooling of the 2 sham arms. The comparison for pegcetacoplan and sham injection within each dose regimen (ie, PM vs SM and PEOM vs SEOM) will be conducted
- Multiple imputation (MI) methods and other sensitivity analyses will be explored, and details will be provided in the SAP

Analysis for Key Secondary and Secondary Endpoint(s)

The key secondary and secondary endpoints will be analyzed in the same fashion as the primary endpoint using mixed effect model. The binary secondary endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. Hypothesis testing for 3 key secondary endpoints will be performed in the order specified. The SAP will provide more details on multiplicity adjustment and the approach for alpha spending among the endpoints.

Sample Size Justification

Subjects will be randomized in a 2:2:1:1 ratio to receive treatment with pegcetacoplan monthly, pegcetacoplan every other month, sham monthly, or sham every other month. 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 pegcetacoplan monthly, pegcetacoplan every-other-month, and sham-pooled groups, respectively, as estimated from the results of a Phase 2 trial for 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.[27] ie, With a sample size of 200 subjects in each group (ie, a total enrollment of 600 subjects) and the observed annual growth rate in GA lesion area from Phase 2 trial for pegcetacoplan, the study will have 99.2% power to show the difference between PM and sham group and 81.5% power to show the difference between PEOM and sham group using the common standard deviation of 1.5 mm^2 and 2-sided alpha of 0.05. The approximation is calculated using PROC POWER one-way analysis of variance, SAS 9.4. The study power is likely larger when utilizing the longitudinal data to model the primary endpoint. The actual study power may also vary based on the distribution of the stratification factors (ie, lesion area at screening, presence of CNV in fellow eye), and site enrollment.

3. ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AMD	age-related macular degeneration
ATA	anti-therapeutic antibodies
BCVA	best corrected visual acuity
CH50	classical pathway of complement functional test
CNV	choroidal neovascularization
CRF (eCRF)	case report form (electronic CRF) (used interchangeably)
DA	disk area
DCFP	digital color fundus photography
DMC	data monitoring committee
EDC	electronic data capture
EOM	every other month
ERG	electroretinography
ERM	epiretinal membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	fundus autofluorescence
FFA/FA	fundus fluorescein angiography or fluorescein angiography
FRI	functional reading independence index
FSH	follicle-stimulating hormone
GA	geographic atrophy
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
IB	investigator's brochure
ICF	informed consent form form
ICH	International Council for Harmonisation
IEC	independent ethics committee

Abbreviation	Term
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVT	intravitreal
IWR	interactive web response
LH	luteinizing hormone
LL-BCVA	low luminance best corrected visual acuity
LLD	low luminance deficit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat
MNREAD	Minnesota Low-Vision Reading Test
MOP	manual of procedures
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25-Item Version
NIR	near infrared reflectance
NOEL	no observable effect level
NL-BCVA	normal luminance best corrected visual acuity
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PEG	polyethylene glycol
PEG40	polyethylene glycol (40-kDa nominal molecular weight)
PEOM	pegcetacoplan every-other-month
PI	principal investigator
PK	pharmacokinetics
PM	pegcetacoplan monthly
PP	per protocol
RPE	retinal pigment epithelium
SAE	serious adverse event
SC	subcutaneous

Abbreviation	Term
SC5b-9	soluble terminal complement complex
SD-OCT	spectral domain optical coherence tomography
SEOM	sham every-other-month
SM	sham monthly
SOP	standard operating procedures
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal elimination half-life
VA	visual acuity
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential
WONCBP	women of nonchildbearing potential

4. INTRODUCTION

4.1. Background

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan for advanced Age-related Macular Degeneration (AMD) (neovascular AMD and geographic atrophy [GA]). The trial will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will comprise adult male and female subjects with GA secondary to AMD.

4.1.1. Age-Related Macular Degeneration

Age-related macular degeneration is the leading cause of severe vision loss in people over the age of 65 in the United States and other Western countries.[2] In the United States, about 1.75 million people have the advanced forms of AMD.[3] The early signs of AMD (drusen and pigmentary changes) are common in individuals over age 65 and precede the late stage forms, which are visually devastating. The late stage forms of AMD are classified into either macular neovascularization (neovascular, wet, or exudative AMD) or GA.

Geographic Atrophy is a disease characterized by thinning and loss of the retinal pigment epithelium (RPE) and concurrent atrophy of photoreceptors and choriocapillaris.[4,5,6] Clinically, GA is characterized by gradually expanding atrophy leaving islands of dead retinal cells in the back of the eye. Although GA can result in significant visual function deficits in reading, night vision, and dark adaptation, and produce dense, irreversible scotomas in the visual field, the initial decline in visual acuity may be relatively limited if the fovea is spared. When the fovea is involved, GA quickly causes blindness.

Genetic susceptibility has become increasingly recognized as a risk factor and important contributor to AMD. More than 19 genetic polymorphisms have been demonstrated to influence AMD risk, with as many as 5 of these encoded by genes that modulate the complement system. Inflammatory processes, especially those mediated by complement are thought to play a key role in AMD.[5] It is thought that these may contribute to loss of choriocapillaris, photoreceptors, and RPE cells.

GA is responsible for approximately 20% of all cases of legal blindness in North America (ie, BCVA 20/200 or worse) with increasing incidence and prevalence owing to a higher life expectancy.[4] While there is treatment for exudative AMD with anti-VEGF therapies, no approved therapy exists for GA which is usually bilateral and relentlessly progressive. It represents a significant unmet need as it leads to significant visual impairment and affects more than 5 million people worldwide.[13]

An overview of available information regarding pegcetacoplan follows below. Further details can be found in the pegcetacoplan investigator's brochure (IB).[26]

4.1.2. Pegcetacoplan

Pegcetacoplan is a PEGylated cyclic peptide inhibitor of complement C3. Pegcetacoplan is formed by 2 identical pentadecapeptides (combining a bioactive cyclic tridecapeptide C3-

inhibiting moiety and a 2-amino acid linker) covalently coupled to each end of a linear 40 kDa polyethylene glycol (PEG) chain. There are 2 peptide moieties per molecule of pegcetacoplan.

The peptide portion of the drug binds to complement C3 and is a broad inhibitor of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. The PEGylation of the molecule imparts slower clearance from the vitreous humor following administration.

Pegcetacoplan Intravitreal Injection 15 mg/0.1 mL will be provided as a 150 mg/ mL sterile solution of pegcetacoplan in stoppered glass vials. Pegcetacoplan is a sterile, isotonic solution in acetate-buffer, pH 5.0, containing trehalose. The drug product is packaged in 2R clear Type I glass vials with 13 mm FluroTec-coated chlorobutyl grey stoppers and sealed with 13 mm aluminum/polypropylene flip-off type seals.

4.1.3. Nonclinical Data

This section is intended to briefly summarize information on the safety, tolerability, and PK of intravitreal (IVT), intravenous (IV) and subcutaneous (SC) injections of pegcetacoplan. For complete and detailed information, refer to the IB.

As pegcetacoplan is only pharmacologically active in primates, the pivotal IVT toxicological studies have been conducted in cynomolgus monkeys. The safety and tolerability of IVT-administered pegcetacoplan has been assessed in a Good Laboratory Practice (GLP)-compliant pivotal chronic (9-month) repeat-dose study in cynomolgus monkeys. In addition, 2 GLP-compliant 2-month ocular bridging studies (the first comparing drug substance from 2 different CMOs, the second assessing the safety and tolerability profiles of 3 different formulations to support the Phase 3 clinical study) have been conducted in cynomolgus monkeys as well. . Pegcetacoplan was observed to be minimally immunogenic in the 9-month study as evidenced by a lack of circulating antibodies in the majority of monkeys studied. The NOEL for chronic (9-month) IVT dosing was concluded to be >24.8 mg/eye. The results of this 9-month chronic study in cynomolgus monkeys support the safety of chronic IVT injections of pegcetacoplan at monthly or bimonthly intervals in humans.

PK assessments included in the chronic (9-month) study revealed serum concentrations of pegcetacoplan that were approximately dose-proportional 24 hours after the first IVT dose. The serum $t_{1/2}$ of IVT-administered pegcetacoplan, determined in a separate PK assessing a 10 mg/eye dose (in 50 µL), was 10.4 days although the pegcetacoplan levels measured in the serum following infrequent IVT administration are orders of magnitude lower than pharmacological serum levels achieved with SC or IV administration.

Additional nonclinical studies in monkeys and rabbits, including assessments of other routes of administration (SC and IV), have further defined pegcetacoplan's safety profile. . Pegcetacoplan has been shown to be generally tolerated through all 3 routes of administration assessed (IVT, SC, and IV), with no adverse effects observed in safety pharmacology studies (*in vivo* cardiopulmonary telemetry and *in vitro* hERG inhibition assay) and genotoxicity studies (Ames, *in vitro* aneugenicity and clastogenicity in TK6 cells, and *in vivo* clastogenicity in mouse micronuclei).

CCI

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4.1.4. Clinical Data

The initial safety and tolerability of pegcetacoplan following IVT administration in humans was tested in an open-label, single dose escalation, Phase I clinical study in patients with wet age-related macular degeneration under protocol POT-CP043014 (NCT02461771). The study was conducted in multiple ophthalmology clinical sites in the US and Australia. A single dose of pegcetacoplan was administered on Day 1 to patients suffering from wet AMD currently receiving anti-VEGF standard of care. Three escalating doses of pegcetacoplan administered IVT were studied. Three subjects received 4 mg; 3 subjects received 10 mg, and 7 subjects received 20 mg. No serious adverse events (SAEs) or drug-related adverse events (AEs) of concern were observed. It was concluded that administration of a single dose of pegcetacoplan IVT up to 20 mg is safe and well tolerated.

A Phase 2 study (Protocol POT-CP121614; NCT02503332) to assess the safety, tolerability, and evidence of activity of multiple intravitreal injections of pegcetacoplan in subjects with geographic atrophy secondary to AMD has been completed. The study was conducted at multiple ophthalmology clinical sites in the US, Australia, and New Zealand. Subjects were randomized in a 2:1:2:1 manner to either receive pegcetacoplan IVT 15 mg monthly for 12 months; sham IVT monthly for 12 months; pegcetacoplan IVT 15 mg every other month for 12 months; or sham IVT every other month for 12 months.

This study demonstrated a statistically significant slowing of disease progression at Month 12 at the prespecified alpha of 0.1. Pegcetacoplan administered monthly showed a 29% (P=.008) reduction in the rate of GA lesion growth compared to sham and pegcetacoplan administered every other month showed a 20% (P=.067) reduction. Pegcetacoplan has been generally well tolerated. The most frequently reported AEs have been related to the injection procedure (intravitreal injection), which are commonly found in this type of study. An imbalance in new active choroidal neovascularization (CNV) in subjects treated with pegcetacoplan was observed and the risk of developing new exudation may be increased in subjects with a prior history of neovascular AMD in the fellow eye. One subject in the sham arm, 1/81 (1%) was observed to have developed new active study eye exudation compared with 25/165 (15%) subjects that received pegcetacoplan IVT injections, 26 subjects in total. Of the 25 pegcetacoplan treated subjects with new active CNV, 18 subjects received PM treatment and 7 subjects received PEOM treatment.

Seventeen of the 25 (68%) subjects that developed new active study eye CNV had a prior history of neovascular AMD in the nonstudy fellow eye. No significant imbalance in history of neovascular AMD in the fellow eye was observed among the 3 arms to explain the imbalance in new exudation observed in study eyes. Visual acuity data did not demonstrate clear differences between subjects developing new study eye exudation compared with those that did not.

A Phase 1b study (Protocol APL2-103; NCT 03777332) to assess the safety of pegcetacoplan in subjects with GA secondary to AMD and low vision is currently ongoing. This study is being conducted at multiple ophthalmology clinical sites across the US. Subjects receive monthly treatment with intravitreal pegcetacoplan for 24 months.

4.1.5. Rationale

4.1.5.1. Rationale for Pegcetacoplan for Treatment of Geographic Atrophy

The rationale for the use of a complement inhibitor in patients with AMD is based on evidence from both human and animal studies. Human biochemical, genetic, and clinical lines of evidence indicate that the complement system plays a role in the etiology of AMD. Complement components including C3, the membrane attack complex, and complement factor H, are present in drusen and basal laminar deposits in eyes from patients with AMD.[7,8,9,10] Genetic variants of complement factor H,[8,11,12,13,14] C3,[15,16] complement factor I[17] and other complement components[18,19,20] have been associated with altered risks for the development of both the neovascular and atrophic forms of AMD. Patients with AMD also have signs of systemic complement activation, exhibiting higher serum levels of Complement Factor B, C3a, C5a, SC5b-9 (soluble terminal complement complex), C3d, and Ba compared to age-matched controls.[21,22,23,24]

4.1.6. Dose Selection

A single dose of 15 mg/0.1 mL injection administered monthly or EOM for 24 months will be tested in this study (see Section 7.3.1). Pegcetacoplan was well tolerated in a panel of animal toxicology studies. A 9-month, repeat-dose GLP study in cynomolgus monkeys was conducted to evaluate the safety of IVT injections of pegcetacoplan at doses up to 24.8 mg/eye at a frequency of 1 injection every 4 weeks.

In this pivotal chronic toxicological study conducted in monkeys, the NOEL was established as >24.8 mg of pegcetacoplan delivered intravitreally every 4 weeks for 9 months using a 100 µL injection. The volume of the human vitreous is approximately 4 mL, which is approximately 2.7-fold larger than the mean vitreous volume of cynomolgus monkeys, 1.5 mL.[25] Based on the difference in vitreous volume between man and cynomolgus and the NOEL defined in nonhuman primates, the human equivalent dose was determined to be 67 mg/eye every 4 weeks. The dose (15 mg/injection) of pegcetacoplan that will be evaluated in this clinical study is expected to result in drug concentrations approximately 4.5-fold lower that the NOEL observed in cynomolgus monkeys.

To support appropriate assessments of dose response to pegcetacoplan, pegcetacoplan is administered in 2 different frequencies in the study: monthly and every other month.

Physician feedback injecting a 200 mg/mL solution in the Phase 1 (Study POT-CP043014; NCT02461771) trial confirmed that 150 mg/mL is the highest practical concentration that can be routinely administered, which set the dose of the Phase 2 trial to 15 mg (ie, 0.1 mL of a 150 mg/mL solution). The 15-mg dose given monthly was found to be the most efficacious in the Phase 2 trial. The 15 mg dose given every other month demonstrated slightly less efficacy but offers a reduced treatment burden for patients and physicians.

4.2. Risk/Benefit

The Phase 1 (Study POT-CP043014; NCT02461771) and Phase 2 (Study POT-CP121614; NCT02503332) studies provide supporting evidence of a positive benefit-risk profile for the use of pegcetacoplan in treating patients with AMD, specifically patients with GA. These

preliminary results of an up to 28% reduction of GA progression rate support the evaluation of pegcetacoplan in a Phase 3 study.

The reported safety data from these studies demonstrated an acceptable safety and tolerability profile with no clinically significant safety concerns observed. A total of 178 patients have received at least 1 dose (15 mg/injection) of pegcetacoplan as part of these studies. In the Phase 2 study in patients with GA an imbalance in new exudation in subjects treated with pegcetacoplan was observed. Section 4.1.4 provides a summary of the study design and key results from both studies.

The safety monitoring practices employed by this protocol (complete ophthalmologic exam, IOP monitoring, OCT, fluorescein angiography, vital signs, hematology, serum chemistry, urinalysis, physical exam, vital signs, and AE questioning) are adequate to protect the subjects' safety. There are also risks associated with the ophthalmic procedures required for participants in this study. However, these are all standard procedures that are widely performed in ophthalmology.

In the days following any IVT injection, patients are at risk of developing sterile or infectious intraocular inflammation (eg, endophthalmitis). In recent studies conducted with pegcetacoplan IVT from a single manufacturer, events of transient moderate and severe intraocular inflammation have been observed. Other risks of IVT injection include traumatic cataract, retinal detachment, increased IOP, and hemorrhage.

The amount of blood (See Section 9.16) planned for collection from each subject over the 24 months of the study does not pose an undue risk in this patient population.

There is a potential health benefit for trial participants from receipt of study drug. If efficacious, pegcetacoplan is expected to alter the course of GA and slow its rate of progression.

5. STUDY OBJECTIVES

5.1.1. Primary Objective

To evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD assessed by change in the total area of GA lesions from baseline as measured by fundus autofluorescence (FAF).

5.1.2. Key Secondary Objectives

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

- Monocular maximum reading speed (study eye), as assessed by Minnesota Low-Vision Reading Test (MNREAD) or Radner Reading Charts (in select countries)
- Functional Reading Independence (FRI) index score
- Normal luminance best corrected visual acuity score (NL-BCVA) in the study eye

5.1.3. Secondary Objectives

- To evaluate the efficacy of pegcetacoplan compared to sham injection in patients with GA secondary to AMD with respect to:
    - Low luminance best corrected visual acuity score (LL-BCVA) 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)
    - Macular functional response as assessed by mesopic microperimetry

5.1.4. Safety Objectives

- To evaluate the safety and tolerability of pegcetacoplan compared to sham injection in patients with GA secondary to AMD as indicated by:
    - Incidence and severity of ocular and systemic treatment-emergent adverse events
    - Incidence of anti-therapeutic antibodies directed against pegcetacoplan
    - Incidence of new active CNV in the study eye

5.1.5. Exploratory Objectives

- To evaluate the efficacy of pegcetacoplan compared to sham injection in patients 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 in change in GA lesion size
    - To evaluate the binocular maximum 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)

6. PATIENT POPULATION

The study population includes approximately 600 subjects to be randomized at approximately 100 multinational sites. To participate in the study, subjects must be diagnosed with GA of the macula secondary to AMD in the study eye.

6.1.1. Inclusion Criteria

The study eye must meet all inclusion criteria. If both eyes meet the inclusion criteria, the eye with the worst normal luminance visual acuity at the screening visit will be designated as the study eye. If both eyes have the same visual acuity, the right eye will be selected as the study eye.

Ocular-specific inclusion criteria apply to the **study eye** only, unless otherwise specified.

1. Age ≥60 years.
2. Normal Luminance best corrected visual acuity of 24 letters or better using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (approximately 20/320 Snellen equivalent).
3. Clinical diagnosis of GA of the macula secondary to AMD as determined by the investigator and confirmed by the reading center.
4. The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
    a. Total GA area must be ≥2.5 and ≤17.5 mm2 (1 and 7 disk areas [DA] respectively).
    b. If GA is multifocal, at least 1 focal lesion must be ≥1.25 mm2 (0.5 DA), with the overall aggregate area of GA as specified above in 4a.
    c. 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.
    d. Presence of any pattern of hyperautofluorescence in the junctional zone of GA. Absence of hyperautofluorescence (ie, pattern = none) is exclusionary.[1]
5. Adequate clarity of ocular media, adequate pupillary dilation, and fixation to permit the collection of good quality images as determined by the investigator.
6. Meets the following criteria related to microperimetry:
    a. Able to detect fixation target.
    b. Total elapsed time to complete the 10-2 68-point exam is ≤30 minutes in duration.
    c. Fixation losses must be ≤20%.
    d. Subject is willing and able to undertake microperimetry assessment in the opinion of the investigator.
7. Female subjects must be:
    a. Women of non–childbearing potential (WONCBP), or
    b. Women of childbearing potential (WOCBP) with a negative serum pregnancy test at screening and must agree to use protocol defined methods of contraception for the duration of the study and refrain from breastfeeding for the duration of the study.

