AN OPEN-LABEL EXTENSION (OLE) PHASE 3 TRIAL TO ASSESS THE SAFETY OF INTRAVITREAL ADMINISTRATION OF AVACINCAPTAD PEGOL (COMPLEMENT C5 INHIBITOR) IN PATIENTS WITH GEOGRAPHIC ATROPHY WHO PREVIOUSLY COMPLETED PHASE 3 STUDY ISEE2008 (GATHER2)

PROTOCOL NO: ISEE2009

(GATHER2 OLE)

Amendment 01

Version Date: 27 Feb 2024

SPONSOR:
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FOR MEDICAL EMERGENCIES REFER TO THE "SAFETY CONTACT LIST" PROVIDED SEPARATELY

Regulatory Agency Identifier Number(s):

Registry	ID
IND	77,902
EudraCT	2022-002860-59

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1 GLOSSARY OF ABBREVIATIONS

ADA	anti-drug antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
C3	Cleavage of Complement 3
CF	Count fingers
CI	Confidence Interval
CFP	Color fundus photography
CFR	Code of Federal Regulations
CNV	Choroidal Neovascularization
CRA	Central Retinal Artery
CRF	Case Report Form
CSR	Clinical Study Report
EC	Ethics Committee
EOS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
EW	Early Withdrawal
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FE	Fellow Eye
FSH	Follicle-stimulating Hormone
GA	Geographic Atrophy
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
IV	intravenous
IVT	Intravitreous
LLVA	low luminance best correct visual acuity
MAC	Membrane attack complex
NF	National Formulary
OCT	Optical Coherence Tomography
OLE	Open-label Extension
OU	Both Eyes
PEG	Polyethylene glycol
PK	Pharmacokinetic

RC	Reading Center
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral-Domain Optical Coherence Tomography
SE	Study Eye
US	United States
USP	United States Pharmacopeia
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

2 SYNOPSIS OF PROTOCOL ISEE2009

SYNOPSIS	
TITLE:	An Open-label Extension (OLE) Phase 3 Trial to Assess the Safety of Intravitreal Administration of avacincaptad pegol (Complement C5 Inhibitor) in Patients with Geographic Atrophy Who Previously Completed Phase 3 Study ISEE2008 (GATHER2)
OBJECTIVES:	The objectives of this trial are to assess long-term safety of avacincaptad pegol intravitreal administration for patients with geographic atrophy (GA) who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham).
TRIAL DESIGN:	Approximately 280 patients who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham) and consent to participate will be administered monthly avacincaptad pegol 2 mg from Month 1 through Month 17 (maximum 17 total doses). All patients will have a final follow up visit at Month 18 or if the study is terminated early, Month 18 final follow up procedures will be followed. Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/ Ethics Committee (EC), or at the discretion of Astellas.
ENDPOINTS:	Primary Endpoint: • Adverse events (AEs) Secondary Endpoints: • Immunogenicity • Pharmacokinetics Exploratory Endpoints: • Ophthalmic findings (best corrected visual acuity [BCVA], low luminance visual acuity [LLVA], intraocular pressure [IOP], and ophthalmic examination)
PLANNED SAMPLE SIZE:	Approximately 280 patients will be enrolled. This is based on the number of currently enrolled patients in Study ISEE2008 (GATHER2) who will have completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham).

SYNOPSIS	
SUBJECT SELECTION:	Male or female patients aged 50 years or greater diagnosed with GA inside and/or outside of the fovea who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment, regardless of whether they received treatment with avacincaptad pegol or Sham previously.
FORMULATION:	Avacincaptad pegol is formulated at a concentration of 20 mg/mL (oligonucleotide mass) in phosphate buffered saline as a sterile aqueous solution and will be supplied in a sealed vial by the Sponsor. The product is preservative -free and intended for intravitreous injection only. The product should not be used if cloudy or if particles are present. The 2 mg dose will have a total injection volume of 0.1 mL (100 µL).
INVESTIGATIONAL DRUG DOSAGE:	Patients will receive a maximum 17 doses (1 dose/month) of avacincaptad pegol at a dose of 2 mg (100 µL injection volume).
STUDY SITES	All study sites participating with active patients in the ISEE2008 trial will be used for this ISEE2009 OLE trial.
STATISTICAL METHODS	The sample size is estimated based on the number of ISEE2008 patients that completed the study through the ISEE2008 Month 24 visit ("ISEE2008 completers") and the expected number of eligible ISEE2008 completers willing to participate in the ISEE2009 study. Data will be summarized using descriptive statistics or listed. No statistical inference will be made.

3 STUDY ASSESSMENTS

Assessments	M1[a]	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18/EOS (EW)
Informed Consent	X[b]																	
Refraction and ETDRS BCVA[c,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LLVA[c]	X					X						X						X
Tonometry[c,d,e]/Ophthalmologic Examination[c,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography[c]	X					X						X						X
Fluorescein Angiography[c]												X						X
Optical Coherence Tomography[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus Autofluorescence[c]	X					X						X						X
Urine Pregnancy (If Applicable)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity Sampling[h]	X[i]	X		X			X						X					X
PK Sampling[h]	X[i]	X		X			X						X					X
Avacincaptad pegol 2 mg Administration	X	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	X
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BCVA = best corrected visual acuity; EOS = end of study; ETDRS = Early Treatment Diabetic Retinopathy Study; EW = early withdrawal; IOP = intraocular pressure; LLVA = low luminance visual acuity; M = month; OLE = open-label extension; OU = both eyes; PK = pharmacokinetic; SE = study eye.
Refer to Section 10.2 Trial Assessments for additional details on assessments.
[a]Enrollment into this OLE trial must be within 90 days of the patient's Month 24 visit in Study ISEE2008.
[b]Informed consent must be signed before any other assessments are performed at Month 1 in this OLE trial.
[c]Ocular assessments are to be performed on both eyes (OU) pre-injection (as applicable) at Month 12 and Month 18/EOS (EW). Ocular assessments at all other trial visits are performed only on the study eye (SE). Refer to Appendix 17.1 for details on procedures for refraction and vision testing.
[d]Goldmann applanation tonometry must be performed at Month 12 and Month 18/EOS (EW), pre- and post-injection (as applicable). The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must also be used to verify intraocular pressure (IOP) reading of ≥ 30 mmHg occurring at any time.
[e]Tonometry should be measured prior to the injection and at least 30 minutes after the injection as per Section 10, Trial Conduct.
[f]A full ophthalmic examination is performed prior to the injection and again at least 30 minutes after the injection. An abbreviated exam assessing Gross Visual Function and Direct Visualization, to ensure the health of the eye post-injection, will be performed 0 to 5 minutes and again at least 30 minutes after injection.
[g]Urine Pregnancy Test will be done at each monthly visit for any female subject of childbearing potential.
[h]Blood samples will be collected prior to avacincaptad pegol administration and analyzed using validated methods. Two blood samples should be collected at each timepoint indicated (one for primary analysis and one for back-up).
[i]Blood samples taken at Month 1 will be considered baseline samples for patients crossing over from Sham to avacincaptad pegol (i.e., drug-free baseline).
[j]Adverse events are to be recorded starting after the first dose of study drug.
[k]BCVA is required at the indicated visits and at any other timepoints in the event of an ocular AE in the study eye.
VISIT WINDOWS: It is essential that patients adhere to their prescheduled trial visits within the visit window as per Section 10, Trial Conduct. Monthly doses will be administered at least 21 days apart.

4 INTRODUCTION

4.1 GA Disease State Overview

Geographic atrophy (GA) is a progressive disease characterized by, irreversible, and severe loss of functional vision, with a potential loss on average of 22 letters over 5 years, that ultimately leads to blindness. GA is associated with a major impact on functional vision, quality of life, and independence (Boyer 2017, Mitchell 2018). GA occurs during the late stage of dry age-related macular degeneration (AMD) and is the most prevalent form of AMD in the general population, accounting for 85% to 90% of AMD cases (Miller 2017). GA may also affect patients with the wet (neovascular) form of AMD, even after treatment with anti-vascular endothelial growth factor (VEGF) agents, so that development or progression of GA over time contributes significantly to vision loss in patients with AMD (Bhisitkul 2015, Abdelfattah 2016, Grunwald 2017). Once GA advances to cover the foveal center, vision loss is rapidly accelerated (Brown 2005, Bagheri 2019).

GA causes progressive and irreversible loss of retinal tissue (photoreceptors, retinal pigment epithelium [RPE], and choriocapillaris) leading to a loss of visual function over time (Lindner 2019, Lindblad 2009, Bonilha 2008, Sunness 1999). Globally, approximately 5 million people have GA, with approximately 1 million patients living in the United States (Wong 2014, Chakravarthy 2018, Rudnicka 2012). The prevalence of GA increases exponentially with age and approximately quadruples per decade beyond 50 years (Rudnicka 2012). GA is typically a condition with about half of patients developing GA in both eyes within 7 years of initial diagnosis (Boyer 2017, Lindblad 2009).

