A PHASE 2B RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ESTABLISH THE SAFETY AND EFFICACY OF ZIMURA™ (COMPLEMENT C5 INHIBITOR) COMPARED TO SHAM IN SUBJECTS WITH AUTOSOMAL RECESSIVE STARGARDT DISEASE

PROTOCOL NO: OPH2005

Amendment C

Version Date:

21 Mar 2025

SPONSOR:
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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Protocol Version	**Protocol Version Date**
Protocol Amendment C	21 Mar 2025
Protocol Amendment B	06 Feb 2024
Protocol Amendment A	26 Jul 2021
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Amendment C [21 Mar 2025]
This amendment is considered to be nonsubstantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament.

Overall Rationale for Amendment C:
To align the endpoints throughout the protocol in the three sections where they are listed: Summary of Protocol Section: Synopsis, Trial Objectives: Section 5.2, Statistical Methods: Section 11.2. To clarify the trial imaging assessments collection timepoints and the timepoints that were analyzed by the independent reading center (RC). Additional administrative updates and clarifications were also made, prior to unmasking of the study. Refer to the table below for the description and brief rationale for each change.

Section # and Name	Description of Change	Brief Rationale
• Section 2 Summary of Protocol OPH2005: Synopsis Table Endpoints • Section 5.2: Endpoints	Adjusted wording of endpoint descriptions: • For applicable endpoints, revised description to delete “over 18 months”. • For endpoints of rate of change, revised description to use “through Month 18”. • For endpoints of change from baseline, revised description to use “at Month 18”. Secondary and supportive endpoints were split under separate headings. Removed “mean” from applicable endpoint descriptions.	For clarity and consistency in endpoint presentation throughout the protocol.
• Section 2 Summary of Protocol OPH2005: Synopsis Table Endpoints • Section 5.2: Endpoints	Removed “at the position of maximum width of ellipsoid zone loss” from the applicable supportive endpoint.	Following the internal sponsor review and discussions with the RC, it was decided that the secondary endpoint of outer nuclear layer (ONL) alignment will now be analyzed through the foveal center instead of at the position of maximum ellipsoid zone loss. Measuring the maximal ONL thickness through the fovea center in the same B-scan is more accurate, as the position of the maximum width of the ellipsoid zone loss can vary over time. This variability can cause inconsistencies. Therefore, ONL measurements will be conducted through the foveal center to ensure consistency.
• Section 2 Summary of Protocol OPH2005: Synopsis Table Endpoints • Section 5.2: Endpoints	Removed secondary endpoint: Mean rate of change in the horizontal width of undetectable ellipsoid zone measured by a horizontal scan through the foveal center with SD-OCT over 18 months.	The primary endpoint captures the overall ellipsoid zone area defect. Measuring the area is more effective than measuring the width, as ellipsoid zone width can vary between adjacent scans and with degeneration of ellipsoid zone. Measuring one scan can also yield variability; as

Section # and Name	Description of Change	Brief Rationale
		disease progresses, you may capture areas of degeneration of the ellipsoid zone versus areas of absent ellipsoid zone. Area measurement takes into account multiple scans, providing a more consistent assessment. The initial inclusion of this secondary endpoint was included as a potential practical clinical surrogate of the ellipsoid zone defect using one measurement (one number) versus area, which requires a calculation.
Section 3: Schedule of Assessments	Superscripted footnote #7 added to Microperimetry Testing row in the continued portion of the table.	For consistency and clarity in presentation of this optional assessment.
Section 7: Procedures	Added text under section heading: Imaging assessments are collected at the timepoints specified in Section 10.2 “Trial Assessments”. The RC will analyze the data from three timepoints prior to database lock: Screening, Month 9 and Month 18. The additional imaging assessments collected at Month 3, Month 6, Month 12 and Month 15 will be stored and made available if needed.	To clarify which timepoints will be analyzed by the RC.
Section 11.2: Endpoints	Removed endpoint details from the section and added cross-reference to Section 5.2.	For document conciseness.
Section 11.3: Study Design	Revised study design description as follows: This is a randomized, double masked, Sham controlled, Phase 2b **trial** that will obtain evidence regarding the effect of avacincaptad pegol on the ~~mean~~ rate of change in the area of ellipsoid zone defect (**defined as ellipsoid zone attenuation in addition to total RPE loss**) measured by en face SD-OCT ~~over~~	For consistency with the change to the description of the primary endpoint and to provide clarity and accuracy to the meaning of ellipsoid zone defect.

Section # and Name	Description of Change	Brief Rationale
	from Baseline through Month 18, when compared with Sham.	
Section 11.4.3: Statistical Analyses	Revised primary endpoint analysis description as follows: Primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) with all available data, using response variable of the area of ellipsoid zone defect measured by en face SD-OCT over time up to Month 18 including baseline and post-baseline **assessments**. The MMRM will be used to assess the difference between the treatment groups in terms of the rate **of change** (slope) ~~of~~**in** the area of ellipsoid zone defect **from Baseline through Month 18** ~~over time of 18 months~~. ~~For the model,~~**The** fixed effects will include treatment **group (avacincaptad pegol or Sham),** time, **pooled geographic region (North America or Rest of World) and** treatment by time interaction.	• To clarify for readability. • To parsimoniously adjust for the randomization stratification factor “Site” in the analysis.
Section 11.4.3: Statistical Analyses	Revised efficacy analysis population as follows: The efficacy analysis will be conducted on all randomized ~~and treated~~ subjects according to the intention-to-treat principle.	To clarify that all randomized patients, irrespective of whether they were treated with study drug, will be included in the analysis, following the intention-to-treat principle.
Entire document	Administrative updates.	To provide updated information and clarification throughout the protocol.

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1. GLOSSARY OF ABBREVIATIONS

A2E	N-Retinylidene-N-Retinylethanolamine
AAV	Adeno Associated Virus
ABC	ATP-Binding Cassette
AE	Adverse Event
atRal	All-*Trans*-Retinal
ALT	Alanine Aminotransferase
AMD	Age-Related Macular Degeneration
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BCVA	Best corrected visual acuity
Bsl	Baseline
BUN	Blood Urea Nitrogen
CFH	Complement Factor H
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
CRO	Contract Research Organization
CRRY	Complement Receptor 1-Like Protein Y
DDAF	Definite Decrease in Autofluorescence
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FE	Fellow Eye
FP	Color Fundus Photography
GA	Geographic Atrophy
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HbA1c	Hemoglobin A1c
hERG	Human Ether-a-go-go-Related Gene
HRA	High resolution angiography
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFU	Instructions for Use
IND	Investigational New Drug
INN	International non-proprietary name

IOP	Intraocular Pressure
IPCV	Idiopathic Polypoidal Choroidal Vasculopathy
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
MAC	Membrane Attack Complex
MMRM	Mixed model for repeated measures
NLP	No Light Perception
NVAMD	Neovascular Age-Related Macular Degeneration
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OGTT	Oral glucose tolerance test
ONL	Outer Nuclear Layer
OU	Both Eyes
PEG	Polyethylene Glycol
RC	Reading Center
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Scr	Screening
SD-OCT	Spectral Domain-Optical Coherence Tomography
SE	Study Eye
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard operating procedure
STGD	Stargardt Disease
STGD1	Stargardt Disease 1
WBC	White Blood Cell

2. SUMMARY OF PROTOCOL OPH2005

SYNOPSIS	
TITLE:	A Phase 2b Randomized, Double-masked, Controlled Trial to Establish the Safety and Efficacy of Zimura™ (Complement C5 Inhibitor) Compared to Sham in Subjects with Autosomal Recessive Stargardt Disease
OBJECTIVES:	The objectives of this study are to evaluate the safety and efficacy of avacincaptad pegol intravitreal injection compared to Sham in subjects with autosomal recessive Stargardt disease 1 (STGD1).
STUDY DESIGN:	Subjects will be randomized in a 1:1 ratio to the following dose groups: • Avacincaptad pegol (Zimura™) • Sham Note: The international non-proprietary name [INN] of the investigational product, Zimura™, is avacincaptad pegol. All subjects will be treated as follows: **Induction Phase:** Administered on Day 1, Month 1, and Month 2 in the following sequence, 14 days apart: • D0: Avacincaptad pegol 2 mg/eye or Sham • D14: Avacincaptad pegol 2 mg/eye or Sham **Maintenance Phase**: Administered monthly (Month 3 – Month 17): • Avacincaptad pegol 4 mg/eye (administered as two injections of avacincaptad pegol 2 mg) • Sham + Sham Monthly doses should be targeted for every 30 days from the last monthly visit and must be administered at least 21 days apart. There will be a final follow-up visit for all subjects at Month 18.
ENDPOINTS:	<u>Primary Efficacy Endpoint</u> • Rate of change in the area of ellipsoid zone defect measured by en face spectral domain-optical coherence tomography (SD-OCT) from Baseline through Month 18. <u>Secondary Endpoints</u> • Change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from Baseline at Month 18. • Change in photopic and/or mesopic macular sensitivity measured by microperimetry (optional assessment) from Baseline at Month 18. <u>Supportive Endpoints</u> • Rate of change in the area of atrophic lesion (definite decrease in autofluorescence, DDAF) measured by fundus autofluorescence (FAF) from Baseline through Month 18. • Rate of change in the thickness of the outer nuclear layer

SYNOPSIS	
	(ONL) measured by a horizontal scan through the foveal center using SD-OCT from Baseline through Month 18. • Time to persistent vision loss (defined as BCVA loss ≥ 10, 15 or 20 letters from Baseline at two or more consecutive visits through Month 18). • Emergence of at least one new atrophic lesion (DDAF) measured by FAF through Month 18. <u>Safety Endpoints:</u> • Adverse events, vital signs, ophthalmic variables [ophthalmic examination, intraocular pressure (IOP), fluorescein angiogram (FA), FAF, SD-OCT, microperimetry], ECG and laboratory variables.
PLANNED SAMPLE SIZE:	Approximately 120 subjects will be enrolled in this study, 60 per dose group.
SUBJECT SELECTION:	Subjects of either gender, aged 18 – 60 years of age (inclusive), with the diagnosis of STGD1.
TEST DRUG DOSAGE:	Subjects randomized to avacincaptad pegol will receive 6 doses of avacincaptad pegol 2 mg and 15 doses of avacincaptad pegol 4 mg.
FORMULATION AND PRESENTATION:	**<u>Formulation</u>** Avacincaptad pegol is formulated at a concentration of 20 mg/mL (oligonucleotide mass) in 10 mM phosphate buffered saline at pH 6.8-7.8 as a sterile aqueous solution. The drug product is preservative-free and intended for intravitreal injection only. The drug product should not be used if cloudy or if particles are present. **<u>Presentation</u>** The clinical supply kits contain either an avacincaptad pegol standard 2R vial [Schott] or an empty 2R vial, along with BD syringe and BD filter needle. The drug product was originally presented in a USP Type I high recovery glass vial that contained a 0.5 mL v-shaped well sealed with FluoroTec®-coated, halobutyl rubber stoppers and red aluminum crimp seals. In March 2023, the drug product was transitioned to presentation in a 2 mL (ISO 2R) Type I glass vial, stoppered with FluoroTec-coated, halobutyl rubber stopper, and sealed with aluminum crimp seals. Instructions for Use (IFU) are provided directly to the study site. **<u>Dosing Information</u>** The avacincaptad pegol 2 mg/eye dose will be administered in a total injection volume of **<u>0.1 mL (100 µL).</u>** Avacincaptad pegol 4 mg/eye will be administered as **<u>two 0.1 mL (100 µL)</u>** injections. **<u>Comparator Sham Procedure</u>** To preserve the randomized treatment arm masking, subjects will have the sham procedure performed at study treatment visits.

3. SCHEDULE OF ASSESSMENTS

Assessment	Scr	Day 1[1] (Bsl)		Month 1		Month 2		Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
		D0	D14	D0	D14	D0	D14										
Informed Consent	X																
Medical & Ophthalmic History	X																
Vital Signs/Physical Exam[2]	X										X						X
Tonometry [3,4,5]/ Ophthalmic Examination[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol Refraction and ETDRS VA[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography [4]	X													X			
Fluorescein Angiography [4]	X													X			
SD-Optical Coherence Tomography [4]	X							X			X			X			X
Fundus Autofluorescence[4]	X							X			X			X			X
Microperimetry Testing[4, 7]	X													X			
12-Lead ECG	X																
Laboratory Tests	X																
Serum Pregnancy Test (if applicable)	X										X						X
Genetic Sampling[8]	X																
Randomization		X															
Randomized Treatment (Avacincaptad pegol or Sham)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening assessments should be performed within 14 days prior to trial drug injection (Day 1).
[2] Physical examination is performed at Screening, and at the investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3] Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Month 6, Month 9, and Month 18/Early Withdrawal. The Tono-Pen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4] Ocular assessments performed at Screening, Month 6, Month 9, Month 12, Month 18, and Early Withdrawal (if indicated above) should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[5] Tonometry should be measured prior to the injection, and after each injection as per Section 10, Trial Conduct.
[6] All AEs are to be recorded after first injection.
[7] Microperimetry is an optional assessment to be performed if the site has the necessary equipment.
[8] Genetic testing done as part of the standard of care by a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory prior to informed consent is acceptable to satisfy Inclusion Criteria 8.2.1. Genetic sampling for the Complement Factor H (CFH) gene may also be taken during the study, at any visit prior to or at the Month 18 visit.

