A Multicenter, Multiple-Dose Study in Neovascular Age-related Macular Degeneration (nAMD) to Evaluate the Safety, Tolerability, Pharmacodynamics, Immunogenicity, and Clinical Effect of Repeat Intravitreal (IVT) Injections of GEM103 as an Adjunct to Standard of Care Aflibercept Therapy

Protocol Number:	GEM-CL-10311
Date of Protocol:	5 May 2021
Protocol Version:	Version 3.0
(P)IND Number:	141036
Product:	Recombinant Human Complement Factor H (GEM103)
Indication:	Neovascular Age-related Macular Degeneration
Sponsor:	Gemini Therapeutics, Inc. 300 One Kendall Square, 3rd Floor Cambridge, MA 02139, USA

The study will be conducted according to the International Council for Harmonisation tripartite guideline E6(R2): Good Clinical Practice

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REVIEWED/APPROVED BY:

PPD

PPD

Sponsor approval	Signature	Date

PPD

Title of sponsor approver

INVESTIGATOR STATEMENT

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol.

I understand that I may terminate or suspend enrollment in the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated at any time by the Sponsor, with or without cause.

I agree to personally conduct and supervise this investigation at my institution and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of subjects.

I will ensure that the requirements relating to Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval are met. I will provide the Sponsor with any material that is provided to the IRB/IEC for ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the IRB/IEC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC and Sponsor approval, except where necessary to ensure the safety of study subjects.

Investigator Name	Investigator Signature	Date

Investigational site or name of institution

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antidrug antibody(ies)
AE(s)	adverse event(s)
AMD	age-related macular degeneration
AP	alternative pathway
AUC	area under curve
BCVA	best corrected visual acuity
BLA	Biologics License Application
CFH	complement factor H
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CNV	choroidal neovascularization
CPT	center point thickness
CSR	clinical study report
CST	central subfield thickness
ECG	electrocardiogram
eCRF	electronic case report form
EOM	every other month
EOS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAF	fundus autofluorescence
FAS	Full Analysis Set
FDA	Food and Drug Administration
GA	geographic atrophy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IVT	intravitreal
LLVA	low luminance visual acuity
MA	macular atrophy
MedDRA	Medical Dictionary for Regulatory Activities
MNRead	Minnesota Low-vision Reading Test
MRC	Medical Review Committee
nAMD	Neovascular Age-Related Macular Degeneration
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25

Abbreviation	Definition
NIR	near infrared reflectance imaging
OCT	optical coherence tomography
OCT-A	optical coherence tomography – angiogram/angiography
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
rhCFH	recombinant human CFH
RPE	retinal pigment epithelium
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
SOA	schedule of assessments
SoC	standard of care
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States (of America)
VA	visual acuity
VEGF	vascular endothelial growth factor

CLINICAL STUDY SYNOPSIS

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<tr><td>Protocol Title</td><td colspan="2">A Multicenter, Multiple-Dose Study in Neovascular Age-related Macular Degeneration (nAMD) to Evaluate the Safety, Tolerability, Pharmacodynamics, Immunogenicity, and Clinical Effect of Repeat Intravitreal (IVT) Injections of GEM103 as an Adjunct to Standard of Care Aflibercept Therapy</td></tr>
<tr><td>Protocol Number</td><td colspan="2">GEM-CL-10311</td></tr>
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<tr><td>(P)IND Number</td><td colspan="2">141036</td></tr>
<tr><td>Indication</td><td colspan="2">Neovascular Age-Related Macular Degeneration</td></tr>
<tr><td>Objectives and Endpoints</td><td colspan="2">The primary endpoint will assess the safety and tolerability of GEM103+standard of care (SoC) vs sham+SoC (SoC is defined as aflibercept every other month [EOM]) through 12 months. Secondary and exploratory endpoints will assess GEM103+SoC vs sham+SoC at month 12 and over time.</td></tr>
<tr><td></td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td></td><td colspan="2">Primary</td></tr>
<tr><td></td><td>• Describe the safety and tolerability of GEM103+SoC vs sham+SoC</td><td>• Ocular and non-ocular treatment-emergent adverse events (TEAEs)
• Changes in ophthalmic exams
• Results of visual function assessments</td></tr>
<tr><td></td><td colspan="2">Secondary</td></tr>
<tr><td></td><td>• To evaluate total complement factor H (CFH) in aqueous humor after GEM103 IVT injection, whenever possible</td><td>• Aqueous humor concentrations of total CFH</td></tr>
<tr><td></td><td>• Describe the effect on best corrected visual acuity (BCVA)</td><td>• Mean change in BCVA from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letters</td></tr>
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</table>

	• Describe the effect on incidence of new MA in subjects without MA at baseline	• New MA evaluated by FAF
	• Describe the effect on choroidal neovascularization (CNV) size • Describe the effect on thickness of retinal layers • Describe the effect on subretinal and intraretinal fluid • Describe the effect on low luminance visual acuity (LLVA) • Describe the effect on National Eye Institute Visual Functioning Questionnaire 25 item Version (NEI-VFQ-25) • Describe the effect on Minnesota Low-vision Reading Test (MNRead)	• Mean reduction from baseline in CNV size as evaluated by fluorescein angiography (FA) • Mean change from baseline in center point thickness and central subfield thickness in µm as evaluated by spectral domain optical coherence tomography (SD-OCT) • The proportion of patients with intraretinal or subretinal fluid as evaluated by SD-OCT • Mean change in LLVA from baseline in ETDRS letters • Mean change in score from baseline on NEI-VFQ-25 • Mean change in maximum reading speed from baseline on MNRead Test
Methodology	Gemini Therapeutics, Inc. (the Sponsor) is developing GEM103 (recombinant human complement factor H [rhCFH]) as an alternative pathway (AP) complement modulatory therapy for the treatment of neovascular age-related macular degeneration (nAMD). GEM103 is being developed to restore appropriate regulation of the complement system in nAMD patients. GEM103 is intended to be used as an AP complement modulatory therapy for the treatment of nAMD by providing supraphysiological rhCFH by IVT injection. This is a Phase 2a, single-masked, sham-controlled, multicenter, multiple-dose study in subjects with nAMD to evaluate the safety, tolerability, immunogenicity, pharmacokinetic/pharmacodynamic, complement biomarkers, and clinical effect during 12 months of GEM103 IVT injections EOM as an adjunct to SoC aflibercept therapy. Study drug or sham, along with SoC aflibercept, will be administered to 1 eye only, which will be designated during the screening process, based on eligibility, and prior to any baseline measurements. If both eyes meet all eye-specific entry criteria, then the study eye will be determined by the Investigator and the subject together. All assessments will be performed in the study eye as well as the fellow eye whenever feasible. Detailed assessments of intraocular pressure (IOP), visual acuity (VA) and function, and retinal parameters such as CNV and MA lesion size will be performed for each subject enrolled.	

	Data will be collected on demographics, medical and ocular history, family history, and concomitant medications. Additionally, ophthalmic anatomic assessments and multimodal imaging, exploratory genetic and biomarker analyses, and aqueous humor sampling will be done for each subject enrolled. The Investigator will monitor the safety of study procedures according to local institutional policy. All AEs will be recorded in the electronic case report form. Accumulating safety data will be reviewed on an ongoing basis.
Study Duration	The minimum planned duration of each subject's participation is approximately 13 months: 1 month for screening and 12 months for dosing and follow-up.
Study Centers	It is anticipated that approximately 40 study centers will participate in this study.
Number of Subjects Planned	Approximately 45 subjects (~ 30 treated with GEM103+SoC and ~ 15 treated with sham+SoC) are planned for inclusion in the study.
Inclusion and Exclusion Criteria	**Inclusion Criteria:** Subjects must meet <u>all</u> of the following inclusion criteria to be considered for participation: 1. At least 50 years old at the time of signed informed consent; subjects younger than 50 may be considered for participation after consultation with the Medical Monitor 2. CNV related to nAMD with the following features, as determined by the Image Reading Center a. Maximum CNV lesion size of 12 disc areas b. Subretinal hemorrhage ≤50% of lesion size 3. Must be on aflibercept treatment prior to Day 1 (with at least one aflibercept dose received within 2 months prior to Day 1) AND be able to continue aflibercept at an every-other-month frequency for the duration of the study 4. BCVA in the study eye of 24 to 75 letters using the ETDRS Chart VA Scale (approximately equivalent to Snellen VA of between 20/32 and 20/320) 5. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and able to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment in the study eye 6. Understands the full nature and purpose of the study, including possible risks of study procedures, and provides informed consent prior to initiation of any study procedure 7. All subjects with reproductive potential must agree to use effective contraceptive methods through the end of study (EOS) visit. **Exclusion Criteria:** A subject who meets <u>any</u> of the following exclusion criteria will be ineligible to participate: 1. Presence of the following ocular conditions **in the study eye**:

	a. Any active ocular disease or condition that could confound the assessment of the macula or be a contraindication to IVT injection, e.g., retinal pigment epithelium tears or rips involving the macula, macular hole (any stage, including lamellar hole), epiretinal membrane, MA or maculopathies due to any disease other than AMD, uncontrolled glaucoma (IOP of >24 mmHg when on 2 or more IOP-lowering medications), severe glaucoma (cup to disc ratio of ≥0.8), diabetic retinopathy graded as moderate nonproliferative diabetic retinopathy or worse (with or without diabetic macular edema) b. Any intraocular surgery, e.g., any glaucoma surgeries including microinvasive glaucoma surgery and/or any intraocular surgery requiring vitrectomy. However, stable intraocular lens replacement surgery that was performed more than 3 months prior to consent will be allowed. c. Aphakia or complete absence of the posterior capsule d. Prior corneal transplant e. Scar or fibrosis ≥50% of CNV lesion or involving center of fovea 2. Presence of any of the following ocular conditions – **in either eye**: a. History of herpetic infection, idiopathic polypoidal choroidal vasculopathy (PCV), pathologic myopia, central serous chorioretinopathy (CSCR), adult-onset foveal pattern dystrophy b. Concurrent disease that could require medical or surgical intervention during the study period c. Active/suspected ocular/periocular infection or active intraocular inflammation d. History of idiopathic or autoimmune-associated uveitis 3. In the opinion of the Investigator, the subject has any prior or ongoing medical condition (e.g., ocular other than wet AMD, systemic, psychiatric) or clinically significant screening laboratory value that may present a safety risk, interfere with study compliance, interfere with consistent study follow-up, or confound data interpretation throughout the longitudinal follow-up period 4. Subject has experienced a cardiovascular or cerebrovascular event within 12 months of informed consent 5. Female subjects must not be pregnant or lactating, nor plan to become pregnant during the study

	6. Current use of medications known to be toxic to the lens, retina, or optic nerve (deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides). (Current use is defined as the administration of first dose of GEM103 within 5 half-lives of the prohibited medication). Past use of these medications, without history of ocular side effects, is not considered exclusionary. Use of medications that may potentially exacerbate macular edema or macular degeneration is permitted if, in the opinion of the Investigator, in consultation with the Medical Monitor, such use will not confound the interpretation of study results 7. Use of any investigational new drug or other experimental treatment in the last 6 months, and/or receipt at any time of any prior gene therapy (e.g., Adeno-associated virus), cell therapy, or ocular device implantation (other than posterior chamber intraocular lens placement after cataract surgery)
Investigational Product (and Reference Therapy), Dose, Route, Regimen	GEM103 (rhCFH) will be supplied in single-use vials with a 0.25 mL fill volume at a concentration of 10 mg/mL rhCFH. Aflibercept administered IVT EOM is SoC therapy. Subjects assigned to the GEM103+SoC group will be administered aflibercept (2 mg/50 µL) first, followed by GEM103 (500 µg/50 µL) 15 minutes (±5 minutes) later. Study drug must not be mixed in the same syringe with other products. Subjects will be randomized to 1 of 2 treatment groups: GEM103+SoC or sham+SoC. Subjects randomized to the GEM103+SoC treatment group will receive treatment EOM (6 doses). All subjects assigned to the GEM103+SoC treatment will be treated with 500 µg GEM103 per eye. Subjects randomized to the sham+SoC treatment group will receive SoC with a sham IVT injection instead of GEM103, to keep the subject masked to their treatment assignment.
Statistical Methods	**General Considerations** Descriptive summary statistics will be provided for demographics, disposition, and dose exposure. The number and percentage of subjects who discontinued from the study, along with reasons for discontinuations, will be tabulated and described in listings. All descriptive summaries will be provided by treatment group (GEM103 vs sham). Continuous data will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation, and two-sided 95% confidence intervals (CI); categorical data will be summarized by sample size, proportions, and two-sided 95% CIs. Any reported p-values will be considered part of the descriptive analyses (i.e., hypothesis-generating) and will not be adjusted for multiplicity. The phrase "statistically significant" may be used interchangeably with "nominally statistically significant" to indicate that a nominal p-value was ≤ 0.05.