The chronic nature of GA leads to loss of visual function. This often results in difficulties performing daily tasks including reading, driving, face recognition, and ultimately, severe detriment on independence (Brown 2014, DeCarlo 2003). Initially, patients may present with adequate visual acuity (VA) if GA lesions are not involved in the central macular or foveal region of the retina (Sadda 2016, Lindner 2015) and standard vision tests can underrepresent the visual deficit experienced by GA patients (Sunness 1996). Reading speed is often initially unaffected due to foveal sparing but worsens progressively as the area of atrophy enlarges (Kunzel 2021, Lindner 2019, Sunness 2008). As the disease progresses, vision-related quality of life declines markedly and patients become at higher risk for developing advanced wet AMD (Kunzel 2020).

GA is quantified in terms of the area of RPE atrophy and can be observed clinically by slit-lamp biomicroscopy (Fleckenstein 2018). It is documented using multiple imaging modalities, with

the most common being a combination of color fundus photography (CFP), fundus autofluorescence (FAF) imaging, and optical coherence tomography (OCT) (Shi 2021, Pfau 2017, Schmitz-Valckenberg 2011). GA presents as sharply demarcated atrophic lesions at the macula secondary to the loss of photoreceptors, RPE, and choriocapillaris (Fleckenstein 2018). The atrophic lesions tend to arise in the perifoveal regions initially, preserving the fovea ('foveal sparing') before these lesions expand and coalesce over time to affect the fovea (Fleckenstein 2018). Recent data suggest that photoreceptor degeneration is not limited to the area of RPE atrophy but extends beyond this area. These more subtle changes can be quantified by volumetric analyses of OCT data (Pfau 2020b, Reiter 2020).

The pathogenesis of GA is not fully understood and is likely multifactorial, triggered by intrinsic and extrinsic stressors of a poorly regenerative RPE including oxidative stress (caused by the high metabolic demand of photoreceptors), photo-oxidation, and environmental stressors (e.g., cigarette smoke) (Pfau 2020b). Variations in several genes, particularly in the complement system, have been implicated in the development of GA (Pfau 2020a). The current hypothesis is that with aging, damage caused by stressors accumulates, which coupled with a genetic predisposition, results in the appearance of drusen and lipofuscin deposits. These and other products of oxidative stress then trigger inflammation via multiple pathways, particularly the complement cascade, leading to loss of photoreceptors, RPE, and choriocapillaris, culminating in atrophic lesions that spread over time (Abdelfattah 2016, Holz 2014).

The rate of progression of GA is highly variable, ranging from 0.53 to 2.6 mm^2/year depending on the technology used to evaluate GA and various patient-related prognostic factors, including larger baseline lesion size, presence of multifocal lesions, specific autofluorescence patterns, and parafoveal atrophic lesions (Fleckenstein 2018, Lindblad 2009, Sunness 2008, Holz 2007). The median time for parafoveal GA to expand into the fovea was determined as ~2.5 years (Lindblad 2009). In an observational study, 53% of GA participants (initially not involving the fovea) suffered a 3-line loss of VA by 4 years.

4.1.1 Role of Complement in GA

The complement pathway and C5 have been identified as important mediators of inflammation (Brandstetter 2015) with complement proteins identified in the subretinal drusen deposits characteristic of GA (Hageman 2001, Cao 2016).

The complement cascades result in generation of complement C5 convertase which cleaves complement C5 into C5a and C5b, the main terminal effector components of the complement cascade, leading to cell death (Holers 2014). Physiologically, C5a is involved in inflammasome priming and activation leading to pyroptosis, a rapid inflammatory form of lytic programmed cell

death (Brandstetter 2015), and C5b leads to the generation and accumulation of membrane attack complex (MAC; C5b-9) of targeted cell membranes, also leading to cell death (Holers 2014).

4.1.2 Unmet Medical Need

Given the long-term natural history of GA, there is a substantial medical need for new therapies that target the underlying cause of disease, alter its progression, and preserve the anatomical architecture needed for visual function While there have been longstanding, established anti-VEGF treatments for wet AMD, the absence of or limited availability of treatment options for GA represents a major public health concern and unmet medical need for the rapidly growing aging population (Brown 2006, Rosenfeld 2006, Heier 2012, Martin 2012, Boyer 2017).

4.2 Avacincaptad Pegol (ARC1905)

Avacincaptad pegol is a polyethylene glycol (PEG)-conjugated single-stranded RNA aptamer. It is a potent and specific inhibitor of complement activation that acts by binding to human complement factor 5 with high affinity (KD = 0.69 ± 0.148 nM at 37°C) and specificity. It consists of a 12,882 Da modified nucleotide aptamer that is conjugated at the 5’ terminus to a ~43 kDa branched PEG moiety. The aptamer portion of avacincaptad pegol is 39 nucleotides in length and modified with a primary amine at the 5’ terminus to provide a reactive site for site-specific conjugation (“PEGylation”). The nucleotide composition consists of purine ribonucleotides and modified 2'-fluoro pyrimidines and 2’ methoxy purines. The modified nucleotides minimize susceptibility to endonuclease digestion. The 3’ terminus is capped with an (“inverted”) 3’-3’ phosphodiester linkage to a deoxythymidine nucleotide to maximize resistance to 3’-exonuclease degradation. PEGylation is employed to improve residence time in vivo. All concentrations and doses for avacincaptad pegol (20 mg/mL = 1.55 mM) are based on the mass of the aptamer, exclusive of the PEG mass.

Avacincaptad pegol inhibits C5 and prevents the formation of key terminal fragments (C5a and C5b-9), regardless of which initial activation pathway (classical, alternative, or lectin) is induced in their generation. By inhibiting these C5-mediated inflammatory and MAC activities, avacincaptad pegol provides a therapeutic approach to treat GA by preserving the anatomical architecture needed for visual function and preventing the loss of photoreceptors and disease progression inside and outside the fovea. Despite complete inhibition of C5 activation, avacincaptad pegol does not inhibit cleavage of complement 3 (C3) to C3a and C3b, the latter of which is an important component of host defense mechanisms. Thus, the beneficial effects of the complement pathway, such as host defenses against pathogens, can be maintained.

4.3 Nonclinical Development Program

A battery of nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies were conducted for avacincaptad pegol. The primary pharmacology studies included binding assays, complement activity inhibition assays, and radioligand binding assays. Safety pharmacology studies included in vitro human ether-à-go-go channel electrophysiology and toxicology assessments in cynomolgus monkeys. Investigations of ocular and systemic disposition, as well as chronic toxicity studies, have been performed in rabbits and dogs following intravitreal (IVT) administration of avacincaptad pegol. There have been no findings in nonclinical studies that would preclude the further development of avacincaptad pegol. Specifically, these nonclinical studies demonstrate that avacincaptad pegol has high selectivity and specificity for inhibition of complement activation at the C5 activation step without affecting other host defense mechanisms. Because avacincaptad pegol is delivered via IVT injection, systemic levels following slow egress out of the vitreous cavity are very low, in the nanogram per milliliter range, and hence, the inhibition of C5 is likely limited to the eye. Clinical and nonclinical PK data have confirmed that avacincaptad pegol migrates slowly out of the eye compartment and is associated with very low plasma levels. These systemic concentration levels appear to remain below levels that would be of any toxicological concern as evidenced by the repeat dose toxicology study results. Additionally, avacincaptad pegol shows no deleterious effects with long-term dosing and has not demonstrated concerns for genetic toxicity.

An overview of these extensive studies is presented in the current Investigator Brochure.

The Sponsor notes that initially the development program for avacincaptad pegol was intended for other routes of administration, hence the numerous studies using the intravenous (IV) route of administration than typical for an IVT administered therapy.

4.4 Completed and Ongoing Clinical Trials

A summary of completed and ongoing intravitreal avacincaptad pegol clinical trials is presented below with additional information described in the IB.