Scr: Screening; Bsl: Baseline; EW = Early Withdrawal Visit

VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the visit window as per Section 10, Trial Conduct.

SCHEDULE OF ASSESSMENTS (CONTINUED)

Assessment	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18/EW
Informed Consent						
Medical & Ophthalmic History						
Vital Signs/Physical Exam[2]						X
Tonometry [3,4,5]/ Ophthalmic Examination[4]	X	X	X	X	X	X
Protocol Refraction and ETDRS VA[4]	X	X	X	X	X	X
Color Fundus Photography [4]						X
Fluorescein Angiography [4]						X
SD-Optical Coherence Tomography [4]			X			X
Fundus Autofluorescence[4]			X			X
Microperimetry Testing[4, 7]						X
12-Lead ECG						X
Laboratory Tests						X
Serum Pregnancy Test (if applicable)						X
Genetic Sampling						
Randomization						
Randomized Treatment (Avacincaptad pegol or Sham)	X	X	X	X	X	
3-Day Post-Injection Telephone Safety Check	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events[6]	X	X	X	X	X	X

[1] Screening assessments should be performed within 14 days prior to trial drug injection (Day 1).
[2] Physical examination is performed at Screening, and at the investigator's discretion thereafter. Vital Signs at all indicated timepoints.
[3] Goldmann applanation tonometry must be performed at Screening and pre-injection at Day 1, Month 6, Month 9, and Month 18/Early Withdrawal. The Tono-Pen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4] Ocular assessments performed at Screening, Month 6, Month 9, Month 12, Month 18, and Early Withdrawal (if indicated above) should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
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[6] All AEs are to be recorded after first injection.
[7] Microperimetry is an optional assessment to be performed if the site has the necessary equipment.
[8] Genetic testing done as part of the standard of care by a CLIA certified laboratory prior to informed consent is acceptable to satisfy Inclusion Criteria 8.2.1. Genetic sampling for the Complement Factor H (CFH) gene may also be taken during the study, at any visit prior to or at the Month 18 visit.
Scr: Screening; Bsl: Baseline; EW = Early Withdrawal Visit
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the visit window as per Section 10, Trial Conduct.

4. INTRODUCTION

4.1 Stargardt Disease

Stargardt disease (STGD) was first described by the German ophthalmologist Karl Stargardt in 1909 in seven patients from two families with visual loss (Stargardt, 1909; Fishman, 1976). Patients presented with an atrophic lesion in the macula that was subsequently surrounded with white flecks in the first or second decade of life (Fishman, 1976; Rotenstreich et al., 2003). Although, Stargardt is the most common inherited macular dystrophy in both children and adults, it is a rare condition with an estimated incidence of 10-12.5 in 100,000 with no treatments approved by the Food and Drug Administration (FDA) in the United States or by the European Medicines Agency in Europe (Strauss et al., 2016).

Stargardt disease is most commonly inherited in an autosomal recessive manner caused by mutations in the *ABCA4* gene (Stargardt disease 1 [STGD1]; Allikmets et al., 1997; Yi et al., 2012; Strom et al., 2012). The ATP-binding cassette (ABC) transporters are the largest and most diverse membrane transport system and associated with many important biological processes as well as various severe pathological conditions (Higgins, 1992). ABCA4, also known as ABCR, is a 250-kDa glycoprotein and a member of the ABCA subfamily of ABC. During the visual cycle, in absence of adenosine triphosphate (ATP), ABCA4 binds with high affinity and clears N-retinylidene-phosphatidylethanolamine (Beharry et al., 2004). Adenosine triphosphate, converts the high affinity retinoid binding site to a low affinity site releasing the retinoid as part of the transport mechanism (Beharry et al., 2004). Lacking ABCA4 causes the accumulation of retinaldehyde and N-retinylidene-phosphatidylethanolamine in the photoreceptor outer segments which in turn leads to the accumulation of N-retinylidene-N-retinylethanolamine (A2E) bisretinoids in the retinal pigment epithelial (RPE) cells (Parish et al., 1998; Weng et al., 1999; Mata et al., 2000; Radu et al., 2008; Wu et al., 2009; Sparrow et al., 2012). The accumulation of bisretinoids in the RPE cells is toxic and potentially contributes to the pathogenesis of STGD1 (Sparrow et al., 2000; Schutt et al., 2000; Finnemann et al., 2002; Lenis et al., 2017).

The seriousness of the disease and absence of treatment options for patients with STGD represents an area of urgent unmet medical need.

4.2 Stargardt Disease and Membrane Attack Complex (MAC)

Accumulation of bisretinoids leads to the activation of complement system and accumulation of membrane attack complex (MAC) in RPE cells, potentially contributing to their deterioration over time and resulting in photoreceptor loss and decrease in vision (Zhou et al., 2006; Zhou et al., 2009; Lenis et al., 2017). Bisretinoids and C5b-9 complex have a damaging effect on the RPE cell function by impacting both lysosomes and mitochondria inside the cells (Georgiannakis et al., 2015).

Photo-oxidation of A2E in RPE cells activates the complement cascade in vitro and potentially could contribute to the chronic inflammatory process in the RPE-Bruchs membrane interface (Zhou et al., 2006; Zhou et al., 2009). Bisretinoid pigments of lipofuscin other than A2E were also capable in activating the complement system in RPE cells (Zhou et al., 2009).

Activation of complement cascade results in the formation of MAC. In RPE cells MAC is cleared by endocytic pathway and lysosomal degradation (Georgiannakis et al., 2015). A2E accumulation leads to lysosomal dysfunction in RPE cells. This prevents the clearance of MAC and leads to its accumulation, inducing cellular distress (Schutt et al., 2002, Bergmann et al., 2004, Georgiannakis et al., 2015). These findings indicate that Bistretinoids/A2E not only activate the complement system but also prevent the clearance of MAC in RPE cells, creating a vicious cycle that makes RPE cells further susceptible to complement activation.

The accumulation of MAC not only impacts lysosomes but also leads to mitochondrial perturbation in RPE cells (Georgiannakis et al., 2015). MAC accumulation leads to a significant decrease in the quantitative number of mitochondria as a function of area and induces ultrastructural defects i.e. smaller size, rounder morphology, and fewer cristae. These changes potentially have a deleterious impact on the energy production and subsequently the function of RPE cells. In addition, the accumulation of A2E inside RPE cells also impacts mitochondria. Mitochondria are significantly more sensitive to A2E when compared to lysosomes and their latency decreases at a lower concentration and a shorter period of time (Schutt et al., 2002). Further, accumulation of MAC leads to the complete lysis and destruction of RPE cells in a concentration dependent manner (Li et al., 2010).

Taken together, the accumulation of A2E and MAC synergistically damages both lysosomes and mitochondria inside the RPE cells, leading to their dysfunction.

In human RPE cell cultures, all-*trans*-retinal (atRal) sensitized RPE cells to complement mediated cell death. The combined effect of atRal pre-treatment and complement activation was significantly greater than was expected from the additive effects of each independent treatment (Berchuck et al., 2013). Incubation with anti-C5 antibody protected the RPE cells and prevented the combined atRal and complement mediate decrease in RPE cell viability (Berchuck et al., 2013).

In the albino *abca4*$^{-/-}$ mice, an animal model for STGD1, the accumulation of lipofuscin fluorophores led to the activation of complement cascade with the deposition of complement proteins and MAC inside the RPE cells *in vivo*. Further, the complement negative regulatory proteins were down regulated (Radu et al., 2011). The complement receptor 1-like protein y (CRRY) is an important complement negative regulatory protein in mice and its downregulation leads to complement activation (Yang et al., 2009; Lenis et al., 2017). Complement receptor 1-like protein Y prevents the generation of cytolytic MAC by inhibiting the cleavage of C3 and C5 complement components (Morgan, 2015). Complement receptor 1-like protein Y is down regulated in the albino abca4$^{-/-}$ mice. The subretinal injection of recombinant adeno-associated virus containing the CRRY coding increased the expression of CRRY in the RPE cells of albino *abca4*$^{-/-}$ mice and significantly decreased the expression of complement factors in these cells (Lenis et al., 2017).

The down regulation of complement activation led to an approximately 2.5-fold decrease in the bisretinoid accumulation levels in mice that had received the CRRY when compared with the adeno-associated virus (AAV)-null virus. Further, the RPE autofluorescence decreased in the AAV-CRRY injected *abca4*$^{-/-}$ mice with an approximately 30% decrease in the lipofuscin granules when compared with the AAV-null–injected albino *abca4*$^{-/-}$ mice. Most unexpectedly, decreasing the complement activation lead to the rescue of the photoreceptors with an approximately 30% increase in the number of photoreceptor nuclei in the transduced area (Lenis et al., 2017). These findings indicated that the inhibition of complement activation and MAC accumulation would lead to healthier RPE cells which in turn are better capable of processing the bisretinoids in STGD1 mice.

These pre-clinical findings indicate that the activation of complement pathway and accumulation of MAC may play a significant role in the progression of STGD1 and their inhibition or modulation may decrease the accumulation of bisretinoids in RPE cells and potentially rescue the degeneration of photoreceptors in STGD1 patients.

4.3 Avacincaptad Pegol

4.3.1 Non-Clinical Pharmacodynamics

Preclinical data demonstrating the complement C5 inhibitory properties of avacincaptad pegol are described in detail in the Investigator's Brochure (IB).

4.3.2 Non-Clinical Pharmacology of Avacincaptad Pegol

Numerous nonclinical pharmacology studies were conducted with avacincaptad pegol, and, in some cases, with related anti-C5 aptamers. Primary pharmacology studies included binding assays, complement activity inhibition, and radioligand binding. Safety pharmacology studies included human ether-a-go-go-related gene (hERG) channel electrophysiology (in vitro), neurotoxicity in rats, and cardiovascular and respiratory safety in cynomolgus monkeys.

The safety pharmacology studies did not reveal any effects on cardiovascular, respiratory, or neurologic function that would raise concerns for the intended ocular administration.

Further information regarding the pharmacology of avacincaptad pegol is presented in detail in the IB.

4.3.3 Toxicology

Chronic intravitreal toxicity studies were conducted in rabbits and dogs with 10 doses of avacincaptad pegol given at 4-week intervals. These studies included interim termination of animals after a single dose (i.e., within a few days and at 4 weeks after the first dose). The full 9-month duration has been completed for both studies.

Additional details of the results of these studies, as well as the results of the various intravenous toxicity studies that were previously conducted, can be found in the IB.

4.3.4 Clinical Data

Clinical trials investigating the safety, tolerability, and/or pharmacokinetic profile of intravitreal injections of avacincaptad pegol (alone or in combination with Lucentis® 0.5 mg) have been conducted or are ongoing in subjects with neovascular age-related macular degeneration (NVAMD) (OPH2000, OPH2004, OPH2007), geographic atrophy (GA) secondary to dry AMD (OPH2001, OPH2003, ISEE2008 and ISEE2009), and idiopathic polypoidal choroidal vasculopathy (IPCV) (OPH2002).

Additional details, including results of these studies, can be found in the IB.

4.4 Trial Rationale

The preclinical evidence indicates that bisretinoid accumulation inside RPE cells results in complement activation and MAC accumulation. This further impairs the retinoid recycling capacity of RPE cells, causing more accumulation and cellular dysfunction. RPE cell dysfunction may lead to photoreceptor degeneration and potentially loss of vision (Travis et al., 2007; Lenis et al., 2017). In human RPE cell cultures, incubation with anti-C5 antibody protected the RPE cells and prevented the atRal and complement mediate decrease in RPE cell viability (Berchuck et al., 2013). Further, the inhibition of complement activation decreased the bisretinoid accumulation and photoreceptor degeneration in albino *abca4*$^{-/-}$ mice (Lenis et al., 2017). Thus, molecules involved in inhibition or regulation of complement activation and MAC accumulation become prime targets for therapeutic intervention in STGD1.

Avacincaptad pegol is FDA approved for the treatment of GA secondary to dry AMND and is currently being developed by Astellas for the treatment of STGD1. Avacincaptad pegol is a PEGylated ribonucleic acid (RNA) aptamer. Avacincaptad inhibits C5, a central component of the complement cascade, which plays multiple roles in innate immunity and inflammatory diseases. Inhibition of this key step in the complement cascade at the level of C5 prevents the formation of key terminal fragments (C5a and C5b-9) regardless of which pathway (alternate, classical or lectin) induced their generation. The C5a fragment is an important inflammatory activator inducing the recruitment and activation of phagocytes. C5b is involved in the formation of MAC (C5b-9) which initiates cells lysis. By inhibiting MAC formation therapeutic benefit may be achieved in STGD1.

5. TRIAL OBJECTIVES

5.1 Objectives

The objectives of this study are to evaluate the safety and efficacy of avacincaptad pegol intravitreal injection compared to Sham in subjects with autosomal recessive Stargardt disease 1 (STGD1).

