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Short Title

Proof-of-concept study of intravitreal CLG561 and LFG316 in subjects with geographic atrophy

Long Title

A randomized, multi-center, single masked, sham controlled, proof-of-concept study of intravitreal CLG561 as a monotherapy and in combination with LFG316 in subjects with geographic atrophy

Protocol Number:	CLG561-2201 (CCLG561X2201A)
Study Phase:	Phase 2
Sponsor Name and Address:	Alcon Research, Ltd.
	Corporate Confidential Information
Investigational Product:	CLG561, LFG316
Indication Studied:	Ophthalmology

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CLG561

Clinical Trial Protocol CCLG561X2201A
(Alcon Protocol CLG561-2201)

A randomized, multi-center, single masked, sham controlled, proof-of-concept study of intravitreal CLG561 as a monotherapy and in combination with LFG316 in subjects with geographic atrophy

Personal Data

Authors:

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Manual of Operations (MOP)

A Manual of Procedures (MOP) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for SAEs (within 24 hours after awareness of the SAE document the event on the SAE eCRF).

Contact information is listed in the MOP.

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Corporate Confidential Information

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List of abbreviations

µL	microliter
ADA	anti-drug antibodies
AE	adverse event
AEF	adverse event form
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AREDS	age-related eye disease study
ARMS2	Age-related maculopathy susceptibility 2
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C3GN	C3 glomerulonephropathy
CFH	Complement Factor H
CFP	color fundus photography
CFR	code of federal regulation
CK	creatinine kinase
CNV	choroidal neovascularization
CRC	central reading center
CSM	clinical site manager
CSR	clinical study report
CV	coefficient of variation
DDD	dense deposit disease
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture

ELISA	enzyme-linked immunosorbent assay
EOS	end of study
ESI	event of special interest
ETDRS	early treatment diabetic retinopathy study
Fab	fully-human antibody
FA	fluorescein angiography
FAF	fundus autofluorescence
FU	follow up
GA	geographic atrophy
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
HIV	human immunodeficiency virus
HTRA1	high temperature requirement A serine peptidase 1
IAG	image acquisition guidelines
IB	Investigator's brochure
IC50	inhibitor concentration 50%
ICH	international conference on harmonization
IEC	independent ethics committee
Ig	immunoglobulin
IOP	intraocular pressure
IRB	Institutional Review Board
IRC	independent review charter
IRT	interactive response technology
IVT	Intravitreal
IV	Intravenous
kg	kilogram
LASIK	laser-assisted in situ keratomileusis
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification

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MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mmHG	millimeters of mercury
MMRM	mixed-effect model repeated measure
MOP	manual of procedures
MPGN II	membranoproliferative glomerulonephritis type II
N or n	sample size
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire – 25
nM	nanometer
No.	number
NOAEL	no observed adverse effect level
OD	Right eye
OS	left eye
PD	pharmacodynamic(s)
pH	negative log of the activity of the hydrogen ion in an aqueous solution
PK	pharmacokinetic(s)
pM	picometer
POC	proof of concept
PP	per-protocol
PRK	photorefractive keratectomy
PT/INR	prothrombin time/international normalized ratio
q2w	biweekly
q4w	every 4 weeks
RBC	red blood cell(s)
RPE	retinal pigment epithelium
SAD	single-ascending dose
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SNP	single nucleotide polymorphism

ULOQ	upper limit of quantification
VEGF	vascular endothelial growth factor
WBC	white blood cell(s)
WHO	world health organization

Pharmacokinetic definitions and symbols

AUC	The area under the plasma (or serum or blood) concentration-time curve
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Tmax	The time to reach the maximum concentration after drug administration [time]

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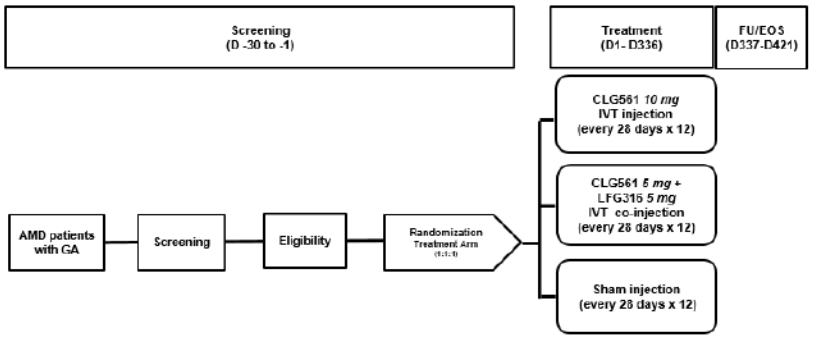
Protocol synopsis

Protocol number	CCLG561X2201A(CLG561-2201)
Title	A randomized, multi-center, single masked, sham controlled, proof-of-concept study of intravitreal CLG561 as a monotherapy and in combination with LFG316 in subjects with geographic atrophy
Brief title	CLG561 (anti-properdin) proof-of-concept study as a monotherapy and in combination with LFG316 (anti-C5) for subjects with geographic atrophy (GA).
Sponsor and clinical phase	Alcon Research, Ltd., a Novartis company Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	To identify whether CLG561 as a monotherapy and in combination with LFG316 has the desired clinical profile in treatment of GA to warrant further development.
Primary Objectives	• To evaluate the safety of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham • To evaluate in the study eye the efficacy of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham on the growth of GA lesion size as assessed by FAF based on the change from baseline to Day 337