Protocol Number[a]	Status (Date)	Study Design	Phase of Study	Objectives	Total Subjects Enrolled and/or Planned	Dose (N)	Study Duration
OPH2000	Completed (final CSR on 27 Jun 2011)	OL, PG, MD, CWA	Phase 1	Safety, tolerability, and PK in nAMD subjects	60 subjects	ARC1905 0.03 mg (N=3) ARC1905 0.3 mg (N=19) ARC1905 1 mg (N=16) ARC1905 2 mg (N=15) ARC1905 3/1 mg[b] (N=7)	3 to 6 months
OPH2001	Completed (final CSR on 26 Jul 2018)	OL, MD	Phase 1	Safety and tolerability in GA AMD	47 subjects	ARC1905 0.3 mg (N=24) ARC1905 1 mg (N=23)	12 months
OPH2002	Completed (final CSR on 05 Oct 2018)	OL, MD, CWA	Phase 2a	Safety and tolerability in IPCV subjects	4 subjects	ARC1905 1 mg (N=4)	3 months
OPH2003	Completed (final CSR on 25 Feb 2022)	R, MC, DM, SC, MD	Phase 2/3	Efficacy and safety in GA AMD subjects	286 subjects	ARC1905 1 mg (N=26) ARC1905 2 mg (N=25) Sham (N=26) ARC1905 2 mg + Sham (N=42) ARC1905 4 mg (2 mg + 2 mg) (N=83) Sham + Sham (N=84)	18 months
OPH2004	Completed (final CSR on 07 Mar 2022)	OL, MD, CWA	Phase 2a	Safety and tolerability in nAMD subjects	1 subject	ARC1905 2 mg (N=1)	18 months

Protocol Number[a]	Status (Date)	Study Design	Phase of Study	Objectives	Total Subjects Enrolled and/or Planned	Dose (N)	Study Duration
OPH2005	Ongoing	R, MC, DM, SC, MD	Phase 2b	Efficacy and safety in patients with Stargardt Disease	121 subjects	ARC1905 (N=60) Induction Phase: ARC1905 2 mg Maintenance Phase: ARC1905 4 mg/eye (2 mg + 2 mg) Sham (N=61) Induction Phase: Sham Maintenance Phase: Sham + Sham	18 months
OPH2007	Completed (final CSR on 10 Jul 2020)	OL MC, MD, CWA	Phase 2a	Safety and tolerability in nAMD subjects	65 subjects	Cohort 1 (N=10): Lucentis® 0.5 mg + ARC1905 4 mg (2 mg + 2 mg); Cohort 2 (N=11): Lucentis® 0.5 mg + ARC1905 2 mg Cohort 3 (n=22): Induction Phase: D0, Lucentis® 0.5 mg + ARC1905 2 mg; D14, ARC1905 2 mg Maintenance Phase: Lucentis® 0.5 mg + ARC1905 2 mg Cohort 4 (n=22): Induction Phase: D0, Lucentis® 0.5 mg + ARC1905 2 mg; D14, ARC1905 2 mg Maintenance Phase: D0, ARC1905 2 mg; D2, Lucentis® 0.5 mg + ARC1905 2 mg	6 months
ISEE2008	Completed (final CSR on 06 Dec 2023)	R, MC, DM, SC, MD	Phase 3	Efficacy and safety in GA AMD subjects	448[c] subjects	ARC1905 2 mg (N=225) Sham (N=222)	24 months

AMD=age-related macular degeneration; CSR=clinical study report; CWA=combined with anti-VEGF therapy; DM=double-masked; GA=geographic atrophy; IPCV=idiopathic polypoidal choroidal vasculopathy; MC= Multicenter; MD=multidose; nAMD=neovascular AMD; NDA=new drug application; OL=open-label; PG=Parallel Group; PK=pharmacokinetic; R=randomized; SC=Sham-controlled.

Note: ARC1905 is interchangeable with the name avacincaptad pegol for the purposes of this table.

[a]All studies listed in this table are to be included in NDA.

[b]Due to a drug stability matter with the 3 mg/eye dose, subjects in Part 1 originally assigned to 3 mg/eye have been transitioned to the 1 mg/eye dose under Amendment D.

[c]447 subjects enrolled and treated; 1 subject randomized to the Sham group never received treatment.

4.5 Trial Rationale

In the first pivotal trial (Study OPH2003 [GATHER1]), the primary endpoint was GA measured by FAF at 3 time points: Baseline, Month 6, and Month 12. At Month 12, the primary efficacy objective was met. The mean rate of GA lesion growth in the avacincaptad pegol 2 mg dose group was 0.697 mm^2 per year (95% confidence interval [CI] = 0.204; 1.190) less than that of the Sham control group (p-value = 0.0059). The avacincaptad pegol treatment effect on GA growth was evident at first evaluation time (Month 6) with patients in the avacincaptad pegol 2 mg dose group, whose GA on average grew 0.323 mm^2 (95% CI = 0.068; 0.579) less than that of the GA lesions in the Sham group. The treatment differences between the avacincaptad pegol groups compared to the corresponding Sham group were maintained through the last evaluation time (Month 18), with patients in the avacincaptad pegol 2 mg dose group whose GA on average grew 1.156 mm^2 (95% CI = 0.480;1.833) less than that of the GA lesions in the Sham group. The most frequently reported ocular adverse events (AEs) with avacincaptad pegol were related to the injection procedure.

Study ISEE2008 (GATHER2), the second pivotal trial, was a 24-month study and the primary endpoint was GA measured by FAF in at least three timepoints: Baseline, Month 6 and Month 12. At Month 12, the primary efficacy objective was met. The average GA lesion growth of patients in the avacincaptad pegol 2 mg group was 0.376 mm^2 per year (95% CI = 0.122; 0.631) less than that of the GA lesions in the Sham group (p-value = 0.0039). Study ISEE2008 has completed data analysis. At Month 24, a statistically significant difference of 0.362 mm^2/year (95% confidence interval [CI] = 0.066; 0.657) in the mean GA growth rate was demonstrated in favor of avacincaptad pegol 2 mg every month treated group compared to sham (p = 0.0165).

The primary endpoint in both OPH2003 and ISEE2008 as measured by FAF, is reflective of loss of photoreceptors and disease progression inside and outside the fovea. As of this protocol's effective date, there are two FDA approved treatments available for patients with GA secondary to AMD, each expressing a unique benefit risk profile. IZERVAY™ (avacincaptad pegol intravitreal solution) is one of the available treatment options in the US, approved by the FDA on August 4, 2023. The limited availability or absence of treatment options for GA represents a major public health concern for the rapidly increasing aging population.

This open-label extension (OLE) trial will continue to assess the long-term safety of monthly intravitreal administration of avacincaptad pegol 2 mg, while continuing to allow patients with GA, who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham), access to avacincaptad pegol treatment.

4.6 Benefit/Risk Assessment

The safety and efficacy of avacincaptad pegol were demonstrated in two pivotal randomized, multi-center, double-masked, sham-controlled, 18- and 24-month studies (OPH2003 [GATHER1] and ISEE2008 [GATHER2], respectively) in patients with GA secondary to AMD. A total of 733 patients were treated in these studies. Patient ages ranged from 51 to 97 years with a mean of 77 years. In total 26, 292, and 83 patients were treated with avacincaptad pegol 1 mg, 2 mg, and 4 mg respectively, and 332 patients received sham.

The most frequently reported Treatment Emergent Adverse Events (TEAEs) in those participants receiving avacincaptad pegol 2 mg in the pivotal clinical studies OPH2003 and ISEE2008 were related to injection procedure. The most common adverse reactions (≥ 5% and greater than sham) reported up to 12 months were conjunctival hemorrhage (13%), increased IOP (9%), and Choroidal Neovascularization (CNV; 7%).

Both Study OPH2003 and Study ISEE2008 demonstrated robust statistical superiority of avacincaptad pegol over sham, through a substantial reduction in GA lesion growth, after one year of treatment. In both pivotal studies, avacincaptad pegol was shown to elicit a treatment effect by Month 6 that was persistent and continued to increase over time as measured by the absolute difference of GA growth between intervention groups.

The consistent safety and efficacy results from two independent, randomized, adequately well-controlled studies in patients with GA secondary to AMD support a favorable benefit/risk profile of avacincaptad pegol 2 mg for treatment in patients with GA secondary to AMD, a serious progressive disease that leads to irreversible blindness, especially in an increased aging population with limited, or no effective and safe treatment options available.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of avacincaptad pegol can be found in the IB.

Adherence to eligibility criteria and study assessments may minimize potential risks to study participants. The safety of study participants will be monitored by the sponsor through remote data review and will be facilitated by timely entry of clinical data into the electronic data capture system (EDC) and reporting of serious adverse events (SAEs) by the investigator during study conduct.

5 TRIAL OBJECTIVES

5.1 Objectives

The objectives of this trial are to assess long-term safety of avacincaptad pegol monthly intravitreal administration for patients with GA who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham).