5.2 Endpoints

Primary Efficacy Endpoint

- Rate of change in the area of ellipsoid zone defect measured by en face spectral domain-optical coherence tomography (SD-OCT) from Baseline through Month 18.

Secondary Endpoints

- Change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from Baseline at Month 18.
- Change in photopic and/or mesopic macular sensitivity measured by microperimetry (optional assessment) from Baseline at Month 18.

Supportive Endpoints

- Rate of change in the area of atrophic lesion (definite decrease in autofluorescence, DDAF) measured by fundus autofluorescence (FAF) from Baseline through Month 18.
- Rate of change in the thickness of the ONL measured by a horizontal scan through the foveal center using SD-OCT from Baseline through Month 18.
- Time to persistent vision loss (defined as BCVA loss ≥ 10, 15 or 20 letters from Baseline at two or more consecutive visits through Month 18).
- Emergence of at least one new atrophic lesion (DDAF) measured by FAF through Month 18.

Safety Endpoints:

- Adverse events, vital signs, ophthalmic variables [ophthalmic examination, intraocular pressure (IOP), fluorescein angiogram (FA), FAF, SD-OCT, microperimetry], ECG and laboratory variables.

6. TRIAL DESIGN

Subjects will be randomized in a 1:1 ratio to the following dose groups:

- Avacincaptad pegol (Zimura™)
- Sham

Note: The international non-proprietary name [INN] of the investigation product, Zimura™, is avacincaptad pegol.

All subjects will be treated as follows:

Induction Phase: Administered on Day 1, Month 1, and Month 2 in the following sequence, 14 days apart:

- D0: Avacincaptad pegol 2 mg/eye or Sham
- D14: Avacincaptad pegol 2 mg/eye or Sham

Maintenance Phase: Administered every month (Month 3 – Month 17):

- Avacincaptad pegol 4 mg/eye (administered as two injections of avacincaptad pegol 2 mg)
- Sham + Sham

Monthly doses should be targeted for every 30 days from the last monthly visit and must be administered at least 21 days apart.

There will be a final follow-up visit for all subjects at Month 18.

7. PROCEDURES

Imaging assessments are collected at the timepoints specified in Section 10.2 “Trial Assessments”. The RC will analyze the data from three timepoints prior to database lock: Screening, Month 9 and Month 18. The additional imaging assessments collected at Month 3, Month 6, Month 12 and Month 15 will be stored and made available if needed.

7.1 Procedures for Refraction and Vision Testing

Refraction and Vision Testing will be performed at all timepoints specified in Section 10.2 “Trial Assessments”.

For ETDRS testing, retroilluminated modified Ferris-Bailey ETDRS (Early Treatment Diabetic Retinopathy Study) charts are used starting at 4 meters (see Appendix 17.3).

When protocol refraction and best-corrected visual acuity measurement is required by the trial protocol, this will be performed only by certified visual acuity examiners. The examiner will be supplied with the previous protocol refraction only.

7.2 Tonometry

Tonometry will be performed at all timepoints specified Section 10.2 “Trial Assessments”. On days when two injections are given, the second injection may not be administered until the IOP is ≤ 21 mmHg or within 5 mmHg of the pre-injection IOP, at which time the IOP is recorded. After the second injection and also on days with only one injection, tonometry must be performed at least 30 minutes after the injection and IOP must return to < 30 mmHg before the subject leaves the clinic. For the post-injection tonometry, proper care should be taken to minimize the risk of contamination.

Goldmann applanation tonometry must be performed at Screening, Pre-Injection (Day 1, Month 6, Month 9, Month 18) and Early Withdrawal. Tono-Pen tonometry may be used at all other timepoints, but Goldmann applanation tonometry must be used to verify IOP for a post-injection reading of ≥ 30 mmHg occurring more than 30 minutes post-injection, or for a reading of ≥ 30 mmHg at any other time.

7.3 Ophthalmologic Examination

The following examinations will be performed at all timepoints specified in Section 10.2 “Trial Assessments”.

- Inspection of the eyelids
- Examination of the extra-ocular muscle movement
- Inspection of the cornea

- Examination of the anterior chamber for inflammation (Appendix 17.1)
- Examination of the pupils
- Examination of the iris
- Inspection of the lens
- Inspection of the vitreous body (Appendix 17.2)
- Inspection of the retina and optic disc

7.4 Fundus Photography, Fluorescein Angiography, and Fundus Autofluorescence

Color stereoscopic fundus photography, fluorescein angiography (FA), and fundus autofluorescence (FAF) will be performed at all timepoints specified in Section 10.2 “Trial Assessments”. Heidelberg Spectralis® High Resolution Angiography (HRA) will be used for fundus autofluorescence.

An image RC will be used for this study. The RC will determine eligibility of all subjects prior to enrollment. Color fundus photos, FAs, and FAFs that are collected at protocol-specified times must be sent to the RC as specified in the RC procedure manual. The RC will provide instructions for the color fundus photographs as well as FA and FAF procedures.

7.5 Spectral-Domain Optical Coherence Tomography (SD-OCT)

Spectral domain-optical coherence tomography will be performed at all timepoints specified in Section 10.2 “Trial Assessments”. Heidelberg Spectralis® OCT is the preferred instrument.

SD-OCTs that are collected at protocol-specified times must be sent to the RC as specified in the RC procedure manual. The RC will provide instructions.

7.6 Retinal Sensitivity by Microperimetry

Retinal sensitivity by microperimetry is an optional assessment to be performed if the site has the necessary equipment. If performed, it will be done at all timepoints specified in Section 10.2 “Trial Assessments”.

The Sponsor will provide the Principal Investigator with instructions for the microperimetry procedures.

7.7 Laboratory Tests

The following laboratory tests will be performed as specified in Section 10.2 “Trial Assessments”:

- Hematology: hemoglobin, platelet count, white blood cell (WBC) and differential
- Renal function: serum creatinine and blood urea nitrogen (BUN)
- Hepatic function: serum bilirubin, alkaline phosphatase, gamma-glutamyl-transferase (GGT), serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT)
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium and phosphate
- Complete urinalysis (including specific gravity, protein, blood, etc.)
- Serum pregnancy test (if of child-bearing potential)

Additional urine or serum pregnancy testing may be performed during the course of the study at the discretion of the investigator, or in accordance with local requirements or regulations.

If the Investigator judges a laboratory value outside of the normal range as clinically significant, the Investigator will repeat the laboratory determination as judged appropriate to ensure the validity of the abnormal result. If any clinically significant abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered clinically significant by the investigator, or an explanation for the change is obtained.

7.8 Genetic Samples

Genetic testing will be performed at Screening for ABCA4 gene mutations to verify eligibility for the study. Genetic testing done by a CLIA certified laboratory as part of the standard of care prior to informed consent is acceptable to satisfy Inclusion Criteria 8.2.1.

Genetic sampling for the Complement Factor H (CFH) gene may also be taken during the study, at any visit prior to or at the Month 18 visit. CFH testing performed by a CLIA certified laboratory prior to this study may also be acceptable (upon review). This sample would be collected only once during the course of this study.

Analysis will be performed by a CLIA-certified laboratory. All supplies and instructions related to obtaining, processing, and shipping the sample will be provided by the

sponsor. The deoxyribonucleic acid (DNA) samples will not be identified by subject number, date of birth, or initials.

7.9 Vital Signs and Physical Examination

A physical examination will be performed at Screening and at the Investigators' discretion thereafter. Assessment of vital signs will be performed at all timepoints specified in Section 10.2 "Trial Assessments".

7.10 12-Lead Electrocardiogram

A 12-lead ECG will be performed at all timepoints specified in Section 10.2 "Trial Assessments".

8. SUBJECT POPULATION

8.1 Sample Size

Approximately 120 subjects will be enrolled in this study.

8.2 Inclusion Criteria

Subjects must meet the following criteria to be eligible to participate in this study.

Ophthalmic Inclusion Criteria

The following inclusion criteria apply to the study eye:

8.2.1 At least two pathogenic mutations of *ABCA4* gene confirmed by a CLIA-certified laboratory.

8.2.2 Best corrected visual acuity in the study eye between 20/20 - 20/200 Snellen equivalent, inclusive.

8.2.3 Presence of at least one identifiable location of at least 250 micrometers contiguous width of ellipsoid zone loss on SD-OCT within the total 9 ETDRS subfields.

8.2.4 The total area of thinned layer(s) on OCT not extending beyond the outer ring of the total 9 ETDRS subfields (e.g., not extending beyond fields 5-9).

8.2.5 Fundus autofluorescence may show heterogeneous signals (areas of increased and/or decreased autofluorescence) but no area of subfoveal definitely decreased autofluorescence (DDAF).

8.2.6 Clear ocular media and adequate pupillary dilatation in both eyes (OU) to allow for all imaging procedures, including good quality stereoscopic fundus photography, fundus autofluorescence, and spectral domain ocular coherence tomography.

8.2.7 Intraocular pressure of 21 mmHg or less in the study eye.

General Inclusion Criteria

8.2.8 Subjects of either gender aged between 18 and 60 years, inclusive.

8.2.9 Women must be using two forms of effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile; if of child-bearing potential, a serum pregnancy test must be performed within 14 days prior to the first injection with a negative result. The two forms of effective contraception

must be implemented during the trial and for at least 90 days following the last dose of test medication. Male subjects should use a condom during the time of study drug exposure and for 90 days following last exposure of study drug.

8.2.10 Provide written informed consent.

8.2.11 Ability to return for all trial visits.

8.3 Exclusion Criteria

Subjects will ***not be eligible for the trial*** if subjects cannot attend all of the trial required visits, or if any of the following criteria are present in the study eye or systematically:

Ophthalmic Exclusion Criteria

The following exclusion criteria apply to the SE unless otherwise noted:

8.3.1 Macular atrophy secondary to any condition other than STGD1 in either eye (e.g., drug-induced).

8.3.2 Any prior treatment for STGD1 including gene therapy, stem cell therapy or any prior intravitreal treatment for any indication in either eye.

8.3.3 Participation in an interventional study of a vitamin A derivative ≤ 3 months prior to screening.

8.3.4 Any ocular condition in the study eye that would progress during the course of the study that could affect central vision, microperimetry testing or otherwise be a confounding factor.

8.3.5 Concomitant treatment with any ocular or systemic medication that is known to be toxic to the lens, retina or optic nerve.

8.3.6 Presence of intraocular inflammation (≥ trace cell or flare), macular hole, pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), epiretinal membrane, evidence of significant vitreo-macular traction, vitreous hemorrhage or aphakia (pseudophakia with or without an intact capsule is not an exclusion criteria).

8.3.7 Presence or history of idiopathic or autoimmune-associated uveitis in either eye.

8.3.8 Significant media opacities, including cataract, which might interfere with visual acuity, assessment of toxicity, fundus photography or fundus autofluorescence. Subjects should not be entered if there is likelihood that they will require cataract surgery in the study eye during the study.

8.3.9 Any intraocular surgery or thermal laser within 3 months of trial entry. Any prior thermal laser in the macular region, regardless of indication.

8.3.10 Any ocular or periocular infection or ocular surface inflammation in the past 12 weeks.

8.3.11 History of any of the following procedures: Posterior vitrectomy, filtering surgery (e.g. trabeculectomy), glaucoma drainage device, corneal transplant or retinal detachment.

General Exclusion Criteria

8.3.12 Any of the following underlying diseases including:

- Diabetes mellitus (regardless of HbA1c level)
- HbA1c value of ≥6.5%*:

  If the HbA1c value is ≥ 6.5% and ≤ 6.9%, and the patient has no signs or symptoms of diabetes mellitus, has a normal creatinine, has no diabetic retinopathy and no glycosuria, then the patient may have an oral glucose tolerance test (OGTT) at the discretion of the investigator. If the 2-hour glucose value on OGTT is <200 mg/dL (<11.1mmol/L), then the patient may be enrolled.[1]
- History of other disease, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications.
- History or evidence of severe cardiac disease (e.g., New York Heart Association (NYHA) Functional Class III or IV - see Appendix 17.5), history or clinical evidence of unstable angina, acute coronary syndrome, myocardial infarction or revascularization within last 6 months, ventricular tachyarrhythmia requiring ongoing treatment.

[1] The OGTT will be performed at a local laboratory as follows: (1) A fasting baseline plasma glucose is drawn; (2) the subject is administered 75 gm oral dextrose; (3) a 2-hour plasma glucose level is drawn.

- Subjects with a clinically significant laboratory value. Laboratory tests may be repeated once before randomization.
- Stroke within 12 months of trial entry.
- Any major surgical procedure within one month of trial entry or anticipated during the trial which may interrupt trial participation.

8.3.13 Previous therapeutic radiation in the region of the study eye.

8.3.14 Any treatment with an investigational agent in the past 60 days for any condition.

8.3.15 Women who are pregnant or nursing.

8.3.16 Known serious allergies to the fluorescein dye used in angiography, povidone iodine, or to the components of the avacincaptad pegol formulation.

8.3.17 History of systemic treatment with any complement inhibitor agent in the past or the likelihood of treatment with any systemic complement inhibitor agent during the study.