	Sample Size The planned total sample size of approximately 45 subjects (~ 30 treated with GEM103+SoC, ~ 15 treated with sham+SoC) is based on feasibility considerations, rather than any specific statistical test. **Analysis Sets** The Consented Subject Set will include subjects who signed the informed consent form and will be used to create a diagram to illustrate subject flow from consent through disposition (similar to a Consolidated Standards of Reporting Trials [CONSORT] diagram for a randomized trial). The Biomarker Set will include subjects with sufficient data to assess biomarker results. The Full Analysis Set (FAS) will include all subjects who receive at least 1 dose of study drug/reference therapy (GEM103 or sham). Safety analyses will be performed on the FAS. Analyses on the FAS are consistent with the intention-to-treat principle. **Safety Analysis** Descriptive statistics will be computed for safety parameters, as appropriate. Number and percentage of subjects who discontinued from the study because of AEs will be tabulated across dose cohorts; severity and frequency of AEs and serious adverse events (SAEs) will also be tabulated across treatment groups. All other safety data will be provided in listings. Physical examination findings, clinical laboratory values, and vital signs will be summarized by dose cohort. The proportion of subjects with measurable antibodies to GEM103 will be displayed. Further statistical evaluations will be applied for select endpoints, if warranted. All baseline data and safety data collected during the study will be listed for each subject. All AEs will be coded using a consistent version of the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). AE analyses will include the following tabular summaries: • Summary of all AEs • Incidence of AEs by SOC and PT • Incidence of AEs by severity • Incidence of SAEs • Incidence of treatment-related AEs **Biomarker, Imaging, and Clinical Endpoint Analysis** Aqueous humor will be collected prior to the first dose, and just prior to each subsequent IVT injection of GEM103 to evaluate complement proteins and possibly inflammatory cytokine profiles to determine their potential as PD biomarkers for usefulness in a pivotal study. Total CFH concentrations in aqueous humor will be evaluated.

	Imaging endpoints such as CNV lesion size, MA lesion size, retinal layer thickness or presence of fluid, and clinical endpoints such as BCVA, LLVA, and low luminance deficit, will be collected as described in the schedule of assessments. Analyses of biomarkers, imaging assessments, and clinical endpoints will be descriptive, and will summarize actual values and changes from baseline over time. Graphical displays will also be created. Analysis of biomarker, imaging, and clinical endpoint changes from baseline will primarily employ the Wilcoxon rank-sum test. Full analysis details will be provided in the Statistical Analysis Plan.

1 INTRODUCTION

This study will be conducted according to Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) and the ethical principles underlying European Union (EU) Directives 2001/20/EC and EU Directives 2005/28/EC; the United States (US) Code of Federal Regulations (CFR), Title 21, Parts 50 and 312 (21 CFR 50, 21 CFR 312); and all applicable government regulations and institutional research policies and procedures.

1.1 Background

1.1.1 Disease

Age-related macular degeneration (AMD) is a condition affecting older people that involves the progressive loss of the central field of vision and it is the leading cause of irreversible blindness in the western world (World Health Organization [WHO] 2019). Two forms of advanced AMD can be distinguished: neovascular (wet) AMD (nAMD) and dry AMD. Neovascular AMD is characterized by infiltration of abnormal blood vessels into the retina, and is a leading cause of vision loss in the western world in individuals 55 years or older. Although nAMD accounts for approximately 10% of all AMD cases, it is responsible for up to 90% of vision loss associated with the disease (Khanani 2020, Holekamp 2019). The current standard of care (SoC) for nAMD is the intravitreal delivery of functional antagonists of vascular endothelial growth factor (VEGF), a protein involved in the molecular orchestration of the pathologic neovascular cascade (Sahni 2020, Jaffe 2016). However, there are several practical limitations to anti-VEGF therapy, including the need for frequent intravitreal injections, incomplete response, and/or failure to maintain response in some patients (Jaffe 2016). Additionally, there is some concern that long-term use of anti-VEGF agents may have an undesirable effect on the macula, possibly related to the role that VEGF plays in maintaining the integrity of the retinal pigment epithelium (Gillies 2020). Development of macular atrophy (MA) in eyes with neovascular AMD treated with agents targeting VEGF has also been reported in several studies (Sadda 2018, Gillies 2020).

Neovascular AMD is characterized by the uncontrolled proliferation of abnormal macular blood vessels that can leak fluid and blood, resulting in damage to the photoreceptors and the retinal pigment epithelium (RPE), a process known as choroidal neovascularization (CNV) (Holekamp 2019). VEGF, the principal driver of neovascularization in AMD, induces angiogenesis and increases vascular permeability and inflammation. Over time, this causes progressive degeneration of photoreceptors and the RPE, and retinal fluid can accumulate, leading to edema and functional deterioration (Holekamp 2019, Khanani 2020). Dysregulation of RPE-derived VEGF is associated with neovascularization in nAMD. Since genetic variants in complement factor H (CFH) are known risk factors for AMD; in a metanalysis, CFH polymorphism rs1061170 was a predictor of treatment response of neovascular AMD, especially for anti-VEGF agents ranibizumab and bevacizumab (Chen 2012). Individuals homozygous for the variant risk C-allele corresponded to a decreased response to treatment by approximately 1.6-fold when compared with patients carrying homozygous for T-allele (Chen 2012). Drusen deposits associated with genetic variants of interest to the Sponsor have also been shown to increase the risk of progression from early or intermediate AMD to advanced AMD (geographic atrophy [GA] and nAMD) (Chavali 2015, Merle 2020). In both dry and nAMD patients, ocular complement activation has been reported with complement deposits detected in drusen, on RPE

cells, Bruch's membrane, choriocapillaris, and complement activation products have also been shown in aqueous humor (Keir 2017, Schick 2017, Altay 2019).

Endogenous (intraocular) CFH is crucial in regulating the alternative pathway (AP) of complement amplification loop. Intraocular human recombinant CFH has also been shown to reduce CNV as efficiently as currently used anti-VEGF antibody in a mouse model for nAMD (Borras 2020). Functional CFH also has roles in AMD that are necessary to maintain homeostasis in the subretinal space, including assistance in RPE clearance of products of lipid oxidation and cellular debris that are necessary to maintain homeostasis in the subretinal space, and which are non-canonical and separate from the complement regulation provided by functional CFH (Calippe 2017, Mattapallil 2017, Landowski 2019, Yu 2020). Therefore, providing supraphysiological rhCFH (GEM103) as an AP complement modulatory therapy has potential to be an effective treatment for nAMD to adequately address hyperactive complement activation, RPE functional deficits, and resultant retinal atrophy caused by CFH insufficiency (Keir 2017, Borras 2020). Taken together, these results clearly identify novel mechanisms of CFH in the nAMD process and demonstrate the potential of GEM103 as a novel, therapeutic option for patients with nAMD.

1.1.2 Medical Rationale for GEM103

Gemini Therapeutics, Inc. (the Sponsor) is developing GEM103 (recombinant human complement factor H [rhCFH]) as an AP complement modulatory therapy for the treatment of nAMD. GEM103 is a glycoprotein of approximately 155 kilodaltons (kDa) made up of 20 of the CFH control protein modules joined by short linkers (3 to 8 amino acids in length). The current SoC for nAMD is the intravitreal delivery of functional antagonists of VEGF, a protein involved in the molecular orchestration of the pathologic neovascular cascade (Sahni 2020, Jaffe 2016). However, significant unmet need exists with anti-VEGF monotherapy (Jaffe 2016). Thus, novel, alternative, and multi-target therapies that provide restoration of retinal health, improved efficacy and extended durability over anti-VEGF therapy are needed for patients with nAMD (Sahni 2020, Borras 2020).

Functional CFH is critical for regulating the AP amplification loop as well as C3 convertase activity (Brodszki 2020, Triebwasser 2015, Geerlings 2017). Restoring retinal health by providing functional CFH has a potential for benefit to patients with nAMD. CFH has an ability to address RPE functional deficits and resultant retinal atrophy caused by CFH insufficiency (Keir 2017, Borras 2020). Additionally, in a murine model of nAMD, intraocular human recombinant CFH has been shown to reduce CNV as efficiently as currently used anti-VEGF antibody (Borras 2020). GEM103 is intended to both restore appropriate regulation of the complement system and to help maintain retinal health. In vitro analyses support the hypothesis that GEM103 restores appropriate regulation by blocking the detrimental effects (e.g., inappropriate cell lysis, immune response) while retaining the beneficial effects (e.g., clearance of extracellular debris, repair of oxidative damage) of physiologic complement activity. Functional CFH also has roles in the ocular compartment, including assistance in RPE clearance of products of lipid oxidation and cellular debris that are necessary to maintain homeostasis in the subretinal space, and which are non-canonical and separate from the complement regulation provided by functional CFH (Calippe 2017, Mattapallil 2017, Yu 2020). GEM103 is intended to

be used as an AP complement modulatory therapy for the treatment of nAMD by providing supraphysiological rhCFH by intravitreal (IVT) injection.

GEM103 has been tested in a variety of biochemical assays and nonclinical studies (Section 1.3) and had appropriate activity, ocular exposure, and safety profile to support clinical testing of GEM103 in nAMD patients. In addition, GEM103 was evaluated in an ongoing Phase 1 single ascending dose study (GEM-CL-10301) and is being evaluated in an ongoing Phase 2a multiple-dose study (GEM-CL-10302) in patients with dry AMD. Available preliminary clinical data as of 30 September 2020 from the ongoing studies in patients with dry AMD, primarily after single doses of GEM103, indicate that GEM103 is well-tolerated, achieves supraphysiological levels of GEM103 in aqueous humor, shows a trend for positive effects on exploratory biomarkers of complement activation, and shows a trend for maintained or improved visual acuity (VA) (Section 1.4). These data support the planned clinical evaluation of GEM103 in nAMD patients in this Phase 2a clinical study.

1.2 Investigational Medicinal Product (GEM103)

GEM103, rhCFH, is a glycoprotein of approximately 155 kilodaltons made up of 20 of the CFH control protein modules joined by short linkers (3 to 8 amino acids in length). GEM103 is formulated in 0.02 molar sodium phosphate, 0.15 molar sodium chloride, 0.01% weight by volume polysorbate 20, pH 7.0 for administration via IVT injection, providing direct access into the target organ (or) tissue. The GEM103 drug product will be manufactured as a formulated, buffered solution at 10 mg/mL rhCFH concentrated liquid that, can be diluted (as needed) to the appropriate concentration prior to dosing at the site.

1.3 Nonclinical Summary

The pharmacology, pharmacokinetics (PK), and toxicology of GEM103 were evaluated in a series of in vitro and in vivo nonclinical studies.

The biological activity of GEM103 was found to be comparable to endogenous human plasma-purified CFH, and consistent with literature-reported values of CFH in the same in vitro models. These data demonstrate that GEM103 exerts the desired biological effect, and the potency of GEM103 is comparable and equivalent to that of endogenous human CFH. In addition, GEM103 ex vivo activity evaluated by the complement factor I cofactor assay on vitreous samples obtained from GEM103-treated cynomolgus monkeys showed that activity was maintained from 14 to 27 days after a single IVT administration of GEM103 at doses ranging from 150 µg/eye to 1000 µg/eye. Literature supports the ability of CFH to address the RPE functional deficits and resultant retinal atrophy caused by CFH insufficiency (Keir 2017, Borras 2020, Ding 2015). Additionally, in a murine model of nAMD, intraocular human recombinant CFH has been shown to reduce CNV as efficiently as currently used anti-VEGF antibody (Borras 2020).

GEM103 in vivo studies were all conducted in cynomolgus monkeys based on the 88% CFH sequence homology between humans and cynomolgus monkeys compared with other species' homology (59% to 66%), and also based on the in vitro erythrocyte study where GEM103 protected cynomolgus monkey erythrocytes from hemolysis in CFH-depleted human serum but did not protect rabbit erythrocytes in the same assay. The results of these studies demonstrated that nonhuman primates are the most relevant species for the nonclinical safety assessment of GEM103.

Safety pharmacology assessments of central nervous, respiratory, and cardiovascular systems after single and 3-month once monthly repeated doses of IVT administration in cynomolgus monkeys showed no GEM103-related effects on the function of these organ systems at 50, 100, or 250 µg/eye.

The PK, toxicokinetic, and distribution properties of GEM103 were evaluated based on the serum, vitreous humor, aqueous humor, retina, RPE, and choroid after single or repeated IVT administration to cynomolgus monkeys. After IVT injection, the vitreous humor, aqueous humor, retina, RPE, and choroid concentration of GEM103 were sustained in cynomolgus monkeys, supporting the intended IVT route of administration in humans. GEM103 exposure increased with increase in dose in an approximately proportional manner after IVT injection. GEM103 rapidly distributed to aqueous humor, retina, RPE, and choroid with elimination half-life ranging from 2.98 to 4.43 days in vitreous humor, from 2.86 to 4.27 days in aqueous humor, from 2.53 to 6.83 days in retina, from 6.27 to 8.27 days in RPE, and from 6.12 to 9.50 days in choroid. GEM103 was found to be relatively stable in the dose site (vitreous humor) and at the target tissue (RPE). GEM103 efficiently distributed into the aqueous humor, retina, RPE, and choroid with maximum concentration (C_{max}) of approximately 29.5%, 45.5%, 60.9%, and 16.4% that of vitreous humor C_{max}, respectively, and with area under curve (AUC) values of approximately 19.4%, 51%, 58.8%, and 18.7% that of vitreous AUC. The GEM103 volume of distribution at steady-state is approximately 1-fold to 5.9-fold greater than cynomolgus monkey vitreous volume, and is approximately 0.7-fold to 3.9-fold greater than cynomolgus monkey whole eye volume that suggest that GEM103 is mainly contained to the eye. The total clearance of GEM103 is approximately the rate of drainage of aqueous humor from the uveo-scleral routes by the anterior chamber or by conventional routes.

The systemic exposure of GEM103 after a single injection was minimal at approximately ≤0.04% of vitreous exposure. After repeated (once monthly) doses for a total of 3 doses at 50, 100, or 250 µg/eye, systemic GEM103 exposure was minimal and observed in the 100 and 250 µg/eye dose groups after the first dose but not after the second or third dose. This may be a result of the moderate to severe inflammation observed in the animals after the first dose due to generation of GEM103 antidrug antibodies (ADA), as ADA detection generally corresponded with toxicokinetic samples that were below the limit of quantification.