5.2 Endpoints

Primary Endpoint:

- AEs

Secondary Endpoints:

- Immunogenicity
- Pharmacokinetics

Exploratory Endpoints:

- Ophthalmic variables
    - best corrected visual acuity (BCVA)
    - low luminance visual acuity (LLVA)
    - intraocular pressure (IOP)
    - ophthalmic examination

6 TRIAL DESIGN

This is an open-label, multicenter, 18-month extension study. Approximately 280 patients who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham) will be administered avacincaptad pegol 2 mg monthly from Month 1 through Month 17. All patients, regardless of treatment received in ISEE2008 (avacincaptad pegol or Sham), will receive avacincaptad pegol 2 mg monthly.

All patients will have a final follow up visit at Month 18 or if the study is terminated early, Month 18 final follow up procedures will be followed. The end of the study is defined as the date of the last study assessment (See Section 3) for the last subject in the study globally.

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the Institutional Review Board (IRB)/Ethics Committee (EC), or at the discretion of Astellas.

7 PROCEDURES

7.1 Refraction, Visual Acuity, and Low Luminance Visual Acuity

Refraction, Vision Testing, and Low Luminance Vision Testing will be performed at all time-points specified in Section 10.2 “Trial Assessments”. BCVA is also required at any other time-point in the event of an ocular AE in the study eye. Retro-illuminated modified Ferris-Bailey Early Treatment Diabetic Retinopathy Study (ETDRS) charts are used starting at 4 meters (see Appendix 17.1).

When refraction and ETDRS BCVA measurements are required by the trial protocol, these will be performed only by certified VA examiners with access to the previous VA measurement and the previous protocol refraction.

All necessary materials and instructions for these assessments will be provided by Astellas.

These assessments should always be performed in the following order: Refraction, ETDRS BCVA, and Low Luminance Visual Acuity.

7.2 Tonometry

Tonometry will be performed at all time-points specified in Section 10.2 “Trial Assessments”. The IOP should be measured and recorded pre-injection and at least 30 minutes after the injection and IOP must be < 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 Month 12 and Month 18/End of Study (EOS) or Early Withdrawal (EW), pre- and post-injection (as applicable). Tono-Pen may be used at all other timepoints. Goldmann applanation tonometry must also be used to verify IOP reading of ≥ 30 mmHg occurring at any time.

7.3 Ophthalmologic Examination

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

- Examination of the eyelids
- Examination of extra-ocular muscle movement
- Examination of the cornea
- Examination of the anterior chamber
- Examination of the pupils

- Examination of the iris
- Examination of the lens
- Examination of the vitreous body
- Examination of the retina and optic disc

7.4 Fundus Photography, Fluorescein Angiography, Fundus Autofluorescence, and Optical Coherence Tomography (SD-OCT)

Color stereoscopic fundus photographs, fluorescein angiography (FA), FAF, and spectral-domain optical coherence tomography (SD-OCT) will be performed at all time-points specified in Section 10.2 “Trial Assessments”.

All color fundus photos, FAs, FAFs, and SD-OCTs that are collected at protocol-specified time points must be sent to the reading center (RC) as specified in the RC procedure manual. The RC will provide instructions for the CFP, FA, FAF, and SD-OCT procedures.

7.5 Pregnancy Tests and Birth Control

A urine pregnancy test will be performed for women of childbearing potential prior to avacincaptad pegol intravitreal administration at the visits as indicated in Section 3, “Study Assessments”, and in Section 10.2 “Trial Assessments”.

For patients who are women of childbearing potential, the same protocol approved highly effective contraceptive method must be used for at least one month prior to study entry and during the trial until at least 90 days following the last dose of test medication. Protocol approved highly effective contraceptive methods are:

- Hormonal contraceptives (i.e., combined oral contraceptive, patch, vaginal ring, injectable, or implant),
- Intrauterine devices or intrauterine systems,
- Vasectomy, and/or tubal ligation,
- Abstinence, defined as refraining from heterosexual intercourse during the entire period of the study and until at least 90 days following the last dose of study medication if in accordance with usual lifestyle.

If the patient is a woman of childbearing potential, she must have no plans to donate ova during the duration of the trial and for at least 90 days following the last dose of test medication.

Non-childbearing potential is defined as follows:

- A woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
- A woman ≥ 60 years of age
- A woman ≥ 40 and < 60 years of age who fulfills at least one of the following:
    - A cessation of menses for at least 12 months and a follicle-stimulating hormone (FSH) test confirming non-childbearing potential (refer to laboratory reference ranges for confirmatory levels)
    - A cessation of menses for at least 24 months without FSH levels confirmed

Czech Republic, Poland, France, Italy: If the patient is male, he should use a condom and not donate sperm during the time of study drug exposure and for 90 days following the last exposure of study drug.

7.6 Immunogenicity

Assessments of anti-drug antibodies (ADA) will be performed at pre-dose at Month 1, Month 2, Month 4, Month 7, Month 13, and Month 18 as specified in Section 10.2 “Trial Assessments”. The pre-dose sample taken at Month 1 will be considered the serum sample taken prior to dosing of avacincaptad pegol for Sham patients crossing over to avacincaptad pegol to capture a drug-free baseline.

Two serum samples of 2 mL will be collected at each timepoint specified: one for primary analysis and one as a back-up.

The Sponsor may request ad-hoc ADA sampling in the event of an adverse drug reaction.

7.7 Pharmacokinetics

The concentration of avacincaptad pegol in K_2EDTA human plasma samples will be quantified using validated electrochemiluminescence dual hybridization assay and expressed in terms of ng/mL. Plasma PK samples will be collected at pre-dose at Month 1 (baseline), Month 2, Month 4, Month 7, Month 13, and Month 18 as specified in Section 10.2 “Trial Assessments” prior to administration of avacincaptad pegol in order to evaluate the effect of ADA on the plasma concentrations of avacincaptad pegol.

8 SUBJECT POPULATION

8.1 Sample Size

Approximately 280 patients will be enrolled.

8.2 Inclusion Criteria

Male or female patients aged 50 years or greater diagnosed with GA inside and/or outside of the fovea who completed Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment, regardless of whether they received treatment with avacincaptad pegol or Sham previously, refer to Section 8.2 of the ISEE2008 protocol for inclusion criteria details. Patients must provide new written informed consent for this OLE trial prior to participating and have the ability to return for all trial visits for the duration of the 18-month trial.

Information on the conduct of patients who are or are not women of childbearing potential and contraception usage in men and women is provided in Section 7.5.

8.3 Exclusion Criteria

Patients will ***not be eligible for the trial*** if:

1. Patient did not complete Study ISEE2008 (GATHER2) through the Month 24 visit on study treatment (either avacincaptad pegol or Sham),
2. Any patients who had the study drug permanently withdrawn for an AE are not eligible; patients who had study drug temporarily withheld for an AE(s) or elective ocular surgery will be reviewed on case by case basis for eligibility,
3. Patient did not enroll into this OLE trial within the 90 days enrollment period.
4. Patients who are pregnant or nursing

9 TRIAL MEDICATION

9.1 Drug Supply

9.1.1 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 PEG moiety. The aptamer portion of avacincaptad pegol is 39 nucleotides in length and modified to a primary amine at the 5' terminus to provide a reactive site for subsequent conjugation ("PEGylation"). The nucleotide composition consists of purine ribonucleotides and modified 2'-fluoro pyrimidines and 2'-methoxy purines. The modified nucleotides minimize minimize susceptibility to endonuclease disgestion. The 3' terminus is capped with an ("inverted") 3'-3' phosphodiester linkage to a deoxythymidine nucleotide to maximize resistance to 3'-exonuclease degradation. PEGylation is employed to improve residence time in vivo. 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 at pH 6.8 to 7.8 as a sterile aqueous solution and will be supplied in a sealed vial by the Sponsor. Sodium hydroxide or hydrochloric acid may have been added for pH adjustment. The product is a preservative-free clear solution and intended for intravitreous (IVT) injection only. The product should not be used if cloudy or if particles are present.

Avacincaptad pegol will be supplied in single use sterile glass vials for intravitreal injection.

Active ingredient:	avacincaptad pegol
Avacincaptad pegol is formulated as:	20 mg/mL solution for injection
Excipients:	Sodium Chloride, United States Pharmacopeia (USP) Sodium Phosphate Monobasic, Monohydrate, USP Sodium Phosphate Dibasic, Heptahydrate, USP Sodium Hydroxide, National Formulary (NF; as needed) Hydrochloric acid, NF (as needed) Water for injection, USP

9.1.2 Treatment Regimen and Duration

Patients may receive monthly injections of 0.1 mL (100 µL) avacincaptad pegol 2 mg for up to 18 months (maximum 17 total doses), starting at Month 1 through Month 17. Monthly doses will be administered at least 21 days apart.

All patients will have a final follow up visit at Month 18.

Subjects will continue in the trial for up to 18 months or until one of the following occurs: the subject withdraws consent and discontinues from the trial, the subject is discontinued from the trial at the discretion of the Investigator or the Sponsor, or the trial is terminated. Refer to Section 10.4 and Section 10.510.6 for patient withdrawal and trial discontinuation information, respectively.