9. TRIAL MEDICATION

9.1 Avacincaptad Pegol

Avacincaptad pegol is a PEGylated RNA aptamer consisting of a 13 kDa modified RNA aptamer that is conjugated at the 5' terminus to a 43 kDa branched polyethylene glycol (PEG) moiety. The aptamer portion of avacincaptad pegol (known as ARC672) is 39 nucleotides in length and modified to a primary amine at the 5' terminus to provide a reactive site for site specific conjugation ("PEGylation"). The nucleotide composition consists of 2'-hydroxyl purines and modified 2'-fluorinated pyrimidines and 2'-methoxy purines. The modified nucleotides minimize endonuclease digestion and contribute to activity. The 3' terminus is capped with an "inverted" 3'-3' phosphodiester linkage to a deoxythymidine nucleotide to minimize 3'-exonuclease degradation. PEGylation is employed because it confers delayed clearance in vivo without diminishing affinity or activity. All concentrations and doses for avacincaptad pegol (1 μM = 13 μg/mL) are based on the mass of the aptamer, exclusive of the PEG mass.

Avacincaptad pegol drug product is formulated at a concentration of 20 mg/mL (oligonucleotide mass) in 10 mM phosphate buffered saline as a sterile aqueous solution.

The drug product was originally presented in a USP Type I high recovery glass vial that contained a 0.5 mL v-shaped well sealed with FluoroTec-coated, halobutyl rubber stoppers and red aluminum crimp seals. In March 2023, the drug product was transitioned to presentation in a 2 mL (ISO 2R) Type I glass vial, stoppered with FluoroTec-coated halobutyl rubber stopper, and sealed with aluminum crimp seals. The product is preservative-free and intended for intravitreal injection only. The product should not be used if cloudy or if particles are present.

The 2 mg/eye dose will be administered in a total injection volume of **0.1 mL (100 μL)**. The 4 mg/eye dose will be administered as **two 0.1 mL (100 μL)** injections of avacincaptad pegol 2 mg (see Section 17.4 Intravitreal Administration Protocol).

Active Ingredient:

Avacincaptad pegol

Excipients:

Sodium Chloride
Sodium Phosphate Monobasic, Monohydrate
Sodium Phosphate Dibasic, Heptahydrate
Nitrogen
Water for injection

9.2 Dose and Administration

9.2.1 Preparation

Avacincaptad pegol will be injected without dilution.

Avacincaptad pegol is supplied in a single-use vial. To prepare for injection, use the 19-gauge filter needle (supplied by the sponsor) and a 1-mL Luer-Lok™ sterile syringe (supplied by the sponsor) to withdraw all avacincaptad pegol content from the vial using aseptic technique. Remove and discard the filter needle and replace it with the sterile 30 gauge injection needle (supplied by the sponsor). Expel any air bubbles and adjust the injection volume to **0.1 mL (100µL)**.

Refer to the Instructions for Use (IFU).

9.2.2 Treatment Regimen and Duration

Subjects will be randomized in a 1:1 ratio to the following dose groups:

- Avacincaptad pegol
- Sham

Interactive Randomization Technology (IRT) will be used to randomize study subjects and assign drug to study subjects. All subjects will be treated as follows:

Induction Phase: Administered on Day 1, Month 1, and Month 2 in the following sequence, 14 days apart:

- D0: Avacincaptad pegol 2 mg/eye or Sham
- D14: Avacincaptad pegol 2 mg/eye or Sham

Maintenance Phase: Administered monthly (Month 3 – Month 17):

- Avacincaptad pegol 4 mg/eye (administered as two injections of avacincaptad pegol 2 mg)
- Sham + Sham

Monthly doses should be targeted for every 30 days from the last monthly visit, and must be administered at least 21 days apart.

There will be a final follow-up visit for all subjects at Month 18.

9.2.3 Administration of Trial Drug

The method for intravitreal administration of avacincaptad pegol is described in detail in Section 17.4.

Subjects randomized to avacincaptad pegol will receive 6 doses of avacincaptad pegol 2 mg and 15 doses of avacincaptad pegol 4 mg. The 2 mg/eye dose will be administered in a total injection volume of **0.1 mL (100 µL).** Avacincaptad pegol 4 mg/eye will be administered as **two 0.1 mL (100 µL)** injections of avacincaptad pegol.

Intravitreal administration of avacincaptad pegol is contraindicated if active inflammation and/or suspected or active ocular or peri-ocular infection is present. If active inflammation and/or suspected or active ocular or peri-ocular infection is present, study drug should not be administered and inflammation/infection should be treated at the discretion of the Investigator, according to standard-of-care. Intravitreal administration of study drug should only resume after treatment and full resolution of ocular inflammation and/or ocular or peri-ocular infection.

9.2.4 Storage

The investigator, or an approved representative (e.g., pharmacist), will ensure that all trial drugs are stored in a secured area, under labeled storage conditions and in accordance with applicable regulatory requirements. Store trial drug under standard refrigeration conditions (2°C – 8°C; 36°F – 46°F); do not freeze. Prior to use, allow the trial drug to reach room temperature (20°C – 25°C [68°F – 77°F]). The unopened glass vial of trial drug may be kept at room temperature, 20°C – 25°C (68°F – 77°F), for up to 24 hours. Ensure that the injection is given immediately after preparation of the dose. All study drug vials should be protected from light and stored in the original carton, as provided, until the time of use.

9.3 Previous or Concomitant Therapy

Any previous or concomitant treatment for Stargardt disease (systemically or in either eye) prior to Day 1 or during the study period is not permitted.

Interventional treatment with a vitamin A derivative ≤ 3 months prior to Screening, any treatment with any investigational agent for any condition in the 60 days prior to Screening, or treatment with an investigational agent for any condition during the trial, is not permitted.

9.3.1 Prohibited Medications

Prior or concomitant treatment with any ocular or systemic medication that is known to be toxic to the lens, retina or optic nerve is not permitted. These medications may include, but are not limited to amiodarone, deferoxamine, chloroquine/hydroxychloroquine sulfate (Plaquenil), tamoxifen, phenothiazines and ethambutol, and fingolomod (Gilenya).

9.3.2 Concomitant Ocular Surgeries and Procedures

For subjects requiring any ocular surgeries or procedures during the study period, the Investigator should consult with the study Sponsor prior to the surgery/procedure.

10. TRIAL CONDUCT

10.1 Subject Enrollment

Before recruitment of subjects into the trial, written Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol and informed consent must be obtained.

Subjects who meet the eligibility criteria and have provided written informed consent will be enrolled in the trial. If any inclusion or exclusion criteria are not met, treatment with trial drug should not commence without prior written approval from Astellas or its designee.

Written informed consent must be obtained before any of the Screening procedures listed below are performed. However, if a routine office procedure (e.g., FA, OCT) has been previously performed independent of this clinical trial, and subsequently the subject provides informed consent for this study, these procedures performed prior to informed consent may be used as screening assessments for this study, provided the 14-day period of screening evaluations is respected and provided the assessments are acceptable to the standards of the study. An explanation of the trial and discussion of the possible risks and discomforts will be given by the investigator.

For the Screening visit only, assessments can be broken into 2 days if necessary. For all other visits, all assessments indicated must be performed on the same day.

The RC will determine eligibility of all subjects prior to enrollment. Only those subjects who fulfill all eligibility criteria will be entered into the trial.

10.2 Trial Assessments

The following dosing days apply to the Induction Phase.

D0	D0 = The first day of dosing at each monthly timepoint.
D14	D14 = The second day of dosing, 14 days after D0.

The following evaluations, as outlined in the Study Assessments Chart (Section 3) will be performed on the days specified below:

Note:

- ***Concomitant medications should be assessed at every study visit.***
- ***Adverse events should be assessed starting at Day 1 after the first dose of trial drug.***

10.2.1 Screening Assessments

The following Screening evaluations, as outlined in the Study Assessments Chart (see Section 3) will be performed ***within 14 days*** prior to Day 1.

- Informed consent
- Medical history
- Ophthalmologic history (OU)
- Vital signs/Physical examination
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Color fundus photography (FP) (OU)
- Fluorescein Angiography (FA) (OU, transit study eye)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)
- Microperimetry testing (OU) (optional assessment)
- Serum pregnancy test (if applicable)
- Laboratory tests
- Genetic sampling (if necessary to confirm eligibility)
- 12-Lead ECG
- Concomitant medication assessment

10.2.2 Reconfirmation of Eligibility at Day 1

To remain eligible for randomization on Day 1, the subject must continue to meet the inclusion criteria. If the subject does not meet the inclusion criteria, the subject must NOT be randomized.

10.2.3 Day 1 (D0 Visit) – Induction Phase

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and ophthalmologic examination (SE)
- Randomization

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.4 Day 1 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Goldmann applanation tonometry and ophthalmologic examination (SE)

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.5 Month 1 (± 7 days) (D0 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.6 Month 1 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.7 Month 2 (±7 days) (D0 Visit)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and Ophthalmologic Examination (SE)

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.8 Month 2 (D14 Visit ± 1 day)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- Randomized Treatment

Post-injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (±1 day)

Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.9 Month 3 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.10 Month 4 Visit (± 7 days) – Maintenance Phase

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.11 Month 5 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.12 Month 6 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Ophthalmologic examination and Goldmann applanation tonometry (OU)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)

- Fundus Autofluorescence (FAF) (OU)
- Vital signs
- Serum pregnancy test (if applicable)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.13 Month 7 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.14 Month 8 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.15 Month 9 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Goldmann applanation tonometry and ophthalmologic examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein Angiography (FA) (OU, transit study eye)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)
- Microperimetry testing (OU) (optional assessment)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic Exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.16 Month 10 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.17 Month 11 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.

- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.18 Month 12 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and ophthalmologic examination (OU)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)
- Vital signs
- Serum pregnancy test (if applicable)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.19 Month 13 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.20 Month 14 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.

- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.21 Month 15 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.22 Month 16 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.
    - Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.
- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.23 Month 17 Visit (± 7 days)

Pre-injection

- Protocol refraction and visual acuity (4 meters) using ETDRS chart (SE)
- Tonometry and ophthalmologic examination (SE)

Injection

- 1st Injection - Randomized Treatment
    - Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the injection to assure that the optic nerve is perfused.

- Tonometry (SE) – After the injection, IOP must be ≤ 21 mmHg or within 5 mmHg of pre-injection before the 2nd injection can be given.

- 2nd Injection - Randomized Treatment

Post 2nd injection

- Indirect Ophthalmoscopy (SE) – 1 to 2 minutes after the second injection to assure that the optic nerve is perfused.
- Ophthalmologic exam/Tonometry (SE) – At least 30 minutes after the second injection, a full ophthalmologic exam must be performed and IOP must be < 30 mmHg before the subject leaves the clinic.

3-Day Post-Injection Safety Check (± 1 day)

- Telephone call to subject to ensure there are no signs or symptoms of retinal detachment or endophthalmitis.

10.2.24 Month 18 Visit (± 7 days)/Early Withdrawal

- Vital Signs
- Protocol refraction and visual acuity (4 meters) using ETDRS chart (OU)
- Tonometry and Ophthalmologic Examination (OU)
- Color fundus photography (FP) (OU)
- Fluorescein Angiography (FA) (OU, transit study eye)
- Spectral Domain Optical Coherence Tomography (SD-OCT) (OU)
- Fundus Autofluorescence (FAF) (OU)
- Microperimetry Testing (OU) (optional assessment)
- Serum pregnancy test (if applicable)
- Laboratory Tests
- 12-Lead ECG

10.3 Withdrawal from Trial

Subjects have the right to withdraw from the trial at any time for any reason. The Investigator (after consultation with the Sponsor) or Sponsor also have the right to withdraw subjects from the trial in the event of concurrent illness, AEs, treatment-failure after a prescribed procedure, protocol violations, cure, administrative or other reasons.

Final trial assessments as outlined in the Study Assessments Chart, Section 3, should be performed on all subjects who withdraw. Subjects who withdraw due to an AEs

should be followed until resolution of the AEs, or an adequate explanation for the event is obtained.

Subjects who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule. The subject must not receive an alternative treatment for Stargardt until he or she is withdrawn from the trial. If an alternative treatment for Stargardt is initiated before completing the study dosing, the subject will no longer be evaluated according to this protocol.

10.4 Trial Discontinuation

The reason for a subject discontinuing from the trial will be recorded in the case report form (CRF). A discontinuation occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. A discontinuation must be reported immediately to the clinical monitor or his/her designated representative if it is due to a serious adverse reaction (SAE; see Section 12.3). The final evaluation required by the protocol will be performed at the time of trial discontinuation. The investigator will record the reason for trial discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition.

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Astellas.

The study will be considered completed when the last subject completes the final study visit.

11. STATISTICAL METHODS

11.1 Interventions

Subjects will be randomized in a 1:1 ratio to the following dose groups:

- Avacincaptad pegol
- Sham

All subjects will be treated as follows:

Induction Phase: Administered on Day 1, Month 1, and Month 2 in the following sequence, 14 days apart:

- D0: Avacincaptad pegol 2 mg/eye or Sham
- D14: Avacincaptad pegol 2 mg/eye or Sham

Maintenance Phase: Administered every month (Months 3 – Month 17):

- Avacincaptad pegol 4 mg/eye (administered as two injections of avacincaptad pegol 2 mg)
- Sham + Sham

There will be a final follow-up visit for all subjects at Month 18.