Secondary Objectives	• To evaluate the time course of the change in GA lesion size of the active arms as compared to sham as measured by FAF in the study eye
	• To evaluate the time course of the change in BCVA/low luminance visual acuity/low luminance visual acuity deficit up to Day 337 of the active arms as compared to sham in the study eye
	• To evaluate the average change in BCVA/low luminance visual acuity/low luminance visual acuity deficit from baseline to the period Day 281 to Day 337 of the active arms as compared to sham in the study eye
	• To evaluate the time course of the proportion of study eyes losing or gaining ≥15 letters, ≥10 letters, and ≥5 letters in BCVA from baseline up to Day 337 in each of the active arms as compared to sham in the study eye
	• To describe:
	  • The systemic exposure of total CLG561 after IVT administration of CLG561 as a monotherapy up to Day 421
	  • The systemic exposure of total CLG561 and total LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421
	• To describe the immunogenicity of CLG561 after IVT administration of CLG561 as a monotherapy and the immunogenicity of CLG561 and LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421

Study design	This study employs a multi-center, randomized, sham-controlled, single-masked design. Approximately 114 elig ble subjects with GA will be randomized in a 1:1:1 ratio to obtain approximately 90 evaluable subjects completing the study per protocol. Subjects will receive one of three treatment modalities: 1. CLG561 (10 mg/100 µL) 2. CLG561 (5 mg/50 µL) + LFG316 (5 mg/50 µL) 3. Sham injection The treatment modalities will occur every 28 days for a total of 12 injections (or sham injections).  Randomization is performed within an IRT system. The IRT will randomize the subject into 1 of 3 treatment modalities. The following are masked to treatment assignment: • Subjects • Visual acuity assessor at the study site • Technicians obtaining images at the study site • CRC staff Both eyes must have GA. Only one eye must meet the other inclusion/exclusion criteria to be eligible for study participation. Randomization is 1:1:1 (CLG561: CLG561 + LFG316: Sham Injection). The study consists of up to 30-Day screening period, approximately 336-Day treatment period (12 IVT injections occurring approximately every 28 days), and a follow up period consisting of two visits occurring 4 and 16 weeks after the last administered injection. If a subject prematurely exits the study, then he/she must return to the clinical site approximately 4 weeks after their last injection (or the earliest possible date after 4 weeks) for the end of study (EOS) evaluation. In this case, all assessments must be completed at the EOS visit.

Population	Male or female subjects (≥ 50 years old) with GA are deemed most appropriate for this study for the following reasons: • Both CLG561 and LFG316 are being developed for subjects with GA • Due to reduced visual acuity, eyes with GA are less likely to sustain incremental loss of visual acuity from an ocular AE • Eyes with GA may experience a benefit from CLG561 monotherapy or in combination with LFG316 • Administration of multiple doses of CLG561 as a monotherapy and in combination with LFG316 to eyes with GA will provide information regarding the efficacy of monotherapy with CLG561 or its combination with LFG316 • The age range of subjects over 50 corresponds to the typical age range of the subjects with advanced AMD The study plans to recruit approximately 114 subjects (38 in each treatment arm) in order to yield 30 evaluable subjects in each treatment arm.
Inclusion criteria	Subjects eligible for inclusion in this study have to fulfill all of the following criteria: 1. Able and willing to provide written informed consent and in the opinion of the Investigator, the subject is able to complete the duration of the study. Note: Informed consent must be obtained before any assessment is performed 2. Male or female GA subjects ≥ 50 years of age 3. GA in BOTH EYES. One eye MUST meet the following criteria with lesion size assessed by FAF and measured by the CRC. • IF GA lesion is multifocal, THEN the total lesion area must be between 3-16 mm^2 and at least one lesion with an area of at least 1.25 mm^2 • IF GA lesion is unifocal, THEN the lesion area must be between 8-16 mm^2 4. Presence of hyper-autofluorescence adjacent to at least 10% of perimeter of GA in the study eye 5. Best-Corrected Visual Acuity of 20/20 or worse in both eyes at Screening
Exclusion criteria	Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible subjects. 1. Pregnant or lactating women and women of child-bearing potential (defined as all women physiologically capable of becoming pregnant). Women are considered post-menopausal and not of child bearing potential if they have had: • 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) • Total hysterectomy • Surgical bilateral oophorectomy (with or without hysterectomy) • Tubal ligation for at least six weeks • Oophorectomy alone is acceptable ONLY when the reproductive status of the woman is confirmed by follow up hormone level assessments and she is considered to be not of child bearing potential 2. Subjects demonstrating any medical condition (systemic or ophthalmic) that may, in the opinion of the Investigator, and based on the content of the IB, preclude the safe administration of test article or safe participation in this