The toxicity profile of GEM103 has been well-characterized in single-dose range-finding studies, Good Laboratory Practice (GLP)-compliant, expanded, acute, single-dose, 3-month and 6-month repeated-dose (once monthly) toxicology studies, as well as single-dose and 3-month repeated dose (once monthly) safety pharmacology studies in cynomolgus monkeys. There were no GEM103-related systemic toxicities in clinical pathology or systemic histopathology effects observed. GEM103-attributable ocular findings in the toxicology studies were consistent across studies and limited to ocular inflammatory reactions that were likely immune-related responses resulting from the generation of GEM103 ADA after the administration of a recombinant human protein to cynomolgus monkeys (Short 2008, Biologics License Application [BLA] 125156, BLA 125387). GEM103 ADAs were mostly observed starting on Day 15 in all GEM103-treated animals across studies and tested doses. Toxicology studies indicated that findings of inflammation in the eye coincided with the time of ADA generation in most animals.

A no-observable-adverse-effect level could not be determined for either the single-dose, 3-month or 6-month repeat-dose (once monthly) studies because of antibody production against a human protein. These GLP-compliant studies indicated that GEM103 was tolerable up to the high dose

of 250 µg/eye, with only ocular inflammatory findings due to an immunogenic response of GEM103 ADA generation as anticipated for an IVT-administered human protein (Short 2008).

Further details on the nonclinical pharmacology, PK, and toxicology of GEM103 may be found in the Investigator's Brochure.

1.4 Clinical Summary

As of 23 September 2020, 12 dry AMD subjects (3 per dose) with bilateral GA had received a single dose of GEM103 in the Phase 1 single ascending dose clinical study (GEM-CL-10301) at 50, 100, 250 and 500 µg/eye. No dose-limiting toxicities and no related adverse events (AEs) were reported. Based on available preliminary data, there were no signs of intraocular inflammation and no clinically relevant changes in best corrected visual acuity (BCVA), intraocular pressure (IOP), endogenous plasma CFH levels, or safety laboratory results. In addition, the preliminary results evaluating the generation of antibodies against GEM103 in serum of patients receiving 50 µg/eye to 500 µg/eye at all assessed timepoints were negative.

GEM103 mean concentration in aqueous humor was maintained at or above 68.3 ng/mL (mean endogenous level of CFH in normal subjects) for a duration of at least 28 days after IVT injection at all doses tested, indicating achievement of supraphysiological levels of GEM103.

Available preliminary mean pharmacodynamic (PD) data showed a trend for positive effects on exploratory markers of complement activation (C3a and Ba), at all doses.

As of 30 September 2020, 10 dry AMD subjects have also received a single dose of GEM103 in the Phase 2a multiple-dose) clinical study (GEM-CL-10302); the first dry AMD subject in this study has received 2 doses of GEM103. No serious adverse events (SAEs) were reported. Serum ADA for the 1 subject who received 2 doses and who had post-dose sampling after their first dose as per protocol was negative at Day 30; the next sampling timepoint for serum ADA per protocol is after the fourth dose. Based on available preliminary PK data from the first subject that received 2 doses as of 30 September 2020, supraphysiological levels of CFH were maintained. No PD data were available from this study as 30 September 2020.

Details on the clinical profile of GEM103 are provided in the Investigator's Brochure.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Study Dose Rationale

This Phase 2a study (GEM-CL-10311) will evaluate the safety, tolerability, immunogenicity, PK/PD, complement biomarkers, and clinical efficacy of repeat IVT injections of GEM103+standard of care (SoC) defined as aflibercept every other month [EOM]; compared with sham+SoC) in subjects with nAMD.

Data from each dose in the Phase 1 single ascending dose study (GEM-CL-10301) in dry AMD patients has been evaluated for safety, GEM103 exposure, and biomarker response, and has been used to inform the selection of the 500 µg/eye dose for evaluation in this Phase 2a multiple-dose study in subjects with nAMD.

Repeat doses of GEM103 will be administered by IVT injection to subjects with nAMD. The 500 µg/eye was based on safety data from single- and repeat-dose (up to 3 and up to 6 once monthly) IVT toxicology studies in cynomolgus monkeys, PK modeling and simulation of the profiles of GEM103 after a single IVT injection in cynomolgus monkeys, and the endogenous level of CFH in human RPE (the target ocular tissue of GEM103 replacement therapy in dry

AMD patients), as well as data from the Phase 1 single ascending dose study (GEM-CL-10301) as described in Section 1.4. The 500 µg/eye dose level (in GEM-CL-10302 protocol version 2.0) was based on the clinical experience with 50, 100, 250, and 500 µg in the Phase 1 single ascending dose study (GEM-CL-10301).

Nonclinical GLP-compliant, single- and repeat-dose (once monthly) IVT studies indicated that GEM103 was tolerable up to the high dose of 250 µg/eye, with only ocular inflammatory findings due to an immunogenic response of GEM103-ADA generation as anticipated for an IVT-administered human protein (Short 2008). The human equivalent dose for the highest tested tolerable dose (250 µg/eye) in cynomolgus monkeys (for the expanded acute single-dose and 3-month repeat-dose [once monthly for a total of 3 doses] and 6-month repeat dose [once monthly for a total of 6 doses] toxicity studies) is 500 µg/eye, calculated based on a 2-fold larger human vitreous volume (human vitreous volume is approximately 4 mL, whereas cynomolgus monkey vitreous volume is approximately 2 mL). A brief summary of available clinical safety data is provided in Section 1.4.

Dose selection was based on both the PK modeling and simulation of the profiles of GEM103 after a single IVT injection in cynomolgus monkey, and the endogenous level of CFH in human RPE, the target ocular tissue of GEM103 replacement therapy in AMD. The average endogenous level of CFH in RPE isolated from frozen cadaver human eyes is 1577 ng/g (range from 488.06 to 3469.7 ng/g). This was assumed to be the normal endogenous level for the purpose of projection of effective GEM103 concentrations and duration of effect post IVT administration. CFH haploinsufficiency has been identified as a risk factor for dry AMD, which would result in the expression of functional CFH at levels approximately 50% of normal (Triebwasser 2015, Geerlings 2017). Therefore, for CFH replacement therapy in AMD patients, the replacement of 50% (approximately 800 ng/g) of the normal endogenous concentrations of CFH in RPE is considered to be sufficient for clinical effect. Based on this assumption, PK modeling and simulation were conducted using cynomolgus monkey PK parameters to project the duration of GEM103 concentrations in RPE at ≥800 ng/g after a single IVT administration in humans at doses ranging from 50 to 750 µg/eye. The PK model assumed that the half-life of GEM103 in human RPE is 2- to 3-fold longer than in cynomolgus monkey RPE, and that the vitreous volume in human is 2-fold greater than in cynomolgus monkey (Gaudreault 2005, Krohne 2012, Xu 2013). GEM103 RPE concentrations are expected to be >800 ng/g for 87 to 132 days after a single IVT dose of 500 µg/eye in humans. Overall, the data indicate that the nonclinical ocular PK, distribution, and systemic PK characteristics of GEM103 support the intended clinical route of administration (IVT injection), dose, and regimen (once monthly, or less frequently) for the treatment of AMD.

1.5.2 Risk/Benefit Assessment for Study Drug and Study Procedures

Potential Risks of GEM103: Immunogenicity and Inflammation

The predominant ophthalmic and histopathologic findings in cynomolgus monkeys were sequelae associated with, and secondary to, an immunogenic response, consistent with an expected immunogenic response to a human protein. No degenerative or apoptotic disruptions were noted. These immunogenic responses are less likely to be generated in the clinic since GEM103 is a human recombinant protein.

Most IVT biologics produce ocular inflammation in nonclinical test species, and inflammation was observed with GEM103 in cynomolgus monkeys. In general, mild, drug-induced inflammation is considered to be an acceptable safety risk in posterior segment diseases, since it

is reversible, treatable, and monitorable in humans (Short 2008). Development of ADA will be monitored in the study.

The Phase 1 single ascending dose study (GEM-CL-10301) did not have any findings of ocular inflammation following doses ranging from 50 to 500 mg administered intravitreally in dry AMD subjects. Furthermore, there were no ADAs detected in this study, consistent with the expectation that a human protein should not elicit an immune response in human subjects.

Potential Risks of anti-VEGF Standard of Care treatment:

Ophthalmologists are accustomed to providing frequent IVT injections for nAMD. A report by the American Academy of Ophthalmology concluded that intravitreal anti-VEGF pharmacotherapy is a safe and effective treatment for neovascular AMD over a 2-year period (Bakri 2019). Adverse ocular events after IVT injection of anti-VEGF agents, including endophthalmitis, retinal detachment, and increased IOP are rare. Arterial thromboembolic events in association with use of anti-VEGF agents have been reported in 2.4 to 5.6% of nAMD patients (Bakri 2019). A recent publication (Baumal, 2020), reiterates the importance of effectively managing the spectrum of intraocular inflammation after treatment with anti-VEGF agents in nAMD patients. It is recommended that as soon as a patient is diagnosed with intraocular inflammation, retinal vasculitis, and/or a retinal vascular occlusive event, anti-VEGF treatment should be suspended. The patient should be monitored regularly and future treatment options for nAMD may be determined based on the outcomes of the above events and the patient's clinical status. The clinician may consider treatment modalities based on an individualized approach and the locally available SoC (Baumal, 2020).

Potential Risks of GEM103 together with anti-VEGF Standard of Care treatment:

Currently there is no nonclinical or clinical information on effects of administering GEM103 as an adjunct to a SoC aflibercept therapy including any potential side effects. However, IVT recombinant human Factor H has been used in a CNV murine model in combination with anti-VEGF (Borras 2020).

Study drug will not be injected with other products in the same syringe, as the compatibility of GEM103 in solution with other products has not been evaluated. Aflibercept is administered first, followed by GEM103 15 minutes (±5 minutes) later (see Section 6.5.2).

Procedural Risks: IVT Injection and Aqueous Humor Sampling

The risk of severe complications after IVT injection such as uveitis, retinal detachment, extensive IVT hemorrhage, raised IOP, or endophthalmitis is low (<0.1%) (Avery 2014). Ophthalmologists are accustomed to providing frequent (monthly) IVT injections for nAMD, sometimes for years. Anterior chamber paracentesis (used to acquire aqueous humor samples) has been widely used and is considered safe, simple, and necessary for the reduction of IOP in a multitude of eye emergencies, including acute angle closure glaucoma, uveitis, hyphema, retinal artery occlusion, and endophthalmitis in order to prevent further irreversible vision loss, especially if used in conjunction with other medical modalities.

Potential Benefit: Restoration of Complement Regulation

The current SoC for nAMD is IVT delivery of functional antagonists of VEGF (Sahni 2020, Jaffe 2016). However, there are several practical limitations to anti-VEGF therapy, including the need for frequent IVT injections, incomplete response, and/or failure to maintain response in some patients (Jaffe 2016). GEM103 is intended to both restore appropriate regulation of the complement system and to help maintain retinal health. In vitro analyses support the hypothesis that GEM103 restores appropriate regulation by blocking AP hyperactivity and the detrimental effects (e.g., inappropriate cell lysis, immune response) while retaining the beneficial effects (e.g., clearance of extracellular debris, repair of oxidative damage) of physiologic complement activity. Functional CFH also has roles in the ocular compartment, including assistance in RPE clearance of products of lipid oxidation and cellular debris that are necessary to maintain homeostasis in the subretinal space, and which are non-canonical and separate from the complement regulation provided by functional CFH (Calippe 2017, Mattapallil 2017, Yu 2020). The benefit of a therapy that can restore normal CFH and AP complement function, and which has an ability to address RPE functional deficits in nAMD patients is likely to outweigh the above-mentioned potential risks.

2 STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are presented in Table 1. The primary endpoint will assess the safety and tolerability of GEM103+SoC vs sham+SoC (SoC is defined as aflibercept EOM) through 12 months. Secondary and exploratory endpoints will assess GEM103+SoC vs sham+SoC at month 12 and over time.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives and Endpoints	
• Describe the safety and tolerability of GEM103+SoC vs sham+SoC	• Ocular and non-ocular treatment-emergent adverse events (TEAEs) • Changes in ophthalmic exams • Results of visual function assessments
Secondary Objectives and Endpoints	
• To evaluate total CFH in aqueous humor after GEM103 IVT injection, whenever possible	• Aqueous humor concentrations of total CFH
• Describe the effect on BCVA	• Mean change in BCVA from baseline in ETDRS letters
• Describe the effect on MA size in subjects with MA present at baseline	• Mean change in size of MA evaluated by FAF
Exploratory Objectives and Endpoints	
• To evaluate the immunogenicity of GEM103 in serum after GEM103 IVT injection, whenever possible	• Generation of serum GEM103-ADA
• Describe the effect of GEM103 IVT injection on biomarkers in aqueous humor	• Change from baseline in complement protein, complement split products, and related cytokines protein values in aqueous humor
• Describe the effect on new MA in subjects without MA at baseline	• New MA evaluated by FAF
• Describe the effect on CNV size	• Mean reduction from baseline in CNV size as evaluated by FA
• Describe the effect on thickness of retinal layers	• Mean change from baseline in CPT and CST in µm as evaluated by SD-OCT
• Describe the effect on subretinal and intraretinal fluid	• The proportion of patients with intraretinal or subretinal fluid as evaluated by SD-OCT

Objectives	Endpoints
• Describe the effect on LLVA	• Mean change in LLVA from baseline in ETDRS letters
• Describe the effect on NEI-VFQ-25	• Mean change in score from baseline on NEI-VFQ-25
• Describe the effect on MNRead	• Mean change in maximum reading speed from baseline on MNRead Test

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BCVA=best corrected visual acuity; CFH=complement factor H; CNV=choroidal neovascularization; CPT=center point thickness; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; FA=fluorescein angiography; FAF=fundus autofluorescence; IVT=intravitreal; LLVA=low luminance visual acuity; MA=macular atrophy; MNRead=Minnesota Low-vision Reading Test; NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; OCT=optical coherence tomography; SD-OCT=Spectral Domain Optical Coherence Tomography; SoC = Standard of Care (2 mg aflibercept every other month)

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This is a Phase 2a, single-masked, sham-controlled, multicenter, multiple-dose study in subjects with nAMD to evaluate the safety, tolerability, immunogenicity, PK/PD, complement biomarkers, and clinical efficacy during 12 months of GEM103 IVT injections EOM as an adjunct to SoC aflibercept therapy.