8. Males with female partners of childbearing potential must agree to use protocol defined methods of contraception and agree to refrain from donating sperm for the duration of the study.
9. Willing and able to give informed consent and to comply with the study procedures and assessments.

6.1.2. Exclusion Criteria

Ocular specific exclusion criteria apply to the **study eye** only, unless otherwise specified.

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.
2. Spherical equivalent of the refractive error demonstrating > 6 diopters of myopia or an axial length >26 mm.
3. Any history or active CNV, associated with AMD or any other cause, including any evidence of retinal pigment epithelium rips or evidence of neovascularization anywhere based on SD-OCT imaging and/or fluorescein angiography as assessed by the reading center.
4. Presence of an active ocular disease that in the opinion of the investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (eg, clinically significant epiretinal membrane [ERM], full thickness macular hole) or uncontrolled glaucoma/ocular hypertension). Benign conditions in the opinion of the investigator such as peripheral retina dystrophy are not exclusionary.
5. Intraocular surgery (including lens replacement surgery) within 3 months prior to randomization.
6. History of laser therapy in the macular region.
7. Aphakia or absence of the posterior capsule. Note: YAG laser posterior capsulotomy for posterior capsule opacification done at least 60 days prior to screening is not exclusionary.
8. Any ocular condition other than GA secondary to AMD that may require surgery or medical intervention during the study period or, in the opinion of the investigator, could compromise visual function during the study period.
9. Any contraindication to IVT injection including current ocular or periocular infection.
10. History of prior intravitreal injection.
11. Unable to perform microperimetry reliably in the opinion of the investigator.
12. Prior participation in another interventional clinical study for intravitreal therapies in either eye (including subjects receiving sham).
13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo.
14. Participation in any systemic experimental treatment or any other systemic investigational new drug including within 6 weeks or 5 half-lives of the active ingredient

(whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.

15. Medical or psychiatric conditions that, in the opinion of the investigator, make consistent follow-up over the 24-month treatment period unlikely, or would make the subject an unsafe study candidate.
16. Any screening laboratory value (hematology, serum chemistry or urinalysis) that in the opinion of the investigator is clinically significant and not suitable for study participation.
17. Known hypersensitivity to fluorescein sodium for injection or hypersensitivity to pegcetacoplan or any of the excipients in pegcetacoplan solution.

6.2. Women of Childbearing Potential

WOCBP are defined as premenopausal women physiologically capable of becoming pregnant.

6.3. Women of Nonchildbearing Potential

WONCBP are defined as women meeting any of the following criteria:

- Older than 45 years with amenorrhea for > 2 years or older than 60 years with amenorrhea for > 1 year. Both confirmed by follicle-stimulating hormone (FSH) and LH levels.
- Has undergone hysterectomy,
- Has undergone bilateral oophorectomy,
- Has undergone bilateral salpingectomy.

6.4. Approved Methods of Contraception

Approved methods of contraception include:

- Combined (estrogen-and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner *(provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success)*
- Sexual abstinence *(defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). Sexual abstinence is only accepted when it is the preferred and usual lifestyle of the subject.*

Subjects must agree to use an approved method of contraception during the study and 90 days after their last dose of study drug.

6.5. Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from treatment with the investigational product (IP) with the medical monitor, when possible.

Subjects who discontinue treatment with the IP can continue participation in the study and should be encouraged to return to the clinical site for as many follow-up visits as they can. In the event that a subject terminates early from the study, all early termination procedures should be performed even if they are outside the allowed study window.

The reason for termination, date of stopping treatment with IP, all follow-up information and the total amount of IP administered must be recorded in the case report form (CRF) and source documents.

7. TREATMENT OF SUBJECTS

7.1. Allocation to Treatment

Each subject will be assigned a unique screening number after signing the informed consent. Subjects who complete the study screening assessments and meet all the eligibility criteria will be scheduled to enter the study and randomized on Day 1. As part of the screening process, the reading center will evaluate FAF, OCT, Digital Color Fundus Photograph (DCFP), Near Infrared Reflectance (NIR), and fluorescein angiography (FA) to provide an objective assessment of subject eligibility. Subjects will be randomized 2:2:1:1 to receive treatment with PM, PEOM, sham injection monthly (SM) or sham injection every other month (SEOM), respectively. Table 1 presents the treatment arms along with the approximate number of subjects and injections per arm.

The randomization scheme will be generated and maintained by the sponsor, or designee. Subject randomization will be stratified by GA lesion area at screening (< 7.5 mm^2; ≥ 7.5 mm^2) and presence of CNV in the fellow eye (yes; no). Further details on the randomization procedures will be described in the statistical analysis plan.

7.2. Masking and Minimization of Bias

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the subject and the masked assessors associated with the conduct of the study until all such opportunities for bias have passed.

This is a double-masked study. Designated masked study site staff (eg, assistant(s), visual acuity technicians, 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 not allowed to discuss treatment and/or patient outcome 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. Documentation 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.

7.2.1. Unmasking

In the event of a medical emergency where the knowledge of subject treatment by masked individuals (eg, the subject or his/her physician) is required, an individual investigator (or designee) will have the ability to unmask the treatment assignment for a specific subject and share that information with the appropriate parties. All documentation indicating unmasking must be retained with the subject's source documentation in a secure manner. A DMC will be set-up to monitor patient safety and review data. The DMC will be provided unmasked safety data but will be masked to efficacy data unless this data is deemed medically necessary. Procedures for DMC unmasking will be documented in a DMC Charter.

For regulatory reporting and if required by local regulations, the sponsor will unmask study treatment for all serious, unexpected adverse reactions that are considered to be related to study drug. Subjects who have had their treatment assignment unmasked secondary to a serious or unexpected AE or medical emergency will no longer receive study treatment. However, they should continue to complete as many of the follow-up visits as possible.

The study unmasking for the primary analysis at 12 months will be limited to the analysis team and personnel only on an as-needed basis. All other personnel in the "masked" role will remain masked until the end of study. A document listing out the roles and responsibilities of the individuals participating in the unmasking analysis will be provided prior to the unmasking.

7.3. Dosage and Administration

7.3.1. Dose Levels and Treatment Arms

After randomization and during the treatment phase beginning at Day 1, all subjects will receive a single dose of 15 mg pegcetacoplan/0.1 mL or sham injection intravitreally either monthly or every other month depending on treatment designation as presented in Table 1 below.

Table 1: Treatment Arms with Approximate Number of Subjects

Treatment Arms
Pegcetacoplan 15 mg/0.1 mL monthly for 24 months (n= approximately 200 subjects; 24 pegcetacoplan injections)
Pegcetacoplan 15 mg/0.1 mL EOM for 24 months (n= approximately 200 subjects; 12 pegcetacoplan injections)
Sham monthly for 24 months (n= approximately 100 subjects; 24 sham injections)
Sham EOM for 24 months (n= approximately 100 subjects; 12 sham injections)

7.3.2. Treatment Administration

Only qualified study staff and those delegated the responsibility of study drug administration on the delegation of authority log should perform this procedure. All staff should be appropriately trained on all procedures prior to performing the procedures. Sites should follow the Visit Schedule for order of procedures and assessments.

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 IOP preinjection.

If a subject falls outside the visit window for a dosing visit, the dose should be skipped and the subject should be scheduled on time for the next dosing visit.

7.3.3. Drug Supplies

7.3.3.1. Identity of Investigational Product

Pegcetacoplan will be supplied as a liquid solution in stoppered glass vials and should be stored according to the label. Specific instructions for preparing pegcetacoplan for the IVT injection procedure will be provided in the manual of procedures. Pegcetacoplan Intravitreal Injection 15 mg/0.1 mL (150 mg/mL) is a sterile, isotonic solution of pegcetacoplan in acetate-buffer, pH 5.0, containing trehalose. The drug product is packaged in 2R clear Type I glass vials with 13 mm FluroTec-coated chlorobutyl grey stoppers and sealed with 13-mm aluminum/polypropylene flip-off type seals.

Sham will be provided as empty stoppered glass vials and should be stored according to the label.

7.3.3.2. Storage

Vials should be automatically stored as per the instructions until ready for use. Each vial should only be used once. Vials should not be shaken and should be protected from sunlight.

7.3.3.3. Accountability

Pegcetacoplan drug product and sham vials will be provided to a designee at the study site and must be stored in a pharmacy or otherwise locked and secured, at the temperature specified on the label. The drug product supply is accessible only to those individuals authorized by the PI. The sponsor will supply sufficient quantities of pegcetacoplan drug product and sham to allow completion of this study. The site should only use the investigational medicinal product provided by the sponsor for use in the study.

Designated unmasked study staff will provide the study treatments to the subjects in accordance with their assigned subject numbers and the randomization schedule. During the study, the receipt of the drugs supplied at the clinical site and of study treatment dispensation for each subject will be documented in drug accountability records. These drug accountability records are to be kept separate from the patient medical records and other source documents.

All used vials should be retained by the clinical site until drug accountability monitoring is performed and then returned to the sponsor or designee or destroyed per sponsor instructions. At the conclusion of the study, any unused IP returned to the sponsor or designee, or destroyed per sponsor instructions, and this will be documented in the drug accountability records.

7.3.4. Intravitreal Pegcetacoplan Administration

Subjects receiving active treatment will be administered 0.1 mL IVT injection of pegcetacoplan according to their treatment designation using a thin wall needle. Detailed instructions on drug preparation, preinjection procedures, administration of pegcetacoplan, and postinjection procedures will be provided in the manual of procedures.

Clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to minimize the risk of potential AEs associated with IVT injections.

Administration of pegcetacoplan is only allowed if preinjection IOP ≤21 mm Hg. If necessary, antiglaucomatous medication can be given to lower the IOP. To minimize transient IOP elevation after IVT injection of pegcetacoplan, decompression of the eye **must** be performed before all pegcetacoplan injections. This is done by applying moderate pressure to the globe with cotton swabs for 30-60 seconds during anesthetic preparation.

In addition to the procedures outlined in the protocol and manual of procedures (MOP), adherence to specific institutional policies associated with IVT injections will be observed.

7.4. Sham Injection Administration

The procedure for sham injection will be the same as that used for IVT injection until the actual injection but no actual injection will occur. The injecting physician will only touch the study eye with the blunt end of the syringe. No needle or medication will be injected inside the eye. Detailed instructions on sham injection procedures and postinjection procedures will be provided in the manual of procedures.

Subjects randomized to the monthly or every-other-month sham-injection groups will receive sham injection monthly or every other month, respectively. The same assessments will be performed as for the subjects in the pegcetacoplan groups.

7.5. Concomitant Therapies

Any concomitant medications a participant is receiving at the start of the study, within 30 days prior to screening, or that are given for any reason during the study (except for routine medications given for ocular procedures required by the protocol, such as topical anesthetic) must be recorded in the source documents and CRF including start and stop date and time, dose, route, and indication. In addition, all invasive intraocular procedures from the previous 5 years must also be recorded in the source documents and CRF including start and stop dates. Surgical anesthetics, paramedical or alternative therapies (eg, acupuncture, herbal supplements) should also be recorded in the source documents and CRF within 30 days prior to screening.

Metoclopramide or other agents to prevent nausea induced by fluorescein injection may be administered at the discretion of the PI.

7.5.1. Treatment of New Exudation Related to Active Choroidal Neovascularization in the Study Eye and/or Fellow Eye

The suspected onset or presence of new exudation related to active CNV secondary to AMD in the study eye and/or fellow eye must be documented in the source documents and CRF. If the

investigator suspects new exudation related to active CNV in the study eye based on fundus examination and/or OCT findings (eg, subretinal fluid, intraretinal fluid, cystoid macular edema, serous pigment epithelial detachment), a fluorescein angiography and Optical Coherence Tomography Angiography (OCT-A; select sites only) must also be captured following the imaging protocol procedure. All images, as outlined above, must be sent to the reading center. The reading center will provide a report indicating whether or not evidence of active, exudative AMD is present or absent, based on the images sent for assessment.

The determination about initiation of anti-VEGF treatment for the exudation related to active CNV is the sole responsibility of the investigator. Treatment with anti-VEGF should start after the report is received by the site from the reading center, with the exception of cases with clear evidence of disease activity (eg,; subretinal hemorrhage, extensive subretinal fluid and/or edema, and/or presence of subretinal hyperreflective material) that, in the opinion of the investigator, may have a detrimental visual impact if not treated immediately.

If it is determined that the subject requires anti-VEGF therapy, ranibizumab or aflibercept should be selected and administered by the injecting (unmasked) physician. Ranibizumab should be given monthly and aflibercept every other month after 3 monthly loading doses. The frequency of aflibercept can be changed to monthly if deemed necessary by the investigator, however the physician should refrain from using as-needed treatment (PRN) or treat and extend protocols. Every effort should be made to use the same anti-VEGF therapy for a subject during the course of the study and all treatments should be documented in the CRF.

If anti-VEGF therapy is administered in the study eye on the same day as an pegcetacoplan (or sham) injection, the anti-VEGF therapy shall be administered first and the pegcetacoplan or sham injection shall occur at least 30 minutes after the anti-VEGF injection and only if the IOP is ≤21 mm Hg. Anti-glaucomatous medication can be given to lower the IOP to the appropriate range to allow for the pegcetacoplan injection.

In order to avoid potential unmasking, if anti-VEGF and pegcetacoplan are given at the same visit, the unmasked physician must perform both procedures. If the anti-VEGF therapy is given on a separate day from the pegcetacoplan administration, either the masked or the unmasked physician may perform this injection.

Treatment with anti-VEGF is allowed in the fellow eye. The treatments for the fellow eye can be administered according to the site's standard protocol for CNV treatment. Any treatments or therapies administered to the fellow eye within 5 years of screening and while on study should be recorded as a concomitant medication.

7.5.2. Prohibited Therapies

The PI should make a determination regarding patient continuation of therapies used to treat concomitant medical conditions. Therapies as noted in the inclusion/exclusion criteria are prohibited as specified.

7.5.3. Endophthalmitis Treatment

Endophthalmitis cases must be reported as SAEs. The decision to treat a participant for endophthalmitis or suspected endophthalmitis will be guided by the clinical judgment of the investigator and in accordance with local guidelines (as applicable). A culture sample should be

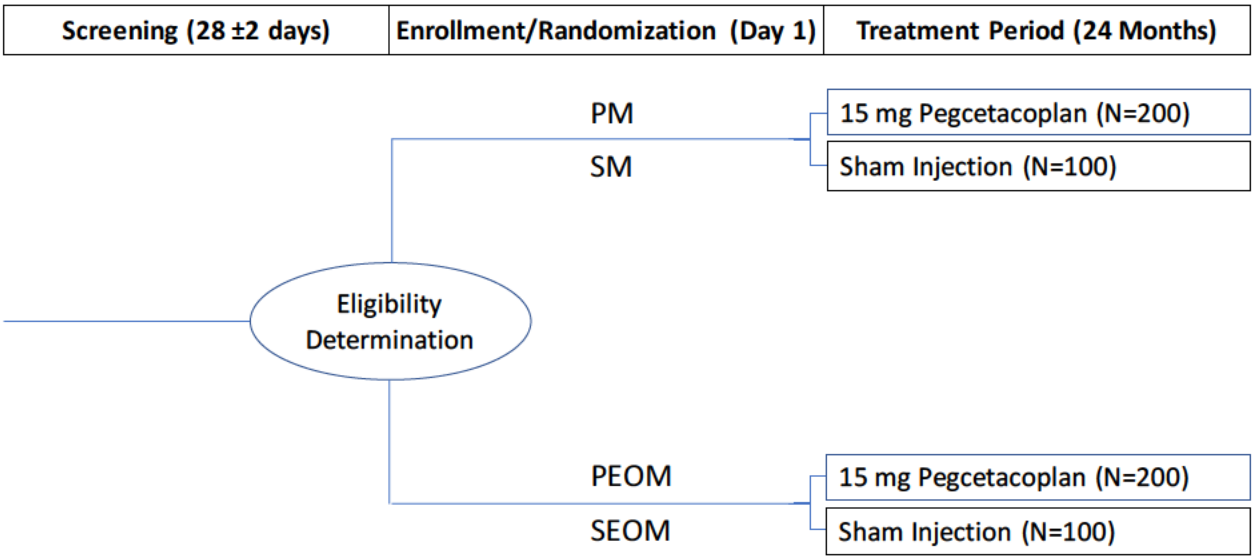
performed prior to making a decision on treatment. The treatment method (pars plana vitrectomy vs intravitreal injection of antibiotics) and choice of antimicrobial agents are also at the discretion of the physician and should follow current standard practice patterns. The decision to use IVT steroids (eg, dexamethasone) for the treatment of endophthalmitis is also at the discretion of the physician.

8. STUDY PROCEDURES

A study schema is presented below in Figure 1. All randomized subjects will return every month to the clinical site for assessments and additional pegcetacoplan or sham injections according to their randomization scheme until Month 12. From Month 12 onwards, subjects will return to the clinical site based on their randomized treatment schedule (monthly or EOM) and will follow the treatment regimen and assessments outlined in the Visit Schedule until Month 24. In addition, subjects will be contacted via phone by masked study staff 4 (±2) days after the first 3 study treatments to collect safety information.

The end of this trial for each subject is defined as when the subject completes their Month 24 study visit, approximately 30 days (monthly treatment group) and approximately 60 days (EOM treatment group) after the last visit at which IP is administered. The period following the last dose of IP is sufficient to evaluate the safety of pegcetacoplan based on its half-life in the vitreous; further details can be found in the pegcetacoplan IB. At the end of the 24-month study period, subjects will be offered entry to enroll into a separate open-label study.

Figure 1: Study Schema



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

Subjects who discontinue study treatment should return to the clinic for study assessments as per the outlined visit schedule for their assigned treatment arm.

Safety will be assessed throughout the study by a number of evaluations including: monitoring of AEs, preinjection and postinjection monitoring, blood and urine samples will be collected, physical examination, vital signs, and follow-up phone calls will be performed. Blood samples will also be collected for anti-therapeutic antibodies, genotyping, and clinical repository (if the subject consents to this portion).

The planned length of participation in the study for each subject is approximately 25 months (from the beginning of the screening period through completion of the Month 24 visit). After completion of the 24-month treatment period, subjects will be offered entry into a separate open-label study.

8.1. Study Visit Schedule

Below is a condensed description of the study visits and the procedures and examinations that will be performed. Please refer to the Visit Schedule in Appendix A to Appendix D for a detailed schedule of procedures/assessments for the monthly and EOM visit schedules. Additional safety assessments not listed in this section or the flow chart may be performed if considered necessary at the discretion of the investigator.