9.1.3 Administration of Study Drug

Each study medication kit contains a 5-micron filter needle, a 30 G injection needle, a 1 mL empty syringe, and a vial of avacincaptad pegol 2 mg, to be administered by IVT injection. The method for IVT administration of avacincaptad pegol is described in detail in Appendix 17.2.

After administration, discard the contents inside of the carton in accordance with local regulations, complete the vial tear-off label, and place in the subject source documents for the monitor to conduct study drug reconciliation.

9.1.4 Drug Accountability

A drug accountability log will be provided by the Sponsor and must be maintained by the clinical site. The drug accountability log must be kept current and must contain the date and drug units [lot number, subject number, date of dispensation and initials of the dispenser].

At the end of the trial or when indicated by the Sponsor, all unused study medication should be destroyed locally by the study site. Where local laws or site procedures do not permit local site destruction the Sponsor will provide instructions for the return of unused medication to a local depot. Sites that destroy study medication locally must be able to produce a certificate of destruction upon request of the Sponsor.

9.1.5 Storage

The Investigator, or an approved representative (e.g., pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study medication kits should be stored at all times under refrigeration (2 to 8°C; 36 to 46°F) as per the study medication label; do not freeze. All vials should be protected from light and stored in the originally provided carton or clinical kit,

until the time of use. Any deviations in storage temperature should be reported to the Sponsor prior to administering the drug to study subject. The Sponsor will determine if the study drug remains stable and can be administered to subjects.

9.2 Previous or Concomitant Therapy

Only patients completing the Month 24 visit of Study ISEE2008 are eligible for this OLE trial, patients who discontinued for any reason are not eligible. Therefore, patients enrolled will have had no previous treatment for GA except for previous treatment with avacincaptad pegol 2 mg in Study ISEE2008.

If subject has a history of wet AMD or if wet AMD were to develop during the trial, in either the study eye (SE) or the fellow eye (FE), please refer to Section 10.3 for guidance on the use of concomitant treatment.

9.2.1 Prohibited Medication

Use of medications listed in the below table are not permitted after start of study intervention.

Prohibited Medication

Medication	Recommended Action
Study Eye	
Anti-VEGF therapy (licensed, unlicensed or investigational) other than Eylea, Lucentis, or Vabysmo; use of other biologics	Discontinue study treatment
Other investigational treatment	Discontinue study treatment
Fellow Eye	
Anti-VEGF therapy (licensed, unlicensed or investigational) other than Eylea, Lucentis, or Vabysmo	None
Other investigational treatment	Discontinue study treatment
Systemic	
Anti-complement therapy	Discontinue study treatment
Any new systemic medication known to be toxic to the lens, retina, or optic nerve (including, but not limited to hydroxychloroquine, tamoxifen)	Discontinue study treatment
Any investigational drug, biologic or device (with the exception of over-the-counter vitamins, supplements or diets)	Discontinue study treatment

Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor.

All treatments administered to the study eye, fellow eye, and systemically must be recorded in the case report form (CRF).

10 TRIAL CONDUCT

10.1 Subject Enrollment

Before recruitment of patients into the trial, written IRB or EC approval of the protocol and informed consent must be obtained.

Enrollment into this OLE trial must be within 90 days of the patient's Month 24 visit in Study ISEE2008.

Patients 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 study drug should not commence. Waivers are not permitted.

10.2 Trial Assessments

Written informed consent must be obtained before any of the procedures listed below are performed. An explanation of the trial and discussion of the possible risks and discomforts will be given by the Investigator or appropriate designee. Only those patients who fulfill all eligibility criteria will be entered into the trial.

Ocular assessments performed at Month 12 and Month 18 (and at an EW visit, if performed) should be performed pre-injection (as applicable) on both eyes (OU). Ocular assessments at all other trial visits are performed only on the SE.

Screening and Day 1 (ISEE2008 Baseline) assessments were performed as part of enrollment into Study ISEE2008 (GATHER2), and therefore, are not repeated for this OLE trial. Refer to the ISEE2008 (GATHER2) protocol for Screening and Day 1 assessments and corresponding procedures (Section 10.2 and Section 7, respectively).

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

Note:

- **IVT injection is contraindicated in patients with active ocular or peri-ocular infections and in patients with active intraocular inflammation.**
- **Concomitant medications should be assessed at every trial visit.**
- **AEs and serious AEs (SAEs) should be assessed starting at Month 1 (first visit of this OLE trial) after the first dose of study drug until 30 days after the last dose of study drug or until the last follow up visit of the trial, whichever comes later.**

Month 1

- **Pre-Injection:**
    - Informed consent (must be signed before any other assessments are performed at Month 1)
    - Urine pregnancy test (if applicable)
    - Immunogenicity and PK sampling
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - LLVA
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Color fundus photography (SE)
    - Fundus autofluorescence (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): To ensure that the injection procedure has not endangered the health of the eye, the study eye will be assessed immediately (0 to 5 minutes) and 30 minutes after an active injection with an abbreviated ophthalmic exam. A full ophthalmic examination and tonometry will also be performed 30 minutes after injection. Assessments will continue to ensure the central retinal artery (CRA) is adequately perfused and the IOP is within 10 mmHg of the pre-injection value and stable in the opinion of the Investigator.
        - Immediately (0 to 5 minutes) post-injection:
            - Examine the gross visual function of the SE: CF, hand motion, light perception, no light perception
            - Perform direct visualization to:
                - Verify the status of the CRA: CRA is perfused and not pulsating, CRA is perfused and pulsating, CRA is pulsating, or CRA is closed.
                - Verify the retina is attached and there are no new intraocular hemorrhages.

- At 30 minutes post-injection:
    - If no CF at the previous measurement examine the gross visual function of the SE
    - Perform direct visualization to:
        - Verify the status of the CRA: CRA is perfused and not pulsating, CRA is perfused and pulsating, CRA is pulsating, or CRA is closed.
        - Verify the retina is attached and there are no new intraocular hemorrhages.
    - Perform full ophthalmic examination
    - Measure IOP
- Continue beyond 30 minutes post-injection until the CRA is adequately perfused and IOP is within 10 mmHg of the pre-injection value and is stable in the opinion of the Investigator.

Month 2 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Immunogenicity and PK sampling
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 3 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)

- Optical coherence tomography (SE)
- Treatment with IVT avacincaptad pegol 2 mg

- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 4 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Immunogenicity and PK sampling
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full ophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 5 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full ophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 6 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - LLVA
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Color fundus photography (SE)
    - Fundus autofluorescence (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 7 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Immunogenicity and PK sampling
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 8 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction

- BCVA (4 meters) using ETDRS chart (SE)
- Tonometry (SE)
- Full ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Treatment with IVT avacincaptad pegol 2 mg

- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 9 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full oophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 10 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full ophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 11 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 12 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - LLVA
    - Goldmann applanation tonometry and full ophthalmologic examination (OU)
    - Color fundus photography (OU)
    - Fluorescein angiography (OU, transit SE)
    - Optical coherence tomography (OU)
    - Fundus autofluorescence (OU)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1 (Note: Goldmann applanation tonometer must be used).

Month 13 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Immunogenicity and PK sampling
    - Refraction

- BCVA (4 meters) using ETDRS chart (SE)
- Tonometry (SE)
- Full ophthalmologic examination (SE)
- Optical coherence tomography (SE)
- Treatment with IVT avacincaptad pegol 2 mg

- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 14 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full ophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 15 (±7 days)

- **Pre-Injection:**
  - Urine pregnancy test (if applicable)
  - Refraction
  - BCVA (4 meters) using ETDRS chart (SE)
  - Tonometry (SE)
  - Full ophthalmologic examination (SE)
  - Optical coherence tomography (SE)
  - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
  - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 16 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 17 (±7 days)

- **Pre-Injection:**
    - Urine pregnancy test (if applicable)
    - Refraction
    - BCVA (4 meters) using ETDRS chart (SE)
    - Tonometry (SE)
    - Full ophthalmologic examination (SE)
    - Optical coherence tomography (SE)
    - Treatment with IVT avacincaptad pegol 2 mg
- **Post-injection:**
    - Ophthalmic exam (SE) and Tonometry (SE): Following same procedures as outlined at Month 1.