	3. Any contraindications or hypersensitivities to any component of the LFG316 or CLG561 solution 4. Any contraindications to IVT injections 5. Retinal disease, other than AMD, in either eye Note: Benign conditions of the vitreous or peripheral retina are NOT excluded. Significant peripapillary atrophy either present at the time of Screening or which is expected to merge with the GA lesion during the course of the study **IS** excluded. 6. Any history of, or current evidence of, CNV in either eye, as determined by FA at screening 7. Media opacity that interferes with fundus imaging in either eye, or is likely to require surgery during the study period 8. Any active ocular or periocular infection or active intraocular inflammation in either eye at screening or at baseline (e.g., infectious blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis) 9. Any history of the following in either eye at screening: • herpes simplex keratitis • herpes zoster keratitis • infectious uveitis 10. Penetrating ocular surgery requiring cutting of ocular tissue (e.g., cataract surgery, PRK, LASIK, Epilasik, pterygium removal, etc.) or ocular trauma requiring medical or pharmacological treatment in the study eye within 90 days of screening. Note: Ocular laser procedures are not excluded 11. Macular atrophy in either eye due to anything other than AMD 12. Concomitant treatment for AMD in either eye within 90 days of screening Note: Concomitant use of vitamins/supplements is not excluded 13. Any periocular or IVT injections in either eye within 90 days of baseline 14. Any of the following abnormal vital signs at screening: temperature > 100.5° F (38° C); heart rate> 100 bpm; systolic blood pressure <90 mmHg or > 160 mmHg, diastolic blood pressure > 95 mmHg. Note: Out of range vital signs may be repeated once. If the values are still out of range the visit must be rescheduled. If out of range vitals are observed again and persistent at re measurement, the subject must be disqualified from the study. Subjects may be rescreened when values have stabilized. 15. Uncontrolled ocular hypertension or glaucoma in the study eye (IOP >25 mmHg despite current pharmacological or non-pharmacological treatment) 16. Participation in any interventional clinical trial within 12 weeks prior to screening 17. Any history of participation in interventional clinical trials involving gene therapy or extended release products, or any product with expected long term efficacy

Investigational and reference therapy	Investigational Products/Treatments: CLG561 (anti-properdin Fab) • IVT Injection • 10 mg/100 µL • Every 28 days for total of 12 injections CLG561 (anti-properdin Fab) combined with LFG316 (anti-C5 IgG) • IVT Injection (co-injection) • CLG 561 5 mg/ 50 µL mixed with LFG316 5 mg/ 50 µL (total 100 µL) are mixed in a vial and will be administered as a 100 µL total volume via a single syringe • Every 28 days for total of 12 injections Control Products/Treatments: • Sham injections • Hub of an empty syringe (without a needle) will be placed against the eye • Every 28 days for total of 12 sham-injection procedures
Efficacy /PK/PD assessments	• GA lesion as measured by FAF (both eyes) • BCVA (both eyes) • Low luminance visual acuity (both eyes) • Serum concentration of total CLG561 and total LFG316 • Serum levels of anti-drug antibodies (ADA; anti-CLG561 and anti-LFG316 antibodies)
Safety assessments	• AEs (AEs) (incidence, severity, overall assessment) • Vital signs (blood pressure, heart rate) • Laboratory evaluations • Hematology • Chemistry including liver function tests • Urinalysis • Complete ophthalmic exam (slit lamp, dilated fundus exam, BCVA, IOP)
Other assessments	

Data analysis	**Primary Endpoint** Change in GA lesion size from baseline to Day 337 **Hypotheses** One-sided hypotheses of superiority of active related to the comparison of each of the two active arms vs control (sham injections). The comparison of the two active arms will be done descriptively. **Primary analysis data set** The primary efficacy analysis data set is a per-protocol (PP) set. Key PP criteria are compliance with the GA specific inclusion criteria, the monthly injection schedule up to Day 337 (not missing greater than 1 in any 6 months period or not missing 2 consecutive doses) and available baseline and Day 337 and/or Day 253 lesion size assessments. Missing values of lesion size on Day 337 will be imputed based on linear regression/extrapolation. **Statistical testing strategy** For hypotheses–testing a global one-sided alpha of 0.2 is considered. With the two hypotheses being tested in parallel using the Bonferroni multiplicity adjustment, the nominal one-sided alpha for each single hypothesis will be 0.1. **Statistical method** The lesion size change from baseline to Day 337 will be analyzed by an ANOVA model including but not limited to the class variable representing categories of baseline lesion size (edge length) and categories of lesion location. **Sample size** A sample size of 30 per-protocol (PP) evaluable subjects per treatment arm will allow identification of a treatment difference of 0.67 mm^2 in lesion size change from baseline to Day 337 (representing a 33% reduction in lesion growth rate, assuming an average natural disease progression of 2.0 mm^2 per year) at a one-sided alpha level of 0.1 with a power of 80% assuming a standard deviation of 1.2 mm^2. In anticipation of a drop-out /protocol deviation rate of 20%, a total sample size of ~114 randomized subjects (~38 subjects/arm) is planned for the current study to ensure sufficient study completers for the above described PP analysis. Depending on ongoing monitoring of the drop-out/protocol deviation rate the need for additional recruitment will be assessed to ensure 90 PP evaluable subjects are available for the Day 337 analysis.
Key words	Geographic atrophy, GA, macular degeneration, dry AMD, IVT, intravitreal, retinal diseases, FAF

1 Introduction

1.1 Background

The current study is designed to investigate monthly IVT doses of CLG561 as a monotherapy and in combination with LFG316. The protocol is designed to test the hypothesis that the inhibition of properdin by CLG561 either as a monotherapy or in combination with C5 inhibition by LFG316 may slow or arrest GA lesion growth and thereby preserve visual function.