Study drug or sham, along with SoC aflibercept, will be administered to 1 eye only, which will be designated during the screening process, based on eligibility, and prior to any baseline measurements. See Section 5.4 for determination of study eye.

Detailed assessments of IOP, VA and function, and retinal parameters such as CNV and MA lesion size will be performed as described in the schedule of assessments (SOA) in Appendix A.

Data will be collected on demographics, medical and ocular history, family history, and concomitant medications. Additionally, ophthalmic anatomic assessments and multimodal imaging, exploratory genetic and biomarker analyses, and aqueous humor sampling will be done for each subject enrolled.

The Investigator will monitor the safety of study procedures according to local institutional policy. All AEs will be recorded in the electronic case report form (eCRF).

The minimum planned duration of each subject's participation is approximately 13 months: 1 month for screening and 12 months for dosing and follow-up.

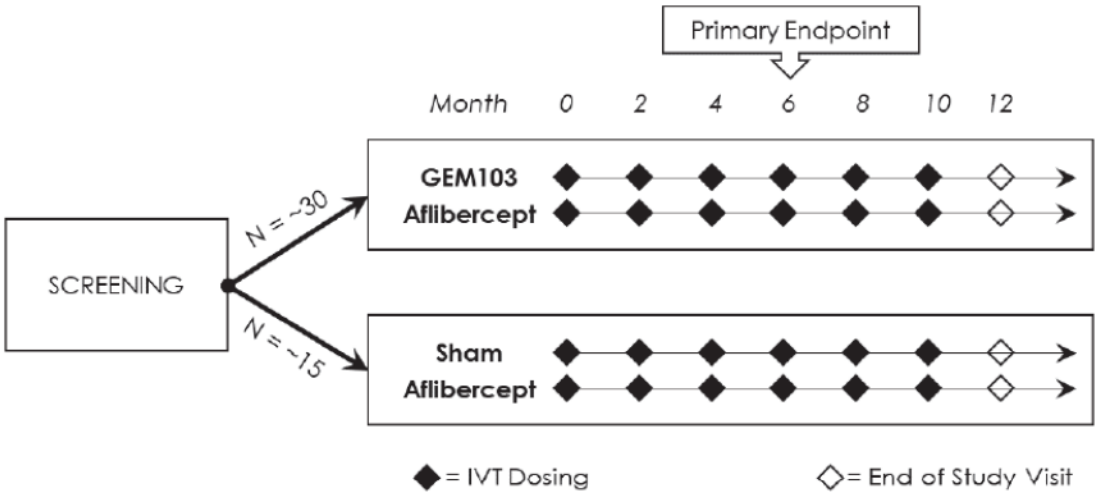
3.2 Study Design and Criteria for Dosing

Subjects will be randomized to 1 of 2 treatment groups: GEM103+SoC or sham+SoC (SoC defined as 2 mg aflibercept EOM). See Section 6.6 for randomization of the study drug).

All subjects treated with GEM103 will receive 500 µg GEM103 IVT, which was the highest dose tested in the Phase 1 single ascending dose study in dry AMD (GEM-CL-10301) and is thus determined to be the highest tolerable dose that achieved supraphysiological levels of GEM103 in aqueous humor and was associated with PD activity. One dosing regimen (EOM) will be evaluated in each treatment group. A study schematic is presented in Figure 1.

Accumulating safety data will be reviewed on an ongoing basis (See Section 7.4).

Figure 1 Study Design



3.3 Rationale for Study Design

GEM103 is being developed to restore appropriate regulation of the complement system in subjects with nAMD being treated with anti-VEGF therapy. GEM103 is intended to be used as an AP complement modulatory therapy for the treatment of nAMD by providing supraphysiological rhCFH by IVT injection. The proposed design and duration of this study will address evaluate safety, tolerability, PD, immunogenicity as well as the efficacy of repeat IVT injections of GEM103 (compared with sham) used as an adjunct to SoC aflibercept therapy in subjects with nAMD.

Since nAMD is a progressive disease, repeat-dose treatment and assessments are required to detect potential clinical efficacy. The available nonclinical toxicology data support multiple-dose regimens of GEM103 in humans (Section 1.3) and clinical trials with other IVT anti-VEGF therapies have shown efficacy signals as early as 6 months in nAMD patients. Therefore, the primary endpoint will be evaluated through 12 months for this study. This duration is sufficient to evaluate the safety, tolerability, and immunogenicity of GEM103, and may provide potential efficacy via biomarkers, and functional and imaging endpoints.

Eligible subjects will have nAMD with some visual impairment in the study eye, since limited information about the potential for GEM103 to impact vision or visual function was available at the time of initiation of this study. In addition to evaluation of change in CNV size, the development and/or progression of MA is a relevant anatomical endpoint (MA size) to evaluate as development of MA has been reported in nAMD patients treated with aflibercept (Sadda 2018, Gillies 2020). All subjects will be on treatment with aflibercept prior to enrollment in the study. CNV secondary to AMD will be determined by the Image Reading Center and eligibility will not be dependent on the presence of markers of activity e.g., fluid/hemorrhage.

GEM103/sham treatments will be administered EOM as an adjunct to EOM SoC. Subjects will be randomly assigned to a treatment group at a 2:1 (GEM103:sham) randomization schedule. A

total of 6 IVT injections will be administered over the 12-month study period. The EOM IVT injection regimen of aflibercept is used in standard clinical dosing in subjects with nAMD and is also similar to the dosing frequency being evaluated in other MA studies conducted with anti-complement agents (Liao 2020, Jaffe 2020). PK modeling and simulation as well as ocular PK data from the ongoing Phase 1 single ascending dosing study (GEM-CL-10301) supports both the proposed dose and dosing regimen of GEM103 in this study.

3.4 Rationale for Dose

Study dose rationale is described in Section 1.5.1.

3.5 Study Endpoints

Study endpoints are described in Table 1.

4 STUDY POPULATION

4.1 Target Population

The target population for this study is subjects with nAMD who are undergoing treatment (at least 1 prior dose) with aflibercept therapy.

4.2 Number of Subjects

Approximately 45 subjects (~30 treated with GEM103+SoC and ~15 treated with sham+SoC; SoC defined as aflibercept EOM) are planned for inclusion in the study.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be considered for participation:

1. At least 50 years old at the time of signed informed consent; subjects younger than 50 may be considered for participation after consultation with the Medical Monitor
2. CNV related to nAMD with the following features, as determined by the Image Reading Center
    a. Maximum CNV lesion size of 12 disc areas
    b. Subretinal hemorrhage ≤50% of lesion size
3. Must be on aflibercept treatment prior to Day 1 (with at least one aflibercept dose received within 2 months prior to Day 1) AND be able to continue aflibercept at an every-other-month frequency for the duration of the study
4. BCVA in the study eye of 24 to 75 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) Chart VA Scale (approximately equivalent to Snellen VA of between 20/32 and 20/320)
5. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and able to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment in the study eye
6. Understands the full nature and purpose of the study, including possible risks of study procedures, and provides informed consent prior to initiation of any study procedure
7. All subjects with reproductive potential must agree to use effective contraceptive methods listed in Section 4.5.2 through the end of study (EOS) visit.

4.3.2 Exclusion Criteria

A subject who meets any of the following exclusion criteria will be ineligible to participate:

1. Presence of the following ocular conditions **in the study eye:**
    a. Any active ocular disease or condition that could confound the assessment of the macula or be a contraindication to IVT injection, e.g., RPE tears or rips involving the macula, macular hole (any stage, including lamellar hole), epiretinal membrane, MA or maculopathies due to any disease other than AMD, uncontrolled glaucoma (IOP of >24 mmHg when on 2 or more IOP-lowering medications), severe glaucoma (cup-to-disc ratio of ≥0.8), diabetic retinopathy

graded as moderate nonproliferative diabetic retinopathy or worse (with or without diabetic macular edema)

b. Any intraocular surgery, e.g., any glaucoma surgeries including microinvasive glaucoma surgery and/or any intraocular surgery requiring vitrectomy. However, stable intraocular lens replacement surgery that was performed more than 3 months prior to consent will be allowed.

c. Aphakia or complete absence of the posterior capsule

d. Prior corneal transplant

e. Scar or fibrosis ≥50% of CNV lesion or involving center of fovea

2. Presence of any of the following ocular conditions **in either eye:**

   a. History of herpetic infection, idiopathic polypoidal choroidal vasculopathy (PCV), pathologic myopia, central serous chorioretinopathy (CSCR), adult onset foveal pattern dystrophy

   b. Concurrent disease that could require medical or surgical intervention during the study period

   c. Active/suspected ocular/periocular infection or active intraocular inflammation

   d. History of idiopathic or autoimmune-associated uveitis (grading scale for uveitis is available in Appendix K)

3. In the opinion of the Investigator, the subject has any prior or ongoing medical condition (e.g., ocular other than nAMD, systemic, psychiatric) or clinically significant screening laboratory value that may present a safety risk, interfere with study compliance, interfere with consistent study follow-up, or confound data interpretation throughout the longitudinal follow-up period

4. Subject has experienced a cardiovascular or cerebrovascular event within 12 months of informed consent

5. Female subjects must not be pregnant or lactating, nor plan to become pregnant during the study

6. Current use of medications known to be toxic to the lens, retina, or optic nerve (deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides). (Current use is defined as the administration of first dose of GEM103 within 5 half-lives of the prohibited medication). Past use of these medications, without history of ocular side effects, is not considered exclusionary. Appendix L provides a list of medications that may potentially exacerbate macular edema or macular degeneration. Use of these medications is permitted if, in the opinion of the Investigator, in consultation with the Medical Monitor, such use will not confound the interpretation of study results.

7. Use of any investigational new drug or other experimental treatment in the last 6 months prior to Day 1, and/or receipt at any time of any prior gene therapy (eg Adeno-associated

virus), cell therapy, or ocular device implantation (other than posterior chamber intraocular lens placement after cataract surgery)

4.4 Method for Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to a treatment cohort in a 2:1 randomization pattern with 2 subjects assigned to treatment with GEM103+SoC (SoC defined as aflibercept EOM) for every 1 subject assigned to treatment with sham+SoC.

4.5 Subject Restrictions During the Study

4.5.1 General and Dietary

Not applicable.

4.5.2 Contraception and Pregnancy Avoidance Procedures

If of childbearing potential (all female subjects unless amenorrheic for >1 year or have undergone surgical sterilization), subjects are required to practice at least 2 medically approved and highly effective methods of contraception (defined as those which result in a low failure rate [i.e., less than 1% per year] when used consistently and correctly).

All female subjects of childbearing potential must have a negative pregnancy test at screening and before dosing with study drug. Women of childbearing potential must agree to abstain from heterosexual sexual intercourse from date of informed consent, and at a minimum through the 3 months after the last IVT injection, or agree to consistently use at least 2 of any of the following methods of contraception from date of informed consent and for at least 3 months after the last IVT injection: condoms (male or female) with spermicide, diaphragm with spermicide, cervical cap with spermicide, intrauterine device, hormonal contraception (e.g., oral or patch contraceptives, Norplant®, Depo-Provera®), or other Food and Drug Administration (FDA)-approved contraceptive method designed to protect against pregnancy. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male subjects must agree to consistently use appropriate contraception and to refrain from sperm donation from consent through 3 months after the final dose.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign an informed consent form (ICF) stating that they understand the requirements for acceptable measures of birth control.

4.6 Concomitant Medications and Treatments

Concomitant medications include prescription and over-the-counter medications, prophylactic and therapeutic vaccines, herbal medications, vitamins, and dietary/nutritional supplements, as well as any investigational medications the subject may have received. See Appendix L for a list of medications that may potentially exacerbate macular edema or macular degeneration. Concomitant treatments include diagnostic, palliative, or interventional procedures (e.g., hematopoietic stem cell transplant, bone marrow transplant).

At the screening visit, information on all medications and treatments received by the subject within the preceding 4 weeks will be recorded. Thereafter, reasonable efforts will be made to ascertain all changes in concomitant medications and treatments from screening until the subject completes the EOS visit. Subjects who are on a stable dosing regimen for any of the medications listed in Appendix L at the time of screening, may be enrolled and remain on the dosing regimen

during the study if, in the opinion of the Investigator, such use will not confound the interpretation of study results. If during the course of the study a subject develops a condition that requires treatment with one of the medications listed in Appendix L, the subject should be treated as clinically indicated; however, the Medical Monitor must be consulted prior to continuing treatment in the study. Information on all concomitant medications and treatments will be recorded in the eCRF and will include the name of the medication (brand or generic) or therapy, reason for use, start date, and stop date.