8.1.1. Screening Period—Within 28 Days Prior to Randomization/ Treatment (Day –28 to –1)

8.1.1.1. Visit 1—All Subjects

Note: All ophthalmic procedures (including imaging) are to be performed on both eyes, except where specified.

Before any study-specific procedures are performed, the purpose and nature of the study should be explained and the patient should read, sign, and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved Informed Consent Form (ICF). The individual obtaining consent from the patient and a witness, if applicable, should also sign and date the ICF. Once the patient has signed the ICF, a screening number should be assigned to the patient. Demographic information, significant medical/surgical history within the previous 5 years, invasive ocular procedures within the previous 5 years, and concomitant medications used within 30 days prior to screening should be collected (including vitamins and all over-the-counter as well as prescription medications). Complete smoking/ tobacco history should also be collected.

Subject eligibility should then be determined by reviewing the inclusion/exclusion criteria and the study eye should be selected. Prior to the administration of fluorescein, blood and urine should be collected for safety labs (including blood for human chorionic gonadotropin/follicle-stimulating hormone/luteinizing hormone [HCG/FSH/LH], if applicable) and vital signs along with a physical examination including weight and height should be performed.

A complete ophthalmic exam including slitlamp exam of the cornea, iris, anterior chamber, aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina, and intraocular pressure (IOP) measurement. Normal luminance BCVA should be performed prior to dilating the eyes. Images should be captured as outlined in the Visit Schedule (FAF, NIR, DCFP, FFA) and forwarded to the reading center for determination of eligibility if applicable.

Mesopic microperimetry should be performed on both eyes post dilation of the eyes and forwarded to the reading center.

8.1.2. Randomization/ Initial Treatment—Day 1—Within 28 Days of Screening

8.1.2.1. Visit 2—All Groups

At this visit, all inclusion/exclusion criteria should be reviewed prior to randomization and dosing, including the determination of eligibility by the reading center. Subjects will be randomized using the Interactive Web Response (IWR) System. A complete ophthalmic exam including slitlamp exam of the cornea, iris, anterior chamber, lens, and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina, and IOP measurement will be performed and imaging collected as per the Visit 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.

Blood should be drawn for anti-pegcetacoplan antibodies.

Prior to dilating the eyes, all functional tests should be performed (NL-BCVA, LL-BCVA, and MNREAD or Radner Reading Charts [in select countries]). Subjects at select sites will be trained on how to use the home-based digital applications for visual function and reading speed if the subject decides to participate in this portion. This training must occur after completion of all functional tests (NL-BCVA, LL-BCVA). Tests completed using the digital application at select sites (optional) should be completed prior to dilating the eyes but after completion of all functional tests and quality of life measures (NL-BCVA, LL-BCVA, MNREAD or Radner Reading Charts [in select countries], NEI VFQ-25, and FRI). The subject should be instructed to take the electronic device home and to complete the digital application weekly on the same day each week, if possible. The quality of life measures (NEI VFQ-25 and FRI) should be administered by the masked site staff.

Imaging should be performed including FAF, SD-OCT, OCT-A (select sites), endothelial cell count (select sites) and NIR and sent to the reading center for evaluation.

Study drug or sham injection should be performed by the unmasked physician as described in the manual of procedures and the study eye should be monitored post injection as outlined in Section 9.16. A follow-up phone call should be scheduled with the subject 4 ± 2 days after randomization Day 1 to assess for any AEs.

8.1.3. Treatment Phase—24 Months

8.1.3.1. Months 1-12

8.1.3.1.1. Visits 3-14 (Monthly and Every-Other Month Group)

During this phase, there will be clinic visits every month. Dosing and assessments will occur monthly in the monthly pegcetacoplan and sham injection treatment arms. Dosing will occur every other month in the EOM pegcetacoplan and sham injection treatment arms, however, the subjects will return monthly for assessments (with no dose given).

A complete ophthalmic exam including slitlamp exam of the cornea, iris, anterior chamber, lens, and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina, and IOP measurement will be performed and imaging collected as per the Visit Schedule.

Blood will be drawn for safety labs, anti-pegcetacoplan antibodies, and genotyping (Month 2 only) prior to the administration of fluorescein as per the Visit Schedule. Samples will be collected for the clinical repository for those subjects that consent to this portion.

Prior to dilating the eyes, all functional tests will be performed (NL-BCVA, LL-BCVA, and MNREAD or Radner Reading Charts [in select countries]). Tests completed using the digital application at select sites (optional) will be completed prior to dilating the eyes but after completion of all functional tests and quality of life measures (NL-BCVA, LL-BCVA, MNREAD or Radner Reading Charts [in select countries], NEI VFQ-25, and FRI). At select sites the subject should be instructed to take the electronic device home and to complete the digital application weekly on the same day each week, if possible. The subject will be instructed to bring back the electronic device for the visits specified in the schedule of events. The quality of life measures (NEI VFQ-25 and FRI) will be administered by the masked site staff.

Mesopic microperimetry should be performed on both eyes (where specified) post dilation of the eyes and forwarded to the reading center.

Imaging will be performed including FAF, FFA, SD-OCT, OCT-A (select sites), endothelial cell count (select sites) and NIR and sent to the reading center for evaluation per the visit schedule.

Study drug or sham injection should be performed by the unmasked physician as described in the manual of procedures and the study eye should be monitored post injection as outlined in Section 9.16. A follow-up phone call should be scheduled with the subject as outlined in the schedule of events.

In the event that a subject is early terminated from the study, all early termination procedures should be performed even if they are outside the allowed study window.

If the subject would like to discontinue dosing but is amenable to continuing in the study, the site should make every effort to have the subject complete as many follow-up visits as possible.

8.1.3.2. Months 13-24

8.1.3.2.1. Visits 15-26 (Monthly Group) and 15-20 (Every-Other-Month Group)

During this phase, clinic visits will follow treatment designation (ie, the monthly subjects will return monthly for dosing and assessments and the EOM group will return EOM for dosing and assessments). At select sites, subjects will complete the home-based digital assessments weekly during this period.

A complete ophthalmic exam including slitlamp exam of the cornea, iris, anterior chamber, lens, and aqueous reaction (cells and flare), dilated fundus exam of the vitreous and retina, and IOP measurement will be performed and imaging collected as per the Visit Schedule.

Blood should be drawn for safety labs, genotyping, and anti-pegcetacoplan antibodies prior to the administration of fluorescein as per the Visit Schedule. Samples will be collected for the clinical repository for those subjects that consented to this portion.

Prior to dilating the eyes, all functional tests should be performed (NL-BCVA, LL-BCVA, and MNREAD or Radner Reading Charts [in select countries]). The quality of life measures (NEI VFQ-25 and FRI) should be administered by the masked site staff.

Mesopic microperimetry should be performed on both eyes (where specified) post dilation of the eyes and forwarded to the reading center.

Imaging should be performed including FAF, FFA, SD-OCT, OCT-A (select sites), endothelial cell count (select sites) and NIR and sent to the reading center for evaluation per the visit schedule.

IVT (or sham) injection should be performed by the unmasked physician as described in the manual of procedures and the study eye should be monitored post injection as outlined in Section 9.16.

In the event that a subject is early terminated from the study, all early termination procedures should be performed even if they are outside the allowed study window.

If the subject would like to discontinue dosing but is amenable to continuing in the study, the site should make every effort to have the subject complete as many follow-up visits as possible.

The completion of the 24-month study period occurs approximately 30 days (monthly treatment group) and approximately 60 days (EOM treatment group) after the last visit at which investigational product (IP) is administered. The period following last dose of IP is sufficient to evaluate the safety of pegcetacoplan based on its half-life in the vitreous; further details can be found in the pegcetacoplan IB. At the end of the 24-month study period, subjects will have the option to enroll in a separate open-label study.

8.1.4. Early Termination Visit

A list of all assessments to be performed at the early termination visit can be found on the Visit Schedule. All subjects who end the study early for any reason must complete the early termination visit, however all efforts should be made to have the subject return for as many follow-up visits as possible even if dosing does not occur. All ophthalmic procedures are to be performed on **BOTH EYES**.

8.1.5. Unscheduled Visits

If a subject returns to the clinical site before their next scheduled visit for an assessment of an AE or at the request of the physician, all safety assessments should be performed and any additional assessments as deemed medically necessary by the physician.

9. ASSESSMENTS

The following evaluations will be performed during the study as outlined in the Visit Schedule in Appendix A to Appendix D. Refer to the MOP for detailed descriptions of study-related procedures.

9.1. Informed Consent

Written informed consent for participation must be obtained before performing any study-specific assessments. Informed consent for all subjects should be maintained within the subject source documentation.

9.2. Demographic Information/ Medical/ Surgical History

Demographic information will be collected from all subjects including but not limited to date of birth, race/ ethnicity (where locally permitted). All significant medical conditions and surgeries within the past 5 years should be captured for the subject including chronic and ongoing conditions. Any history or current use of tobacco is to be collected.

9.3. Ocular History/ Ocular Procedures

Ocular history within the previous 5 years should be collected and recorded for all subjects. The history should include any significant previous ocular surgeries, procedures and/ or medications or treatments used for these conditions.

9.4. Vital Signs

Vital signs consist of body temperature, respiratory rate, blood pressure (systolic and diastolic), and heart rate measurements.

On injection visits, vital signs will be measured prior to dosing. Vital signs should be taken with the patient in a seated position after resting for 5 minutes. Vital signs will be measured before venipuncture.

9.5. Physical Examination

A physical exam will be performed and should include but should not be limited to an evaluation of the eyes, ears, nose, throat, lymph nodes, head, and neurological function. A patient's height and weight should also be measured at screening. If any abnormalities are noted at screening, the PI, or designee, should determine the clinical significance of the finding and whether this will pose any safety risk to the subject. Any changes from baseline should be noted and the clinical significance assessed. Any new, clinically significant, findings should be documented as AEs.

9.6. Laboratory Analysis of Blood and Urine

Collection of blood and urine will occur at the study site and the samples will be shipped to a central laboratory for analysis. All samples (including urine) should be collected prior to treatment and FFA/OCT-A assessments (if applicable). Procedures for the collection and processing of blood and urine are provided in the laboratory manual.

Table 2 presents the laboratory and urine analysis that will be performed.

Table 2: Laboratory Sampling and Analysis

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Blood urea nitrogen	pH	Genotyping
Hematocrit	Creatinine	Specific gravity	Anti-pegcetacoplan Ab
Red blood cell count	Bilirubin (total, direct and indirect)	Protein	Human chorionic gonadotropin[a]
White blood cell count with differential	Albumin	Glucose	Follicle-stimulating hormone[b]
Platelet count	Alkaline phosphatase	Ketones	Luteinizing hormone[b]
	Aspartate aminotransferase	Bilirubin	
	Alanine aminotransferase	Blood	
	Creatine kinase	Nitrite	
	Glucose	Urobilinogen	
	Electrolytes (sodium, potassium, chloride, bicarbonate)	Leukocyte esterase	

[a] Serum Pregnancy Test (ie, HCG) will be performed for females of childbearing potential at screening only.
[b] FSH and LH will be performed for postmenopausal females at screening only.

The principal investigator, or designee, must review the results of the screening visit clinical laboratory tests (including any retest results) and confirm that these results do not show evidence of any medical condition that would make study participation inappropriate. The principal investigator, or designee, should also assess any changes from baseline at the follow-up visits and the final visit. Clinically significant laboratory values are to be recorded as AEs.

9.7. Genotyping Samples

The genetic marker sample will be used to evaluate the relationship between genetic polymorphisms associated with AMD with disease progression and response to pegcetacoplan.

A whole-blood sample will be collected for genetic marker analysis. These samples will be collected only for those subjects who consent to this analysis.

These samples will be stored as per the clinical repository guidelines outlined in Section 9.17 if the subject consents to this portion of the study. These samples will be stored up to 15 years after the date of the final closure of the associated clinical database if the patient consented to the clinical repository.

9.8. Urine Pregnancy Test

Urine pregnancy test will be performed in WOCBP only as outlined in the Visit Schedule in Appendix A to Appendix D.

9.9. Patient-Reported Outcomes

Data will be collected via interview-administered questionnaires to assess patient-reported outcomes during scheduled visits as outlined in the Visit Schedule. The questionnaire should be administered by the masked site staff and should be performed prior to any other assessments being performed that day.

Questionnaire data will be used to assess subject-reported efficacy of pegcetacoplan and changes in quality of life over time. Questionnaires will be translated into the appropriate language for each country or region.

9.9.1. The National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI-VFQ)

The NEI-VFQ is an interviewer-administered questionnaire designed to assess patient-reported visual function (Appendix E). The NEI-VFQ is to be administered by the masked staff. It is a 25-item questionnaire with a composite score and covers 12 domains of functional health status and well-being (general health, general vision, ocular pain, near activities (select countries), distance activities (select countries), social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision). Scoring yields 12 subscales based on the 12 domains covered in the questionnaire. These scales are scored from 0 to 100 with higher scores indicating better visual function. The recall period is not specified; however, it is important that the patient uses the same recall period each time the questionnaire is administered throughout their participation in the study.

9.9.2. The Functional Reading Independence (FRI) Index

The FRI will be interviewer-administered and is an individualized assessment of functional reading independence (Appendix F). The questionnaire has 7 items with 1 total index score. Higher levels on the scale represent higher functional reading independence. The recall period is 7 days.

9.10. Best Corrected Visual Acuity and Low Luminance Best Corrected Visual Acuity

Best corrected visual acuity (including best corrected visual acuity under low luminance [LL-BCVA]) will be measured at each visit as per the visit schedule by certified study staff. The study staff performing visual acuity should be masked to the treatment assignment. Best corrected visual acuity testing will be assessed on ETDRS chart starting at a distance of 4 m, performed by a certified VA examiner, and should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye.

The LL-BCVA acuity will be measured by placing a neutral density trial lens causing a reduction of 2.0 log units in luminance. The same requirements apply to measurement of low luminance visual acuity as described above for best corrected visual acuity. Low luminance deficit will be auto-calculated.

A Visual Acuity Specifications procedure manual and training materials will be provided to all sites. All examiners will require certification prior to performing this assessment as part of the study.

9.11. Minnesota Low-Vision Reading (MNREAD) Test or Radner Reading Charts (in select countries)

MNREAD Test or Radner Reading Charts (Appendix G) should be administered first monocularly for both eyes and then binocularly. The Manual of Operations should be referenced for a list of versions that should be administered based on country. These tests should be administered prior to dilating the eyes.

9.12. Home-Based Functional Digital Applications (optional, select sites)

In addition to in-clinic assessments, visual function and reading speed will also be evaluated using applications on an electronic device. Subjects who decide to participate in this portion will be trained on how to use the digital applications during the Day 1 visit and will complete the assessments using the digital application in the clinic at Day 1, Months 1-3, Month 6, 12, 18, and 24. 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 (NL-BCVA, LL-BCVA, MNREAD or Radner Reading Charts [in select countries], NEI VFQ 25, and FRI).

Subjects will also take home the electronic device to complete visual function and reading speed assessments weekly beginning at Day 1. 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.

9.13. Complete Ophthalmic Exam

The complete ophthalmic exam will consist of the following:

- External examination of the eye and adnexa.
- Routine screening for eyelids/pupil responsiveness (including ptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light, and afferent pupillary defect).
- Slitlamp examination (cornea, anterior chamber, iris, lens, aqueous reaction [cells and flare]). Please see Appendix H for grading scales.
- Dilated fundus exam including evaluation of retina and vitreous (ie, posterior segment abnormalities, retinal hemorrhage/detachment, and vitreal hemorrhage density and vitreous cells). Vitreal hemorrhage density and vitreous cells grading scales are outlined in Appendix I.
- IOP measurement—A measurement of intraocular pressure will be conducted using either Tono-Pen or Goldmann applanation tonometer as outlined in the MOP. This should be performed prior to dilating the eyes and the same method should be used for all measurements in the same subject throughout the study.

9.14. Ocular Imaging and Microperimetry

The following ocular images will be obtained and sent to the reading center as outlined in the visit schedule. A reading center manual along with training materials will be provided to all sites which will provide information on standardized procedures for the collection, storage, and transmission of all images. Prior to any images being taken at the site, site personnel must be

properly trained and certified and test images and systems and software must be certified and validated by the reading center. Only trained and certified site staff delegated the responsibility of image collection should perform this task. Ocular images obtained as part of this study are:

- Digital Color Fundus Photographs
- Fluorescein Angiography
- Spectral Domain Optical Coherence Tomography imaging
- Fundus Autofluorescence (Heidelberg Spectralis Instrument)
- Near Infrared Reflectance
- Endothelial Cell Count (Specular Microscopy): Select sites only
- Mesopic Microperimetry of the study eye only (at screening, performed on both eyes)
    - To account for the learning curve of this test, the patient is allowed up to 3 attempts to meet the criteria for this portion
- Optical Coherence Tomography Angiography (OCT-A): Select sites only

If a patient misses a visit during which ocular images should have been taken, the images should be collected at the next scheduled study visit.

In the event that a subject is suspected to have new active CNV in the study eye and/or the fellow eye, an SD-OCT and FFA using the protocol specified procedures should be performed and sent to the reading center to confirm the diagnosis (Section 7.5.1). In addition, in select sites, OCT-A should also be captured according to the study imaging protocol and sent to the reading center.

9.15. Postinjection Assessment

The study eye will be assessed after the intravitreal injection of pegcetacoplan or sham to ensure that the injection procedure and/or the study medication have not endangered the health of the eye. The initial postinjection assessments should be done within 5 minutes post injection and include a gross assessment of vision (light perception, hand motion). If the subject passes the gross vision test, he/she can be released from the clinic. If the subject does not pass the gross vision test, IOP must be measured at that time. Additional IOP measurement must be taken approximately every 30 minutes thereafter until IOP ≤30 mm Hg and the subject is able to be released from the clinic.

All subjects receiving an anti-VEGF (ranibizumab or aflibercept) and pegcetacoplan/sham injection on the same day, should have the IOP measured prior to and after the anti-VEGF (prepegcetacoplan). The second injection (pegcetacoplan/sham) can only be given if the IOP ≤21 mm Hg. Antiglaucomatous medication can be given to lower the IOP. The subject can only be released from the clinic if the IOP is ≤30 mm Hg.

Any subject who develops a significant and sustained raise in IOP (>30 mm Hg) after any injection, should be monitored according to the investigator's clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol

as well as IOP lowering procedures. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the physician's clinical judgment.

9.16. Blood Volume for Study Assessments

Table 3: Total Study Blood Volume

Assay	Number of time points	Approximate volume per time point * (mL)	Approximate sample volume over course of study (mL)—all groups
Anti-pegcetacoplan antibodies	9	2	18
*Hematology	8	4	32
**Chemistry (incl. HCG/LH)	8	5	40
FSH/LH (postmenopausal women only)	-	5	-
Genotyping sample[a]	1	8	8
Clinical repository (select sites and only subjects that consent to clinical repository)	5	14	70
Total blood volume			168 [a]

Abbreviations: HCG=human chorionic gonadotropin; FSH=follicle-stimulating hormone ; LH=luteinizing hormone
[a] Represents the standard collection volume planned over the duration of the study, actual volume may vary by group and across sites.
* Volume will vary slightly between regions and analyzing labs based on the standard methodology.
** In some regions, may be included in the chemistry sample based on local methodology.