AMD is the leading cause of legal blindness in the United States and the rest of the developed world (Klein et al 2011). The early signs of AMD are common in individuals over the age of 65 and precede the advanced forms, which are visually devastating. Advanced AMD is divided into two forms: neovascular AMD and GA, which affect approximately 1 million people in the United States (Klein et al 2011), and millions more worldwide. Besides nutritional practices of modest value, there is no treatment to prevent the progression of the early AMD to advanced AMD, or to slow GA once it begins. For the neovascular form of advanced AMD, prompt initiation of anti-VEGF therapies such as Lucentis® can improve visual outcomes in many patients (Rosenfeld et al 2006).

No therapy currently exists for GA, which is usually bilateral and relentlessly progressive. Once the cells of the retina have been lost, they cannot be replaced so improvement in anatomical or functional outcomes is not possible. The only approach to treating this disease is to delay the progression, and prolong the life of the functional retina.

Numerous independent studies of patients with AMD have convincingly identified strong associations between the disease and single nucleotide polymorphism (SNPs) in genes encoding key members of the complement alternative pathway, including the negative regulator complement factor H, the protease complement factor B, and complement factor C3 (Klein et al 2005, Haines et al 2005, Maller et al 2006, Yates et al 2007, Hughes et al 2006, Postel et al 2006, van de Ven et al 2013). Many of the SNPs have allele frequencies greater than 5% and carrier frequencies among Caucasians over 10%.

In aggregate, the population attributable risk of these variants is greater than 50%, meaning that if one had a population of humans without the high-risk alleles, the prevalence of AMD would be substantially reduced (Despriet et al 2006, Gold et al 2006). Risk variants of factor H are found not only to be associated with lifetime incidence of early AMD but also with progression of early to late AMD (Gangnon et al 2012). Increased activation of the alternative complement pathway in the vitreous was also found to be correlated to the AMD disease and genetic variation in the complement pathway, supporting a role for complement activation in AMD disease pathogenesis (Loyet et al 2012).

Recently, human genetic studies of rare, highly penetrant mutations have further strengthened the causal link between complement upregulation and AMD pathogenesis (Raychaudhuri et al 2010, Jozsi et al 2006, Ferreira et al 2009, van de Ven et al 2013, Seddon et al 2013).

The genetic data are supported by functional studies showing: i) immunohistochemical detection of C5 and MAC in drusen from AMD eyes (Mullins et al 2000); ii) the presence of the complement activation products C5a and C3a in drusen, RPE cells, and Bruch's membrane (Nozaki et al 2006); iii) detection of complement proteins and immune complexes in drusen and retinal pigmented epithelial cells (Crabb et al 2002, Johnson et al 2001, Hageman et al 2001); iv) AMD patients have increased serum concentrations of complement activation products (Scholl et al 2007, Hecker et al 2010); v) increased affinity of the AMD risk-associated variant of factor B protein (arginine 32) for C3b with associated enhanced formation of activated convertase (Montes et al 2009); and vii) elevated levels of C5a and sC5b-9 in patients with AMD or associated complement risk polymorphisms (Scholl et al 2008, Reynolds et al 2009).

A hallmark of AMD is the development of drusen, which are lipoproteinaceous deposits located between the retinal pigment epithelium and Bruch's membrane and can be a risk factor for disease progression. In membranoproliferative glomerulonephritis type II (MPGN II), or more specifically C3 glomerulonephropathy (C3GN) and Dense Deposit Disease (DDD), systemic hyper-activation of the complement system, either by C3 nephritic factor or mutations in the complement regulatory protein factor H, leads to deposition of C3 activation products within the kidney glomerular basement membrane. Some patients with MPGN II also develop ocular drusen deposits within Bruch's membrane at early ages that resemble drusen seen in AMD patients and the patients may progress to vision loss (Hageman et al 2001, Appel et al 2005).

Investigator led Phase 2 clinical trials with intravenously administered eculizumab (Alexion) (anti-C5 antibody) have been conducted in patients with GA or intermediate AMD (drusen).

Eculizumab was administered at two different doses to cohorts of patients either with intermediate AMD or GA for 6 months with a further follow up period of 6 months (Yehoshua et al 2014, Garcia Filho et al 2014). The drug was well tolerated with no drug-related AEs. There were no differences between the GA lesion sizes or drusen volume in the treatments versus placebo groups at 6 months. The reasons for inability of eculizumab to demonstrate efficacy in GA or intermediate AMD may be due to the short duration of treatment, the route of administration (IV) of the compound, or the small numbers of patients.