During the course of the study, if in the opinion of the Investigator, the protocol required dosing of aflibercept every 60 days is insufficient for managing the subject's clinical condition, additional doses of aflibercept may be administered as needed. The Medical Monitor should be notified that additional dosing has been administered (permission does not need to be requested prior to treatment), and all doses of aflibercept administered must be documented.

4.7 Discontinuation of Subjects

4.7.1 Premature Withdrawal from Study Participation

Subjects have the right to withdraw from the study at any time for any reason.

The Investigator can also withdraw a subject upon the request of the Sponsor or if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor or designee. If a subject is discontinued because of an AE, the event will be followed until it is resolved or until stable, or the Sponsor and Investigator agree that further follow-up is not needed (Section 7).

4.7.2 Procedures for Discontinuation

If a subject discontinues at any time after being treated with GEM103 or sham, all efforts should be made to have the subject complete the follow-up visit procedures, including EOS/Early Withdrawal visit as per the SOA (Appendix A). All subjects who withdraw will be asked about the reason(s) for their discontinuation and about the presence of any AEs. The date and the reason for discontinuation will be recorded in the eCRF.

When a subject fails to return for scheduled assessments, the following efforts should be made to contact him/her to determine a reason for the failure to return: 3 phone attempts, including the date and time, will be documented in the subject's chart. If there is no response to the telephone calls, a certified letter will be sent. After these efforts have been completed, a subject will be considered as lost to follow-up. All attempts at contact should be documented in the subject's medical record.

4.8 Subject Replacement Policy

All subjects who receive at least 1 dose of GEM103 or reference therapy (sham) will be included in summaries of safety results. In this sense, treated subjects are not "replaced."

If a subject discontinues from the study before completing 3 doses, the Sponsor may choose to enroll additional subjects.

4.9 Subject Rescreening

During the 35-day screening period, subjects will be allowed to retest a screening procedure(s) with approval from the Sponsor and Medical Monitor. Retests beyond the 35-day window will require the subject to be reconsented.

5 STUDY PROCEDURES

5.1 Study Assessments

The SOA is presented in Appendix A. The SOA provides detailed information regarding the timepoints for all of these assessments.

5.1.1 Informed Consent

The Investigator is required to obtain informed consent according to this protocol and appropriate local requirements and regulations prior to enrolling a subject in this study. A copy of the signed and dated ICF will be given to the subject. The original form shall be maintained in the subject's medical records at the site. If the ICF is revised during the course of the study, sites will reconsent all active participating subjects.

5.1.2 Genetic Sample Collection

All subjects will provide a whole blood sample for exploratory genetics prior to their first study drug dose. Refer to the laboratory manual for further details. The samples will be sent to a contract laboratory selected by the Sponsor for targeted sequencing using the Sponsor's genetic testing assay (Section 5.2.1).

5.1.3 Medical and Ocular History

A medical history for the past 6 months, plus any significant, relevant medical history such as prior cardiovascular events, diabetes mellitus, or cancer will be obtained for each subject at screening. Conditions ongoing at baseline will be documented. Social history, to include smoking history and use of multivitamin supplements, will also be obtained.

An ophthalmic medical history will be obtained to include any past or current ocular conditions, surgeries, and symptoms, as well as conditions for which the subject is undergoing pre-emptive observation, e.g., glaucoma screening. Specifically, any history of AMD including history of IVT injections will be captured. Subjects will also be requested to provide a family ophthalmic history if available.

Refer to Section 4.6 for details on collection of medication history and concomitant medications/treatments.

5.1.4 Demographic Information

The following demographic information will be collected at screening according to local regulations: date of birth, gender, race, and ethnicity.

5.1.5 Physical Examination

Physical examinations will be performed by the Investigator or qualified designee at the timepoints specified in the SOA in Appendix A. Complete physical examinations will include an assessment of the subject's general appearance; skin, HEENT (head, eyes, ears, nose, throat), heart, lungs, abdomen, extremities/joints, and neurological status. A 12-lead electrocardiogram (ECG) will be taken at screening, after lying supine for 5 minutes, as part of the cardiac examination. Abnormal findings will be recorded in the eCRF and referred for appropriate investigation by a primary care physician or other healthcare provider at the determination of the Investigator.

5.1.6 Ophthalmic Examination

A comprehensive ophthalmic examination of both the study and fellow eye will be performed by the Investigator or qualified designee at the timepoints specified in the SOA in Appendix A. These examinations will include an assessment of the VA (both BCVA and LLVA) and visual function, a complete ophthalmic biomicroscopy examination including fundus examination, IOP (pretreatment IOP is required OU, post treatment IOP is only required in the SE), and ocular imaging tests to visualize the appearance and pathology of the retina and associated ocular tissues. All findings will be recorded in the eCRF. Further details on these examinations are found in respective study manuals.

On dosing days, IOP assessments are obtained prior to the dose OU, and 30±15 minutes after the dose only in the SE (OU optional). An additional assessment from the SE should be taken at 60±15 minutes if the IOP has not resolved to ≤30 mmHg at the 30-minute assessment. If the IOP continues to exceed 30 mmHg, then standard IOP-lowering interventions (per institutional guidelines) should be followed. If IOP is ≤5 mmHg, the subject should be treated per institutional guidelines. Regardless of whether applanation tonometry or a Tono-Pen® is used to measure IOP, the same method should be used for the subject for the entirety of their participation in this study.

5.1.7 Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The subject will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the timepoints indicated in the SOA in Appendix A.

When procedures overlap and are scheduled to occur at the same timepoint, vital signs should be assessed prior to any blood collection.

Management of subject safety regarding vital signs, including the appropriateness of dosing if vital signs are out of range, is the responsibility of the Investigator.

5.2 Clinical Laboratory Assessments

A list of all clinical laboratory tests that will be performed, as well as the timepoints for sample collection, are specified in the SOA in Appendix A.

Central laboratory reference ranges will be used throughout the study. All required tests will be performed by a qualified laboratory.

Clinical laboratory samples will be stored by the Sponsor or designee in a secure and controlled environment until analysis and will be destroyed by the Sponsor or designee after all obligations have been met, or sooner if required by local regulations.

Refer to the laboratory manual for further details regarding the collection, processing, and storage of clinical laboratory samples.

5.2.1 DNA Sample

After consent is provided and prior to dosing, a whole blood sample will be collected from each subject for DNA extraction (Section 5.1.2).

DNA sequences, including both the protein coding sequences and the noncoding sequences involved in transcriptional and translational regulation, and other biological functions, will be

analyzed by the Sponsor for genetic modifications that may contribute to and/or modify the disease phenotype or rate of progression of nAMD. Such DNA sequences, which may be investigated include, but are not limited to the following: genome-wide associated variants for AMD risk and/or progression, and selected protein coding variants in genes near such genome-wide association signals.

DNA samples will be stored by the Sponsor, or designee, in a secure and controlled environment until analysis, and will be destroyed by the Sponsor after all obligations have been met, or sooner if required by local regulations or if requested in writing by the subject.

Refer to Appendix B and the laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.2.2 Exploratory Biomarkers

Blood samples for plasma isolation will be obtained at the timepoints specified in the SOA for exploratory analyses to identify and evaluate disease-related biomarkers, where local regulations and blood volume permits (see Appendix A). A specific sample for exploratory biomarker analysis is being collected in this study; however, remaining blood samples collected in this study may also be used to analyze additional biomarkers of potential clinical interest, if there is sufficient sample and where local regulations permit.

Aqueous humor samples will be obtained at the timepoints specified in the SOAs for exploratory analyses to identify and evaluate disease-related biomarkers (see Appendix A). Aqueous humor samples collected will be obtained for the primary purpose of PD biomarker analysis.

Collection of samples for exploratory biomarker analysis will be subject to discretionary approval from each center's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the specific written consent of the subject. This section of the protocol only applies if approval for collection of these additional samples has been granted by the IRB/IEC and consent is provided by the subject.

Samples will be stored by the Sponsor or designee in a secure and controlled environment until analysis. They will be destroyed by the Sponsor or designee after all obligations have been met, or sooner if required by local regulations.

Refer to the laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.2.3 PK and Immunogenicity Assessments

Aqueous humor samples will be collected for PK (assessed as total CFH concentration in aqueous humor)/PD. Blood samples will be collected for ADA evaluation at the timepoints specified in Appendix A and in the laboratory manual.

5.3 Imaging Assessments

Color fundus photography (Appendix C), fundus autofluorescence (FAF; Appendix D), fluorescein angiography (FA; Appendix E), spectral domain – optical coherence tomography (OCT; Appendix F), optical coherence tomography – angiography (OCT-A; Appendix G), and near infrared reflectance imaging (Appendix H) will be evaluated at the time-points specified in Appendix A.

Full instructions on image acquisition and analysis will be provided in the imaging manual(s).

5.4 Determination of Study Eye

Only 1 eye will be selected as the study eye. If both eyes meet all eye-specific entry criteria, then the study eye will be determined by the Investigator and the subject together. All assessments will be performed in the study eye as well as the fellow eye whenever feasible.

Since study eye selection is based on both VA and imaging assessments, this determination will be made after results for screening assessments are available, but before the baseline visit and randomization.

6 STUDY TREATMENTS

6.1 Treatments Administered

6.1.1 Dose Adjustments

Dose adjustments are not planned for individual subjects. Adjustments to dose level and/or frequency may be implemented based on review of emerging data.

6.1.2 Dose Escalation

Dose escalation is not planned for individual subjects.

6.2 Stopping Rules

6.2.1 Stopping Rules in Individual Subjects

If a subject experiences an SAE considered related to GEM103, the subject's dosing will be paused until the SAE has resolved, or until the Investigator decides, in consultation with the Sponsor, that the subject may continue with study drug.

6.2.2 Stopping Rules for Multiple Subjects

At any time during this study, if ≥2 subjects experience the same (or similar) suspected unexpected serious adverse reaction (SUSAR), the Sponsor will convene the Medical Review Committee (MRC, see Section 7.4) to determine whether to continue the study in a manner such that benefits outweigh risks, or to cease further enrollment. The Sponsor will conduct ongoing reviews for detection of potential safety signals. At any time during this study, if a clinically relevant signal is established, the Sponsor may request a pause in dosing to review reported safety events and all available data. If a pause is instituted, dosing may resume only after review of available data by the MRC.

6.3 Description of Study Drug

The reference document for GEM103 is the Investigator's Brochure. GEM103 must be administered under close supervision of the Investigator, or designee.

The study drug will be provided in sterile, single-use vials as a 10 mg/mL concentrated liquid. The drug product may be aseptically diluted to the appropriate dose concentration according to the procedures outlined in the pharmacy manual as necessary.

Additional details are provided in Section 1.2.

6.4 Storage and Disposition of Study Drug

6.4.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. Receipt of study drug and upload of shipment temperature monitor reports must also occur in the appropriate IRT system in order to make the study drug available for dispensation. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable GEM103 vials in a given shipment will be documented in the study files. If any part of an investigational medicinal product kit is damaged, the entire kit will be replaced. The Investigator must notify the Sponsor of any damaged or unusable study treatments that were supplied to the Investigator's site.

6.4.2 Management of Clinical Supplies

The Sponsor will provide the Investigator and study site with adequate quantities of GEM103. GEM103 will be labeled "for clinical trial use" and have all required labeling per regulations. Each vial will be individually labeled for future subject identification purposes.

GEM103 will be supplied in single-use vials with a 0.25 mL fill volume at a concentration of 10 mg/mL CFH. The study site pharmacy personnel will prepare a single dose for each subject. A pharmacy manual will be made available and training provided to ensure pharmacy staff can comply with all drug storage, preparation, administration, and drug accountability procedures.

6.4.3 Storage

GEM103 must be stored in a secure area with limited access, protected from moisture and light, and be stored at 5°C ±3°C (2-8° C). The refrigerator should have an automated temperature recording and alert system. In addition, drug accountability study personnel are required to keep a temperature log to establish a record of compliance with these storage conditions. Only drug accountability personnel should have access to the product used in this study.

6.4.4 Disposition

The Investigator or designee will be responsible for maintaining accurate records for all supplies used. Opened vials of GEM103 containing residual volume will undergo GEM103 accountability/reconciliation. Following GEM103 accountability, the Sponsor will provide authorization to the Investigator to return or destroy any remaining investigational product as described in Section 6.7.

Under no circumstances will GEM103 be used other than as directed in the protocol. Refer to the pharmacy manual for additional details.

The site is responsible for reporting to the site monitor and to the appropriate Sponsor representative any vials of GEM103 that were not temperature-controlled during shipment or during storage. Such vials will be retained for inspection by the site monitor and next steps will be discussed with the Sponsor's Supply Manager. Vials determined to be questionable or unsuitable may be quarantined or disposed of upon approval by the Sponsor according to approved methods.

It is the Investigator's responsibility to ensure that that the pharmacy personnel maintain accurate records of receipt of all GEM103 vials, including dates of receipt. In addition, accurate records will be kept regarding when and how much GEM103 is dispensed and used by each subject in the study (including documentation of each dilutional record used to prepare the drug for injection). Reasons for departure from the expected dispensing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all GEM103 vials will be reconciled and retained until study conclusion. At that time, GEM103 vials will be destroyed or returned to the Sponsor according to applicable regulations.

6.5 Preparation and Administration of Study Drug

6.5.1 Preparation of Study Drug

Dose preparation and administration should be performed using sterile, nonpyrogenic disposable materials including, but not restricted to syringes, needles, transfer tubing, and stopcocks.