Month 18/End of Study (Early Withdrawal)

- Urine pregnancy test (if applicable)
- Immunogenicity and PK sampling
- Refraction

- BCVA (4 meters) using ETDRS chart (OU)
- LLVA
- Goldmann applanation tonometry (OU)
- Full ophthalmologic examination (OU)
- Color fundus photography (OU)
- Fluorescein angiography (OU, transit SE)
- Optical coherence tomography (OU)
- Fundus autofluorescence (OU)

10.3 Development of CNV During the Trial

If the Investigator suspects the development of CNV in the study eye, or if the subject has > 5 ETDRS letters of VA loss between the current visit and the immediate past visit where VA was assessed, the diagnosis must be assessed with fundus photography, FA and OCT and **confirmed by the Duke RC prior** to initiating anti-VEGF treatment in the study eye. The trigger for imaging studies should be the Investigator's suspicion of CNV. VA change alone does not constitute a requirement for imaging studies.

For patients who develop CNV in the *study eye* **and the diagnosis is confirmed by the Duke RC** during the trial, the study eye should be treated with either Lucentis® (ranibizumab), Eylea® (aflibercept), or Vabysmo® (faricimab) per their label.

If the Investigator plans to administer the anti-VEGF agent on the day of the diagnosis, the Duke RC will confirm the diagnosis within 1 hour after receiving the images. If the anti-VEGF agent and avacincaptad pegol are administered in the SE on the same day, avacincaptad pegol should be administered first, and the anti-VEGF administered second. The anti-VEGF agent may NOT be administered after the avacincaptad pegol injection until the IOP is ≤ 21 mmHg or within 5 mmHg of the baseline IOP on that day (i.e., the "baseline" IOP is the pre-injection IOP before the avacincaptad pegol administration on that day). 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 before proceeding to the anti-VEGF injection.

For the anti-VEGF agent administration, it is ***mandatory*** that, the same injection preparation and administration protocol specified for the avacincaptad pegol administration be followed by the ophthalmologist. Please refer to Appendix 17.2 Intravitreous Administration Protocol; for example, the use of aseptic technique, sterile gloves, anesthesia, eye speculum, and povidone-iodine are required.

IVT injection is contraindicated in patients with active ocular or peri-ocular infections and in patients with active intraocular inflammation.

The subject will continue with the study treatment (avacincaptad pegol) as scheduled.

For patients who develop CNV in the *fellow eye* during the trial, the fellow eye should be treated with either Lucentis® (ranibizumab), Eylea® (aflibercept), or Vabysmo® (facimab) per their label, with no change to trial conduct regarding the study eye. **However, if the study eye is treated on the same day as the fellow eye, the study eye should be treated before the fellow eye.**

10.4 Withdrawal from Trial

Patients 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 patients from the trial in the event of concurrent illness, AEs (including pregnancy in female patients), treatment failure after a prescribed procedure, protocol violations, regulatory authority decision, cure, administrative or other reasons.

Final trial assessments as outlined in the Study Assessments Chart, Section 3, should be performed on all patients who withdraw. Patients who withdraw due to an AE should be followed until resolution of the AE, or an adequate explanation for the event is obtained.

Patients who withdraw for any reason should have assessments performed according to the Early Withdrawal schedule.

10.5 Study Drug Discontinuation

In rare instances, it may be necessary for a subject to permanently discontinue study treatment before the planned study duration. If study treatment is permanently discontinued, the subject should, if at all possible, remain in the study to be evaluated for safety.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should not be considered discontinued from the study unless they withdraw their consent and where possible, they should return for study visits and assessments according to the Study Assessments Chart, Section 3.

10.6 Trial Discontinuation

The reason for a subject discontinuing from the trial will be recorded in the source documentation and 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 an 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 patients, 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, or at the discretion of Astellas.

The trial will be considered completed when the last subject completes the final trial visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

A subject is considered to have completed the study if the subject has completed the final trial visit.

11 STATISTICAL METHODS

The following summarizes the statistical methods that will be employed in this trial.

11.1 Study Endpoints

Primary endpoint:

- All AEs reported whether or not deemed related to the injection procedure or study drug

Secondary endpoints:

- Immunogenicity
- Pharmacokinetics

Exploratory Endpoints:

- Ophthalmic variables (BCVA, LLVA, IOP, and ophthalmic examination)

11.2 Determination of Sample Size and Statistical Rationale

The sample size is estimated based on the number of ISEE2008 subjects that completed the ISEE2008 Month 24 visit ("ISEE2008 completers") and the expected number of eligible ISEE2008 completers willing to participate in the ISEE2009 study.

11.3 Randomization and Masking Procedures

No randomization or masking procedures are necessary for this trial as it is an open-label trial and all eligible patients will be administered avacincaptad pegol 2 mg monthly.

11.4 Analytical Considerations

11.4.1 Safety Analysis

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

AEs will be summarized using Medical Dictionary for Regulatory Activities terms. The incidence and severity of AEs will be listed and grouped by body system.

Summary statistics (i.e., mean, median, standard deviation, minimum and maximum for continuous variables, counts and proportions for categorical variables) will be presented for all endpoints.

11.5 Immunogenicity and PK Analyses

Additional details regarding immunogenicity and pharmacokinetic data analyses will be provided in the statistical analysis plan (SAP) prior to database lock.

Immunogenicity: A patient's overall ADA status will be reported as follows: ADA-negative, ADA-positive, ADA-inconclusive and Unevaluable samples.

Pharmacokinetics: Individual patient concentration-time data will be listed and summarized descriptively in tabular format.

11.6 Interim Analyses

Interim analyses may be performed if deemed appropriate. Details (if applicable) will be described in the SAP.

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.

AEs 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 patient 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, electrocardiogram, 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

AEs will be recorded starting after the first dose of study 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 trial 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 whether the event qualifies as a “serious” AE (Section 12.3).

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 the 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;

AEs are assessed as “not related” or “related” to one of the following: (1) the IVT injection procedure (including eyelid speculum, anesthetic drops, mydriatic drops, antibiotic drops, povidone-iodine, subconjunctival injection of anesthetic, IVT injection of avacincaptad pegol or anti-VEGF) or (2) the study drug (avacincaptad pegol).

The adverse relationship will be assessed using the definitions below. The Investigator will choose either “not related”, or chose the most likely cause of the AE (i.e., only one of the relationships noted in the above paragraph may be chosen):

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

12.3 Definition of AESIs

The selection of adverse events of special interest (AESIs) are based on medical review of avacincaptad pegol AEs throughout the development program and the post-marketing environment. These include identified risks for an IVT injection procedure and potential risks for avacincaptad pegol mechanism of action, considering the frequency, seriousness, and medical plausibility of events.

The AESIs will include the following:

- Endophthalmitis
- Ischemic optic neuropathy
- Intraocular inflammation; any case of uveitis, retinal vasculitis or retinal occlusive vasculitis
- IOP ≥ 30 mmHg at 30 minutes post injection deemed clinically significant by the Investigator
- Transient loss of light perception immediately after injection
- Elevation of IOP post-injection requiring surgical/procedural intervention (i.e., paracentesis; for instruction regarding paracentesis refer to Appendix 17.2
- BCVA decrease ≥30 letters from ISEE2009 Month 1 Visit
- CNV (exudative or nonexudative)

AEs, as defined in Section 12.1, should be reported as per Section 12.2.

An AESI, as defined in this Section 12.3, shall be reported if affecting the study eye. When an AESI occurs, the Investigator will fill out a standardized questionnaire to report the designated event in the same expedited manner as SAEs (Section 12.5).

Adverse events of CNV, endophthalmitis and intraocular inflammation occurring in the fellow eye, while not considered an AESI per protocol, shall be entered in the CRF as expeditiously as possible (i.e., within 24 hours of event).

12.4 Definition of Serious Adverse Events

A 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 inpatient admission. 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)

12.5 Assessment and Reporting of Serious Adverse Events

SAEs will be recorded starting after the first dose of study 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 study 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 Serious Adverse Events must be reported by the site
to the Sponsor or Designee within 24 hours.
Refer to the "Safety Contact List" provided separately

12.6 Exposure in Utero

If any trial patient or the female partner of a male patient becomes or is found to be pregnant while receiving study drug, the Investigator must contact the Sponsor. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The Sponsor will inform the site of the information to be provided. All pregnancies must be followed to conclusion to determine their outcome, as well as the status of the infant for a minimum of 8 weeks.

13 RESPONSIBILITIES

13.1 Emergency Equipment

Each center must adhere to their policies regarding emergency equipment and resuscitation procedures that may be in effect at the individual site or institution.

The Sponsor recommends, if applicable for the participating sites, to 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) and to ensure that all equipment is within specifications for the duration of the trial. If applicable, each center should follow their written policies regarding resuscitation procedures. In addition to the above, any additional measures in adherence to specific site or institutional policies should be followed.

13.2 Case Report Forms and Trial Documentation

The Investigator will complete the appropriate CRF pages within 3 business days 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 Astellas clinical monitors, or its representatives, 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. This Trial File will be reviewed periodically for completeness by Astellas' clinical monitors, or its representatives, 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. The Investigator is responsible for reporting all deviations in drug storage temperatures and should not administer the drug to any subjects until the stability is approved by Astellas.