11.2 Endpoints

Refer to Section 5.2 for detailed study endpoints.

11.3 Study Design

This is a randomized, double masked, Sham controlled, Phase 2b trial that will obtain evidence regarding the effect of avacincaptad pegol on the rate of change in the area of ellipsoid zone defect (defined as ellipsoid zone attenuation in addition to total RPE loss) measured by en face SD-OCT from Baseline through Month 18, when compared with Sham.

This Phase 2b trial will provide evidence suggesting that avacincaptad pegol:

- Is not plausibly more efficacious than Sham;
- Is plausibly more efficacious than Sham; or
- Is more efficacious than Sham, with strength of evidence meeting the standard requirement of a 0.025 one-sided, false-positive error rate.

11.3.1 Determination of Sample Size and Statistical Rationale

Approximately 120 subjects will be enrolled in this study. This statistical rationale for the trial is based on the methodology presented in Fleming and Richardson (2004). Patients will be maintained on their randomized intervention (including those on the Sham control) for 18 months.

The primary analysis of this Phase 2b trial for the comparison of avacincaptad pegol vs the Sham is formally based on a three-category decision guideline. To be specific, if SD_{Δ} is the standard deviation of the rate of change in the area of ellipsoid zone defect measured by en face SD-OCT over 18 months within each treatment group, the decision guideline for this trial is based on whether the difference between avacincaptad pegol and the Sham groups in the estimated mean rate of change in this area is less than 0.1843 SD_{Δ}, is from 0.1843 SD_{Δ} to 0.3577 SD_{Δ}, or is at least 0.3577 SD_{Δ}.

Note that these categories should not be interpreted as providing strict decision rules but rather as guidelines that will be factored into a broader scientific assessment of the benefit to risk profile of avacincaptad pegol. This broader assessment will include consideration of safety, of supportive efficacy endpoints, and of relevant information external to this trial. Specifically, the decision guidelines for this trial are:

1. If the difference between avacincaptad pegol and the Sham groups in the estimated mean rate of change in the area of ellipsoid zone defect measured by en face SD-OCT over 18 months is less than 0.1843 SD_{Δ}, then avacincaptad pegol is not plausibly more efficacious than the Sham.
2. If the difference between avacincaptad pegol and the Sham groups in the estimated mean rate of change in the area of ellipsoid zone defect measured by en face SD-OCT over 18 months is from 0.1843 SD_{Δ} to 0.3577 SD_{Δ}, then avacincaptad pegol is plausibly more efficacious than the Sham.
3. If the difference between avacincaptad pegol and the Sham groups in the estimated mean rate of change in the area of ellipsoid zone defect measured by en face SD-OCT over 18 months is at least 0.3577 SD_{Δ}, then this dose of avacincaptad pegol would be statistically significantly more effective than the Sham, with strength of evidence meeting the standard requirement of a 0.025 one-sided, false positive error rate.

The planned size of 120 subjects for this phase 2b trial was determined based on the number of subjects with STGD1 that could potentially be enrolled within a reasonable

period of time. Based on the actual recruitment rate during the trial, this number may be increased or decreased. As STGD1 is an orphan indication, there is no natural history data currently available regarding the standard deviation of rate of change in the area of ellipsoid zone defect over 18 months in the STGD1 patient population that we plan to enroll in this trial.

11.3.2 Randomization Procedure

Subjects will be centrally allocated to one of the two treatment groups by a dynamic minimization procedure.

Randomization will occur with the use of an IRT system which will assign subjects to treatment in 1:1 ratio to avacincaptad pegol or Sham.

11.4 Masking Procedure

It is the responsibility of the Principal Investigator to ensure that the physician assessing AEs, the visual acuity examiner, all masked study personnel, and the subject remain masked to the subject's treatment assignment. Any unmasking should be documented and reported immediately to the Sponsor.

11.4.1 Visual Acuity Assessments

Refraction and visual acuity measurements will be performed for all subjects by a certified vision examiner. Since this is a double-masked study, subjects and staff at the investigational site, particularly the visual acuity examiners, will be masked to study treatment. All visual acuity assessments will be performed by the trial refractionist/ophthalmologist, who will be masked to the subject's treatment as well as previous visual acuity assessments. The trial refractionist/ophthalmologist will be supplied only with the subject's most recent protocol refraction.

11.4.2 Injections

Each clinical site is required to have a minimum of 2 ophthalmologists – the unmasked injector and the masked assessor. The unmasked injector will perform the avacincaptad pegol/Sham injection as well as the post-injection ophthalmic examination and tonometry measurements. The unmasked injector and designated unmasked assistants (if needed) are not permitted to be involved in the conduct of the study in any other manner and are not to communicate with any other personnel or subjects regarding the treatment assignment. Once the unmasked injector or unmasked assistant breaks the seal on the masked drug kit, no masked study personnel can be present until after the injections are complete and the drug kit and components (vial,

syringe, needles) have been disposed of by the unmasked injector/unmasked assistant; only the empty drug kit box and the tear-off part of the vial label are saved. The masked assessor will perform all other physician assessments including the relationship of all AEs to study drug, including those noted by the unmasked injector.

11.4.3 Statistical Analyses

All statistical analyses will be conducted by the study Sponsor or under the authority of the study Sponsor. The Sponsor and the subjects will remain masked to treatments until the end of the study, except if safety considerations justify breaking the code for individual subjects.

Primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) with all available data, using response variable of the area of ellipsoid zone defect measured by en face SD-OCT over time up to Month 18 including baseline and post-baseline assessments. The MMRM will be used to assess the difference between the treatment groups in terms of the rate of change (slope) in the area of ellipsoid zone defect from Baseline through Month 18. The fixed effects will include treatment group (avacincaptad pegol or Sham), time, pooled geographic region (North America or Rest of World) and treatment by time interaction. Subject is the random effect with repeated measures.

The efficacy analysis will be conducted on all randomized subjects according to the intention-to-treat principle.

A Statistical Analysis Plan (SAP) will provide the details for the statistical analyses.

11.4.4 Descriptive Statistics

Descriptive statistics will be provided on demographic information, treatment administration, baseline characteristics, and protocol deviations, as well as for selected endpoints at relevant timepoints.

11.4.5 Safety Analysis

The safety analysis will be conducted on all subjects who had at least one administration of trial drug.

Adverse events will be summarized using MedDRA terms. The incidence and severity of AEs will be listed and grouped by body system.

All laboratory data will be listed and values falling outside normal ranges will be identified. Summary statistics (i.e., mean, median, standard deviation, minimum and maximum) will be presented for all continuous variables.

Summary statistics will be given on the number of subjects for whom the trial medication had to be permanently stopped.

12. ADVERSE EVENTS

12.1 Definition of Adverse Events

An AE is defined as follows: Any untoward medical occurrence in a patient or subject including unfavorable and unintended signs, symptoms or disease temporally associated with the use of a medicinal product and which does not necessarily have to have a causal relationship to this treatment.

Adverse events include illnesses with onset during the trial, or exacerbations of pre-existing illnesses. Exacerbation of pre-existing illness is defined as a significant increase in the severity of the illness as compared to the start of the trial, and should be considered when a subject requires new or additional treatment for that illness. Lack of or insufficient clinical response or efficacy should not be recorded as an AE.

In addition, clinically significant changes in objective findings (e.g., laboratory, ECG, X-ray, physical examination) should also be considered as to whether they are AEs. The criteria for determining whether an objective finding should be reported as an AE are as follows:

1. Associated with accompanying symptoms; and/or
2. Requires medical/surgical intervention; and/or
3. Leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy; and/or
4. Leads to any of the outcomes included in the definition of a SAE; and/or
5. Is considered to be an AE by the investigator or Sponsor.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.2 Assessment and Reporting of Adverse Events

Adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. An AE that is ongoing at the last follow up study visit is required to be followed up until the event resolves or stabilizes at a level acceptable to the investigator and/or Sponsor. If the subject still presents with any treatment-related toxicity, the follow-up period will be extended until return to

Baseline status or until the condition has stabilized.

All AEs spontaneously reported, elicited or observed by the investigators will be recorded. The events will be recorded in the source documents and onto the AE pages of the CRF, including date of onset and resolution, severity, relationship to trial treatment and determination of “serious”.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

The investigator will take all therapeutic measures necessary for resolution of the AE. Any medication necessary for treatment of the AE must be recorded in the subject’s source documents and on the appropriate pages of the subject’s CRF.

To assist with grading of AE severity, the following definitions are provided:

Mild	=	Aware of sign or symptom, but easily tolerated;
Moderate	=	Discomfort enough to cause interference with usual activity;
Severe	=	Incapacitating with inability to work or do usual activity;

Adverse events are assessed as either related to the intravitreal injection procedure (eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine drops or flush, subconjunctival injection of anesthetic, intravitreal injection), termed “injection procedure-related”, or to avacincaptad pegol.

The relationship to the intravitreal injection procedure or to study drug will be assessed using the following definitions:

Not Related	=	There is not a reasonable possibility that the AE is related to the injection procedure or to the study drug.
Related	=	There is a reasonable possibility that the AE is related to the injection procedure or to the study drug.

12.3 Definition of Serious Adverse Events

An SAE is any event that:

1. Results in death;
2. Is life-threatening (immediate risk of death);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect.

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

A life-threatening AE is any event that places the patient/subject at immediate risk of death from the reaction as it occurred; i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Disability is a substantial disruption of a person's ability to conduct normal life functions.

Hospitalization is defined as any formal inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from the psychiatric wing to a medical floor, from a medical floor to the coronary care unit).

- Inpatient admission does not include the following:
    - Emergency Room/Casualty Department visits
    - Outpatient/same-day/ambulatory procedures and observation/short-stay units
    - Hospice facilities and Respite care (e.g., caregiver relief)
    - Rehabilitation facilities, skilled nursing facilities, nursing homes, custodial care facilities
- Inpatient admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for "seriousness" but is not an AE and thus is not subject to immediate reporting to the Sponsor. For example:
    - Admission for treatment of a pre-existing condition not associated with the

development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)

- Social admission (e.g., subject has no place to sleep)
- Optional admission not associated with a precipitating clinical AE (e.g., yearly physical, elective cosmetic surgery)

12.4 Assessment and Reporting of Serious Adverse Events

Serious adverse events will be recorded starting after the first dose of trial drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. Any SAE occurring at any other time after completion of the trial must be promptly reported if a causal relationship to trial drug is suspected.

If a SAE occurs, the Sponsor is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made regardless of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports.

All SAEs must be reported to the
Sponsor or Designee within 24 hours.
Refer to the "Safety Contact List" provided separately

12.5 Independent Data Safety Monitoring Committee

An Independent Data Safety Monitoring Committee (DSMB), consisting of persons who are independent of the Sponsor, trial coordination center, data coordination center, regulatory agencies, IRB/EC and investigators, and who have no financial, scientific, or other conflict of interest with the clinical trial, will meet regularly to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial, and provide recommendations to continue, modify, or terminate the trial depending upon the analyses. The safety data provided to the committee will be prepared by an independent statistician. For details, please refer to the Independent Data Safety Monitoring Committee (DSMB) Charter.

The Sponsor will ensure the proper conduct of the study, collection of accurate and timely data, and promptly report potential safety concerns to the DSMB, and communicate with

regulatory authorities, IRB/EC, and investigators in a manner that maintains integrity of the data as necessary.

12.6 Exposure in Utero

Astellas Drug Safety or contract research organization (CRO) must be notified of any subject who becomes pregnant or their partner who becomes pregnant, while participating in a clinical trial. The Investigator must immediately notify the Sponsor's Medical Monitor of any pregnancy associated with study medication exposure (at least 90 days after drug administration) and record the event using sponsor provided pregnancy report form. Protocol-required procedures for study discontinuation must be performed on the subject unless contraindicated by pregnancy. All pregnancies must be followed to conclusion to determine their outcome. Infants should be followed for a minimum of 8 weeks, if the pregnant study subject or their pregnant partner provides consent for the follow-up and for access to the newborn's data.

13. RESPONSIBILITIES

13.1 Emergency Equipment

All participating sites should have emergency resuscitation equipment available, including at a minimum, an Ambu bag, IV tubing, D5W IV fluid, oxygen, and epinephrine 1:1000, and Diphenhydramine Hydrochloride (Benadryl). It is each center's responsibility to ensure that all equipment is within specifications for the duration of the trial. Each center should have written policies regarding resuscitation procedures.

13.2 Case Report Forms and Trial Documentation

The investigator will complete the appropriate CRF pages promptly following completion of each procedure or evaluation.

All data recorded on CRFs will be supported by source documents. For certain trial parameters, with prior written agreement by the trial sponsor and monitor, the CRF may be used to record source data.

All source documents will be made available to the Sponsor's clinical monitors during scheduled monitoring visits, to auditors during any audits requested by Astellas, and to regulatory agencies during inspections.

The investigator will maintain a Trial File containing all trial related documentation required by Good Clinical Practice (GCP). This Trial File will be reviewed periodically for completeness by the Sponsor's clinical monitors and must be made available to auditors and regulatory agencies.