Two syringes will be prepared: 1 for aflibercept and 1 for GEM103/sham. Injections will be made with 2 separate syringes according to the methods in the study manual. The syringe

containing GEM103 should be prepared just prior to the start of injection. It is preferable that the prepared syringe is used within 2 hours, although it may be stored at room temperature for up to 4 hours. Part of the preparation may include dilution.

For subjects assigned to the sham+SoC treatment group, a syringe should be prepared to serve as sham to mimic a real IVT injection. For the injection, the needle is removed and only the hub of the syringe is held to the eye.

Prior to preparation of the injection, the vials of study drug should be visually inspected. The solution should not be used if it contains foreign particulate matter or is discolored. The contents should NOT be warmed using a microwave or other heat source. GEM103 is a protein that should be not be shaken and should be handled and mixed gently to prevent foaming.

Refer to the pharmacy manual for detailed instructions regarding the preparation of the injection.

6.5.2 Administration of Study Drug

All IVT injections must be administered by the Investigator, or designee (Subinvestigator) using aseptic technique consistent with accepted guidelines (e.g., AAO Guidelines for Intravitreal Injections 2015, Royal College of Ophthalmologists Ophthalmic Service Guidance for Intravitreal injection therapy May 2018). Study drug must not be injected with other products in the same syringe, as the compatibility of GEM103 in solution with other products has not been evaluated. It is recommended that all injections of GEM103 be administered using a 30-gauge needle and a 1 mL syringe.

Sham injections will be performed using the hub of a 1mL syringe with the needle removed, to mimic the IVT administration of study drug.

At each dosing visit, 2 IVT injections (or sham) will be administered; aflibercept and GEM103 (or sham). They will be administered separately to the same eye, with the second injection administered at 90°, or 3 clock hours distance, from the location of the first injection. GEM103 and aflibercept will under no circumstances be administered as 1 combined injection from the same syringe. The intravitreal injections will be administered in accordance with SoC techniques including the use of 5% povidone iodine and a sterile lid speculum. Administer aflibercept (2 mg/50 µL) first, followed by GEM103 (500 µg/50 µL) 15 minutes (±5 minutes) later. Measure IOP after IVT injections as described in the SOA (Appendix A).

Refer to the pharmacy manual for detailed instructions on the administration of GEM103 and sham. Administer aflibercept following the instructions in the current, approved full prescribing information and any available institutional guidelines, if applicable.

6.6 Randomization of the Study Drug

All subjects in both treatment groups will receive EOM treatment.

Subjects will be randomized to 1 of 2 treatments: GEM103+SoC or sham+SoC (SoC defined as aflibercept EOM) for a total of 6 doses during the 12-month study period.

Possible changes to randomization and subsequent analysis based on discontinuation of assignment to a study arm are described in Section 8.6.

6.7 Destruction of the Study Drug

All study drug vials are single-use. All vials with leftover study drug after administration will be destroyed at the site after accountability/reconciliation is complete and in accordance with site standard operating procedures and policies governing drug destruction.

If any unused study drug material is remaining upon completion of the study, the material will be returned to the Sponsor or designee or destroyed only after the Sponsor or designee has performed final drug accountability/reconciliation and provided written authorization for the return or destruction of the study drug. Refer to the pharmacy manual for further instructions.

7 ASSESSMENT OF SAFETY

The methods for collecting safety data are described below. All personnel involved with the study must ensure they are familiar with the content of this section.

7.1 AEs and Laboratory Abnormalities

7.1.1 Clinical AEs

An AE is any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. Pre-existing conditions that worsen in severity during the course of the study are to be reported as AEs. Vital signs considered clinically significant by the Investigator should be documented as AEs.

All AEs (including procedure-related AEs) occurring during the clinical study following the signing of consent will be reported in the AE eCRF.

The Investigator will assess the severity, causality (relationship to study drug), and seriousness of each AE.

Severity: The Investigator will assess the severity of all AEs as mild, moderate, or severe based on the following definitions developed from the Clinical Data Interchange Standards Consortium Study Data Tabulation Model v3.1.1 standard terminology.

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research subject.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Causality: AEs/SAEs will be assessed as not related, unlikely related, possibly related, probably related, or definitely related to study drug. Table 2 provides general guidance on the assessment of causality. For data reporting purposes, AEs assessed as not related or unlikely related will be classified as unrelated to study drug, and AEs assessed as possibly related, probably related, or definitely related will be classified as related to study drug. Assessment of causality should be based on the Investigator's medical judgment and the observed symptoms associated with the event.

Expectedness: AEs/SAEs will be considered unexpected if the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

Table 2. Assessment of Causality

Relationship to Study Drug	Criteria for Judgment
Definitely Related	Reasonable temporal relationship of the clinical event to study drug administration AND cannot be reasonably explained by other factors (such as the subject's clinical state, concomitant therapy, and/or other interventions).
Probably Related	The temporal relationship of the clinical event to study drug administration makes causal relationship probable but not possible AND other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
Possibly Related	The temporal relationship of the clinical event to study drug administration makes causal relationship possible but not unlikely AND other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
Unlikely Related	The temporal relationship of the clinical event to study drug administration makes causal relationship unlikely but not impossible AND other drugs, therapeutic interventions, or underlying conditions provide a plausible explanation for the observed event.
Not Related	Data are available to clearly identify an alternative cause for the reaction.

Seriousness: AEs will be classified as serious or nonserious according to the definitions provided below.

An SAE is any AE that is or leads to any of the following:

- Death
- Immediately life-threatening. An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect
- Persistent or significant disability or incapacity
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.2 Laboratory Test Abnormality

Laboratory test results either will be recorded on the eCRF or appear on the laboratory reports submitted directly from the central laboratory. Out-of-range laboratory test values should not be reported as AEs unless they are considered clinically significant abnormalities by the Investigator.

7.2 Recording of AEs

At each contact with the subject, the Investigator will elicit information on AEs. Any information on AEs should be recorded in the source documentation and in the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under 1 diagnosis.

Any AEs remaining unresolved should be recorded as "ongoing." Ongoing AEs/SAEs should continue to be followed up for the period specified in Section 7.3.2. However, follow-up information on SAEs must be reported to the Sponsor or designee as described in Section 7.3.1. Any SAE that occurs after the study period and is considered to be related or possibly related to the study treatment or study participation should be recorded and reported immediately.

All AEs will be recorded by time and date. The time and date when the AE started and stopped, the intensity, seriousness, action taken with regard to GEM103, causality assessment, and outcome of the event will be recorded for each AE.

AEs will be reported for a minimum of 30 days after the last administration of study treatment.

7.3 Reporting and Handling of Safety Parameters

7.3.1 SAEs (Immediately Reportable to the Sponsor)

All SAEs must be reported to the Sponsor or designee immediately and no later than 24 hours after the Investigator's first knowledge of the event (expedited reporting). To report such events, an SAE form must be completed by the Investigator. The Investigator will keep a copy of this SAE form on file at the study site.

The Investigator will provide any additional information within 24 hours of becoming aware of this information. This update should include a copy of the completed SAE form, and any other information that will assist with the understanding of the event. Significant new information on ongoing SAEs must be reported to the Sponsor or designee immediately and no later than 24 hours after the Investigator's becomes aware of this information.

Reporting Serious Adverse Events

The following contact information is to be used for SAE reporting:

Syneos Health Pharmacovigilance

To Report an SAE send to: safetyreporting@syneoshealth.com or Fax to: 877-464-7787.

The definition and reporting requirement are in accordance with ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting (Topic E2, 1995).

7.3.2 AE Reporting Period

The study period during which AEs must be reported is defined as the period from signature of the informed consent to the EOS treatment follow-up. For this study, the study treatment follow-up is defined as a minimum of 30 days after the last administration of study treatment. If the

Investigator becomes aware of an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the Sponsor.

7.3.3 Investigator Reporting: Notifying the Sponsor

SAEs must be reported in accordance with the process and timelines described in Section 7.3.1.

7.3.4 Investigator Reporting: Notifying the IRB/IEC

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB/IEC according to local regulations. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Investigator's study file.

7.3.5 Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor is required to report certain study events in an expedited manner to the FDA. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- Immediately and within 7 calendar days
    - Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and fatal or life-threatening
    - Follow-up information must be reported in the following 8 calendar days
- Immediately and within 15 calendar days
    - Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening
    - Any finding from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity
    - Any event in connection with the conduct of the study or the development of the investigational medicinal product that may affect the safety of the study subjects
    - Follow-up information must be reported within 15 calendar days

For the purposes of expedited reporting, the determination of causality will be the responsibility of the Sponsor with consideration of the Investigator's assessment of causality.

The Sponsor will comply with all additional local safety reporting requirements, as applicable.

7.3.6 Sponsor Reporting: Notifying Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

7.3.7 Treatment and Follow-up of AEs

During the study, all SAEs and ocular AEs will be followed up until they have returned to baseline status or stabilized or until the Investigator and Sponsor agree that follow-up is no longer necessary. If a clear explanation is established, it should be documented.

Treatment of AEs is at the discretion of the Investigator and should follow the standards of medical care at the Investigator's institution.

7.3.8 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained clinically significant abnormal laboratory values, the tests should be repeated immediately and followed up until they have returned to baseline values and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded; this follow-up may occur with the subject's primary care physician.

7.3.9 Pregnancy

Contraception and pregnancy avoidance procedures are described in Section 4.5.2.

A female subject must be advised to immediately inform the Investigator if she becomes pregnant during the study and must not receive further GEM103 injections. Pregnancies occurring through the EOS must be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor within 24 hours of notification. The Investigator should counsel the subject discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a subject participating in the study (through the EOS) must also be reported to the Investigator and the Sponsor. The partner should be counseled and followed as described above (Section 4.5.2).

7.4 Medical Review Committee (MRC)

An MRC consisting of Sponsor medical personnel and independent medical expert(s) will meet approximately quarterly to review safety information for the study. The first meeting is planned to occur after at least 3 subjects have completed 3 doses of GEM103+SoC. The MRC may also be convened for an ad hoc meeting to discuss interim safety findings at the discretion of the Sponsor (e.g., if 2 or more subjects report clinically similar study drug-related SAEs).

8 STATISTICAL PLAN

8.1 General Considerations

Descriptive summary statistics will be provided for demographics, disposition, and dose exposure. The number and percentage of subjects who discontinued from the study, along with reasons for discontinuations, will be tabulated and described in listings. All descriptive summaries will be provided by treatment group (GEM103 vs sham).

Continuous data will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation, and two-sided 95% confidence intervals (CI); categorical data will be summarized by sample size, proportions, and two-sided 95% CIs.

Any reported p-values will be considered part of the descriptive analyses (i.e., hypothesis-generating) and will not be adjusted for multiplicity. The phrase "statistically significant" may be used interchangeably with "nominally statistically significant" to indicate that a nominal p-value was ≤ 0.05.

Full analysis details will be provided in a separate Statistical Analysis Plan (SAP).

8.2 Determination of Sample Size

The planned total sample size of approximately 45 subjects (~30 treated with GEM103+SoC, ~15 treated with sham+SoC; SoC defined as aflibercept EOM) is based on feasibility considerations, rather than any specific statistical test.

8.3 Analysis Sets

8.3.1 Consented Subject Set

The Consented Subject Set will include subjects who signed the ICF and will be used to create a diagram to illustrate subject flow from consent through disposition (similar to a Consolidated Standards of Reporting Trials [CONSORT] diagram for a randomized trial).

8.3.2 Biomarker Set

The Biomarker Set will include subjects with sufficient data to assess biomarker results.

8.3.3 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who receive at least 1 dose of study drug (GEM103 or sham). Safety analyses will be performed on the FAS. Analyses on the FAS are consistent with the intention-to-treat principle.

8.4 Demographics and Safety Analysis

Demographic baseline characteristic data will be summarized according to the methods described in Section 8.1.

Various analyses to describe subject characteristics will be performed such as length of prior aflibercept treatment, type of CNV lesions, etc.

Descriptive statistics will be computed for safety parameters, as appropriate. Number and percentage of subjects who discontinued from the study because of AEs will be tabulated across dose cohorts; severity and frequency of AEs and SAEs will also be tabulated across treatment

groups. All other safety data will be provided in listings. Physical examination findings, clinical laboratory values, and vital signs will be summarized by dose cohort.

The proportion of subjects with measurable antibodies to GEM103 will be displayed.

Further statistical evaluations will be applied for select endpoints, if warranted. All baseline data and safety data collected during the study will be listed for each subject.

All AEs will be coded using a consistent version of the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher) and will be classified by MedDRA system organ class (SOC) and preferred term (PT).

AE analyses will include the following tabular summaries:

- Summary of all AEs
- Incidence of AEs by SOC and PT
- Incidence of AEs by severity
- Incidence of SAEs
- Incidence of treatment-related AEs

8.5 Biomarker, Imaging, and Clinical Endpoint Analysis

Aqueous humor will be collected prior to the first dose, and just prior to each GEM103/sham IVT injection to evaluate complement proteins and possibly inflammatory cytokine profiles to determine their potential as PD biomarkers for usefulness in a pivotal study. Total CFH concentrations in aqueous humor and plasma will be evaluated.

Imaging endpoints such as CNV lesion size, MA lesion size, retinal layer thickness or presence of fluid, and clinical endpoints such as BCVA, low luminance visual acuity (LLVA), and low luminance deficit, will be analyzed according to the methods of Section 8.1.

Analyses of biomarkers, imaging assessments, and clinical endpoints will be descriptive, and will summarize actual values and changes from baseline over time. Graphical displays will also be created.