Drug accountability records will be reviewed during monitoring visits. Adequate drug accountability records include documentation of all study drug supplies received, dispensed to trial patients, and returned to Astellas.

At the end of the trial, all drug supplies and documentation will be reviewed and verified by the trial monitors. The sites will be instructed to destroy unused study drug supplies when the trial is completed, or the site may choose to return the drug to an Astellas contracted drug management facility for destruction. If the drug is destroyed at the site, the drug accountability form must be completed and 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.

Prospective approval of protocol deviations to recruitment or enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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 Good Clinical Practice” 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 “Good Clinical Practice” as outlined in the current version of 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Patients”, and part 56, “Institutional Review Boards”.

Expedited reporting will be conducted in accordance with local legislation.

13.6 Institutional Review Board or Ethics Committee 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 patient informed consent
- A list of IRB/EC members, or statement of compliance

Prior to enrollment, written informed consent must be obtained from each patient 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.

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16 SPONSOR SIGNATORY

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 Procedures for Refraction and Vision Testing

Refraction and VA measurements will be performed for all patients by a trained vision examiner. Another examiner should also be trained to serve as a back-up should the primary examiner be absent. The name of the vision examiner should be documented in the subject's source document at each visit. The subject's chart, previous VA testing results, and previous refraction should be made available.

17.1.1 Refraction

Refraction may not be required at every study visit to obtain best corrected vision. Refraction should be conducted prior to VA testing to obtain best corrected vision at the Month 1, M7, M12, and Month 18/EOS (EW) visits. Refraction should be performed on study visits immediately following any refractive procedures (cataract extraction) or if greater than 10 ETDRS letter difference compared to immediate prior visit is observed.

17.1.2 Equipment

Refraction equipment required includes:

1. Retroilluminated light box and Charts R, 1 and 2 from Ferris-Bailey ETDRS distance VA 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

17.1.3 Beginning Approximate Refraction

At the Screening visit (performed at Screening in Study ISEE2008 [GATHER2]), the subject's beginning refraction is determined by one of the following methods:

a) If the subject's VA 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 VA 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 VA 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 VA must NOT be used for refraction. Refraction for each eye should be performed at 4 meters unless the subject's VA measured at 4 meters on the refraction chart (Chart R) is worse than 20/160. If VA 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 patients, including those with intraocular lenses. For uncorrected aphakic patients, a +10.00 diopter sphere should be added to the trial frame as the beginning approximate refraction.

17.1.4 Subjective Refraction

Subjective refraction allows one to determine the best correction for a subject to perform the VA 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.

17.1.5 Procedure

1. Measure the distance vision of each eye using Chart R while occluding the FE. Patients 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 VA 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 patients 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 summary below) and follow a similar procedure.** *Note: Whenever VA is improved to a higher range by improved correction, refraction should be performed with the smaller sphere and cylinder powers given for the better VA 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 VA 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 VA 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 VA chart. Whenever the VA is improved, even by one letter, you may increase the minus by 0.50 (or decrease the plus) and repeat Step 6d. Whenever VA 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 VA 20/10 to 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 VA chart.

b) Test the cylinder power by placing the 0.25 diopter cross-cylinder (for vision of 20/10 to 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 VA 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.

17.1.6 Visual Acuity Testing

Best-corrected VA 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.

17.1.7 Visual Acuity Charts

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

17.1.8 Visual Acuity Lane and Visual Acuity Box

A distance of **4 meters** is required between the subject's eyes and the VA 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 VA 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 VA, the VA of an individual subject should be measured in the same lane at each visit, if possible. If different lanes are used to test VA, they must each meet the same standards.

Retro-illuminated 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 $\pm$ 2 inches from floor.

The VA 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.

17.1.9 Corrected Visual Acuity Measures

- As a reminder, Charts 1, 2, and R are used for testing the right eye, left eye, and refraction, respectively. Patients 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 VA 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 VA. 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 VA of the eye at 4.0 meters (i.e. 20 or more letters read at 4 meters), the VA 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 VA 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 VA score is recorded as 0.

17.1.10 Testing for Count Fingers Vision, Hand Motion Vision and Light Perception/No Light Perception Vision

If the subject's VA 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/No Light Perception 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”.

17.1.11 Procedures for Refraction and Vision Testing under Low Luminance

Once the subject has been refracted and had their vision measured under normal light conditions, a neutral density filter will be added to the trial frame and the ETDRS VA will be measured again using the same refraction noted above. Additional specification of the neutral density filter and procedures will be provided by the Sponsor.

17.1.12 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
20/10 - 20/160 (4 meters)	+1.00 -1.00	+1.00 -1.00	.50 JCC	.50 JCC	+.50 -.50	+.50 -.50	+.50 -.50
20/20 - 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)

17.2 Intravitreous Administration Protocol

This protocol applies to avacincaptad pegol injections.

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

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

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

New bottles of topical eye drops should be used for each patient at each visit.

NOTE: Prior to the IVT 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 IVT drug.

NOTE: Pre-operative antibiotic drops are NOT recommended prior to the scheduled injection(s) of IVT drug. In addition, peri-operative and post-operative antibiotic drops are NOT recommended 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 may be prescribed for subject use at the discretion of the Investigator.

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

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

c. OPTIONAL: Apply 2 to 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 permitted.**

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 swab stick.

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

7) Allow 30 to 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 swab stick. 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 IVT injection should be 3.0 to 3.5 mm from the limbus in aphakic/pseudophakic patients, and 3.5 to 4.0 mm in phakic patients.

   NOTE: During the preparation and injection of the drug, Investigators, ancillary staff, and patients 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 study drug is optional.

Avacincaptad pegol 2 mg (0.1 mL injection volume) Injection Procedure:

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 filter needle attached to a 1-mL sterile syringe (supplied). Please see the study drug manual for appropriate withdrawal technique. 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 mg 0.10 mL on the syringe for avacincaptad pegol 2 mg.

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. Zero to five minutes following the intravitreal injection, patients should be examined with indirect ophthalmoscopy to assure that the optic nerve head is perfused, the retina is attached, and there is no new intraocular hemorrhage.

g. The IOP should be measured and recorded at least 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 injection and the IOP is below 30 mmHg or at a lower level as determined by the Investigator.

After All Injections:

1) Zero to five minutes following intravitreal injection, patients 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, check the IOP:

    a. The IOP should be measured and recorded at least 30 minutes after the injection. Monitor the IOP until it is within 10 mmHg of the pre-injection value; the subject should not be discharged until at least 30 minutes after the injection and the IOP is within 10 mmHg of the pre-injection value.

    b. 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 cleaned as per the standard procedures of the site before using it to measure IOP. Sterile fluorescein strips and single use proparacaine bottles should be used for all patients. “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. IOP 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 no light perception for more than 1 to 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 patients 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. Patients should be informed that some blurring of vision is common post-injection, which is often described as seeing spots floating in the eye. Patients 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.

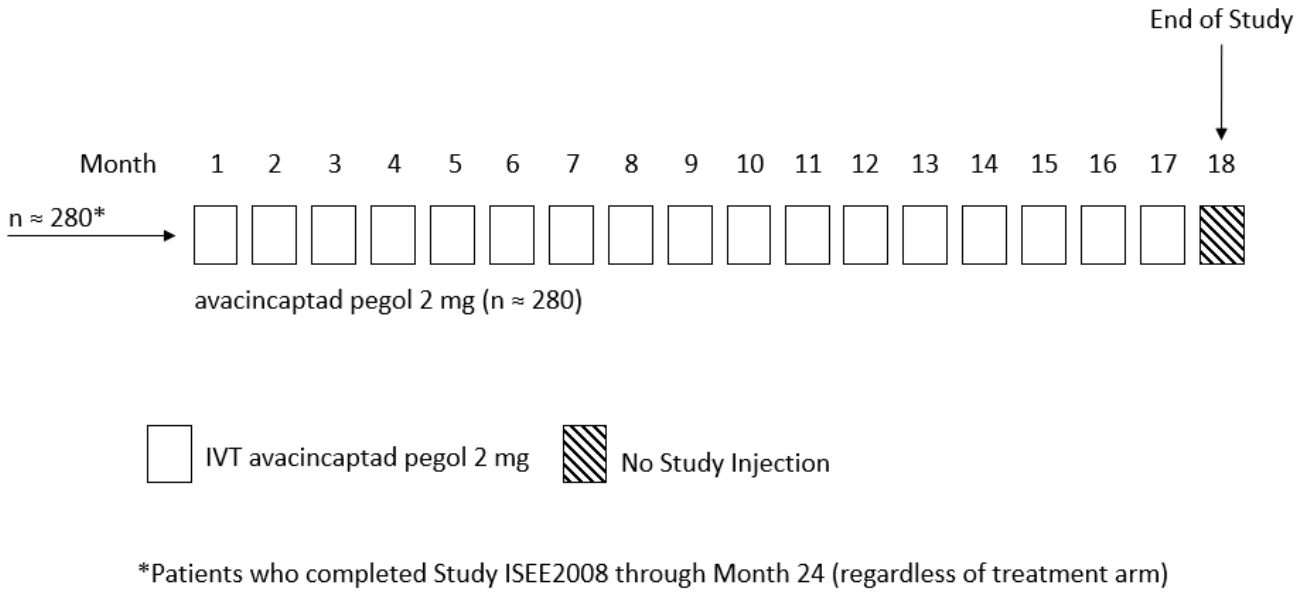
4) After administration, please securely discard the contents inside of the carton, flatten and retain the box for the monitor to conduct drug reconciliation.