More recently, Genentech presented their Phase 2 results with the anti-factor D Fab, lampalizumab, in patients with GA (Regillo et al 2013). They observed a 20.4% reduction in GA lesion growth in overall patients treated with monthly IVT injection of 10 mg of lampalizumab. The observed effect was larger (42%) in patients who had a complement factor I polymorphism.

In summary, there are multiple converging lines of evidence that AMD involves over-activation of the alternative complement cascade and provides a rationale for complement inhibition therapy.

CLG561 is a fully-human antibody Fab fragment that binds and neutralizes properdin activity to prevent alternative pathway activation. Inhibition of properdin blocks both the early and late nodes of AP activation, preventing the formation of the early activation products, C3a and C3b/iC3b, as well as the late activation products, C5a and C5b, and MAC.

It is proposed to test the safety and efficacy of the combination of LFG316 and CLG561 for the treatment of GA. Other combinations of complement inhibitors were evaluated pre-clinically, and only anti-C5 and anti-properdin were synergistic. The exact mechanism underlying the observed synergy remains unclear, but it could be related to target concentration, target half-life, or target function. Ocular levels of properdin are much lower than other complement proteins, such as C3 and C5, and, based on systemic data, the predicted half-life is longer than other complement proteins, such as Factor D. A lower target concentration coupled with a longer half-life might make properdin a more attractive target for complement suppression. However, properdin is a positive regulator of the alternative pathway, and while it is important for convertase stabilization, it is not essential. Consequently, it might be possible that over time, a small amount of terminal complement complex could be formed even in the presence of CLG561. Perhaps the addition of LFG316 to a system containing CLG561 serves to block any low level pathway activation resulting in more potent complement inhibition. Enhanced blockade of the pathway could lead to a better inhibition of complement-dependent lesion growth and an improvement in patient disease.

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1.2 Study purpose

This study is designed as a POC study to identify whether CLG561 as a monotherapy and in combination with LFG316 has the desired clinical profile in the treatment of GA to warrant further development.

2 Study objectives

2.1 Primary objective(s)

Objective	Endpoint
• To evaluate the safety of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham.	• Incidence and characteristics of treatment-emergent AEs. • Treatment-emergent changes from baseline through Day 421 in ocular and systemic parameters.
• To evaluate in the study eye the efficacy of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham on the growth of GA lesion size as assessed by FAF based on the change from baseline to Day 337.	• Change in GA lesion size from baseline to Day 337 as measured by FAF.

2.2 Secondary objective(s)

Objective	Endpoint
• To evaluate the time course of the change in GA lesion size of the active arms as compared to sham as measured by FAF in the study eye	• Change in GA lesion size from baseline to Day 85, 169, 253, and 421 as measured by FAF in the study eye
• To evaluate the time course of the change in BCVA/low luminance visual acuity/low luminance visual acuity deficit up to Day 337 of the active arms as compared to sham in the study eye	• Change in BCVA/low luminance visual acuity/low luminance visual acuity deficit from baseline by visit up to Day 337 as measured by ETDRS in the study eye
• To evaluate the average change in BCVA/low luminance visual acuity/low luminance visual acuity deficit from baseline to the period Day 281 to Day 337 of the active arms as compared to sham in the study eye	• Average change in BCVA/low luminance visual acuity/low luminance visual acuity deficit from baseline to the period Day 281 to Day 337 as measured by ETDRS in the study eye
• To evaluate the time course of the proportion of study eyes losing or gaining ≥15 letters, ≥10 letters, and ≥5 letters in BCVA from baseline up to Day 337 in each of the active arms as compared to sham in the study eye	• Subject status regarding ≥15 letters, ≥10 letters, and ≥5 letters change from baseline in BCVA by visit up to Day 337 as measured by ETDRS in the study eye

• To describe:
  • The systemic exposure of total CLG561 after IVT administration of CLG561 as a monotherapy up to Day 421
  • The systemic exposure of total CLG561 and total LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421
	• Serum concentrations of total CLG561 (CLG561 monotherapy) and serum concentrations of total CLG561 and total LFG316 (CLG561/LFG316 combination) by visit up to Day 421

• To describe the immunogenicity of CLG561 after IVT administration of CLG561 as a monotherapy and the immunogenicity of CLG561 and LFG316 after IVT administration of CLG561 in combination with LFG316 up to Day 421	• Serum anti-CLG561 antibodies (CLG561 monotherapy) and serum anti-CLG561 and anti-LFG316 antibodies (sham and CLG561/LFG316 combination) by visit up to Day 421

3 Investigational plan

3.1 Study design

This study employs a multi-center, randomized, sham-controlled, single-masked design. Approximately 114 eligible subjects (38 in each treatment arm) with GA will be randomized in a 1:1:1 ratio to obtain approximately 90 evaluable subjects completing the study per protocol. Subjects will receive one of three treatment modalities:

1. CLG561 (10 mg/100 µL)
2. CLG561 (5 mg/50 µL) + LFG316 (5 mg/50 µL)
3. Sham injection

The treatment modalities will occur every 28 days for a total of 12 injections (or sham injections). Subjects assigned to receive sham injections will be treated in the same manner as those assigned to the other two treatment arms, except that the hub of an empty syringe (without a needle) is placed against the eye. For the subjects receiving the CLG561 + LFG316 combination, the drugs are mixed extemporaneously and then injected in a single administration.