All CRFs and original source documents including ocular images should be stored for a minimum of two years after a marketing application has been approved, or two years after formal discontinuation of development of the investigational drug, or five years after completion of the trial, whichever is longer. Documents should not be destroyed without the permission of Astellas. In the event of the Principal Investigator leaving the clinical site, it is the Principal Investigator's responsibility to notify Astellas in writing and to designate which trial material will be transferred at the clinical site.

13.3 Drug Accountability/Storage Conditions

The investigator is responsible for the accountability of all used and unused trial medication and for recording and documenting the drug storage temperature at arrival and throughout the trial. Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all trial drug

supplies received, dispensed to trial subjects, and returned to the Sponsor. All drug documentation should be filed at the site and a copy sent to the Sponsor for archiving.

At the end of the trial, all drug supplies and documentation will be reviewed and reconciled by the trial monitors. The sites may destroy unused trial drug supplies when the trial is completed if they have an SOP to cover that activity. Otherwise the site may return the drug to a sponsor-contracted drug management facility for destruction. If the drug is destroyed at the site, the drug destruction documentation must be sent to Astellas for archiving.

13.4 Protocol Compliance

Astellas will not compensate the Investigator for evaluation of cases in which the procedures and evaluations are conducted in a manner other than that specified by the protocol.

13.5 Ethical Aspects

Local Regulations/Declaration of Helsinki

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for GCP" ICH Tripartite Guideline (May 9th 1997) and with local law if it affords greater protection to the subject. For studies conducted in the USA or under US Investigational New Drug (IND), the investigator will additionally ensure adherence to the basic principles of "GCP" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

13.6 Institutional Review Board (IRB) or Ethics Committee (EC) Approval and Informed Consent

The investigator is responsible for obtaining approval of the trial protocol, informed consent, and any advertising used for subject recruitment from the appropriate IRB/EC prior to initiating the trial. The investigator will forward the following documents prior to commencement of subject enrollment:

- IRB/EC approval documentation
- Approved trial subject informed consent
- A list of IRB/EC members, or statement of compliance

Prior to enrollment, written informed consent must be obtained from each subject or his/her legally authorized representative. The informed consent must contain all of the elements prescribed by the relevant regulatory authorities and must be appropriately signed, dated and witnessed. **Any changes by the Investigator or local IRB/EC to the sample consent provided by the Sponsor must be approved by the Sponsor before initiating enrollment.**

13.7 Clinical Trial Insurance

Astellas has insurance coverage for medicine-induced injury and other liabilities incurred during clinical trials with its compounds.

13.8 Trial Report and Publications

The trial will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or investigator may publish or present any results from the trial until a joint, multi-center publication of the trial results is made by Sponsor in conjunction with various participating investigators and appropriate sites contributing data and comments. Subsequently, individual investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language be in conflict with the language addressing publication in the clinical trial agreement, the language in the clinical trial agreement will prevail.

14. MONITORING

The investigator will permit representatives of Astellas to review all CRFs, trial documentation, and subject medical records at regular intervals throughout the trial. These monitoring visits are for the purpose of verifying protocol compliance, subject safety, and the adequacy of data collected.

15. REFERENCES

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16. SPONSOR SIGNATURE PAGE

Required sponsor signatures as required by ICH GCP 4.5.1 are located in the first attachment.

Attachment 1	Electronic Sponsor Signatures

17. APPENDICES

17.1 Method for Evaluating Anterior Chamber Inflammatory Activity

17.1.1 Examination

1. The pupils will be maximally dilated.
2. A slit-lamp biomicroscope will be used with a one by two mm^2 beam at an angle of 30-45°. The number of cells within this wedge will be counted.
3. The grade of anterior chamber inflammatory activity is determined.

17.1.2 Standardized Description of Anterior Chamber Activity

Anterior chamber activity will be graded on a scale of 0, trace, 1+, 2+, 3+, and 4+.

The grading is as follows:

0	None
Trace	< 5 cells in wedge
1+	5 - 10 cells in wedge
2+	11 - 20 cells in wedge
3+	21 - 50 cells in wedge
4+	> 50 cells in wedge

Reference

Hogan MJ, Kimura SJ, Thygeson P (1959). Signs and symptoms of Uveitis. I. Anterior uveitis. Am J Ophthalmol; 47:155-170.

17.2 Method for Evaluating Vitreous Inflammatory Activity

All subjects will have the standard fundus examination followed by evaluation for inflammatory activity in the vitreous.

17.2.1 Marking

The clarity of the optic nerve head, retinal vessels, and the nerve fiber layer are used as landmarks for the marking criteria.

17.2.2 Examination

1. The pupils will be maximally dilated.
2. An indirect ophthalmoscope and a 20+ diopter aspheric lens will be used as the standard.
3. Standard fundus examination is performed with the last view being over the disc and surrounding retina.
4. Inflammatory activity is evaluated by the examiner by determining which standardized description most closely resembles the vitreal haze seen through the indirect ophthalmoscope.

17.2.3 Standardized Description of Vitreous Inflammation

Vitreous activity will be graded on a scale of 0, 1+, 2+, 3+, and 4+.

The grading is as follows[1]:

0	No evident vitreal haze at all.
1+	Minimal haze. Optic nerve head and retinal vessels are both clearly defined.
2+	Retinal vessels are visible, but not clearly defined.
3+	Optic nerve head is visible but the borders are blurry, and cannot see vessels.
4+	Optic nerve head is obscured.

Reference

Nussenblatt RB et al. (1985). Standardization of Vitreal Inflammatory Activity in Intermediate and posterior Uveitis. Ophthalmology 92:467-471.

17.3 Procedures for Refraction and Vision Testing

Refraction and visual acuity measurements will be performed for all subjects by a certified vision examiner. Another examiner should also be certified to serve as a back-up should the primary examiner be absent. The name and certification number of the vision examiner should be documented in the subject's source document at each visit. Visual acuity examiners are "masked" to previous visual acuity testing results. Therefore, visual acuity examiners should not have access to the subject's chart or previous visual acuity testing results. The previous refraction should be made available.

17.3.1 Refraction

Refraction should be conducted prior to visual acuity testing to obtain best-corrected vision.

17.3.2 Equipment

Refraction equipment required includes:

1. Retroilluminated light box and Charts R, 1 and 2 from Ferris-Bailey ETDRS distance visual acuity chart set
2. Trial lens frames
3. Trial lens set with plus or minus cylinder lenses
4. Jackson cross-cylinders of 0.25, 0.5, and 1.00 diopters
5. Pinhole occluder
6. Tissues or eye pads and tape
7. A 1 meter rigid measuring stick

17.3.3 Beginning Approximate Refraction

At the Screening visit, the subject's beginning refraction is determined by one of the following methods:

a) If the subject's visual acuity is 20/100 or better and the subject does not require glasses for distance vision, then the beginning approximate refraction should be no lens correction or plano.
b) If the subject's visual acuity is 20/100 or better and the subject requires glasses for distance viewing, the glasses should be measured using a lensometer, and these measurements are used for the beginning refraction.
c) If the subject's visual acuity is less than 20/100 with or without correction, then retinoscopy or autorefraction should be performed.
d) If the subject wears contact lenses for refraction, a notation should be made that the refraction was over contact lenses. It is suggested that the subject wear the contact lenses for future examinations. If the subject is not a regular contact lens wearer

and wore the lenses in by mistake, they should be removed and you should wait at least 30 minutes before beginning the refraction. The subject should be reminded not to wear contact lenses at subsequent visits.

Refractions are performed with either plus or minus cylinder power. Whichever cylinder type is used at screening (minus or plus) must be used for all subsequent visits. Best correction will be recorded on an examination form for each subject to be included in the source document. At each follow-up visit, the results of the protocol refraction from the previous visit are used as the beginning approximate refraction. If the previous refraction is not available for whatever reason, the procedure described immediately above should be used. *Note: The distance prescription worn in glasses should be used only as the starting point for the Screening Visit. All subsequent visits should use the previous refraction as the starting point.*

The charts used for measuring distance visual acuity must NOT be used for refraction. Refraction for each eye should be performed at 4 meters unless the subject's visual acuity measured at 4 meters on the refraction chart (Chart R) is worse than 20/160. If visual acuity is worse than 20/160 the eye is refracted at 1.0 meter. If during the refraction process at one meter, the subject is reading letters on the eighth line or lower, the refraction should continue at 4 meters. Whenever a subject cannot read any letters on the top line of Chart R at 1.0 meter the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to a larger refractive error. If there is no improvement with the pinhole, then the eye is exempt from refraction.

Subjective refraction as described below should be performed for corrected aphakic subjects, including those with intraocular lenses. For uncorrected aphakic subjects, a +10.00 diopter sphere should be added to the trial frame as the beginning approximate refraction.

17.3.4 Subjective Refraction

Subjective refraction allows one to determine the best correction for a subject to perform the visual acuity tests at specified distances. The “push plus” approach is used in this trial. Add minus diopter spherical corrections only when the subject is able to read at least one more letter on a line or a letter on a smaller line.

17.3.5 Procedure

1. Measure the distance vision of each eye using Chart R while occluding the fellow eye (FE). Subjects should be reminded to blink and encouraged to use eccentric fixation, or their side vision, when necessary.
2. All vision testing must be done at 4 meters or 1 meter from Chart R, depending upon the visual acuity determined at 4 meters. Distance for 4 meters is 13 feet and 1.5 inches or 157.5 inches. The one meter distance is 39 and 3/8 inches.
3. All subjects should be seated for testing. A rigid measuring device should be used to measure the distance from the subject to the chart at each visit if testing is done at 1 meter. The distance is measured from the outer canthus to the center of the second letter (left eye) or fourth letter (right eye) of the third line of the chart. If testing is done at 4 meters, **clear and permanent** floor markings should be used to mark the distance for consistency.
4. Place and adjust the trial frame on the subject’s face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea.
5. Occlude the left eye by lightly patching with an eye pad or tissue and tape.
   a) Place the spherical lens correction in the compartment closest to the eye.
   b) The cylindrical lens correction, if present, is placed in the compartment in front of the spherical correction. Adjust the axis.
6. ***Spherical Correction*****:** To determine the highest plus or least minus sphere, refract the right eye. **The following refraction steps are recommended for visual acuities of 20/10 to 20/80 with the beginning approximate refraction. For visual acuities less than 20/80, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (See 17.3.10) and follow a similar procedure.** *Note: Whenever visual acuity is improved to a higher range by improved correction, refraction should be performed with the smaller sphere and cylinder powers given for the better visual acuity level (See table at end of this appendix).*
   a) Hold a +0.50 sphere in front of the subject’s right eye. The subject should be looking at the smallest legible line on the visual acuity chart. In these exact words, ask the subject, “Is this better, worse, or no change?”

b) If the subject responds that the vision is worse or blurred, remove the +0.50 sphere from in front of the trial frame, record the visual acuity to the nearest letter, and go to Step 6d.
c) If the subject responds better or no change, remove the +0.50 sphere from in front of the trial frame and replace the spherical lens in the trial frame with a spherical lens that is one-half diopter more positive. Continue this procedure by returning to Step 6a and repeating this process until a +0.50 makes the vision worse or blurred and then go to Step 6d.
d) Hold a -0.50 sphere in front of the subject's right eye. In these exact words, ask the subject, "Is this better, worse or no change?" If the subject replies "worse" or "no change", go to Step 6f. If they reply "better" go to step 6e.
e) Hold the -0.50 sphere in front of the eye. If the subject responds that the vision is better, ask the subject to read the visual acuity chart. Whenever the visual acuity is improved, even by one letter, you may increase the minus by 0.50 (or decrease the plus) and repeat Step 6d. Whenever visual acuity is not improved, go to Step 6f.
f) Remove the -0.50 sphere from in front of the eye and hold a +0.50 sphere in front of the right eye. In these exact words, ask the subject, "Is this better, worse, or no change?" If the subject responds that vision is better or unchanged, then return to Step 6c. Otherwise, go to Step 7. Spherical testing should always end with a plus lens.

7. ***Cylinder Axis*:** To determine and refine the cylinder axis for PLUS cylinder, proceed as follows *(If negative cylinders are used, the appropriate technique using minus cylinders must be employed and minus cylinder must be used throughout the trial.)*:
   a) Have the subject look at a line, which is either one or two lines larger than the smallest line the subject is able to read. Ask the subject to focus on a rounded letter such as "C", "D", or "O". The subject should focus on this same letter throughout this procedure.
   b) If a cylinder is present in the beginning approximate refraction, then go to Step 7c. Otherwise, follow one of the options listed below to determine the appropriate cylindrical correction.

Option 1:

Place a +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then at 180°, then 45°, and 135°. If the subject says that vision is improved at any one of these axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and go to Step 7c. If none of the positions are preferred, then proceed to Step 9.