9.17. Samples for Clinical Repository (Optional, Select Sites)

Apellis intends to apply genomic research across the pegcetacoplan development program to explore how genomic variations may affect the clinical parameters associated with and response to pegcetacoplan. Select sites will be asked to collect additional whole-blood samples and derivatives thereof in a centrally administered facility for the long-term storage of human biologic specimens. The collection and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future. Specimens for the Genetic Biorepository will be collected from subjects who give specific consent to participate in this optional research only and this will only be done at a select group of sites.

Specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Future research may suggest other genes, gene categories, proteins, etc. as candidates for influencing not only response to pegcetacoplan but also susceptibility to AMD for which pegcetacoplan may be evaluated. Thus, this additional genomic research may involve the future study of additional unnamed genes or gene categories, but only as they relate to AMD disease susceptibility and drug action.

9.17.1. Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the clinical repository is contingent upon the review and approval of the exploratory research and the clinical repository portion of the N by each site's IRB or IEC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for clinical repository sampling, this section of the protocol (Section 9.17) will not be applicable at that site.

9.17.2. Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (noninherited) biomarkers related to AMD and related diseases, pegcetacoplan, and signaling pathways related to AMD and the complement pathway:

- Residual whole-blood clinical genotyping sample
- 14-mL whole-blood sample collected at the specified time points

For all samples, dates of consent and specimen collection should be recorded on the associated clinical repository page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

All collected specimens will be destroyed no later than 15 years after the date of final closure of the clinical database. The clinical repository storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (eg, health authority requirements).

9.17.3. Confidentiality and Data Ownership

Patient medical information associated with clinical repository specimens is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless required by law.

Data derived from clinical repository specimen analysis on individual subjects will generally not be provided to the subjects or to study investigators unless required by law. The aggregate results of any research conducted using clinical repository specimens will be available in accordance with the effective Apellis policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the clinical repository data will become and remain the exclusive and unburdened property of Apellis, including the right to sell, license, or assign the invention to another entity.

9.17.4. Consent to Participate in the Clinical Repository

The ICF will contain a separate section or separate ICF that will address participation in the clinical repository. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the clinical repository. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. Subjects who decline to participate in the clinical repository can still participate in this clinical study. The investigator should document whether the patient has given consent to participate by completing the clinical repository Research Sample Informed Consent eCRF. In the event of a clinical repository participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the clinical repository research.

9.17.5. Withdrawal From the Clinical Repository

Subjects who give consent to provide clinical repository specimens have the right to withdraw their specimens from the clinical repository at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the sponsor in writing of the patient's wishes using the clinical repository Patient Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the Clinical Repository Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from this study does not, by itself, constitute withdrawal of specimens from the clinical repository. Likewise, a patient's withdrawal from the clinical repository does not constitute withdrawal from this portion of the study.

9.17.6. Monitoring and Oversight

Clinical Repository specimens will be tracked in a manner consistent with GCP by a quality-controlled, auditable, and appropriately validated laboratory information management system to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the ICF. Apellis monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the clinical repository for the purposes of verifying the data provided to Apellis. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the clinical repository samples.

10. SAFETY EVALUATIONS

Any clinically significant abnormalities persisting at the end of the study/ early withdrawal or end of the posttreatment phase will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study includes a number of evaluations to monitor safety including monitoring of AEs, postinjection monitoring, laboratory and urine sampling, physical examination, and vital signs.

10.1. Data Monitoring Committee

An external, independent data monitoring committee (DMC) will be formed with the purpose of reviewing all data across the conduct of the study on an ongoing basis. The DMC will follow a charter that will outline the frequency of meetings and the roles and responsibilities of all members. The DMC will meet at the beginning of the study and approximately every 6 months thereafter and will perform a masked review of all relevant events on an ongoing basis. An ad hoc meeting of the DMC may be convened by the sponsor or the DMC chairperson at any time between the regularly scheduled DMC meetings and data reviews, if warranted by new safety information or for any other reason. The DMC will communicate their recommendations to the sponsor who will notify the appropriate health authorities according to local regulatory requirements.

11. ADVERSE EVENTS

11.1. Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. An AE can, therefore be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP.

Adverse events can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described on the appropriate AE or SAE page of the eCRF.

Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE recording but are still collected and recorded via the appropriate eCRF form, if applicable. If these changes in laboratory values are linked to a diagnosis, this diagnosis should be reported as an AE, especially if the diagnosis constitutes an SAE or leads to discontinuation of administration of IP.

11.2. Recording Adverse Events

Adverse events and SAEs will be collected from the signing of the consent form until the last visit or early termination visit, 30 days after the last IP administration for the monthly treatment groups and 60 days after the last IP administration for the EOM treatment groups.

Any events that occur prior to dosing will be categorized as pretreatment events; events occurring after dosing will be recorded as treatment-emergent adverse events (TEAEs) (start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment).

For each AE, the investigator will evaluate and report the onset date (and time if applicable), resolution date (and time if applicable), intensity, causality, action taken, serious outcome, and whether or not it caused the subject to discontinue the study.

If possible, the outcome of any AE that caused permanent discontinuation or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the IP. Subjects experiencing AEs that cause interruption or discontinuation of IP, or those experiencing AEs that are present at the last visit or early termination visit should receive follow-up as appropriate.

All SAEs must be reported to the sponsor/Apellis Safety via eCRF within 24 hours of becoming aware of the event, whether or not the event is deemed treatment-related. If the electronic data capture (EDC) system is not operational (or for paper-based study[ies]), the site must complete the paper SAE form and email to CCI [redacted] immediately and also within 24 hours of becoming aware of the event. The reported information submitted as a paper SAE must be entered into the EDC system once it becomes operational.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.3. Reporting Adverse Events

The sponsor has the responsibility to inform concerned health authorities, ethic committees, and investigators about suspected unexpected serious adverse reactions in line with GCP guidance and applicable regulatory requirements.

If required, specific SAEs should be reported to the concerned ethic committees in compliance with local requirements

11.3.1. Relationship of Events to Study Treatment

All AEs that occur during this study will be recorded. The investigator will review each event and assess its relationship to study treatment (definitely related, possibly related, unlikely related, not related, unknown). The date and time of onset, time relationship to drug dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown) of each event will be noted.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Definitely Related	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon) Re-challenge satisfactory, if necessary
Possibly Related	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear
Unlikely Related	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations
Not Related	Event or laboratory test abnormality, is plausibly related to the participant's clinical state, underlying disease, or the study procedure/conditions Time relationship to drug intake makes a relationship unreasonable Other obvious causes for event or laboratory test abnormality exist
Unknown	Report suggests an adverse event, however, cannot be judged at this time because information is insufficient or contradictory More data for proper assessment is needed, or additional data is under examination

11.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL [a].
Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]. Note**:** An experience may be severe but may not be serious, eg, severe headache).

Abbreviation: ADL=activities of daily living
A semicolon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.4. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening*, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

**Life-threatening* is defined as an AE or suspected adverse reaction, which in the view of either the investigator or sponsor places the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the Reference Safety Information section of the IB.

11.5. Treatment and Follow-up of Adverse Events

AEs (whether serious or nonserious), including clinically significant abnormal laboratory test values, will be evaluated by the investigator and treated and/or followed up until the symptoms or value(s) return to baseline or are clinically stable. Treatment of AEs will be performed by appropriately trained medical personnel, either at the clinical site or at a nearby hospital emergency room. When appropriate, medical tests and/or examinations will be performed to document resolution of the event(s).

AEs continuing after completion of the study will be followed up by telephone or with visits per the discretion of the investigator. If possible, the outcome of any AE that caused discontinuation from the study or was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the study drug.

11.6. Pregnancy

Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject, must be followed to conclusion to determine their outcome and are considered immediately reportable events.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety within 24 hours of the investigator's awareness using the paper Pregnancy Report Form. The Pregnancy Report Form shall be signed and dated by the investigator and submitted via email to CCI [redacted].

The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc.) and neonatal status up to 12 months postdelivery. An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE Report Form will be required.

11.7. Disease Progression

Normal progression or worsening of the medical condition under study (eg, vision loss due to the progression of GA in either eye), by itself, does not necessarily constitute an AE unless the change can be reasonably attributed to an action of the test article and not only to its lack of efficacy. Disease progression that requires an intervention (eg, administration of IVT anti-VEGF agents for neovascular AMD) should be recorded as an AE in the eCRF.

11.8. Withdrawal

Participants may choose to discontinue from treatment or to completely withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other clinical protocols.

Participants wishing to withdraw from the study completely will be offered an early termination visit. This early termination visit will include the examinations outlined in Section 8.1.5.

Participants wishing to discontinue treatment but willing to continue with other study procedures, will return to the clinical site for follow-up visits, as per protocol, until Month 24.

Additional information on subject discontinuation is provided in Section 6.5.

12. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

12.1. Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

12.2. Clinical Data Management

Data are to be entered into a clinical database as specified in the contract research organization's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

12.3. Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock. All statistical analyses will be performed using SAS (SAS Institute, Cary, NC 27513).

12.4. Planned Interim Analysis and Data Safety Monitoring Committee

No interim analysis is planned for this study. During the study, patient safety will be monitored on a continuous basis by the medical monitor until the last patient completes his or her last scheduled study assessment.

An independent DMC will also be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and

safety of the participating patients in the study. The ongoing review of SAEs and other responsibilities of the DMC will be described in the DMC Charter.

The overall Type I (alpha) error rate for the study will be 0.05. To accommodate DMC data reviews, the alpha available for efficacy hypothesis testing will be reduced by 0.0001 for each DMC review. The study is expected to have 3-4 DMC data reviews prior to the primary analysis of 12-month data and 1 review afterward.

12.5. Sample Size Calculation and Power Considerations

Subjects will be randomized in a 2:2:1:1 ratio to receive treatment with pegcetacoplan monthly, pegcetacoplan every other month, sham monthly, or sham every other month. 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 pegcetacoplan monthly, pegcetacoplan every-other-month, and sham-pooled groups, respectively, as estimated from the results of a Phase 2 trial for 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.[27] The following table provides an approximation of the study power for a sample size of 200 subjects in each group (ie, a total enrollment of 600 subjects) under different alpha values and standard deviations. The approximation is calculated using PROC POWER one-way analysis of variance, SAS 9.4. The study power is likely larger when utilizing the longitudinal data to model the primary endpoint. The actual study power may also vary based on the distribution of the stratification factors (ie, lesion area at screening, presence of CNV in fellow eye), and site enrollment.

Table 4: Power to Detect a Difference Among 3 Groups With an Equal Size of 200 Subjects

Common standard deviation (mm^2)	Alpha (2-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%

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

12.6. Statistical Analysis Sets

The **safety set** will consist of all subjects who receive any amount of IP.

The **intent-to-treat (ITT) set** will include all randomized subjects. Subjects will be analyzed in the treatment arm assigned at randomization with the 2 sham treatment arms being combined into a single ‘control’ group.

The **modified ITT (mITT) set** will include all randomized subjects who receive at least 1 injection of pegcetacoplan or sham and have baseline and at least 1 postbaseline value of GA lesion in the study eye as assessed by FAF.

The **per-protocol (PP) set** will include all ITT subjects who follow the protocol without any major deviation(s) that could impact the integrity of the data. A detailed description of the reasons for exclusion from the PP population will be included in the statistical analysis plan (SAP).

12.7. Efficacy Analyses

The primary, secondary, and exploratory efficacy analyses will be performed using the ITT set and presented by treatment group.

12.7.1. Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline to Month 12 in the total area of GA lesion(s) in eyes injected with pegcetacoplan, either monthly (PM) or every-other month (PEOM), or sham injections. GA lesion area (mm^2) as measured by a quantified central reading center based on FAF images. The primary analysis will be the comparison of pegcetacoplan, either monthly (PM) or every-other month (PEOM) versus the combined 2 sham arms (the 2 sham arms will be combined into a single 'control' group).

The null and alternative hypotheses for the primary efficacy analysis are:

H_0: $\mu_S = \mu_{PM}$ vs H_A: $\mu_S \neq \mu_{PM}$, and

H_0: $\mu_S = \mu_{PEOM}$ vs H_A: $\mu_S \neq \mu_{PEOM}$

Note: here μ indicates each group's respective mean change from baseline to Month 12 in GA lesion area for the comparison of the primary endpoint.

A mixed effect model for longitudinal data will be used to analyze the change from baseline in GA lesion area. The model will include treatment and presence of CNV in the fellow eye as fixed effects; baseline GA lesion area (at screening), time (in months) as a factor; as well as the time × treatment interaction term. All available data up to 12 months will be included in the model for the primary analysis. The mean change from baseline to 12 months will be estimated from the model (ie, least square [LS] mean) and compared between each of the pegcetacoplan arms to the sham control. For other time point of interest, LS mean change from baseline will be estimated and compared between treatments. Unstructured variance covariance will be used.

For the analysis of final study data, a similar model including data up to 24 months will be used and LS means at time points of interest will be estimated and compared between treatment.

As indicated in an earlier section, the study is expected to have an approximately 5 DMC data reviews. Allocating an alpha level of 0.0001 for each DMC data review, the alpha level remains for the efficacy analysis at 0.0495 to maintain an overall study alpha of 0.05.

The hypothesis testing strategy for the primary and secondary efficacy endpoints will be based on the Gate-keeping multiple testing procedures controlling for the study wide type I error strongly at 2-sided 0.0495 as follows:

Step 1. The mean GA lesion growth at 12 months will be compared between the PM group and the Control at the α level of 0.0495. If the null hypotheses of no difference between groups in this step is rejected, the testing proceeds to **Step 2** and **Step 3**. If it's not rejected, the testing procedure stops at this step.

Step 2. The mean GA lesion growth at 12 months will be compared between the PEOM group and the Control at the **α1** level. If the null hypotheses of no difference between groups in this step is rejected, the **α1** level will be passed down to **Step 3**. The actual value of **α1** will be specified in the SAP and it will be defined to ensure an adequate power of at least 80% for the comparison in this step.

Step 3. The mean GA lesion growth at 24 months will be compared between the PM group and the Control at the α level of **0.0495** if the null hypotheses are rejected at both **Step 1** and **Step 2**; or at the α level of **(0.0495 – α1)** if **Step 2** testing does not reject the null hypothesis. If the null hypothesis at this step is rejected, the α level used at this step will be passed down to the next step of testing. If it's not rejected, the testing procedure stops at this step.

Step 4. The prioritization and alpha allocation for the remaining secondary endpoints will be specified in the SAP.

The following sensitivity and supportive analyses will be performed to evaluate the robustness of the results from the primary analysis method:

- Analyses will be repeated using the mITT and PP sets
- Primary and secondary endpoints will also be summarized with no pooling of the 2 sham arms. The comparison for pegcetacoplan and sham injection within each dose regimen (ie, PM vs SM and PEOM vs SEOM) will be conducted
- Multiple imputation methods and other sensitivity analyses will be explored, and details will be provided in the SAP

12.7.2. Secondary Efficacy Analysis

The key secondary and secondary endpoints will be analyzed in the same fashion as the primary endpoint using mixed effect model. The binary secondary endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. Hypothesis testing for 3 key secondary endpoints will be performed in the order specified. The SAP will provide more details on multiplicity adjustment and the approach for alpha spending among the endpoints.

Key Secondary Efficacy Endpoints

- Change from baseline in maximum monocular reading speed (study eye), as assessed by MNREAD or Radner Reading Charts at Month 24 (in select countries)
- Change from baseline in FRI index score, at Month 24.
- Change from baseline in NL-BCVA at Month 24 as assessed by ETDRS chart.

Secondary Efficacy Endpoints

- Change from baseline in LL-BCVA at Month 12 and Month 24 as assessed by ETDRS chart.
- Change from baseline in LLD at Month 12 and Month 24.
- Change from baseline at each planned assessment in the total area of GA lesion(s) in the study eye (in mm^2) as assessed by FAF.

- Change from baseline in monocular critical print size (study eye), as assessed by MNREAD or Radner Reading Charts, at Month 12 and Month 24 (in select countries).
- Change from baseline in the NEI VFQ-25 distance activity subscale score at Month 12 and Month 24 (in select countries).
- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response.
- Change in macular sensitivity as assessed by mesopic microperimetry for the evaluation of the macular functional response.

12.7.3. Exploratory Efficacy Analysis

Summary statistics will be provided for the following exploratory endpoints:

- Change from baseline in NEI VFQ-25 composite score at Month 12 and Month 24.
- Change from baseline in NEI VFQ-25 near activity subscale score at Month 12 and Month 24 (in select countries).
- Comparison between study eye and fellow eye in change in GA lesion size from baseline to Month 12 and Month 24.
- Binocular maximum reading speed as assessed by MNREAD or Radner Reading Charts over time (in select countries).
- Binocular critical print size as assessed by MNREAD or Radner Reading Charts over time (in select countries).
- Relationship between genetic polymorphisms associated with AMD with GA progression and response to pegcetacoplan.
- Incidence of new onset of subclinical CNV in the study eye.
- Assess sensitivity and specificity of a digital reading speed application to detect disease progression / regression (optional, select sites).
- Assess sensitivity and specificity of a digital visual function application to detect disease progression / regression (optional, select sites).

12.8. Safety Analyses

Adverse events will be collected from the time of the first study drug administration until a subject completes the study or discontinues prematurely. Treatment-emergent adverse events are defined as those AEs that develop or worsen after the first dose of study medication and up to 30 days beyond the last dose of study medication. The current version of MedDRA will be used to classify all AEs. Treatment-emergent adverse events will be summarized by System Organ Class and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE Preferred Term will be tabulated for all TEAEs and separately for those considered as related to study treatment by the investigator or designee. Number of

subjects reporting SAEs will also be tabulated. Adverse event summaries will be presented for each treatment group separately.

Adverse events will be summarized by MedDRA coding terms, and separate tabulations also will be produced for related AEs (those considered by the investigator as definitively drug related), SAEs, and discontinuations due to AEs. Vital signs data and findings from physical and ophthalmologic examinations will be tabulated for changes over time on study. Laboratory parameters will be summarized for changes across study by using descriptive statistics. Separate summaries will be prepared for systemic (nonocular) and ocular AEs, with events in the study eye and nonstudy eye summarized separately

12.8.1. Anti-Therapeutic Antibodies

Data on anti-therapeutic antibodies (ATAs) directed against pegcetacoplan will be summarized by the number and percentage of subjects with confirmed positive ATAs.

12.8.2. Death

Patient deaths and primary cause of death will be summarized.

12.8.3. Ocular Assessments

Descriptive summaries will be generated for ocular assessments, such as VA and IOP.

12.9. Handling of Missing Data

All efforts will be made to minimize missing data. A full description of the imputation methods will be provided in the SAP.