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 to 3 drops of povidone-iodine to the paracentesis site, and allow 30 to 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. For repeated paracentesis in the same patient, different clock-hour locations along the corneal circumference should be chosen. Further, IOP reducing drops can be applied prior to the intravitreal injection at the Investigator's discretion. 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 IVT drug.

17.3 ISEE2009 Study Schematic



*Patients who completed Study ISEE2008 through Month 24 (regardless of treatment arm)

17.4 Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Protocol Version	**Protocol Version Date**
Protocol Amendment 01	27 February 2024
Protocol Amendment A (France)	28 November 2022
Original Protocol	27 July 2022

Amendment 01 dated 27 February 2024

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and EU Clinical Trial Regulation.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the sponsor and to apply clarifications to the conduct of the study throughout the protocol.

Substantial Changes

Section # and Name	Description of Change	Brief Rationale
Throughout	The sponsor is updated from Iveric bio to Astellas Pharma Global Development (Astellas).	To reflect the change in sponsor.
2; 6; 8.1	The approximate number of subjects to be enrolled is reduced from 400 to 280	To update the number of subjects expected to complete the ISEE2008 study and be eligible to enroll in ISEE2009, based on current data.

2; 5.2; 11.1	Study safety endpoints clarified as follows: Primary Endpoint: • Adverse Events (AEs) Secondary Endpoints: • Immunogenicity • Pharmacokinetics Exploratory Endpoints: • Ophthalmic findings (BCVA, LLVA, IOP, and ophthalmic examination)	To specify primary, secondary, and exploratory endpoints of existing endpoints as required. Study endpoints were originally specified only as "safety endpoints".

Nonsubstantial Changes

Section # and Name	Description of Change	Brief Rationale
Title Page	Regulatory agency identifier numbers are added.	To include regulatory agency identifiers as required.
Title Page	Sponsor confidentiality statement is updated.	To provide updated confidentiality statement per change in Sponsor.
2; 6; 9.1.2; 10.6	Removal of market authorization of study drug and commercial availability as reason for premature study termination	To reflect that commercial availability of study drug does not impact study duration.
2; 11.2	The justification for sample size is updated	To clarify that the sample size is based on enrollment and eligible subject completion in ISEE2008

3; 10.2	Specified “as applicable” for ocular assessments at Month 12 and Month 18 performed pre-injection on both eyes (OU)	To provide clarity on pre-injection ocular assessments, given that there is no injection at Month 18
3	A cross-reference to Appendix 17.1 for details on procedures for refraction and vision testing is added.	To ensure understanding of study procedures.
3; 10.2	The requirement to perform a full ophthalmic evaluation at 0 to 5 minutes post-injection is revised to an abbreviated exam.	An abbreviated exam is adequate to monitor health of eye immediately post-injection.
3; 7.2; 10.2	The timepoints for performing Goldmann applanation tonometry are updated to pre- and post-injection as applicable.	To clarify the timepoints when this assessment is to be conducted.
4.1	Deletion of concluding paragraph of Section 4.1 GA Disease State Overview	To align with current state of unmet medical need
4.1.2	Revision of Section 4.1.2 Unmet Medical Need	To align with current state of unmet medical need
4.2	Description of avacincaptad pegol is updated	To align with description in current IB
4.4	Updates to Section 4.4 Completed and Ongoing Clinical Trials	To reflect current information

4.5	Clinical data cited in the trial rationale is updated to reflect current information.	To provide current information.
4.6	A benefit/risk assessment is added.	To summarize the benefits and risks of avacincaptad pegol based on current clinical data, and to meet the requirements of European Clinical Trial Regulation. The data in the benefit/risk assessment is updated but the overall benefit/risk ratio is not significantly changed compared to the benefit/risk statement in the most recent IMPD.
6	Added statement “This is an open-label, multicenter 18-month extensions study.”	For clarity on trial design and length of study
6; 10.6	The end of trial definition is added.	To provide a clear definition of the end of the trial.
9.1.1	Avacincaptad pegol composition details updated	For clarity and consistency with program level documents
9.2	The exclusion of previous treatment for CNV in study ISEE2008 is removed.	To align with current requirements for study ISEE2008. Subjects treated for CNV in ISEE2008 are eligible for enrolling into ISEE2009.
9.2	The exclusion of any treatment with investigational agent(s) during the trial is removed.	Placed in tabular format in Section 9.2.1
9.2.1	A table listing prohibited medications is added.	To specify prohibited medications. Prohibited medications was absent from the original protocol
10.1; 13.4	References to waivers from individual protocol criteria are updated to clarify that waivers to the protocol, including inclusion and exclusion criteria, are not allowed.	To preserve trial integrity.

10.3	Vabysmo® (faricimab) is added as a treatment option for CNV.	To reflect additional treatment option for CNV.
10.4	Treatment failure is added as an event qualifying for withdrawal from trial.	Subjects with treatment failure should be withdrawn from trial to avoid continued exposure to ineffective treatment.
10.5	Study drug discontinuation section is added to describe circumstances when a subject may discontinue study treatment but remain on trial for safety evaluation.	To continue to monitor safety of the subject and collect safety data in case of early discontinuation of study treatment.
10.6	Added subject study completion definition to the Section describing Trial Discontinuation.	To clarify the definition of completed subject for analysis purposes.
11.6	New section Interim Analysis with reference to the SAP for details on interim analysis is added.	The full description of interim analysis details is provided in the SAP as applicable.
12.3	Adverse Events of Special Interest are updated as follows: • Endophthalmitis • **Ischemic optic neuropathy** • Intraocular inflammation; any case of uveitis, **retinal** vasculitis or ~~retinal vascular~~	To add clarity to AESI definitions for the Investigator and to aid in management of AESI reporting; Ischemic optic neuropathy added as a new AESI to reflect current events included in safety signal monitoring.

	~~occlusion~~ **occlusive vasculitis** • IOP ≥ 30 mmHg at 30 minutes post injection **deemed clinically significant by the investigator** • Transient ~~vision~~ loss of light perception immediately after injection • Elevation of IOP **post-injection** requiring surgical/procedural intervention (i.e., paracentesis; for instruction regarding paracentesis refer to Appendix 17.2) • BCVA decrease ≥30 letters from ~~Screening in the~~ I**SEE2009 Month 1 Visit** • CNV (exudative or nonexudative) ~~in the SE~~ Clarification of AESI handling for study eye versus fellow eye is also added.	

12.6	Included “or the female partner of a male patient”	For clarity of pregnancy reporting requirements for the study. Reporting of pregnant partners was not specified in the original protocol.
16	Updated Signature Page to Sponsor Signatory	To align with new sponsor standard format
17.2	Examination after intravitreal injection is updated from one to two minutes to zero to five minutes	To allow operational flexibility in performing this assessment; to ensure consistency throughout document
17.2	Included “head” to describe optic nerve as part of the post-injection assessment of the Intravitreous Administration Protocol	For clarity
17.3	A schematic of study visits is added.	To ensure understanding of trial visit timing.
17.4	New section Protocol Amendment Summary of Changes added	To align with new sponsor template
Throughout	Minor administrative-type changes were made, e.g., typos, formatting, definition of abbreviations and other continuity throughout the protocol.	To provide clarification and proper interpretation of the protocol.

Electronic Signature Page

Document Name: ISEE2009-protocol-incorp-subst-amend-01

Signed By: PPD Capacity: Therapeutic Area - Medical	Signature Date: 29-Feb-2024 14:39:55 GMT+0000

Signed By: PPD Capacity: Biostatistician	Signature Date: 29-Feb-2024 15:22:46 GMT+0000

Document Type - Subtype: Clinical - Study Report Appendices

Vault Document Number: VV-CLIN-061222 v1.0