Both eyes must have GA. Only one eye MUST meet the other inclusion/exclusion criteria to be eligible for study participation. Randomization is 1:1:1 (CLG561: CLG561 + LFG316: Sham Injection) and assigned by the IRT.

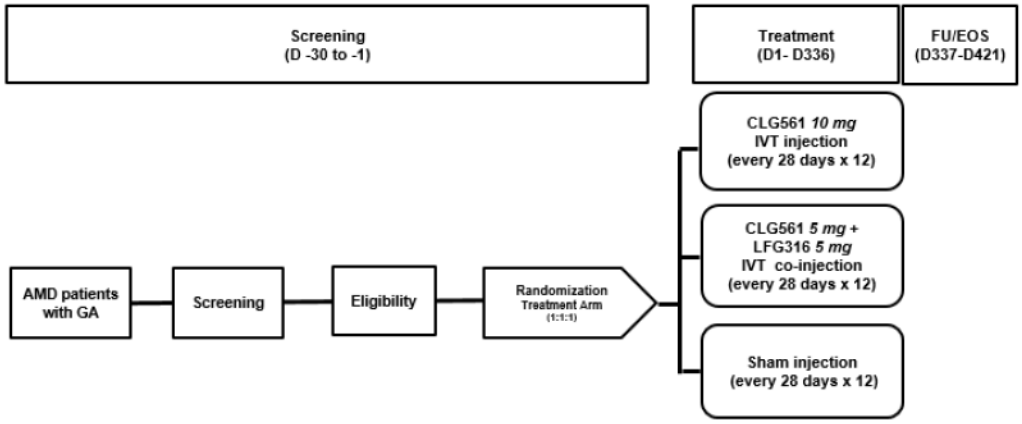
The study consists of up to 30-Day screening period, an approximate 336-Day treatment period (12 IVT injections occurring approximately every 28 days), and a follow up period consisting of two follow up visits occurring 4 and 16 weeks after the last administered injection.

If a subject prematurely exits the study, then he/she must return to the clinical site approximately 4 weeks after their last injection (or the earliest possible date after 4 weeks) for the EOS evaluation. In this case, all assessments must be completed at the EOS visit.

The following will be masked to treatment assignment:

- Subjects
- Visual acuity assessor at the study site
- Technicians obtaining images at the study site

Figure 3-1 Study design



3.2 Rationale of study design

The design of this study will address the primary objectives of efficacy and safety of every 4 weeks IVT injection of monotherapy with CLG561 (10 mg), as well as the combination of LFG316 and CLG561 (5 mg of each) in subjects with GA. Since there is currently no product approved for the treatment of GA, no active comparator is included in the current study. The control for this study will be a sham injection, which is a common and well-established method of control for studies of IVT medications.

Subjects and certain study personnel, but not the Investigator or Sponsor, will be masked to treatment randomization. This approach was chosen for two reasons:

1. Opalescence of the IVT formulation is likely to be visible in the peripheral vitreous, particularly at early visits and would identify actively treated subjects to the study ophthalmologists
2. The primary endpoint is based on objective evaluations by a central reading facility, which will be masked to treatment assignment

Treatment randomization between the active arms and sham allows the evaluation of safety characters of CLG561 as a monotherapy and in combination with LFG316 in a balanced and objective manner. All study subjects will undergo the same study assessments and receive their assigned study treatments under the same dosing interval (every 28 days). All treatment arms will proceed in parallel to each other.

3.3 Rationale of dose/regimen and duration of treatment

Rationale for treatment arms

Since GA is a slowly progressive disease, prolonged treatment and observation are required to detect any potential clinical efficacy with CLG561 as a monotherapy or combination of both CLG561 and LFG316. The every 28 day injection frequency is similar to the standard dosing frequency deployed in the LFG316 monotherapy study and in other GA studies conducted with anti-complement agents [the MAHALO trial by Roche testing every 4 week injection of lampalizumab (anti-factor D Fab)].

Based on power calculations, a 12-month treatment period is adequate to measure a clinically meaningful effect. This period of observation depends on available technology, which is currently FAF with semi-automated area quantification using RegionFinder software (Heidelberg Engineering).

Injection of the maximum deliverable concentration of CLG561 (10 mg) is supported by the 26-week IVT toxicity studies in cynomolgus monkeys. Injection of the maximum deliverable concentration of LFG316 (10 mg) is supported by the 26 week IVT toxicity studies in cynomolgus monkeys (605210) in accordance with ICHS6 (R1). The injection of 5 mg CLG561 and 5 mg LFG316 is supported by the 3 month intravitreal CLG561/LFG316 combination toxicology study in cynomolgus monkeys.