12.10. Visit Windows

Analysis visits will be derived with windows for the monthly visits to assess the primary endpoint. Baseline is defined as the date of randomization. If 2 or more treatment visits occur within a window, the closest visit to the target day will be used as that analysis visit; if 2 visits are equidistant from the scheduled analysis visit day, the later analysis visit will be used.

13. ETHICS

13.1. Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guidance for Good Clinical Practice, E6, R1 (ICH GCP).

13.2. Institutional Review Board/Ethic Committee

The study protocol, any amendments to the protocol, ICF, the IB, and other study-specific information will be reviewed and approved by the IRB/IEC. The study will not be initiated until the IRB/IEC has approved the protocol or a modification thereof. All records pertaining to IRB/IEC submission and approval should be kept in the site's regulatory files and sponsor's Trial Master File.

The IRB/IEC must be constituted and operate in accordance with the principles and requirements described in ICH Guidance E6 and national and local regulations as deemed appropriate.

13.3. Subject Information and Consent

The principal investigator, or designee, is responsible for obtaining an informed consent. A written informed consent, in compliance with ICH Guidance E6, must be obtained from each subject at the screening visit, prior to performing any study-related procedures.

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the subjects in nontechnical terms. The subject will be given sufficient time to consider the study's implications before deciding to participate in the study. The subject and/or legal guardian will be required to sign and date an ICF and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. The PI shall retain the original, signed informed consent for study participation in the subject's medical record and shall provide the subject and/or legal guardian with a copy of the signed consent.

If there are any changes/amendments to the approved protocol, which may directly affect the subject's decision to continue participation in the study, the ICF shall be amended to incorporate the changes to the protocol and the subject must re-sign the IRB/IEC approved amended ICF.

14. ADMINISTRATIVE CONSIDERATIONS

14.1. Direct Access to Source Data/Documents

The principal investigator, or designee, must maintain, at all times, the primary records (ie, source documents) of each subject's data for data verification. Examples of source documents are medical records, laboratory reports, study drug records, and printed CRF pages that are used as the source.

The investigator will permit trial-related monitoring, audits, and inspections by the sponsor and/or its designee, IRB/IEC, and the regulatory agencies at any time during the study. The investigator will ensure that the auditor is allowed direct access to the source data, medical records, eCRFs, and the site's regulatory file for the study and any other pertinent information.

14.2. Quality Control and Quality Assurance

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. The principal investigator, sponsor, and/or its designee are responsible for ensuring that the study staff receive appropriate training on the protocol, study procedures, and any other relevant information.

Quality assurance and quality control systems are implemented and maintained using written Investigative site, sponsor and/or designee Standard Operating Procedures (SOPs) to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s) and local laws, rules, regulations.

Quality control checks will be applied at each stage of data handling (eg, edit checks) to ensure that all data are reliable and have been processed correctly.

14.3. Monitoring

On-site monitoring will be performed by the sponsor's designee for the duration of the study. The monitor will ensure that the study is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements. The monitor will verify the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The investigator, or designee, will provide direct access to source data/documents for study-related monitoring. It is important that the investigator and the investigator site staff are available at these visits. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be documented in writing to the investigator.

14.4. Data Handling and Record Keeping

The investigator must maintain all documentation related to this study. All essential documents (as defined in the ICH Guideline E6 and applicable local regulations) and the data generated in connection with this study, together with the original copy of the final report, will be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there

are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14.5. Protocol Amendments

Any amendments to the study protocol deemed necessary as the study progresses will be discussed between sponsor and the investigator. The investigator will not implement any changes to the protocol without an agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazards to study subject or when the changes involve only logistical or administrative aspects of the study (eg, change in staff, telephone numbers).

Changes resulting in amendments will be made jointly between the sponsor and the investigator and must be confirmed in writing. Amendment(s) will be approved and signed off in the same way as the protocol.

14.6. Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

14.7. Finance and Insurance

Finance and insurance will be addressed in a Clinical Trial Agreement between the sponsor and the investigator/institution.

14.8. Publication Policy

The data generated for this study are considered confidential information and are the property of the sponsor. All study information provided to the PI and site personnel by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

Apellis will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Apellis adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Apellis. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Apellis products or projects must undergo appropriate technical and intellectual property review, with Apellis agreement to publish prior to release of information. The review is aimed at protecting the sponsor’s proprietary information existing either at the

commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the investigator has such sole, joint, or shared rights, the investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Apellis, the institution and investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

14.9. ClinicalTrials.gov

This study will be listed with ClinicalTrials.gov.

14.10. Termination of Study

The sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons at any time. The investigator reserves the right to discontinue dosing subjects at any time for safety reasons.

15. REFERENCES

1. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *American journal of ophthalmology.* 2007;143(3):463-472.

2. Rein DB, Wittenborn JS, Zhang X, et al. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. *Archives of ophthalmology.* 2009;127(4):533-540.

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16. APPENDICES

APPENDIX A: VISIT SCHEDULE—Monthly Group—Screening, Day 1 through Month 12

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	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—anti-pegcetacoplan Ab [D]		x	x	x				x						x	x
Blood draw—genotyping (if applicable) [D]				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
Mesopic microperimetry[L]	x							SE						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 [M]		x						x						x	x
FRI [M]		x						x						x	x
Home-based digital applications [M,N,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

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	8	8	8	8	8	8	8	8	8	8	8	8	
SD-OCT [O]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [O]	x	x		SE		SE		x		SE		SE		x	x
NIR [O]	x	x		SE		SE		x		SE		SE		x	x
DCFP [O]	x													x	x
FFA [O]	x													x	x
OCT-A[S]		x[S]						x[S]						x[S]	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 [P]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Follow-up call [Q]		x	x	x	x										
Concomitant medication/ concomitant ocular procedures [R]	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

Abbreviations: BCVA=best corrected visual acuity; 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; 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/ exculsion 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.
M. 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.
N. 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.
O. 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.
P. 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.
Q. 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.
R. 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.
S. 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.
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.

APPENDIX B: 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	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—anti-pegcetacoplan Ab [D]		x				x						x	x
Blood draw—genotyping (if applicable) [D]													
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
Mesopic microperimetry[L]						SE						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 [M]						x						x	x
FRI [M]						x						x	x
Dilated Indirect Ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
Home-based digital applications [M,N,S]						x						x	
IOP measurement	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [O]	x	x	x	x	x	x	x	x	x	x	x	x	x

	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	
FAF [O]		SE		SE		x		SE		SE		x	x
NIR [O]		SE		SE		x		SE		SE		x	x
DCFP [O]												x	x
FFA [O]												x	x
OCT-A[S]						x [S]						x [S]	x
Study eye determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]	x	x	x	x	x	x	x	x	x	x	x		
Postinjection assessment [P]	x	x	x	x	x	x	x	x	x	x	x		
Follow-up call [Q]													
Concomitant medication/ concomitant ocular procedures [R]	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: BCVA=best corrected visual acuity; 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; 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/ exculsion 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.
M. 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.
N. 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.
O. 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.
P. 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.
Q. 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.
R. 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.
S. 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.
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.

APPENDIX C: VISIT SCHEDULE—Every-Other-Month Group—Screening, Day 1 Through Month 12

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	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—anti–pegcetacoplan Ab [D]		x	x	x				x						x	x
Blood draw—genotyping (if applicable) [D]				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
Mesopic microperimetry[L]	x							SE						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 [M]		x						x						x	x
FRI [M]		x						x						x	x
Home-based digital applications [M,N,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 [O]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [O]	x	x		SE		SE		x		SE		SE		x	x

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	8	8	8	8	8	8	8	8	8	8	8	8	
NIR [O]	x	x		SE		SE		x		SE		SE		x	x
DCFP [O]	x													x	x
FFA [O]	x													x	x
OCT-A[S]		x[S]						x[S]						x[S]	x
Study eye determination	x														
Randomization		x													
Pegcetacoplan administration or Sham Injection[T]		x		x		x		x		x		x		x	
Postinjection assessment [P]		x		x		x		x		x		x		x	
Follow-up call [Q]		x		x		x									
Concomitant medication/ concomitant ocular procedures [R]	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

Abbreviations: BCVA=best corrected visual acuity; 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; 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 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.
M. 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.
N. 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.
O. 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.
P. 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.
Q. 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.
R. 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.
S. 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.
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.

APPENDIX D: 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—anti-pegcetacoplan Ab [D]		x				x						x	x
Blood draw—genotyping (if applicable) [D]													
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
Mesopic microperimetry[L]						SE						x	x
Slitlamp examination		x		x		x		x		x		x	x
Endothelial cell count[S]												x	x
NEI VFQ-25 [M]						x						x	x
FRI [M]						x						x	x
Home-based digital applications [M,N,S]						x						x	
Dilated indirect ophthalmoscopy		x		x		x		x		x		x	x
IOP measurement		x		x		x		x		x		x	x
SD-OCT [O]		x		x		x		x		x		x	x
FAF [O]		SE		SE		x		SE		SE		x	x

	Treatment												
Visit #		**15**		**16**		**17**		**18**		**19**		**20**	**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)		**16**		**16**		**16**		**16**		**16**		**16**	
NIR[O]		**SE**		**SE**		**x**		**SE**		**SE**		**x**	**x**
DCFP [O]												**x**	**x**
FFA [O]												**x**	**x**
OCT-A[S]						**x[S]**						**x[S]**	**x**
Study eye determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]		**x**		**x**		**x**		**x**		**x**			
Postinjection assessment [P]		**x**		**x**		**x**		**x**		**x**			
Follow-up call [Q]													
Concomitant medication/ concomitant ocular procedures [R]		**x**		**x**		**x**		**x**		**x**		**x**	**x**
Adverse events		**x**		**x**		**x**		**x**		**x**		**x**	**x**

Abbreviations: BCVA=best corrected visual acuity; 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; 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 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.
M. 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.
N. 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.
O. 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.
P. 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 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.
Q. 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.
R. 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.
S. 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.
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.

APPENDIX E: NATIONAL EYE INSTITUTE VISUAL FUNCTIONING QUESTIONNAIRE 25-ITEM VERSION

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DRIVING

A10. [This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.....	1	2	3	4	5

APPENDIX F: FUNCTIONAL READING INDEPENDENCE INDEX (FRI)

Kimel M, Yu R, Leidy N. The Functional Reading Independence Index (FRI Index) - User Manual (Version 1.2). Evidera. 2015

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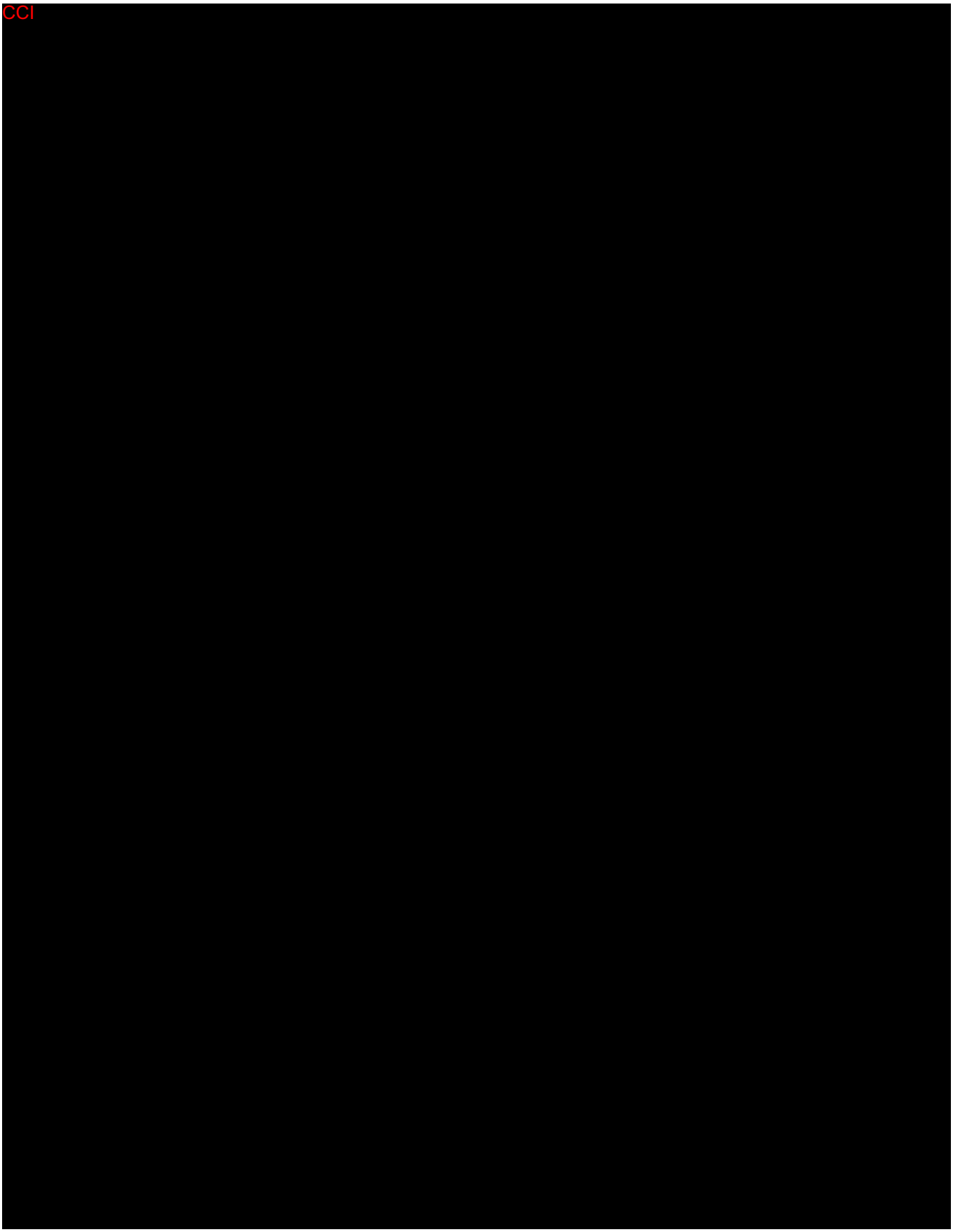
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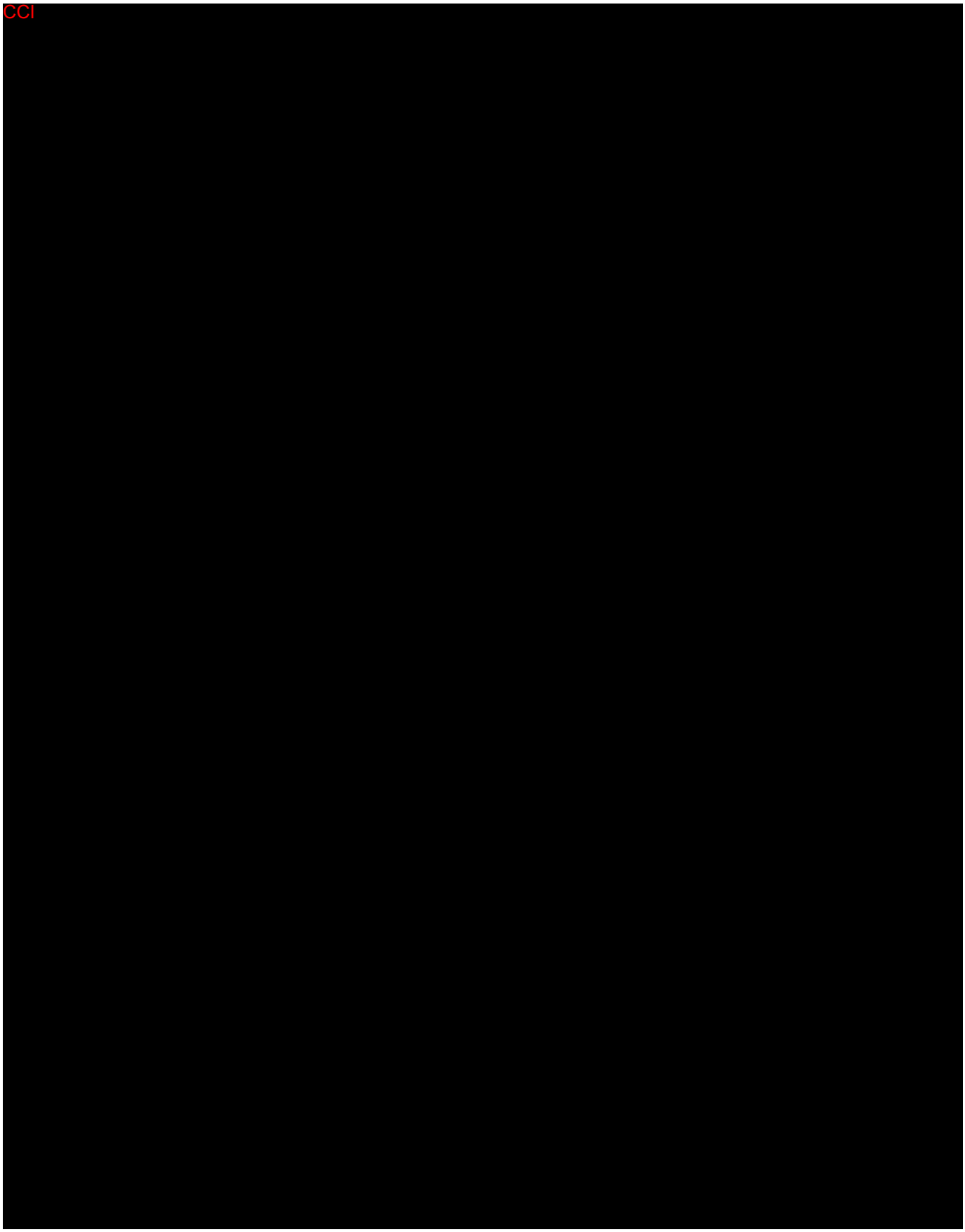