Option 2 (preferred)**:**

Place a +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then compare this to no cylinder; repeat this procedure for 180°, then 45°, and 135° always comparing to no cylinder after each axis position. If the subject says that vision is improved at any one of the four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis. If the subject prefers no cylinder at all four axis positions, then go to Step 9.

c) Place the +0.25 diopter cross-cylinder (for visual acuity 20/10-20/80) first with the positive axis 45° to the right of the preferred cylinder axis (as determined above), and second with the positive axis 45° to the left of the preferred cylinder axis. Ask the subject, “Which do you like better, position one or position two?” Also, tell the subject that both positions may blur their vision. The subject must choose the least blurred position, either one or two. “Neither” is allowed only if both positions are equally blurred or equally good.
d) If “neither” position is better and this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 7c. Otherwise, proceed to Step 7e.
e) When one position is preferred over another, move the cylinder to the preferred positive axis position in the step sizes noted below and return to Step 7c. If no single position is better than another than go to Step 8.

CYLINDER REFINEMENT - AXIS STEP SIZES

Cylinder Power	Axis Step Sizes
< 1.00D	15°
1.00 - < 2.00D	10°
2.00 - < 3.00D	5°
3.00 - < 5.00D	3°
5.0 - < 8.00D	2°

8. ***Cylinder Power:*** **Cylinder power is refined by following the steps:**
   a) Ask the subject to look at the smallest line that can be read on the visual acuity chart.
   b) Test the cylinder power by placing the 0.25 diopter cross-cylinder (for vision of 20/10-20/80) first with the positive axis and second with the negative axis coincident with the cylinder axis. Ask the subject, "Which is better, position one or position two?" Do not give the subject the choice of neither.
   c) If the subject prefers the negative (red) axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. Repeat the process until the subject cannot choose one of the cross cylinder positions over the other. If the subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90°away from the previous axis. Otherwise go to Step 8d.
   d) If the subject prefers the positive (white) axis coincident with the cylinder axis, increase the power of the cylinder by 0.25 diopters and return to Step 8b. Otherwise proceed to Step 8e.
   e) When the subject feels that both positions are equally bad or good, and the cylinder power in the trial frame has changed by more than 0.50 diopter, return to Step 7c and re-adjust the axis if necessary. Otherwise, proceed to Step 9.
   Note: If the cylinder is changed by more than 0.50 diopter, the spherical equivalent should be maintained. (For each 0.50 ***plus*** *CX increase, add –0.25 to the sphere, for each 0.50* ***minus*** *CX increase, add +0.25 to the sphere).*
9. ***Spherical Correction Refinement:*** Recheck the power of the sphere by adding +0.25 and -0.25 spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the subject cannot detect any improvement

in vision. As a reminder, spherical testing should always begin and end with a plus lens.

10. Record the lens corrections obtained by subjective refraction for the right eye on the examination form in the section for visual acuity measurements as the corrections obtained by protocol refraction for the right eye. If the corrective power was changed by more than 2 diopters from the starting refraction, confirm that the subject can read at least as well as the beginning approximate refraction. If not, then begin again at Step 1 and repeat the process.
11. Repeat the entire process (Steps 1-10) for the left eye and record the result on the examination form.

17.3.6 Visual Acuity Testing

Best-corrected visual acuity is measured at all trial visits using standard charts, lighting, and procedures. Best correction is determined by careful refraction at that visit according to the standard protocol for Refraction as described in the previous section.

17.3.7 Visual Acuity Charts

Chart 1 is used for testing the visual acuity of the right eye; Chart 2 for testing the left eye; and Chart R for testing refraction only. Subjects should not be allowed to see any of the charts before the examination.

17.3.8 Visual Acuity Lane and Visual Acuity Box

A distance of **4 meters** is required between the subject's eyes and the visual acuity chart. With the box light off, not more than 15 foot-candles of light (161.4 Lux) should fall on the center of the chart. To measure the amount of light, the room is set up for visual acuity testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one lane is available for testing visual acuity, the visual acuity of an individual subject should be measured in the same lane at each visit, if possible. If different lanes are used to test visual acuity, they must each meet the same standards.

Retroilluminated ETDRS charts are used in this trial. The illuminator box will be either wall-mounted or mounted on a stand manufactured by the Lighthouse Low Vision Services. The light box should be mounted at a height such that top of third row letter is 49 ± 2 inches from floor.

The visual acuity light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and a ballast which partially covers the tubes. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and

by another 5 percent during the next 2000 hours, new tubes should be kept on for 4 days (96 hours) continuously, and should be replaced once a year.

A sticker should be placed on the back of the light box, indicating the date on which the present tubes were installed. A spare set of burned in bulbs should be available on site.

Each tube is partly covered by a 14-inch fenestrated sleeve, which is open in the back. This serves as a baffle to reduce illumination. Each sleeve should be centered on the tube with the opening towards the back.

17.3.9 Corrected Visual Acuity Measures

- As a reminder, Charts 1, 2, and R are used for testing the right eye, left eye, and refraction, respectively. Subjects should not see the charts until the test begins.
- All eyes must be tested at 4 meters first, even if the refraction was performed at 1 meter.
- The subject should be seated comfortably directly in front of the chart so that the eyes remain at the 4 meter distance. Testing always begins with the right eye. Occlude the subject's left eye. A folded tissue or eye pad lightly taped over the eye behind the trial frame serves as an effective occluder that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.
- The lens correction from the subjective refraction should be in the trial frame worn by the subject.
- The subject is asked to read the letters slowly, approximately one letter per second. The subject should be told that only one chance is given to read each letter on the chart. If the subject is unsure about the identity of the letter, then the subject should be encouraged to guess.
- The subject should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the data collection form. An X is put through letters read incorrectly. Letters, for which no guess was attempted, are not circled. When a subject reaches a level where he/she cannot guess, the examiner may stop the test provided that the subject has made errors on

previous guesses, which is a clear indication that the best visual acuity has been obtained.

- When a subject cannot read at least 20 letters on the chart at 4.0 meters, the subject is tested at 1.0 meter. The distance from the subject to the chart should be measured again using the rigid one meter stick. The distance is measured from the outer canthus to the center of the fourth letter (right eye) or the second letter (left eye) of the third line of the chart. The spherical correction in the trial frame should be changed by adding +0.75 to correct for the closer test distance. The subject may fixate eccentrically or turn or shake his/her head to improve visual acuity. If this is done, the examiner must ensure that the FE remains occluded both centrally and peripherally and that the subject does not move forward in the chair. Particular care should be taken to make sure the subject does not move forward when testing at 1 meter. The subject should be reminded to blink.
- The examiner should not tell the subject if a letter was identified correctly. The subject may be encouraged by neutral comments, such as “good”, “next”, and “OK”.
- The examiner should not stand close to the chart during testing. Attention should be focused on the subject and the data collection form. If the subject has difficulty locating the next line to read, the examiner may go up to the chart and point to the next line to be read, but then must move away from the chart.
- When it is possible to measure the visual acuity of the eye at 4.0 meters (i.e. 20 or more letters read at 4 meters), the visual acuity score for that eye is recorded as the number of letters correct plus 30. The subject gets credit for the 30 1M letters even though they did not have to read them. Otherwise, the visual acuity score is the number of letters read correctly at 1.0 meter plus the number, if any, read at 4M. If no letters are read correctly at either 4.0 meters or 1 meter, then the visual acuity score is recorded as 0.

Testing for Count Fingers Vision, Hand Motion Vision and Light Perception/No Light Perception (NLP) Vision

If the subject’s visual acuity is so poor that he/she cannot read any chart letters when tested at one meter then the subject’s ability to count fingers, detect hand motion, or have light perception should be evaluated.

Testing for Count Fingers Vision

In testing for count fingers vision, the examiner's hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. The FE is completely occluded with a patch on the face. A light should be shown directly on the hand from behind the subject. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the subject correctly identifies three of the five presentations, then count fingers vision is noted. If not, then the subject must be tested for hand motion vision.

Testing for Hand Motion Vision

The examiner's hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The FE should be occluded with a patch on the subject's face. A light should be shone directly on the hand from behind the subject. The examiner's hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The subject is instructed that the examiner's hand will be presented and they will have to respond to the question: "What am I doing with my hand?" This should be repeated five times. Three out of five correct responses indicate that hand motion vision is present. If the subject does not correctly identify three of five presentations, then you must test for light perception.

Testing for Light Perception/NLP Vision

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope light should be in focus at 1 meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the subject should be asked to respond when he or she sees the light. If the examiner is convinced that the subject perceives the light, vision should be recorded as "light perception", if not, vision should be recorded as "no light perception (NLP)".

17.3.10 Refraction Sequence Chart

Refraction Protocol Summary							
Vision with Best Correction (Refraction Distance)	**Sphere**		**Cylinder**			**Sphere Refinement**	
	Power (a)	Increment	Axis (b)	Power (c)	Increment	Power (d)	Increment
20/10 - 20/80 (4 meters)	+.50 -.50	+.50 -.50	.25 JCC	.25 JCC	+.25 -.25	+.25 -.25	+.25 -.25
20/100 - 20/160 (4 meters)	+1.00 -1.00	+1.00 -1.00	.50 JCC	.50 JCC	+.50 -.50	+.50 -.50	+.50 -.50
20/200 - 20/400 (1 meter)	+2.00 -2.00	+2.00 -2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00	+1.00 -1.00
<20/400 (1.0 meters)	+2.00 -2.00	+2.00 -2.00	No cylinder test			No refinement	

Sequence of Refraction: (a) - (d)

17.4 Intravitreal Administration Protocol

This protocol applies to avacincaptad pegol and Sham injections.

The injection volume for avacincaptad pegol 2 mg/eye is 0.10 mL (100 µL).

The avacincaptad pegol and Sham injections must be performed by the unmasked ophthalmologist at the clinical site.

Subjects will receive one or two intravitreal injections (including Sham) at each monthly visit. Subjects will receive one of the following treatments at each injection visit:

- Avacincaptad pegol 2 mg/eye
- Avacincaptad pegol 4 mg/eye (administered as two injections of avacincaptad pegol 2 mg)
- Sham
- Sham + Sham

Only an ophthalmologist who is experienced with intravitreous injections may perform the intravitreous injections.

When there are two intravitreal injections to be administered on the same day, this intravitreous preparation and administration procedure MUST be followed for both injections, i.e., subjects MUST undergo a second preparation procedure and povidone-iodine (Betadine®) application prior to the second injection.

In addition to the procedures outlined, any additional safety measures in adherence to specific institutional policies associated with intravitreal injections may be utilized.

NOTE: Prior to the intravitreous injection, direct ocular massage using a sterile cotton-tip applicator at the intended site of injection may be utilized at the Investigator's discretion. However, a paracentesis **MAY NOT** be performed ***prior*** to injection of the intravitreous drug.

NOTE: Pre-operative antibiotic drops are NOT required prior to the scheduled injection(s) of intravitreous drug. In addition, peri-operative and post-operative antibiotic drops are NOT required at the time of the procedure or after the procedure, respectively. However, if it is considered the standard of care at the individual

institution, appropriate broad spectrum topical antibiotics (topical ofloxacin, levofloxacin, or an antibiotic drop with comparable antimicrobial coverage) may be prescribed for subject use at the discretion of the investigator.

NOTE: Intravitreal administration of avacincaptad pegol is contraindicated if active inflammation and/or suspected or active ocular or peri-ocular infection is present.

NOTE: Clinically significant blepharitis should be treated and resolved prior to randomization.

Before the Injection Day

1) If pre-operative topical ofloxacin, levofloxacin, or an antibiotic drop with comparable antimicrobial coverage therapy is ordered by the investigator, the subject should be instructed to initiate the use of such antibiotic drops according to the regimen selected at the discretion of the investigator. The antibiotic drops should be provided to the subject with clear instructions of how to use them at the visit immediately prior to each planned injection.

Preparation on the Day of the Injection

2) Approximately one hour prior to injection, topical 1% tropicamide (e.g., Mydriacyl) and 2.5% phenylephrine (e.g., Neo-Synephrine) from new bottles should be applied topically to achieve adequate pupillary dilation. If 2.5% phenylephrine is not available, another dilating drop may be used at the discretion of the investigator.

3) Injection preparation (for the following, new povidone-iodine bottles must be used and cannot be shared between subjects):
    a. Apply single use topical anesthetic drop(s) to the eye.
    b. Apply 2-3 drops of povidone-iodine to the injection site.
    c. OPTIONAL: Apply 2-3 drops of povidone-iodine to the lower fornix and/or use sterile cotton-tipped applicators soaked in 5% or 10% povidone-iodine to swab the upper and lower eyelid margins and the upper and lower eyelashes.

4) Place a sterile eyelid speculum to stabilize the eyelids.

5) Consider additional anesthesia with the application of one or two cotton-tipped applicators soaked in topical anesthetic over the intended injection site for at least 30 seconds. Subconjunctival anesthesia (0.5 mL of 2% xylocaine without epinephrine subconjunctivally at the intended injection site) can be used if the investigator believes that topical anesthetic is not sufficient to minimize discomfort. Lidocaine gel is not recommended.

6) Encourage the study participant to look superonasally (if injection site is inferotemporal) during the application of the povidone-iodine. Apply one of the following to the conjunctiva directly over and surrounding the intended injection site:

    a. A cotton-tipped applicator soaked in 5% or 10% povidone-iodine.

    b. A 10% povidone-iodine swabstick.

    c. At least 1-3 drops of 5% povidone-iodine (at least enough to cover the intended injection site).