As there are no animal models of GA available, the dose-response relationship is unknown for CLG561 or its combination with LFG316. Thus it is proposed to test the highest safe dose of CLG561 (10 mg) as monotherapy. Further monotherapy dose ranging will take place in phase IIb/phase III studies. The combination of 5 mg of each molecule in 100 µL is the maximum feasible volume that can be safely delivered into the vitreous. The combination of CLG561 and LFG316 has shown synergistic efficacy *in vitro* inhibition of complement activation, and in an in vivo murine in vivo model of complement-dependent ocular inflammation. Thus, it is expected that the combination of CLG561 and LFG316 will have superior efficacy in GA as compared to monotherapy.

3.4 Rationale for choice of comparator

A sham injection is selected as a comparator treatment because there are currently no approved treatments available to subjects with GA.

3.6 Risks and benefits

The risk to subjects in this trial is minimized by adherence to the eligibility criteria, close clinical and safety monitoring, and study/arm(s) stopping rules.

An estimated total of 288.5 mL of blood is planned to be collected over a period of approximately 451 days, from each subject. Additional samples for monitoring of safety findings may be necessary. Blood sampling is not considered to be a risk for this population.

Intravitreal LFG316 up to 5 mg has been administered to over 190 subjects. Over 2000 injections have been administered up to the 10 mg dose. No drug related AEs were noted. CLG561, as a single IVT injection, has been administered to 31 subjects in escalating doses of up to 10 mg. No drug related AEs were noted. A summary of the known and potential risks and benefits associated with CLG561 and LFG316 can be found in the IB.

All IVT injections carry the risk of endophthalmitis, retinal detachment, vitreous or retinal hemorrhage, cataract, elevated intraocular pressure, and ocular inflammation. All of the above conditions are apparent on eye exam, and most cause symptoms that prompt the subject to seek evaluation.

With respect to endophthalmitis, current best clinical practices are used to reduce the risk of endophthalmitis. Despite these practices, endophthalmitis rates may approximate 1 in 1,000 to 1 in 20,000.

As with any antibody, CLG561 or LFG316 are expected to carry the risk of anaphylaxis or hypersensitivity reactions. CLG561 and LFG316 may also elicit the formation of human ADA.

Risks involved in systemic inhibition of properdin

Subjects with inherited properdin deficiency are at increased risks of meningococcal infections (Sjoholm et al 1982; Mathew and Overturf 2006; Fijen et al 1999). Meningococcal infections are the most common presentation of subjects due to properdin deficiency, although recurrent otitis and pneumonia has also been seen (Schejbel et al 2009). The mortality rate in properdin deficient subjects from systemic infections is high (33–75%) (Bathum et al 2006). The specific individual risk of meningococcal infection in properdin deficiency has been calculated at around 50%, a 250-fold increase over the baseline incidence of meningococcal infection in the general population (Linton and Morgan 1999). Investigators should also be aware of other possible infections involving meningococcus, streptococcus, or *H. influenzae*.

After IVT administration of CLG561 there was no clear time-dependent or dose-dependent change in serum complement activity at a dose of up to 10 mg.

In theory CLG561 may predispose to ocular infections, including endophthalmitis or herpesvirus infections. Investigators should be alert to possible ocular infection following IVT administration. Any potential infections must be treated by the Investigator according to the standard of care.

Risks involved in systemic inhibition of C5

Risks involved in systemic inhibition of C5 in humans have been characterized and include risk of serious infections with meningococcus, other encapsulated bacteria, and other agents.

After IVT administration of LFG316 there was no evidence of time-dependent or dose-dependent change in serum complement activity at a dose of up to 5 mg.

However, local immunosuppression could in theory increase the eye's susceptibility to infection, including endophthalmitis. Investigators must always follow strict preventative measures for IVT administration.

Adverse Drug Reactions

CLG561

In clinical study CCLG561X2101A, CLG561 was safely administered to 31 adult and elderly AMD subjects (57 to 86 years) up to a dose of 10 mg. Safety results from this study indicate no dose-dependent AEs associated with IVT administration of CLG561. CLG561 was well tolerated.

LFG316

Four studies with LFG316 have been completed at this time (CLFG316A2101, CLFG316A2102, CLFG316A2201 and CLFG316A2202) and another two studies are currently ongoing Corporate Confidential Information . The AE profiles are described in Section 5.1.1.1 of the Investigator's Brochure.
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In subjects with advanced AMD, there were no drug-related AEs, deaths, serious AEs, or discontinuations.

CLFG316A2201 was a multicenter, multiple dose, 2-cohort study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of intravenous LFG316 in subjects with neovascular age-related macular degeneration. Both cohorts were to employ a randomized, placebo-controlled, double-masked design. Novartis terminated this study and stopped recruitment on 26 March 2013 after just 4 subjects were randomized to LFG316; none were randomized to placebo. The decision to terminate the CLFG316A2201 study was not due to any safety signal with LFG316. It was based upon a consideration of the reported number of subjects with meningococcal infection and unclear risk of death due to meningitis noted after repeated intravenous dosing with Soliris® (eculizumab), which is an approved antibody against complement factor 5 (C5) for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic syndrome. Overall, intravenous infusion of LFG316 was safe and well tolerated and was not associated with any infections.