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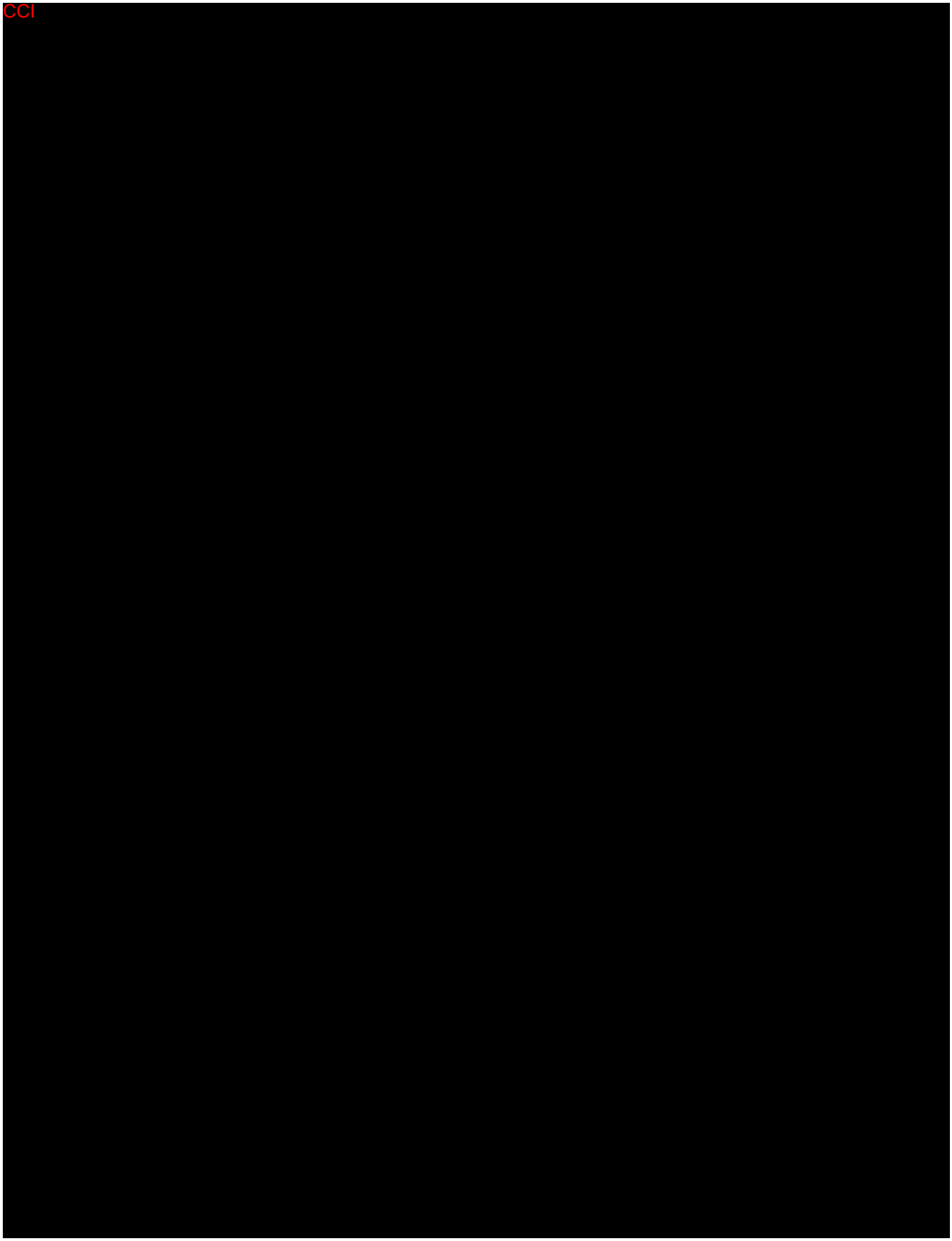
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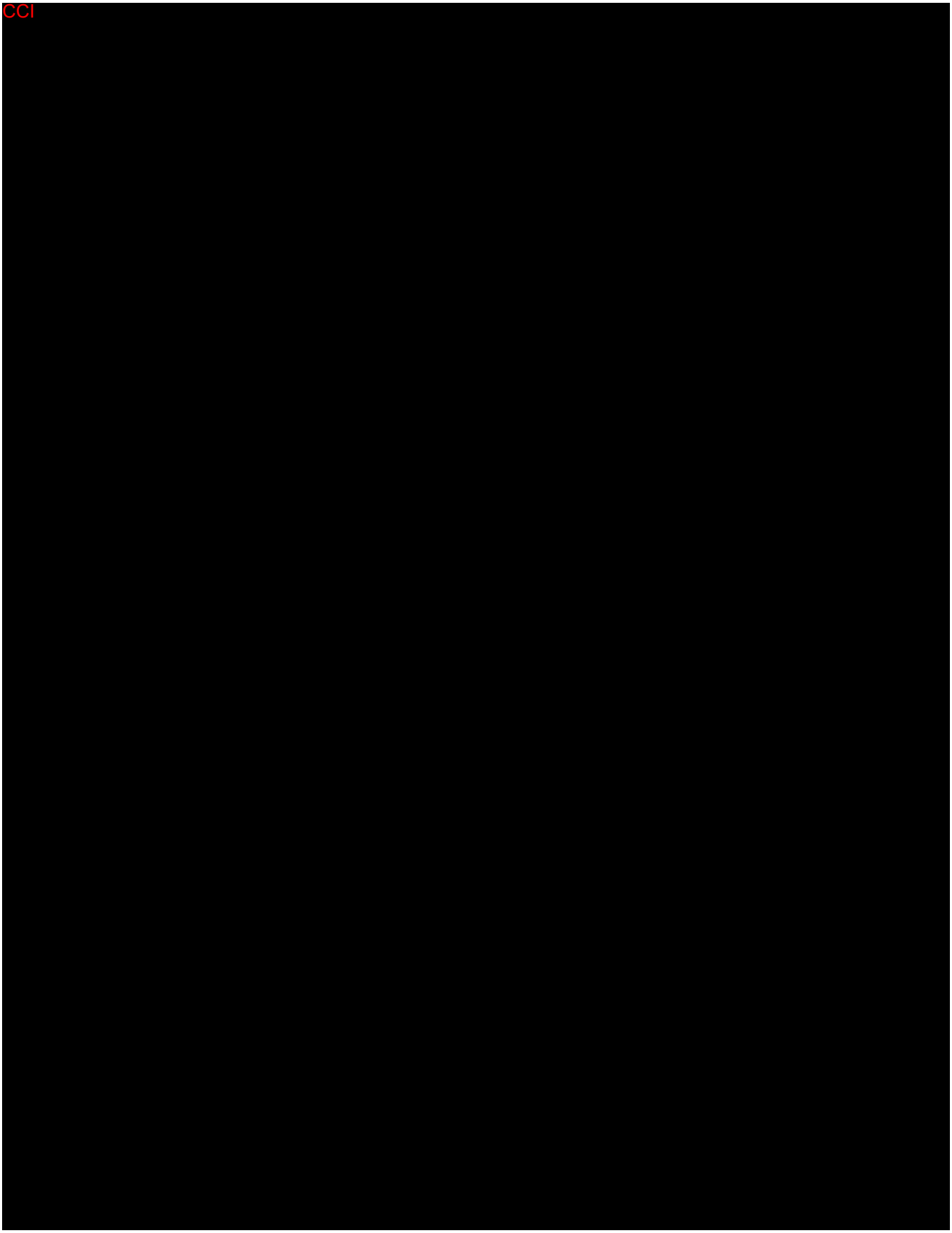

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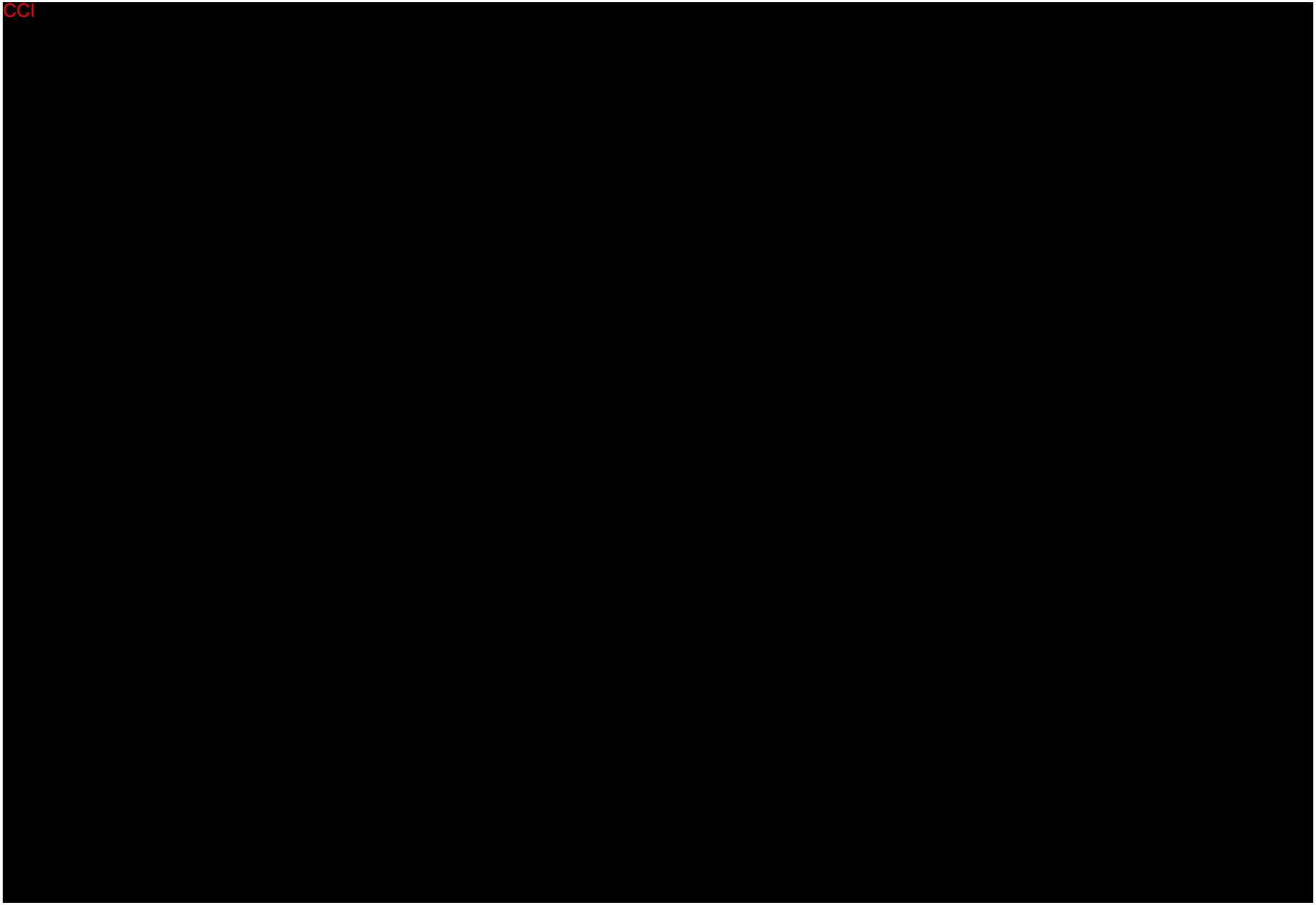
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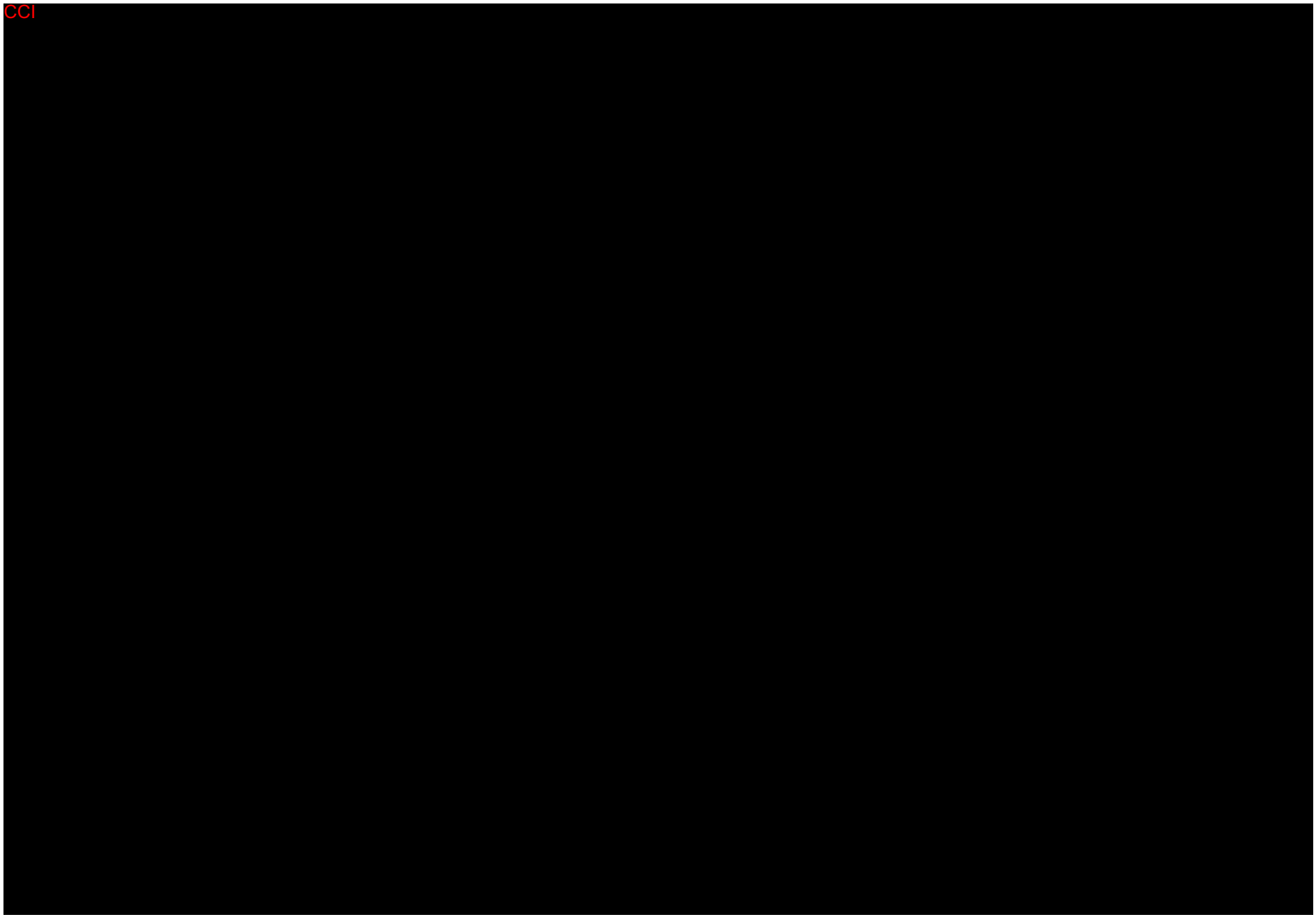
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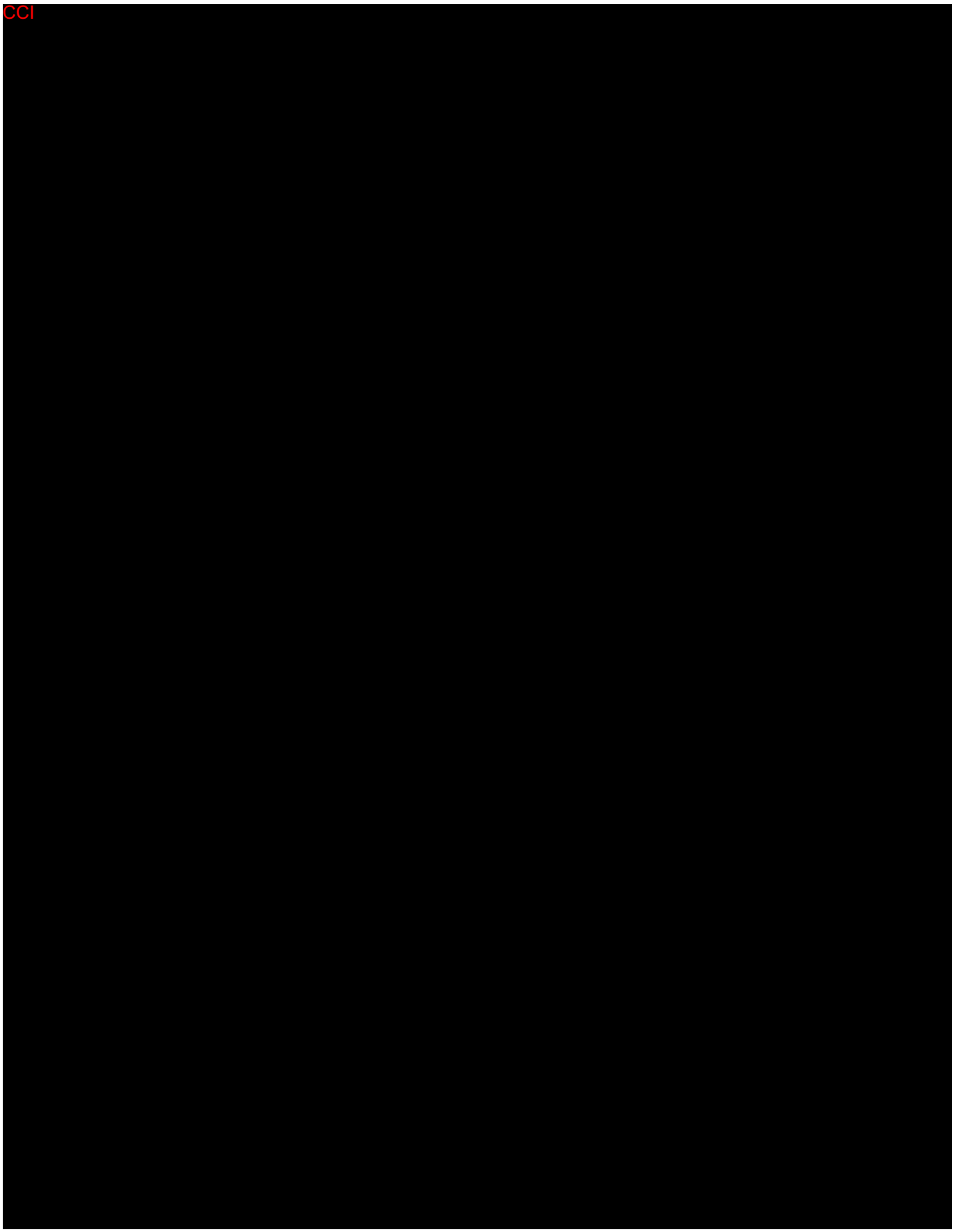