7) Allow 30-60 seconds for the povidone-iodine to be in contact with the injection site before injection.

    NOTE: As indicated above, injection preparation must include the use of povidone-iodine either applied directly to the injection site using topical drops, a cotton-tipped applicator, or a swabstick. If a study participant experiences an adverse reaction to povidone-iodine, other approaches to limit the exposure of povidone-iodine may be permitted. However, **a study participant may not receive a study intravitreal injection without use of povidone-iodine directly to the injection site just prior to the injection.**

8) Sterilized calipers should be used to measure the injection site. The entry site of the needle for the intravitreous injection should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic subjects, and 3.5-4.0 mm in phakic subjects.

    NOTE: During the preparation and injection of the drug, investigators, ancillary staff and subjects should refrain from talking. If talking becomes absolutely necessary, the investigator

should face away from the bare needle and the injection site to avoid contamination of the needle and injection site. Wearing a mask during the preparation and injection of the drug is optional.

1st Injection (avacincaptad pegol 2 mg/eye or Sham)

If the Subject is Randomized to Receive avacincaptad pegol 2mg (0.10 mL injection volume):

a. Use sterile gloves during preparation and administration of the injectable drug.

b. Using aseptic technique, 0.2 mL of the avacincaptad pegol injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to a 1-mL sterile syringe (supplied). Care should be taken to aim the filter needle toward the center of the vial. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with the sterile 30-gauge needle (supplied) for the intravitreal injection. The contents and any air bubbles should be expelled until the plunger tip is aligned with the line that **marks 0.10 mL on the syringe for avacincaptad pegol 2mg.**

c. Insert the drug into the vitreous cavity pointing toward the optic nerve via the pars plana. Once the needle is in place, continuous pressure should be applied to the syringe for approximately 10 seconds to assure slow, even delivery of all drug.

d. As the needle is withdrawn, a sterile cotton tip applicator should be rolled over the entry site to minimize the risk of drug reflux. This should be held in place for a full 10 seconds.

e. The eye can then be irrigated as per the typical practice pattern of the investigator to minimize irritation from the aseptic procedure.

f. Two drops of single use antibiotic may be placed over the injection site at the end of the injection procedure at the discretion of the investigator. This same antibiotic may then be used four times daily for 3 days following the injection at the discretion of the investigator.

g. One to two minutes following the intravitreal injection, subjects should be examined with indirect ophthalmoscopy to assure that the optic nerve is perfused, the retina is attached and there is no new intraocular hemorrhage.

h. **If a second injection is to be administered, the second injection may NOT be administered until the IOP is ≤ 21 mmHg or within 5 mmHg of the baseline IOP on the day of injection.** If the IOP is **not** ≤ 21 mmHg or within 5 mmHg of the baseline IOP, the IOP should continue to be monitored until it is ≤ 21 mmHg or within 5 mmHg of the baseline IOP (record IOP at this time) before proceeding to the second injection.

i. If there is no second injection, the IOP should be measured and recorded 30 minutes after the intravitreal injection is administered. Monitor the IOP until it is below 30 mmHg; the subject should not be discharged until at least 30 minutes after the 1st injection and the IOP is below 30 mmHg or at a lower level as determined by the investigator.

If the Subject is Randomized to Receive Sham:

a. Use sterile gloves during preparation of the empty syringe and during the simulated injection.

b. Use the sterile empty syringe **without** an attached needle.

c. Use the blunt opening of the syringe barrel to indent the conjunctiva in the inferotemporal quadrant to simulate the pressure on the eyeball of an injection.

Note: This procedure should be performed in a manner so that the subject is not aware that the syringe has no needle, and that the globe is not being penetrated (i.e. the subject should be instructed to look away).

d. The eye can then be irrigated as per the typical practice pattern of the investigator to minimize irritation from the aseptic procedure.

e. One to two minutes following the Sham injection, subjects should be examined with indirect ophthalmoscopy to assure that the optic nerve is perfused, the retina is attached and there is no new intraocular hemorrhage.

f. **If a second injection is to be administered, the second injection may NOT be administered until the IOP is ≤ 21 mmHg or within 5 mmHg of the**

Baseline IOP on the day of injection. If the IOP is **not** ≤ 21 mmHg or within 5 mmHg of the baseline IOP, the IOP should continue to be monitored until it is ≤ 21 mmHg or within 5 mmHg of the baseline IOP (record IOP at this time) before proceeding to the second injection.

g. If there is no second injection, the IOP should be measured and recorded 30 minutes after the intravitreal injection is administered. Monitor the IOP until it is below 30 mmHg; the subject should not be discharged until at least 30 minutes after the 1st injection and the IOP is below 30 mmHg or at a lower level as determined by the investigator.

2nd Injection (avacincaptad pegol 2 mg/eye or Sham) (if regimen includes a second injection)

Prepare the eye for the 2nd injection. Repeat the injection preparation steps 3) through 8) above. For convenience, the steps are repeated here:

3) Injection preparation (for the following, new povidone-iodine bottles must be used and cannot be shared between subjects):

   a. Apply single use topical anesthetic drop(s) to the eye.

   b. Apply 2-3 drops of povidone-iodine to the injection site.

   c. OPTIONAL: Apply 2-3 drops of povidone-iodine to the lower fornix and/or use sterile cotton-tipped applicators soaked in 5% or 10% povidone-iodine to swab the upper and lower eyelid margins and the upper and lower eyelashes.

4) Place a sterile eyelid speculum to stabilize the eyelids.

5) Consider additional anesthesia with the application of one or two cotton-tipped applicators soaked in topical anesthetic over the intended injection site for at least 30 seconds. Subconjunctival anesthesia (0.5 mL of 2% xylocaine without epinephrine subconjunctivally at the intended injection site) can be used if the investigator believes that topical anesthetic is not sufficient to minimize discomfort. Lidocaine gel is not recommended.

6) Encourage the study participant to look superonasally (if injection site is inferotemporal) during the application of the povidone-iodine. Apply one of the

following to the conjunctiva directly over and surrounding the intended injection site:

a. A cotton-tipped applicator soaked in 5% or 10% povidone-iodine.

b. A 10% povidone-iodine swabstick.

c. At least 1-3 drops of 5% povidone-iodine (at least enough to cover the intended injection site).

7) Allow 30-60 seconds for the povidone-iodine to be in contact with the injection site before injection.

NOTE: As indicated above, injection preparation must include the use of povidone-iodine either applied directly to the injection site using topical drops, a cotton-tipped applicator, or a swabstick. If a study participant experiences an adverse reaction to povidone-iodine, other approaches to limit the exposure of povidone-iodine may be permitted. However, **a study participant may not receive a study intravitreal injection without use of povidone-iodine directly to the injection site just prior to the injection.**

8) Sterilized calipers should be used to measure the injection site. The entry site of the needle for the intravitreous injection should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic subjects, and 3.5-4.0 mm in phakic subjects.

NOTE: During the preparation and injection of the drug, investigators, ancillary staff and subjects should refrain from talking. If talking becomes absolutely necessary, the investigator should face away from the bare needle and the injection site to avoid contamination of the needle and injection site. Wearing a mask during the preparation and injection of the drug is optional.

If the Subject is Randomized to Receive avacincaptad pegol 2 mg (0.10 mL injection volume):

a. Use sterile gloves during preparation and administration of the injectable drug.

b. Using aseptic technique, 0.2 mL of the avacincaptad pegol injection vial contents are withdrawn through a 5-micron 19-gauge filter needle attached to

a 1-mL sterile syringe (supplied). Care should be taken to aim the filter needle toward the center of the vial. The filter needle should be discarded after withdrawal of the vial contents and should not be used for intravitreal injection. The filter needle should be replaced with the sterile 30-gauge needle (supplied) for the intravitreal injection. The contents and any air bubbles should be expelled until the plunger tip is aligned with the line that **marks 0.10 mL** on the syringe.

c. Insert the drug into the vitreous cavity pointing toward the optic nerve via the pars plana. Once the needle is in place, continuous pressure should be applied to the syringe for approximately 10 seconds to assure slow, even delivery of all drug.

d. As the needle is withdrawn, a sterile cotton tip applicator should be rolled over the entry site to minimize the risk of drug reflux. This should be held in place for a full 10 seconds.

e. The eye can then be irrigated as per the typical practice pattern of the investigator to minimize irritation from the aseptic procedure.

f. Two drops of single use antibiotic may be placed over the injection site at the end of the injection procedure at the discretion of the investigator. This same antibiotic may then be used four times daily for 3 days following the injection at the discretion of the investigator.

g. One to two minutes following the intravitreal injection, subjects should be examined with indirect ophthalmoscopy to assure that the optic nerve is perfused, the retina is attached and there is no new intraocular hemorrhage.

h. The IOP should be measured and recorded <u>30 minutes</u> after the 2nd injection is administered. Monitor the IOP until it is below 30 mmHg; the subject should not be discharged until at least 30 minutes after the 2nd injection and the IOP is below 30 mmHg or at a lower level as determined by the investigator.

If the Subject is Randomized to Receive Sham:

a. Use sterile gloves during preparation of the empty syringe and during the simulated injection.

b. Use the sterile empty syringe **without** an attached needle.

c. Use the blunt opening of the syringe barrel to indent the conjunctiva in the inferotemporal quadrant to simulate the pressure on the eyeball of an injection.

Note: This procedure should be performed in a manner so that the subject is not aware that the syringe has no needle, and that the globe is not being penetrated (i.e. the subject should be instructed to look away).

d. The eye can then be irrigated as per the typical practice pattern of the investigator to minimize irritation from the aseptic procedure.

e. One to two minutes following the Sham injection, subjects should be examined with indirect ophthalmoscopy to assure that the optic nerve is perfused, the retina is attached and there is no new intraocular hemorrhage.

f. The IOP should be measured and recorded 30 minutes after the Sham injection is administered. Monitor the IOP until it is below 30 mmHg; the subject should not be discharged until at least 30 minutes after the 2nd injection (Sham) and the IOP is below 30 mmHg or at a lower level as determined by the investigator.

After All Injections (including Sham injections)

1) One to two minutes following each intravitreal injection, subjects should be examined by ophthalmoscopy to verify reperfusion of the central retinal artery in the immediate post-injection period. Verify that the retina is attached and that there is no new intraocular hemorrhage.

2) After each intravitreal injection (including Sham), check the intraocular pressure (IOP) while maintaining a clean field.

    a. If a second injection is to be administered, monitor the IOP after the 1st injection until it is **≤ 21 mm Hg or within 5 mm Hg of the baseline IOP on the day of injection;** record the IOP at this time.

b. The IOP should be measured and recorded 30 minutes after the last injection (whether it is the first or second injection). Monitor the IOP until it is below 30 mmHg; the subject should not be discharged until at least 30 minutes after the 2nd injection and the IOP is below 30 mmHg or at a lower level as determined by the investigator.

c. If a Tono-Pen is used to check pressure, a clean Tono-Pen condom should be placed on the tip before taking each measurement. If applanation tonometry is used, the applanator tip should be swabbed with alcohol and let to dry before using it to measure IOP. Sterile fluorescein strips and single use proparacaine bottles should be used for all subjects. "Fluoracaine" or other combination fluorescein sodium and proparacaine HCl mixtures should only be used if single use presentation is available, and then only if single use bottles are available. Intraocular pressure may be lowered by pharmaceutical or surgical intervention, if required. Treatment should be initiated whenever IOP is increased to the extent that the central retinal artery remains closed and the subject has NLP for more than 1-2 minutes or as per investigator judgment. Transient graying or obscuration of vision following injection, however, is expected and should not be treated. See below for additional information concerning paracentesis.

3) No special precautions are required before discharge of a subject who has had an uneventful recovery from the intravitreal injection(s), but subjects and/or caregivers should be educated to avoid rubbing the eye and to recognize the signs and symptoms of endophthalmitis, retinal detachment and intraocular hemorrhage, including eye pain or increased discomfort, increased redness of the eye (compared to immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light. Subjects should be informed that some blurring of vision is common post-injection, which is often described as seeing spots floating in the eye. Subjects who experience post-injection AEs that require additional monitoring should remain in the clinic for longer than 30 minutes, and treated according to the investigator's medical judgment.

Instructions Regarding Paracentesis:

Paracentesis should be used **only** in extreme circumstances when the degree of

pressure elevation poses an imminent and irreversible threat to vision. In the rare situation when a paracentesis is warranted, the IOP should be recorded both before and after the procedure. Apply single use topical anesthetic drop(s) to the eye. Use a new pair of sterile gloves. Place a sterile lid speculum to open the eye lids. Apply 2-3 drops of povidone-iodine to the paracentesis site, and allow 30-60 seconds for the povidone-iodine to be in contact with the paracentesis site. A 0.1 mL paracentesis is performed at the temporal limbus using a 27-gauge or 30-gauge needle by the investigator. Antibiotic eye drops are applied per discretion of the investigator. Record pre- and post-paracentesis IOP measurements in the source document and on the appropriate CRF page.

NOTE: A paracentesis **MAY NOT** be performed ***prior*** to injection of the intravitreous drug.

17.5 NYHA Functional Classifications

Class	Subject Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.