Analysis of biomarker, imaging, and clinical endpoint changes from baseline will primarily employ the Wilcoxon rank-sum test.

Full analysis details will be provided in the SAP.

8.6 Summaries of Data Prior to Study Completion

Interim data may be summarized for presentation to regulatory authorities or to the scientific community to facilitate discussions and obtain input on late phase study designs.

As the design of this study is not based on a specific statistical test, no adjustments will be made to the final analyses for this type of change, but the change itself will be noted in the final clinical study report (CSR), and sensitivity analyses will be performed to assess potential impact of the change.

For some of these summaries, CIs may be computed. Additional details of the prespecified statistical analyses will be provided in the SAP.

8.6.1 Handling of Missing Data

In general, missing results will not be imputed. Additional information, including information about missing data related to COVID-19, can be found in the SAP.

9 DATA QUALITY AND ASSURANCE, SUBJECT DATA HANDLING, AND RECORD KEEPING

All aspects of the study will be monitored for compliance with applicable government regulations with respect to current ICH harmonised tripartite guideline E6(R2): GCP and current standard operating procedures. An electronic data capture system that is validated and compliant with US Title 21 of the CFR Part 11 will be used.

Information about study subjects will be kept confidential and managed according to the requirements of applicable local regulations. Further details are described in Section 11.1.

9.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments.

The images plus auxiliary information will be stored locally but also transmitted to the Sponsor in Digital Imaging and Communications in Medicine format for potential further internal analyses and for generation of illustrative images.

9.2 Case Report Forms (CRFs)

Required data for this study will be captured on CRFs via electronic data capture (eCRFs) unless otherwise specified in this document. Except for data points for which the protocol indicates that the eCRF may serve as source documentation, data are to be obtained from the subject's source documents and then entered into the eCRF by authorized personnel. Clinical data that are not recorded on the eCRF will be captured and transferred to the Sponsor or its designee.

9.3 Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application for GEM103 in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of GEM103. These documents should be retained for a longer period if required by the local legislation requirements or an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

10 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

This study will be monitored according to the study monitoring plan. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study-related facilities (e.g., diagnostic laboratory), and has adequate space to conduct the monitoring visit.

The clinical monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the Investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

10.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the Sponsor (or their designee), government regulatory bodies, and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data). In the event of an audit, the Investigator agrees to allow the Sponsor, their representatives, the FDA, the Department of Defense or federal representatives, or other regulatory agencies access to all study records. The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory).

The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

10.3 Management of Protocol Amendments and Deviations

10.3.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval before subjects are enrolled into an amended protocol.

10.3.2 Protocol Deviations

The Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A study deviation is a significant or a nonsignificant deviation from the protocol or to ICH GCP E6R2 or a noncompliance with applicable regulatory requirements. Nonsignificant protocol deviations do not impact the endpoints or the safety or mental integrity of a subject or the

scientific value of the study. A protocol violation or significant deviation occurs when the subject or Investigator did not adhere to the protocol, and the deviation affects primary efficacy and safety assessments, the safety or mental integrity of a subject, or the scientific value of the study.

All deviations, significant and nonsignificant, will be reviewed and documented by the clinical team throughout the course of the study. The Investigator will be notified in writing by the monitor of all deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner. The clinical team will follow all deviations until resolved.

10.4 Study Termination

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last subject completes the last visit (includes the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required to monitor the resolution of a finding or AE may be reported through an amendment to the CSR.

11 INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of applicable local regulations.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (through the ICF), except as necessary for monitoring, auditing, and analyses by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study and future research, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2 Institutional Review

Federal regulations and the ICH E6(R2) guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2) guidelines will be maintained by the site and will be available for review by the Sponsor or its designee.

11.3 Subject Consent

The Investigator is required to obtain informed consent according to Section 5.1.1 of this protocol and appropriate local requirements and regulations prior to enrolling a subject in this study.

11.4 Financial Disclosure and Obligations

The Investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the Sponsor, its delegates, nor the study site is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor, its vendors, nor the study site is financially responsible for further treatment of the disease under study.

11.5 Study Conduct and Adherence to Protocol

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The study will be conducted in compliance with the protocol, current GCP guidelines – adopting the principles of the Declaration of Helsinki – and all applicable regulatory requirements.

11.6 Data Collection

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and similar sources.

Electronic CRFs are accessed through an electronic data capture system that is validated and compliant with 21 CFR 11.

11.7 Reporting Adverse Events

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and methods outlined in this protocol (for details refer to Section 7). In addition, the Investigator agrees to submit annual reports to his IRB as appropriate. The Investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the Investigator's participation in the study.

11.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the Sponsor's responsibility to inform the Investigator/institution as to when these documents no longer need to be retained.

11.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over decisions related to data publication.

Data are the property of the Sponsor and cannot be published without their prior authorization.

12 ETHICAL CONSIDERATIONS

This study is to be conducted in accordance with international standards of GCP (ICH, EU Directives 2001/20/EC and 2005/28/EC, and US 21CFR50 and 21CFR312), as well as all other applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB/IEC, in agreement with local legal requirements, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the applicant and a copy of this decision will be provided to the Sponsor before commencement of this study. The IRB/IEC will be requested to provide a list of IRB/IEC members. A member who is affiliated with the Sponsor should not participate in voting on the IRB/IEC opinion.

Each subject will be given an ICF describing this study and providing sufficient information to allow the subject to make an informed decision about the subject's participation in this study. This ICF will be submitted with the protocol for review and approval by the IRB/IEC for the study. The formal consent of a subject, using the IRB/IEC-approved ICF, must be obtained before that subject undergoes any study procedure. The ICF must be signed by the subject, and the Investigator-designated research professional obtaining the consent.

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved (if applicable) by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval must be returned to the Sponsor or designee. Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB with a summary of the study's outcome, and the Sponsor and regulatory authority(ies) with any reports required.

13 CLINICAL STUDY REPORT AND DATA DISCLOSURE

A CSR will be produced upon completion of the study. A coordinating Investigator will be designated to review and sign the completed CSR.

Information about this study will be posted on the http://clinicaltrials.gov and https://www.clinicaltrialsregister.eu websites (if applicable) and, where applicable, on other websites required by the local regulatory authorities of participating countries.

It is intended that the results from this research will be submitted to a peer-reviewed medical publication, once the study is completed.

13.1 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that a CSR is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports, and have the opportunity to review complete study results.

A CSR will contain all data collected through to the EOS.

Upon completion of the CSR(s), the Sponsor will provide the Investigator(s) with the final approved CSR(s).

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15 APPENDICES

Appendix A: Schedule of Assessments

	IC/EC Screen [a]	Baseline	48 hr Post-dose Phone Call	Week 1 Phone Call	Week 2	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48 EOS
Clinical Visit (C) or Phone Visit (P)	C	C	P	P	C	C	C	C	C	C	C
Study Day (First Dose = Day 1)	-35 to -1	1	3 (±1)	8 (±2)	15 (±2)	57 (±4)	113 (±4)	169 (±4)	225 (±4)	281 (±4)	337 (±4)
Informed consent [b]	X										
Blood sample – exploratory genetics *[a]		X									
Medical and Ocular History *[c]	X										
Inclusion/Exclusion Criteria *[d]	X										
Demographics	X										
Complete Physical Examination	X										X
ECG	X										
Vital Signs *[e]	X	X			X	X	X	X	X	X	X
Concomitant Medications *	X	X	X	X	X	X	X	X	X	X	X
Treatments and AEs											
Randomization†		X									
Aflibercept SoC Administration		SE				SE	SE	SE	SE	SE	X [f]
Treatment (Sham or GEM103) Administration		SE				SE	SE	SE	SE	SE	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X [g]
Ocular Assessments											
Complete Ophthalmic Examination *[h]	OU	OU			OU	OU	OU	OU	OU	OU	OU
Intraocular Pressure Assessment [i]	OU	OU [i]			OU	OU [i]	OU [i]	OU [i]	OU [i]	OU [i]	OU
ETDRS BCVA *[j]	OU	OU			OU	OU	OU	OU	OU	OU	OU
ETDRS BCVA LLVA *[j]		OU					OU	OU			OU
Imaging and Visual Function Assessments ** (Imaging assessments may be optionally performed at any in-clinic visit if deemed medically necessary for subject safety)											
Color Fundus Photography (3-Field) *	OU	OU [k]						OU			OU
Fundus Autofluorescence *	OU	OU [k]				OU	OU	OU	OU	OU	OU
Fluorescein Angiography *[l]	OU							OU			OU
Near Infrared Reflectance Imaging *	OU	OU [k]						OU			OU
Optical Coherence Tomography (SD-OCT)	OU	OU [k]			OU	OU	OU	OU	OU	OU	OU
OCTA [m]		OU [k]						OU			OU
NEI-VFQ-25 *[o]		X						X			X
MNRead *[n]		X						X			X
Other Assessments											
Selection of Study Eye [d]		X									
Pregnancy Testing [p]	X										X
Clinical Safety Laboratory Assessments *[q]	X	X			X	X	X	X	X	X	X
Routine Urinalysis [r]	X										X
Plasma for CFH		X						X			
Blood Sampling – ADA *		X				X	X	X	X	X	X
Aqueous Humor Sampling *		SE				SE	SE	SE	SE	SE	SE

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BCVA=best corrected visual acuity; CFH=complement factor H; EC=exclusion criteria; ECG=electrocardiogram; EOS=End of Study; ETDRS=Early Treatment Diabetic Retinopathy Study; hr=hour; IC=inclusion criteria; IOP=intraocular pressure; LLVA=low luminance visual acuity; MNRead=Minnesota Low-vision Reading Test; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; OCT=optical coherence tomography; OCT-A=OCT angiography; OU=oculus uterque (both eyes; eyes will be tested separately); SAE=serious adverse event; SD-OCT=spectral domain OCT; SE=study eye; SoC=standard of care (2 mg aflibercept every other month); VA=visual acuity

* Assessment obtained prior to dosing, as applicable.

** Imaging (color fundus photography, fundus autofluorescence, fluorescein angiography, near infrared reflectance imaging, SD-OCT) should be repeated at baseline if >28 days after screening assessment, or desired by the Investigator.

† Randomization may occur up to 2 days prior to the baseline visit.

[a] Blood sampling for exploratory genetics will occur prior to first dosing.

[b] Informed consent must be obtained before any study assessment is performed.

[c] Medical and ocular history also includes social history and family ophthalmic history (Section 5.1.3).

[d] Some entry criteria apply only to the SE. Therefore, the SE must be identified during the screening process in order to assess entry criteria (Section 5.4).

[e] Vital sign measurements include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. The subject will be seated for at least 5 minutes before all measurements are taken. When procedures overlap and are scheduled to occur at the same timepoint, vital sign measurements should precede any blood collection (Section 5.1.7).

[f] No IP/Sham treatment will be given at the 48-week EOS visit; however, aflibercept SoC should be administered as clinically indicated. It is acceptable for a different anti-VEGF therapy to be administered at this visit per the investigator's clinical judgement.

[g] AEs will be reported for a minimum of 30 days after the last administration of study treatment. If a subject experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the Sponsor. See Section 7.3 for full AE reporting procedures.

[h] Complete ophthalmic examinations of both the study and fellow eye will include an assessment of the VA and visual function using validated assessment tools, a complete ophthalmic biomicroscopy examination including fundus examination, IOP, and ocular imaging tests to visualize the appearance and pathology of the retina and associated ocular tissues (Section 5.1.6).

[i] On dosing days, IOP assessments are obtained prior to the dose OU, and 30±15 minutes after the dose only in the SE (OU optional). An additional assessment from the SE should be taken at 60±15 minutes if the IOP has not resolved to ≤30 mmHg at the 30-minute assessment. If the IOP continues to exceed 30 mmHg, then standard IOP-lowering interventions (per institutional guidelines) should be followed. If IOP is ≤5 mmHg, the subject should be treated per institutional guidelines. Regardless of whether applanation tonometry or a Tono-Pen® is used to measure IOP, the same method should be used for the subject for the entirety of their participation in this study.

[j] ETDRS BCVA and BCVA LLVA will be performed by masked assessors.

[k] These baseline imaging assessments are only required if the screening images were obtained >28 days prior to baseline. They may be redone at baseline if the Investigator deems it clinically relevant, or if there were quality issues with the screening images.

[l] Baseline assessment of fluorescein angiography is not required, but may be assessed if the Investigator deems it clinically relevant, or if there were quality issues with the screening images.

[m] Assessment is optional and will only be conducted if the site has approval from the Sponsor.

[n] Assessment will be performed as described in Appendix I.

[o] Assessment will be performed as described in Appendix J.

[p] Highly sensitive (serum or urine) human chorionic gonadotropin pregnancy test as needed for women of childbearing potential.

[q] Clinical safety laboratory assessments include the following: hematology (platelet count, red blood cell count, hemoglobin count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, percent reticulocytes, and white blood cell count with differential) and clinical chemistry (blood urea nitrogen, creatinine, glucose, potassium, sodium, total calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, standard electrolytes – magnesium, phosphate, and chloride).

[r] Routine urinalysis includes macroscopic and microscopic examination.

Appendix B: Biological Sample Collection and Shipping Instructions

Biological Samples

Whole blood and aqueous humor samples for the assessment of complement protein concentrations (such as, but not limited to, complement factor H, complement factor I, complement factor B, complement component 3); DNA and cells; and samples for serum chemistry will be collected at the timepoints specified in the SOA in Appendix A.

Refer to the laboratory manual for detailed sample collection, storage, and shipping instructions. All necessary transfer tubes, Vacutainer®tubes, labels, shipping boxes, and forms, will be provided by the central laboratory.