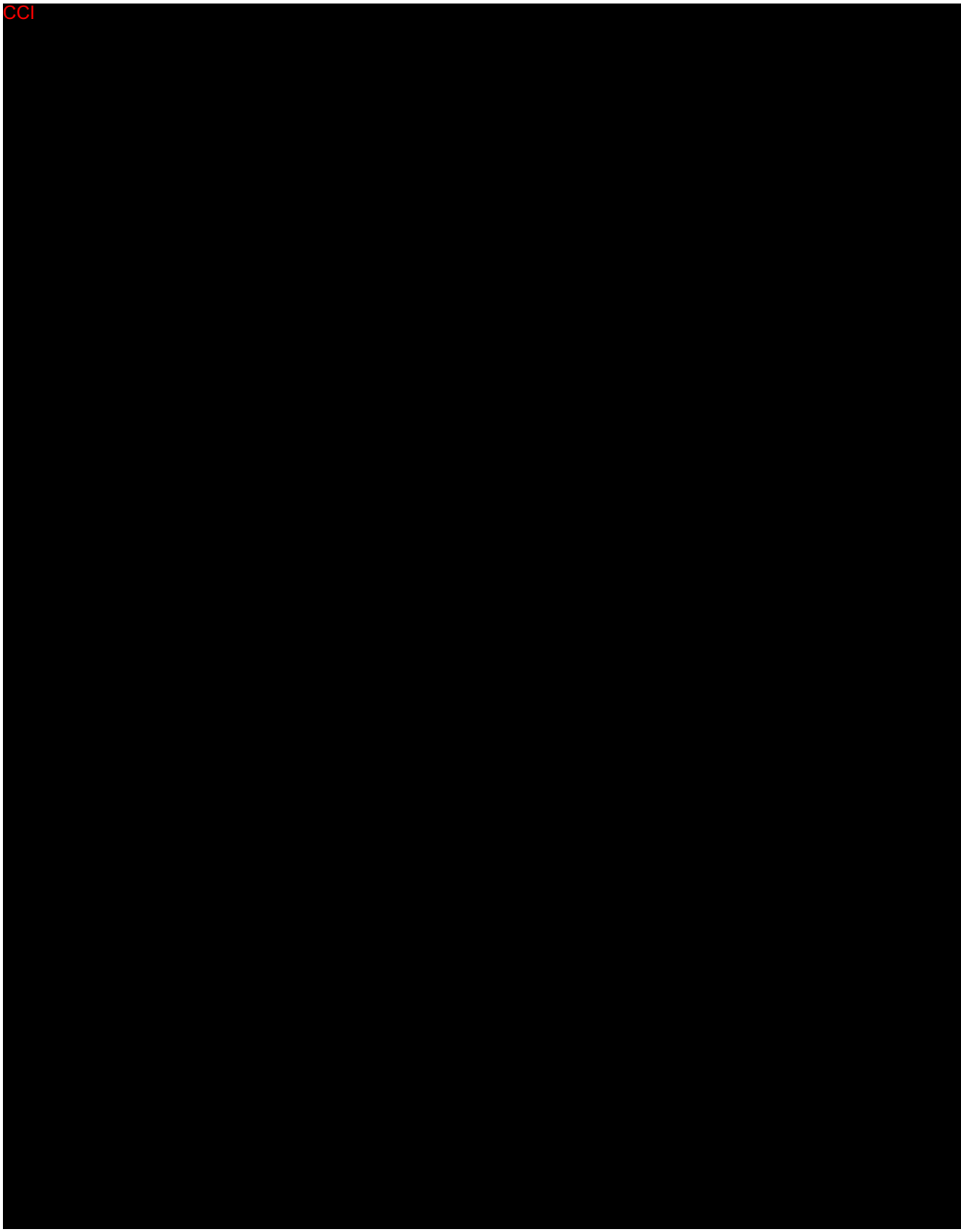
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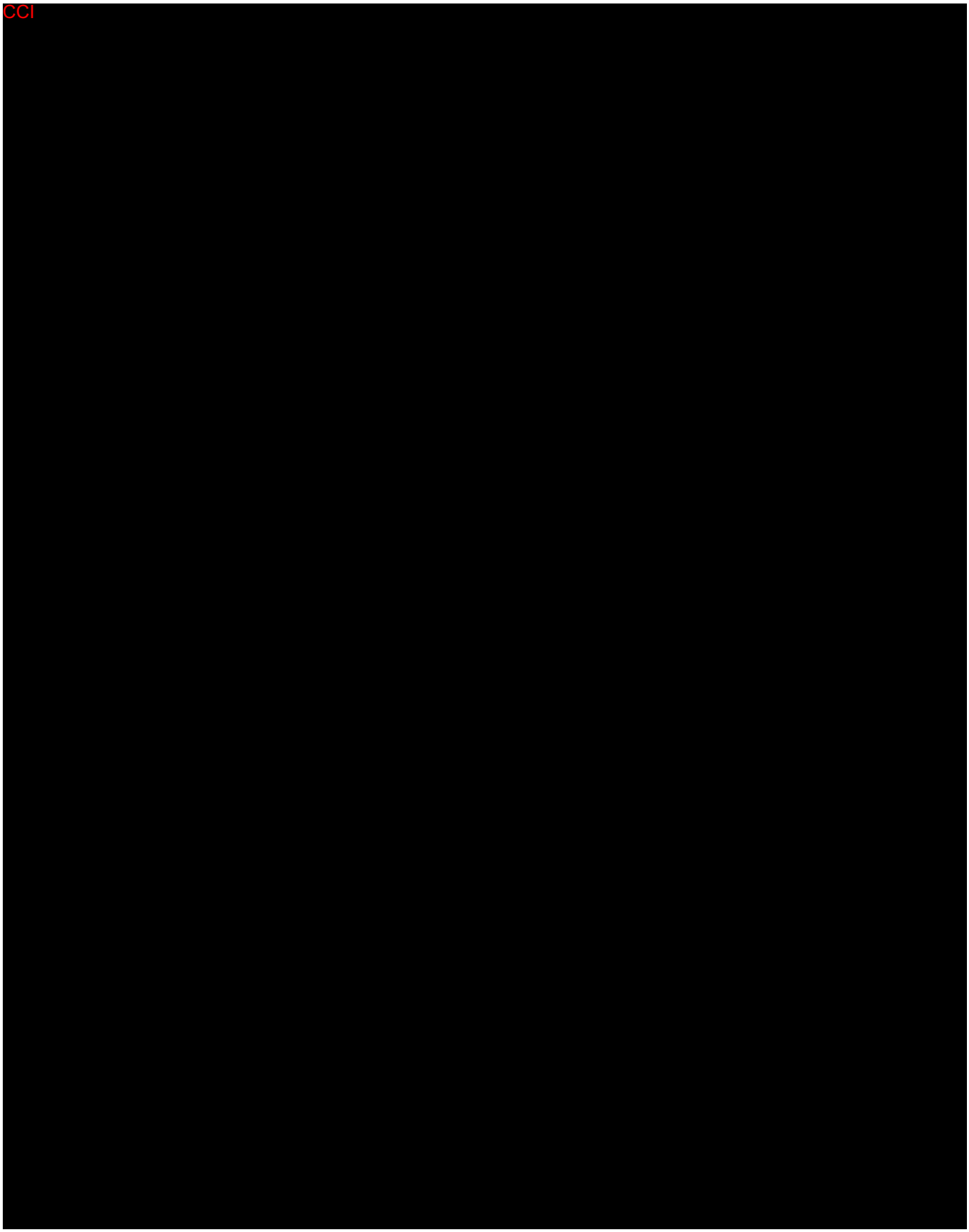

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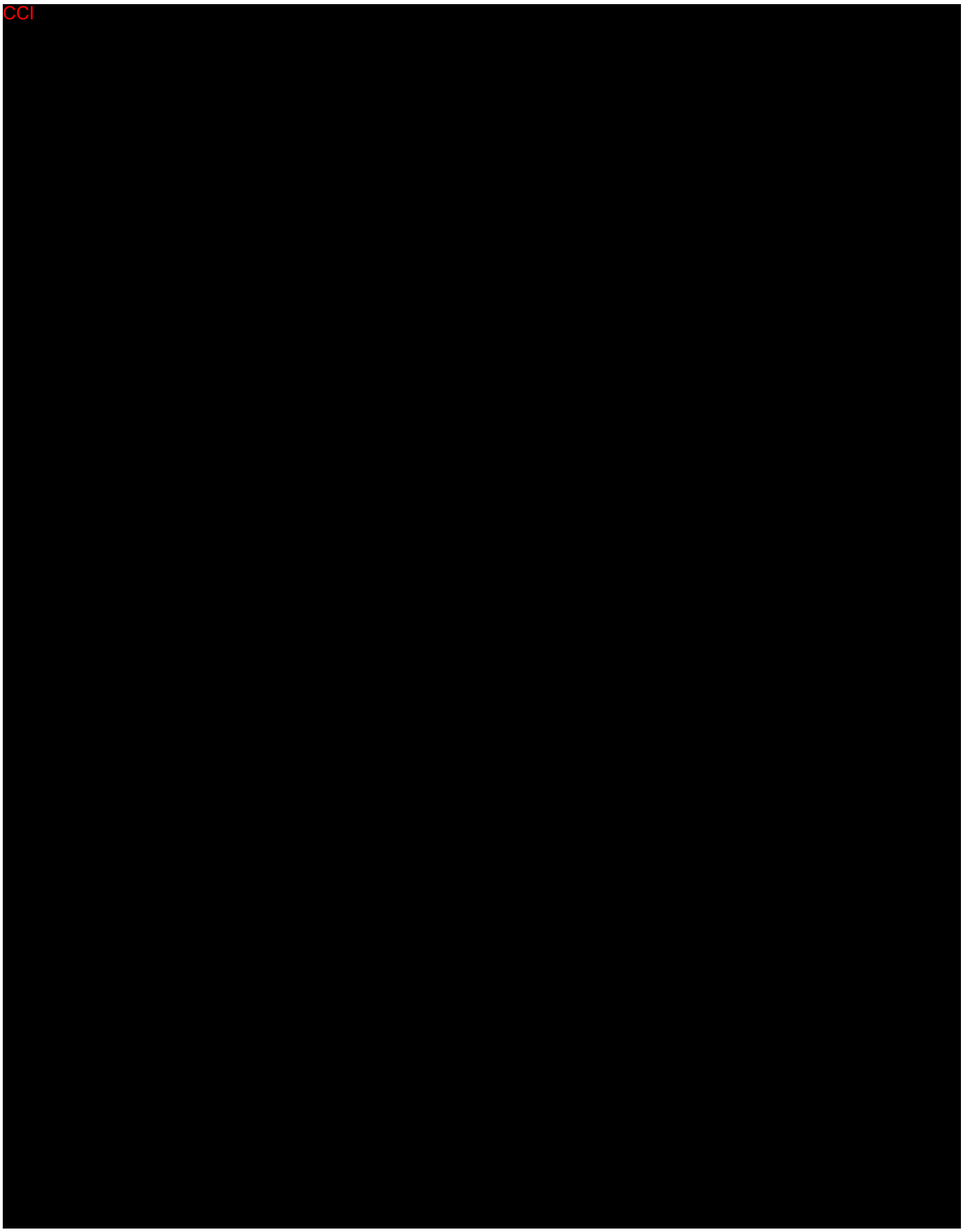

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APPENDIX G: MINNESOTA LOW-VISION READING TEST (MNREAD) AND RADNER READING CARDS

The manual of procedures should be referenced for a detailed table of countries and languages to determine which test will be administered. Equipment and testing procedures will also be described in detail in the manual of procedures for both tests.

Minnesota Low-Vision Reading Test:

The Minnesota Low-Vision Reading Test acuity cards are continuous-text reading-acuity cards used for measuring the reading acuity and speed of normal and low-vision patients. These charts were developed at the Minnesota Laboratory for Low-Vision Research, University of Minnesota, Minneapolis, Minnesota, USA.

The MNREAD Acuity Charts will be used to measure:

- Critical Print Size: the smallest print that the patient can read with maximum speed
- Maximum Reading Speed: the patient's reading speed when reading is not limited by print size

Radner Reading Cards:

The Radner Reading Cards consist of sentence optotypes, which are optimized reading test items, standardized by construction and statistical selection. These cards allow for accurate and comparable measurements of reading acuity and reading speed and measurement of critical print size.

APPENDIX H: GRADING SCALE FOR ASSESSMENT OF ANTERIOR CHAMBER FLARE OR CELLS

AQUEOUS REACTION—FLARE

Grade	Description
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slitlamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Mild amount of protein detectable in the anterior chamber. This protein is immediately apparent to an experienced observer using slitlamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light. Note presence of any fibrin.
2-3+	Moderate amount of protein detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+. Note presence of any fibrin.
4+	A large (severe) amount of protein is detectable in the anterior chamber. Similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It needs to be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood-aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (eg, 1+ flare with fibrin).

AQUEOUS REACTION—CELLS

Grade	Description
0	No cells are seen in any optical section when a large slitlamp beam is swept across the anterior chamber.
Trace	Rare (1-3) cells are observed when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3-10 cells/optical section are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Note stage of hypopyon, if applicable.
2+	10-25 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Note stage of hypopyon, if applicable.
3+	25-50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present. Note stage of hypopyon, if applicable.
4+	More than 50 cells are seen when the slitlamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells or

	hypopyon is noted. As for the fibrin deposition, hypopyon may persist for a period of time after exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible for have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

APPENDIX I: GRADING SCALE FOR ASSESSMENT OF VITREOUS CELLS

Grade	Description	Cells in Retro-Illuminated Field
0	Clear	0
Trace	Few opacities	1-20
1	Scattered opacities	21-50
2	Moderate opacities	51-100
3	Many opacities	101-250
4	Dense opacities	≥ 251

APPENDIX J: AMENDMENT HISTORY

A summary of changes from previous amendments is provided below.

Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 4	**Amendment Date 27 April 2020**	**Global**
Description of Change		**Section(s) Affected by Change**
Non-substantial changes that did not impact content of the document have been made for clarity.		Entire document
Information related to COVID-19-related changes added		Appendix K

Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 3 Version 1.0	**Amendment Date 14 February 2019**	**Global**
Description of Change		**Section(s) Affected by Change**
Non-substantial changes that did not impact content of the document have been made for clarity.		Entire document
PK and complement profile assessments have been removed from this study.		Entire document
It was noted that: <u>In addition, two GLP-compliant 2-month ocular bridging studies (the first comparing drug substance from two different CMOs, the second assessing the safety and tolerability profiles of three different formulations to support the Phase 3 clinical study) have been conducted, in cynomolgus monkeys as well.</u> The previous version of the protocol noted that 1 2-month ocular bridging study was completed and that data from a second study would be performed to assess the safety and tolerability profiles of three different formulations in order to support the Phase 3 formulation.		Section 4.1.3 Nonclinical Data
Updated to include Clinical Study APL2-103.		Section 4.1.4 Clinical Data
Updated to include the following statement: <u>In recent studies conducted with APL 2 IVT from a single manufacturer, events of transient moderate and severe intraocular inflammation have been observed.</u>		Section 4.2 Risk/Benefit

Section revised to further define approved methods of contraception include:
• Combined (estrogen-and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  o Oral
  o Intravaginal
  o Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  o Oral
  o Injectable
  o Implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success)
• Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). Sexual abstinence is only accepted when it is the preferred and usual lifestyle of the subject.
 	
~~Approved methods of contraception include: oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like DepoProvera) or removable birth control device (like NuvaRing or Ortho Evra patches); and/or surgical sterilization (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study and 90 days after their last dose of study drug.~~
	Section 6.4 Approved Methods of Contraception

The following section was added: A subject may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from treatment with the investigational product with the medical monitor when possible. Subjects who discontinue treatment with the investigational product can continue participation in the study and should be encouraged to return to the clinical site for as many follow-up visits as they can. In the event that a subject terminates early from the study, all early termination procedures should be performed even if they are outside the allowed study window. The reason for termination, date of stopping treatment with investigational product, all follow-up information and the total amount of investigational product administered must be recorded in the case report form (CRF) and source documents.	Section 6.5 Discontinuation of Subjects

The requirement to notify the sponsor prior to unmasking was removed: In the event of a medical emergency where the knowledge of subject treatment by masked individuals (e.g., the subject or his/her physician) is required, an individual Investigator (or designee) will have the ability to unmask the treatment assignment for a specific subject and share that information with the appropriate parties. ~~The Investigator (or designee) must endeavor to notify the Sponsor prior to unmasking a subject.~~	Section 7.2.1 Unmasking
Section was revised to allow study treatment administration to occur on a day separate from the assessment visit: Section was revised to allow study treatment administration to occur on a day separate from the assessment visit: Only qualified study staff and those delegated the responsibility of study drug administration on the Delegation of Authority log should perform this procedure. All staff should be appropriately trained on all procedures prior to performing the procedures. Sites should follow the Visit Schedule for order of procedures and assessments. Administration of study treatment (APL-2 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 APL-2 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 pre-injection IOP. If a subject falls outside the visit window for a dosing visit, the dose should be skipped and the subject should be scheduled on time for the next dosing visit.	Section 7.3.2 Treatment Administration
The description of sham injection was modified as there is no requirement for sham to be sterile: Sham will be provided as ~~sterile~~ empty stoppered glass vials and should be stored according to the label.	Section 7.3.3.1 Identity of the Investigational Product
The procedure for sham injection was further described: The procedure for sham injection will be the same as that used for IVT injection until the actual injection but no actual injection will occur. The injecting physician will only touch the study eye with the blunt end of the syringe. No needle or medication will be injected inside the eye.	Section 7.4 Sham Injection Administration

Detailed instructions on sham injection procedures and post-injection procedures will be provided in the Manual of Procedures.	
The end of the trial for each subject was defined: The end of the trial for each subject is defined as when the subject either completes their Month 24 Visit and enrolls in the open-label extension study or, should a subject elect not to enter the open label extension study, when the subject completes their exit visit at Month 30. Through the section it has also been noted that endothelial cell count assessment is for "select sites only". This was previously noted in the schedule of events but not consistently in the body of the protocol. In addition FAF and NAR are no longer "study eye only".	Section 8 Study Procedures
The following assessments were removed as they will no longer be conducted at the screening Visit 1: • ~~Low luminance BCVA~~ • ~~Endothelial cell count~~ • ~~OCT-A~~ The following text was moved to Section 8.1.2 as training for home-based digital applications will now be conducted at Visit 2: ~~Prior to dilating the eyes, subjects at select sites will be trained on how to use the home-based digital applications for visual function and reading speed if the subject decides to participate in this portion. This training must occur after completion of all functional tests (NL-BCVA, LL-BCVA).~~	Section 8.1.1 Visit 1 All Subjects
It was clarified that: All assessments should be performed on the same day. All study visits should be scheduled and projected based on the Day 1 visit. The following text was added as home-based digital application training will now occur at Visit 2: Subjects at select sites will be trained on how to use the home-based digital applications for visual function and reading speed if the subject decides to participate in this portion. This training must occur after completion of all functional tests (NL-BCVA, LL-BCVA). The following assessments were added: • Endothelial cell count • OCT-A (select sites) The following text was removed as subject discontinuation is now covered in Section 6.5. ~~In the event that a subject is early terminated from the study, all early termination procedures should be performed even if they are outside the allowed study window.~~ ~~If the subject would like to discontinue dosing but is amenable to~~	Section 8.1.2 Randomization/Initial Treatment—Day—Within 28 Days of Screening

~~continuing in the study, the site should make every effort to have the subject complete as many follow-up visits as possible.~~	
It has been noted in the text which assessments will be conducted at Month 27 and Month 30.	Section 8.1.4 Follow-up Phase
Instructions were revised to include the following: All AEs encountered during the study will be monitored and reported in detail in the source documents and documented on the eCRF, from signing of the ICF until the Exit Visit. AEs should be recorded by maximum severity. AEs, especially those for which the relationship to ~~test drug~~ study treatment are considered by the Investigator to be possibly or definitely related, should be followed up until they have returned to the baseline status or stabilized. If a clear explanation is established, it should be recorded on the eCRF.	Section 11.2 Recording Adverse Events
Instructions modified as follows: ~~If any AEs are serious, special procedures will be followed. All SAEs will be reported to the Safety Monitor by the Investigator via fax or email within one calendar day of becoming aware of the event, whether or not the serious events are deemed drug-related. SAE reporting contact information will be provided separately and as included in the Safety Monitoring Plan. All SAEs must be reported to the applicable ethics committee by the Investigator in accordance with their regulations.~~ **Special procedures will be followed for reporting SAEs.** All SAEs will be reported to the Safety Monitor by the Investigator via eCRF or fax/email (if eCRF is not available) within **24 hours** of becoming aware of the event, whether or not the event is deemed treatment-related. If the EDC system is not operational, the site must complete the appropriate paper SAE form and fax/email to the number listed on the SAE form, also within 24 hours of becoming aware of the event. The reported information submitted as a paper SAE form must be entered into the EDC system once it becomes operational. SAE reporting contact information will be provided separately and included in the Safety Monitoring Plan. All SAEs must be reported to the applicable ethics committee by the Investigator in accordance with their regulations.	Section 11.5 Serious Adverse Events
The following text was added: A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence (such as a temporal relationship) to suggest a causal relationship between the drug and the AE.	Section 11.6 Unexpected Adverse Events or Unexpected Suspected Adverse Reactions
The analysis description was modified as follows as this will be conducted at all sites. This is an error correction. • Change from baseline at each planned assessment in the total area of GA lesion(s) in the study eye (in mm2) as assessed by FAF ~~(in select sites)~~	Section 12.7.2 Secondary Efficacy Analysis

Section 12.10 was added to describe how visit windows will be used in the assessment of the primary endpoint: Analysis visits will be derived with windows for the monthly visits to assess the primary endpoint. Baseline is defined as the date of randomization. If 2 or more treatment visits occur within a window, the closest visit to the target day will be used as that analysis visit; if 2 visits are equidistant from the scheduled analysis visit day, the later analysis visit will be used.	Section 12.10 Visit Windows
All study schedules were modified to align with the changes noted above, including removal of PK and complement profile study assessments.	Appendix A, B, C, and D: Visit Schedules

Protocol Versions		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment 2 Version 1.0	**Version Date 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Non-substantial changes that did not impact content of the document have been made for clarity and to align with language used in the protocol for Study APL2-303.		Entire document
Exclusion criteria #4 and #10 were modified as follows for clarity and to exclude subjects with history of IVT injection in either eye: 4. Presence ~~in either eye~~ of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including but not limited to, uveitis, other macular diseases (e.g., clinically significant epiretinal membrane [ERM], full thickness macular hole or uncontrolled glaucoma/ocular hypertension). Benign conditions in the opinion of the investigator such as peripheral retina dystrophy are not exclusionary. 10. History of prior intravitreal injection ~~in the study eye~~. Exclusion criteria #14 was modified as follows for clarity: 14. Participation in any systemic experimental treatment or any other systemic investigational new drug including within 6 weeks or 5 half-lives of the active ingredient (whichever is longer) prior to the start of study treatment. Note: clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.		Synopsis Section 6.1.2 Exclusion Criteria
The following exclusion criteria was implemented as Exclusion Criteria #13 (EC criteria following this were renumbered): 13. Prior participation in another interventional clinical study for geographic atrophy in either eye including investigational oral medication and placebo.		Synopsis Section 6.1.2 Exclusion Criteria
Noted that the NEI VFQ-25 distance activity and near activity subscale score endpoints will be conducted in select countries as these subscales are not available in all languages.		Synopsis Section 5.1.3 Secondary Objectives Section 5.1.5 Exploratory Objectives Section 12.7.2 Secondary Efficacy Analysis Section 12.7.3 Exploratory Efficacy Analysis Section 9.9.1 The National Eye Institute Visual Functioning Questionnaire 25-Item Version (NEI VFQ)
Contraception text was updated to align with the Investigator's Brochure and in studies with APL-2 in other indications: Approved methods of contraception include: ~~hormonal contraceptives~~		Section 6.4 Approved Methods of Contraception

~~associated with inhibition of ovulation,~~ oral contraceptives, intrauterine device, ~~intrauterine hormone-releasing system; and/or bilateral tubal occlusion (at least 6 months before dosing)~~ medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives (like DepoProvera) or removable birth control device (like NuvaRing or Ortho Evra patches); and/or surgical sterilization (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study and ~~60~~ 90 days after their last dose of study drug.	
Masking language was modified to indicate that the PI is required to remain masked to subjects' treatment assignments, while the treating physician and any associated support staff involved in IP administration will be unmasked.	Section 7.2 Masking and Minimization of Bias
Guidance on the treatment of new exudation related to active choroidal neovascularization in the study eye and/or fellow eye was modified to clarify that the reading center will provide a report to indicate whether or not there is evidence of active, exudative AMD, and the Investigator will then determine if anti-VEGF treatment should be initiated. The Investigator should wait for the reading center report before making a decision regarding treatment, except in cases where there is clear evidence of disease activity that may have a detrimental visual impact if not treated immediately. It was also clarified that either ranibizumab or aflibercept should be selected as the anti-VEGF therapy, and that the unmasked physician should administer anti-VEGF treatment if the treatment is administered on the same day as APL-2. It was also noted that any treatments of therapies administered to the fellow eye within 5 years of screening should be recorded as a concomitant medication.	Section 7.5.1 Treatment of New Exudation Related to Active Choroidal Neovascularization in the Study Eye and/or Fellow Eye Visit Schedules A-D
The following instruction regarding electronic devices was added: The subject will be instructed to bring back the electronic device for the visits specified in the schedule of events.	Section 8.1.3.1 Months 1-12
Month 6 and Month 12 were added as times of in-clinic assessment. It was noted that subjects will take electronic devices home at Day 1 instead of at Screening.	Section 9.12 Home-Based Functional Digital Applications (in select sites/countries) Visit Schedules A-D.
Clarified that: In the event that a subject is suspected to have new active CNV in the study eye and/or the fellow eye, an SD-OCT and FA using the protocol specified procedures should be performed and sent to the Reading Center to confirm the diagnosis. In addition, in selected sites, OCT-A should also be captured according to the study imaging protocol and sent to the Reading Center.	Section 9.14 Ocular Imaging
It was clarified that if the subject does not pass the gross vision test, IOP must be measured at that time. Additional IOP measurement must be taken approximately every 30 minutes thereafter until IOP ≤ 30 mm Hg	Section 9.15 Post-Injection Assessment; Visit Schedule Footnote "O" (all Visit Schedules)

and the subject is able to be released from the clinic. It was clarified that anti-VEGF treatment will be either ranibizumab or aflibercept, and that IOP should be measured before and after the anti-VEGF injection, but prior to administration of APL-2.	
Blood volume for study assessments was updated based on the lab manual.	Section 9.16 Blood Volume for Study Assessments
It was clarified that ~~15~~14 mL whole blood sample will be collected at the specified time points for research samples.	Section 9.17.2 Sample Collection Visit Schedules A-D
The screening urine pregnancy test was removed as a serum pregnancy test will be performed for screening. Footnotes "M" (All Visit Schedules) was modified to indicate that "Beginning at Day 1 Screening, subjects will complete the functional assessments weekly at home."	Visit Schedules A and C
Week 24 blood draw for clinical repository was added (error correction).	Visit Schedule C
The full version of the NEI VFQ-25 has been included in Appendix E.	Appendix E.
An amendment history appendix was added to show changes enacted by previous amendments.	Appendix J

Amendment 1 Version 1.0 **Version Date 31 May 2018**	**Sections Affected by Change**
Non-substantial changes that did not impact content of the document have been made for clarity and to align with language used in the protocol for Study APL2-303. In addition, section numbering was modified to unify document structure between this protocol and the protocol for Study APL2-303.	Entire document
The changes noted below were also incorporated into the synopsis where applicable.	Synopsis
Study objectives were expanded to describe the endpoints that will be utilized to meet them. Endpoint descriptions were moved to Section 12: DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS.	Section 5. STUDY OBJECTIVES ~~AND ENDPOINTS~~ Section 12. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS
It was noted that exploratory objectives utilizing digital applications will be conducted in select sites/countries only as these applications will be utilized according to local regulation.	Section 5.1.3 Exploratory Objectives Section 8 STUDY PROCEDURES Section 9.13 Home-Based Digital Applications (in select sites/countries)
It was clarified that to participate in the study, subjects must be diagnosed with GA of the macula secondary to AMD in ~~one or both eyes~~ the study eye.	Section 6. Patient Population
It was noted that if both eyes have the same visual acuity score, the right eye will be selected as the study eye. The inclusion criteria for microperimetry was incorporated to the main list of inclusion criteria (as #6) as all patients in this study will now be participating in this portion.	Section 6.1.1 Inclusion Criteria
The exclusion criteria for microperimetry was moved to the main list of exclusion criteria (as #11) as all patients in this study will now be participating in this portion. Exclusion criteria 11 was updated as follows: ~~11~~12. Prior participation in another interventional clinical study for intravitreal therapies in either eye (including subjects receiving sham).	Section 6.1.2 Exclusion Criteria
Contraception requirements were updated as follows based on requirements from ethics committees: Approved methods of contraception include: ~~oral~~ hormonal contraceptives associated with inhibition of ovulation, intrauterine device, ~~medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives or removable birth control device~~ intrauterine hormone-releasing system; and/or ~~sterilization~~ bilateral tubal occlusion (at least 6 months before dosing). Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study and 60 days after their last dose of study drug.	Section 6.4 Approved Methods of Contraception

"Endothelial cell count" was removed as an assessment that will be provided to the reading center for objective assessment of subject eligibility. "Optical Coherence Tomography Angiography (OCT-A, selected sites only)" was added as an assessment that will be provided to the reading center for objective assessment of subject eligibility.	Section 7.1 Allocation to Treatment Section 8.1. Study Visit Schedule Section 8.1.2 Randomization/Initial Treatment
"Country" and "microperimetry eligibility (yes; no)" were removed as a stratification factor.	Section 7.1 Allocation to Treatment
References to "DSMB" updated to "DMC".	Section 7.2.1 Unmasking Section 10.1 Data Monitoring Committee
Reference to preparing APL-2 for injection was removed from the paragraph describing sham.	Section 7.3.3.1 Identity of the Investigational Product
Text was updated to indicate that: The suspected onset or presence of new active choroidal neovascularization (CNV) secondary to AMD in the study eye and/or fellow eye must be documented in the source document and CRF.	Section 7.5.1 Treatment of New Active Choroidal Neovascularization in the Study Eye and/or Fellow Eye Section 9.15 Ocular Imaging
Optical Coherence Tomography Angiography (OCT-A) was added as a monitoring assessment for select sites to confirm the diagnosis of new active CNV.	Section 7.5.1 Treatment of New Active Choroidal Neovascularization in the Study Eye and/or Fellow Eye Section 9.15 Ocular Imaging
Text corrected as follows: The treatment method (pars plana vitrectomy vs intravitreal injection of antibiotics ~~vitreous tap~~) and choice of antimicrobial agents are also at the discretion of the physician and should follow current standard practice patterns.	Section 7.5.3 Endophthalmitis Treatment
Content in these sections was combined.	Section 7.5.1 Treatment of New Active Choroidal Neovascularization in the Study Eye and/or Fellow Eye ~~Section 7.5.2 Treatment of Neovascular AMD in the Fellow Eye~~
References to "biobanking" have been replaced by references to the "genetic biorepository" and the "clinical repository".	Section 8. STUDY DESIGN Section 9.7 Genotyping Samples Section 9.17 Blood Volume for Study Assessments
Protocol updated to specify that microperimetry should be conducted on both eyes.	Section 8 STUDY DESIGN
Noted that blood draws will be conducted for genotyping.	Section 8.1.3.2 Months 13-24
Noted that OCT-A may be conducted, if applicable as per instructions of the protocol.	Section 9.6 Laboratory Analysis of Blood and Urine
Text was modified to clarify that the study staff performing visual acuity	Section 9.11 Best-corrected Visual

should be masked to the treatment assignment only; the protocol previously stated that staff should also be blinded to the study eye.	Acuity and Low Luminance Best-corrected Visual Acuity
Blood volume for genetic biorepository was updated.	Section 9.17 Blood Volume for Study Assessments
The following samples were removed: • ~~All residual serum and whole blood samples collected during the course of the study for PK analysis, genotyping and anti-APL-2 antibody formation~~ • ~~Residual serum PK sample~~ • ~~Residual serum Anti-Therapeutic Antibodies (ATA) sample~~ It was noted that the 15 mL whole blood sample will be collected at Month 2, ~~baseline~~, Month 12 and Month 24 of the study	Section 9.18.2 Sample Collection
It was clarified that the DMC will meet at the beginning of the study and every 6 months thereafter.	Section 10.1 Data Monitoring Committee
Reference to "possibly related" AEs was removed as there is no "possibly related" AE categorization for this study. Resolution outcome possibilities were updated to accurately align with the SAE report forms that will be used for this study.	Section 11.2 Recording Adverse Events Section 11.4.1 Relationship of Events to Study Treatment
Clarified that: All SAEs will be reported to the Safety Monitor by the Investigator via fax or email within one ~~working~~ calendar day of becoming aware of the event, whether or not the serious events are deemed drug-related.	Section 11.5 Serious Adverse Events
Section reorganized, modified, and updated to depict protocol specifications for data management and statistical considerations more clearly, accurately, and thoroughly.	Section 12. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS
Footnote was updated to indicate that: **All assessments should be performed on the same day~~, with the exception of screening~~.** The blood draw for the clinical repository was removed at baseline, Month 1, Month 8, Month 18, and Month 27. OCT-A was added at screening, Month 6, Month 12, Month 18, and Month 24 for select sites. Footnote "R" was added to note that 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.	All Study Schedules (Appendices: A, B, C, and D)

APPENDIX K: 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 study window is as followed:

- 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 consecutives injection 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 APL2-304 (Oaks) 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 safety 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 Appendix A [every month treatment group] and Appendix C [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
- NL-BCVA 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, fundus fluorescein angiography 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 Appendix A [every month treatment group] and Appendix C [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 adverse events (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 documentation 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.

The Schedule of Assessments tables shown below supersede those sent on 30 March 2020. These changes were previously communicated to the sites via a memorandum.

APPENDIX A (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Screening, Day 1 through Month 12

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	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—Anti-Pegcetacoplan Ab [D]		x	~~x~~	~~x~~				~~x~~						x	x
Blood Draw—Genotyping (if applicable) [D]				~~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
Mesopic Microperimetry[L]	x							~~SE~~						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 [M]		x						~~x~~						x	x
FRI [M]		x						~~x~~						x	x
Home-Based Digital Applications [M,N,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 [O]	x	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [O]	x	x		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [O]	x	x		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x

APPENDIX A (TRACKED): COVID-19 VISIT SCHEDULE—Monthly Group—Screening, Day 1 through Month 12

	Screening	Treatment													
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Early Term[A]
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	8	8	8	8	8	8	8	8	8	8	8	8	
DCFP [O]	x													x	x
FFA [O]	x													x	x
OCT-A[S]		x[S]						~~x~~[S]						x[S]	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 [P]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Follow-Up Call [Q]		x	x	x	x										
Concomitant Medication/ Concomitant Ocular Procedures [R]	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

Abbreviations: BCVA=best corrected visual acuity; 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; 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 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.

M. 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.

N. 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.

O. 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.

P. 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.

Q. 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.

R. 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.

S. 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.

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: –8 days to + 15 days after medical monitor approval. Note, interval for consecutive injections must be at least 14 days.</u>

APPENDIX B (TRACKED): COVID-19 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—Anti-Pegcetacoplan Ab [D]		~~x~~				~~x~~						x	x
Blood Draw—Genotyping (if applicable) [D]													
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
Mesopic Microperimetry[L]						~~SE~~						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 [M]						~~x~~						x	x
FRI [M]						~~x~~						x	x
Dilated Indirect Ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
Home-Based Digital Applications [M,N,S]						~~x~~						~~x~~	
IOP Measurement	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT [O]	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [O]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [O]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x

APPENDIX B (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	
DCFP [O]												x	x
FFA [O]												x	x
OCT-A[S]						x[S]						x[S]	X
Study Eye Determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]	x	x	x	x	x	x	x	x	x	x	x		
Postinjection Assessment [P]	x	x	x	x	x	x	x	x	x	x	x		
Follow-Up Call [Q]													
Concomitant Medication/ Concomitant Ocular Procedures [R]	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: BCVA=best corrected visual acuity; 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; 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 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.

M. 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.

N. 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.

O. 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.

P. 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.

Q. 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.

R. 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.

S. 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.

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: –8 days to + 15 days after medical monitor approval. Note, interval for consecutive injections must be at least 14 days.</u>

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

	Screening	Treatment													Early Term[A]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Day	–28 to –1	1	30	60	90	120	150	180	210	240	270	300	330	360	
Week	0	0	4	8	12	16	20	24	28	32	36	40	44	48	
Month	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Window (+ or – days)	2	0	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—Anti-Pegcetacoplan Ab [D]		x	~~x~~	~~x~~				~~x~~						x	x
Blood Draw—Genotyping (if applicable) [D]				~~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
Mesopic Microperimetry[L]	x							~~SE~~						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 [M]		x						~~x~~						x	x
FRI [M]		x						~~x~~						x	x
Home-Based Digital Applications [M,N,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 [O]	x	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	x	x
FAF [O]	x	x		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [O]	x	x		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x

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

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

Abbreviations: BCVA=best corrected visual acuity; 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; 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 genetic biorepository 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.

M. 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.

N. 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 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.

O. 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.

P. 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.

Q. 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.

R. 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.

S. 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.

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: –8 days to + 30 days after medical monitor approval.</u>

APPENDIX D (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	x
Urine Sample Collection [D, E,F]						~~x~~						x	x
Urine Pregnancy Test [D,E,F]		x		x		x		x		x		x	
Blood Draw—Anti-Pegcetacoplan Ab [D]		~~x~~				~~x~~						x	x
Blood Draw—Genotyping (if applicable) [D]													
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
Mesopic Microperimetry [L]						~~SE~~						x	x
Slitlamp Examination		x		x		x		x		x		x	x
Endothelial Cell Count [S]												x	x
NEI VFQ-25 [M]						~~x~~						x	x
FRI [M]						~~x~~						x	x
Home-Based Digital Applications [M,N,S]						~~x~~						~~x~~	
Dilated Indirect Ophthalmoscopy		x		x		x		x		x		x	x
IOP Measurement		x		x		x		x		x		x	x
SD-OCT [O]		~~x~~		~~x~~		x		~~x~~		~~x~~		x	x
FAF [O]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
NIR [O]		~~SE~~		~~SE~~		x		~~SE~~		~~SE~~		x	x
DCFP [O]												x	x

APPENDIX D (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	
FFA [O]												x	x
OCT-A[S]						x[S]						x[S]	x
Study Eye Determination													
Randomization													
Pegcetacoplan administration or Sham Injection[T]		x		x		x		x		x			
Postinjection Assessment [P]		x		x		x		x		x			
Follow-Up Call [Q]													
Concomitant Medication/ Concomitant Ocular Procedures [R]		x		x		x		x		x		x	x
Adverse Events		x		x		x		x		x		x	x

Abbreviations: BCVA=best corrected visual acuity; 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; 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 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. Microperimetry assessments will be performed post dilation. Data will be forwarded to the reading center.

M. 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.

N. 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.

O. 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.

P. 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 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.

Q. 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.

R. 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.

S. 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.

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>