Anterior Chamber (Aqueous Humor) Sample Collection

The following procedures will be followed:

- The aqueous humor paracentesis samples will be collected using aseptic technique by a qualified physician following the instructions outlined in the pharmacy manual.
- The aqueous humor sample collection consists of an anterior chamber paracentesis (ACP) (removing approximately 0.1 mL of aqueous fluid from the anterior chamber of the eye). The procedure will be performed by passing a needle through the limbus using the physician's anesthesia of choice following application of topical anti-bacterial solution (e.g., 5% povidone iodine ophthalmic solution) (see pharmacy manual for complete instructions).

Please refer to laboratory manual for additional details on handling of collected samples.

Samples will be collected with the kit provided by the central laboratory and shipped on dry ice to the central laboratory as soon as possible after the draw.

The samples will be approximately 100 µL, which is expected to be well-tolerated without pain or other side effects.

Appendix C: Color Fundus Photography (CFP)

Scope:

Color fundus photographs will be taken by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the SOA in Appendix A. Analysis of fundus photographs will be performed by the Image Reading Center.

Equipment:

See the Image Reading Center manual.

Procedure:

The Image Reading Center will provide a manual and training materials. The fundus photographer and photography equipment will be certified by the reading center before any study images are taken. See the Image Reading Center manual for further details.

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject, the rationale must be clearly marked in the subject's study binder and made available if requested.

Appendix D: Fundus Autofluorescence (FAF)

Scope:

FAF will be performed by trained personnel at the study site who are certified by the Image Reading Center. FAF imaging will be obtained at the intervals specified in the SOA (Appendix A). Analysis of FAF images will be performed by the Image Reading Center.

Equipment:

Digital imaging systems are required as described in the Image Reading Center manual. The system and software at the site will be certified by the Image Reading Center prior to obtaining any study images. This certification and validation process will ensure that the Image Reading Center will be able to correctly calculate the required measurements.

No printed FAF images will be sent to the Image Reading Center.

Procedures and Certification:

The Image Reading Center will provide a manual. The FAF photographer and equipment, systems, and software will be certified by the reading center before any study images are taken. See the Image Reading Center manual for further details.

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject, the rationale must be clearly marked in the subject's study binder and made available if requested.

Appendix E: Fluorescein Angiography (FA)

Scope:

FA will be performed by trained personnel at the study site who are certified by the Image Reading Center. The fluorescein angiograms will be obtained at the intervals specified in the SOA (Appendix A). Analysis of FAs will be performed by the Image Reading Center.

Equipment:

Digital angiograms must be used while conducting an angiographic evaluation for the study. Film-based angiography is not acceptable.

Digital imaging systems are required. The system and software at the site will be certified by the Image Reading Center prior to obtaining any study angiograms. This certification and validation process will ensure that the Image Reading Center will be able to correctly calculate the required measurements.

Procedures:

The Image Reading Center will provide a manual and training materials. The photographer and photography equipment, systems and software will be certified by the Image Reading Center before any study images are taken. See the Image Reading Center manual for further details.

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject, the rationale must be clearly marked in the subject's study binder and made available if requested.

Appendix F: Spectral Domain Optical Coherence Tomography (SD-OCT)

Scope:

SD-OCT will be performed by trained personnel at the study site who are certified by the Image Reading Center. SD-OCT imaging will be obtained at the intervals specified in the SOA (Appendix A) and forwarded to the Image Reading Center.

Equipment:

Digital imaging systems are required as described in the Image Reading Center manual. The system and software at the site will be certified by the Image Reading Center prior to obtaining any study images. This certification and validation process will ensure that the Image Reading Center will be able to correctly calculate the required measurements.

No printed SD-OCT images will be sent to the Image Reading Center.

Procedures and Certification:

The Image Reading Center will provide a manual and training materials. The SD-OCT technician and equipment, systems, and software will be certified by the Image Reading Center before any study images are taken. See the Image Reading Center manual for further details.

Appendix G: Optical Coherence Tomography – Angiogram (OCT-A)

Scope:

OCT-A will be performed by trained personnel at the study site who are certified by the Image Reading Center. OCT-A imaging will be obtained at the intervals specified in the SOA (Appendix A) and forwarded to the Image Reading Center.

Equipment:

Digital imaging systems are required as described in the Image Reading Center manual. The system and software at the site will be certified by the Image Reading Center prior to obtaining any study images. This certification and validation process will ensure that the Image Reading Center will be able to correctly calculate the required measurements.

No printed OCT-A images will be sent to the Image Reading Center.

Procedures and Certification:

The Image Reading Center will provide a manual and training materials. The OCT-A technician and equipment, systems, and software will be certified by the Image Reading Center before any study images are taken. See the Image Reading Center manual for further details.

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject, the rationale must be clearly marked in the subject's study binder and made available if requested.

Appendix H: Near Infrared Reflectance Imaging (NIR)

Scope:

NIR images are taken to complement the Image Reading Center reading center evaluation of fundus autofluorescence images.

NIR will be performed by trained personnel at the study site who are certified by the Image Reading Center. NIR will be obtained at the intervals specified in the SOA (Appendix A) and forwarded to the Image Reading Center.

Equipment:

Digital imaging systems are required as described in the Image Reading Center manual. The system and software at the site will be certified by the Image Reading Center prior to obtaining any study images. This certification and validation process will ensure that the Image Reading Center will be able to correctly calculate the required measurements.

No printed NIR images will be sent to the Image Reading Center.

Procedures and Certification:

The Image Reading Center will provide a manual and training materials. The NIR technician and equipment, systems, and software will be certified by the Image Reading Center before any study images are taken. See the Image Reading Center manual for further details.

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject, the rationale must be clearly marked in the subjects' study binder and made available if requested.

Appendix I: Minnesota Low-vision Reading Test (MNRead) Charts

MNRead Reading Speed Assessment

The MNRead acuity cards are continuous-text reading acuity cards suitable for measuring the reading acuity and reading speed of normal and low-vision subjects. These cards were developed at the Minnesota Laboratory for Low-Vision Research, University of Minnesota, Minneapolis, Minnesota, in research funded by the National Institutes of Health.

Measuring Reading Speed:

The MNRead acuity cards consist of single, simple sentences with equal numbers of characters. The print is a proportionally spaced font, similar to that found in many newspapers and books. The cards contain sentences with 19 different print sizes. The text is printed with high contrast (approximately 85%). Each sentence contains 60 characters (including space between each word and the end of each line) printed as 3 lines with even left and right margins. The vocabulary used in the sentences are selected from words appearing with high frequency in second- to third-grade reading materials.

Equipment:

MNRead acuity cards are used to measure reading speed at different print sizes to determine the print that supports the subject's maximum reading speed. A stopwatch is required to record time to a tenth of a second. An easel or adjustable stand may be needed for some subjects.

Testing:

Card Illumination:

The cards should be evenly lit so that no shadows or glare will interfere with reading. The luminance of the white background on the cards should be between 80-120 cd/m^2.

Viewing Distance:

The print sizes and markings on the cards are designed for a testing distance of 40 cm, but may be tested at a distance of 32 cm. We recommend using a headrest set to the appropriate viewing distance in front of the cards, to prevent the subject from creeping forward throughout the test. For subjects with central field loss, we find it easier to allow the subject to position the MNRead card so that the sentence to be read will fall into their preferred location for reading.

Testing Procedure:

The MNRead assessment will be conducted first in each eye separately and then with both eyes open. A different card must be used for each test to prevent memorization of the printed material. Rotate cards from one examination to another to vary the text for each eye. Conduct the reading tests in the following order. Start by testing the right eye with the left eye occluded. Next, conduct the speed-reading test in the left eye with the right eye occluded, and lastly with both eyes open.

The card should be read from a distance of exactly 32 cm. To keep the testing distance constant, use a piece of transparent fishing line, pre-measured at 32 cm from the card. Measure the 32 cm to the subject's eye by holding the fishing line parallel to the floor. A ruler or 32 cm measuring device may also be used to set and monitor the distance. Instruct the subject that the card may be moved up and down or side to side, but not closer or farther from the eyes. The card must remain upright and must not tilt away from or toward the subjects. Either the subject or the

examiner may hold the card, depending on the physical ability of the subject. Alternatively, the card may be placed on an easel or adjustable stand.

Check to ensure that the reading card number on the scoring sheet corresponds to the reading card number that you are using. The MNRead scoring sheet contains the test sentences corresponding to the card beginning on the left-hand column in descending order of acuity. Indicate which eye is being tested. Start with the largest sentence and move onto the subsequent sentences. Keep going until the subject cannot read any words in a sentence. Use a blank card to cover each sentence as you work your way down the card: uncover the sentence to be read when you say "start." Present the test sentence; simultaneously, tell the subject to start reading and activate the stopwatch to start the timer. As the subject reads the text, strike out words not read, not attempted, or read incorrectly. Use a stopwatch to record the time taken to read each sentence (to the nearest 0.1 second).

Instructions to the Subject:

"When I say 'start,' read the sentence aloud as quickly as you can without making errors. But if you do make an error, or realize that you have missed a word, read to the end of the sentence and then go back and correct yourself."

Scoring:

Two pieces of information are required to be recorded on the score sheet for each test sentence: the time and the number of errors. Use a stopwatch to record the time taken to read each sentence (to the nearest 0.1 second). For each sentence on the score sheet, mark the total number of words missed, read incorrectly or not able to be read, and the time taken to read the sentence (i.e., the time between when you say 'start' and when the subject finishes uttering the last word in the sentence). Sentences that could not be read or were not attempted due to vision should be recorded as 0 for time and 10 for errors.

Measuring Reading Function:

Subjects' average reading speed, critical print size, and reading acuity will be calculated using the data transcribed from the scoring sheet to the electronic Case Report Form and will not be calculated by the interviewers.

Detailed Table for Administration of MNRead

Selected Countries	Primary Language	MNRead
United States	English, Spanish	X
United Kingdom	English	X
Netherlands	Dutch	X

Study site must make best effort to use the same assessor throughout the study for each subject. If a different assessor is used for the same subject the rationale must be clearly marked in the subject's study binder and made available if requested.

Appendix J: National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI-VFQ-25) with Near and Distance Activity Subscale Scores

The study center and Investigator will include the following credit or attribution statement for the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) questionnaire in any public presentation, publication, or other dissemination or reference to the NEI-VFQ-25 as used in this study.

The following form, based upon NEI-VFQ-25, was developed at RAND (https://www.rand.org) under the sponsorship of the NEI and was adapted by the Sponsor for use in this study.

Six questions from the appendix of optional additional questions for the NEI-VFQ-25, pertaining to the near and distance activities, were added to the form. Minor changes (not affecting the items of the questionnaire) were made to the form, and a header was added with the study number, Sponsor's name, visit, and subject identifiers.

Instructions to Subjects:

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

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

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

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

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

	(Circle One)
READ CATEGORIES:	
Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

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

	(Circle One)
READ CATEGORIES:	
Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

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

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

READ CATEGORIES:	(Circle One)
None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

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

READ CATEGORIES:	(Circle One)
None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

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

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

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

No..... 2

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

(Circle One)

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

Gave up 2

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

(Circle One)

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

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

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

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

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

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

(Circle One)

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

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

(Circle One)

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

PART 3: RESPONSES TO VISION PROBLEMS

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

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

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

(Circle One On Each Line)

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

SUBSCALE: NEAR VISION

A1. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

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

A2. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

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

A3. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

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

SUBSCALE: DISTANCE VISION

A4. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

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

Appendix K: Grading Scale for Uveitis

Endpoint	Grade	Description
Anterior Cells	0	<1 cell in the field
	0.5+	1 to 5 cells in the field
	1+	6 to 15 cells in the field
	2+	16 to 25 cells in the field
	3+	26 to 50 cells in the field
	4+	>50 cells in the field
Anterior Flare	0	No flare
	1+	Faint
	2+	Moderate, iris and lens details clear
	3+	Marked, iris and lens details hazy
	4+	Intense, fibrin or plastic aqueous
Vitreous Haze	0	None, no clinical findings
	1	Minimal, posterior pole clearly visible
	2	Mild, posterior pole details slightly hazy
	3	Moderate, posterior pole details very hazy
	4	Marked, posterior pole details barely visible
	5	Severe, fundus details not visible

Note: Number of cells seen in 1 mm x 1 mm high-powered field.

Appendix L: Medications Known to Potentially Exacerbate Macular Edema or Macular Degeneration

Macular Edema	Macular Degeneration
Acetazolamide Allopurinol Aluminum Nicotinate Betaxolol Broxyquinoline Chymotrypsin Diclorphenamide Dipivefrin Dipivalyl epinephrine (DPE) Epinephrine Ethoxzolamide Griseofulvin Hexamethonium Indomethacin (Indometacin) Iodide and Iodine Solutions and Compounds Iodochlorhydroxyquin Iodoquinol (Diiodohydroxyquinoline) Iothalamate Meglumine and/or Sodium Iothalamic Acid Levobunolol Methazolamide Naproxen Niacin (Nicontic Acid) Niacinamide Nicotinyl Alcohol Phenylephrine Quinine Radioactive iodides Tamoxifen (exclusionary) Timolol	Allopurinol Amodiaquinne Broxyquinoline Chloroquine Clonidine Griseofulvin Hydroxychloroquine Ibuprofen Indomethacin (Indometacin) Iodochlorhydroxyquin Iodoquinol Quinine

Source: "Medication Cautions in Macular Degeneration." www macular.org/medications-use-caution. Accessed 02 October 2019.