CLFG316A2202 was a repeat-dose POC study in subjects with neovascular (wet) AMD. This study used a multicenter, randomized study design to assess the efficacy, safety, tolerability, and serum pharmacokinetics of 3 successive doses of intravitreally administered LFG316. The study was completed as planned. Forty-five subjects were randomized in a 2:1 ratio to either LFG316 5 mg/50 µL IVT injection (30 subjects) or to sham injection (15 subjects) for total of 3 doses. Overall, single intravitreal doses of LFG316, up to 5 mg were found to be safe and well tolerated across all treatment groups. Conjunctival hemorrhage was the most frequently reported ocular AE which can be attributed to the IVT injection procedure. None of the AEs were dose dependent or suspected to be related to the study drug. Remaining clinical safety parameters (vital signs, ECG, etc.) and ocular assessments showed no clinically significant changes.

Results from all studies indicate no dose-dependent AEs associated with IV or IVT administration of LFG316. IV infusion and IVT injection of LFG316 were well tolerated in all doses studied.

Combination of CLG561 and LFG316

The combination of the two compounds, CLG561 5 mg combined with LFG316 5 mg, has not been tested in humans.

There may be unknown risks of CLG561 or the combination of CLG561 and LFG316 which may be serious and unforeseen.

4 Population

The study population is comprised of male and female subjects (≥ 50 years old) with GA.

The study population is deemed most appropriate for this study because of the following:

1. Both CLG561 and LFG316 are being developed for subjects with GA
2. Due to reduced visual acuity, eyes with GA are less likely to sustain incremental loss of visual acuity from an ocular AE
3. Eyes with GA may experience a benefit from CLG561 monotherapy or in combination with LFG316
4. Administration of multiple doses of CLG561 as a monotherapy and in combination with LFG316 to eyes with GA will provide information regarding the efficacy of monotherapy with CLG561 or its combination with LFG316
5. The age range of subjects over 50 corresponds to the typical age range of the subjects with advanced AMD

A total of approximately 114 subjects will be enrolled in the study and randomized. At least 90 evaluable subjects are expected to complete the study. A maximum of 216 subjects (72 per treatment arm) may be enrolled if additional subjects are required to replace drop-outs, and balance stratification factors.

The Investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional eligibility criteria must be applied by the Investigator in order to make sure that the study population is representative of all eligible subjects.

Subject selection is established by checking through all eligibility criteria at screening and confirmed at baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study. If BOTH eyes qualify, the eye with the worse visual acuity will be selected as the study eye.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill all of the following criteria:

1. Able and willing to provide written informed consent and in the opinion of the Investigator, the subject is able to complete the duration of the study
   Note: Informed consent must be obtained before any assessment is performed.
2. Male or female GA subjects ≥ 50 years of age
3. GA in BOTH EYES. **One eye MUST meet the following criteria** with lesion size assessed by FAF and measured by the CRC.
   - IF GA lesion is multifocal, THEN the total lesion area must be between 3-16 mm^2 and at least one lesion with an area of at least 1.25 mm^2
   - IF GA lesion is unifocal, THEN the lesion area must be between 8-16 mm^2
4. Presence of hyper-autofluorescence adjacent to at least 10% of the perimeter of GA the study eye

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Pregnant or lactating women and women of child-bearing potential (defined as all women physiologically capable of becoming pregnant). Women are considered post-menopausal and not of child bearing potential if they have had:
   - 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms)
   - Total hysterectomy
   - Surgical bilateral oophorectomy (with or without hysterectomy)
   - Tubal ligation for at least six weeks
   - Oophorectomy alone is acceptable ONLY when the reproductive status of the woman is confirmed by follow up hormone level assessments and she is considered to be not of child bearing potential
2. Subjects demonstrating any medical condition (systemic or ophthalmic) that may, in the opinion of the Investigator, and based on the content of the IB, preclude the safe administration of test article or safe participation in this study
3. Any contraindications or hypersensitivities to any component of the LFG316 or CLG561 solution
4. Any contraindications to IVT injections
5. Retinal disease, other than AMD, in either eye

   Note: Benign conditions of the vitreous or peripheral retina are NOT excluded. Significant peripapillary atrophy either present at the time of Screening or which is expected to merge with the GA lesion during the course of the study, IS excluded.
6. Any history of, or current evidence of, CNV in either eye, as determined by FA at screening
7. Media opacity that interferes with fundus imaging in either eye, or is likely to require surgery during the study period
8. Any active ocular or periocular infection or active intraocular inflammation in either eye at screening or at baseline (e.g., infectious blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis)
9. Any history of the following in either eye at screening:
   - herpes simplex keratitis
   - herpes zoster keratitis
   - infectious uveitis
10. Penetrating ocular surgery requiring cutting of ocular tissue (e.g., cataract surgery, PRK, LASIK, Epilasik, pterygium removal, etc.) or ocular trauma requiring medical or pharmacological treatment in the study eye within 90 days of screening

    Note: Ocular laser procedures are not excluded
11. Macular atrophy in either eye due to anything other than AMD

12. Concomitant treatment for AMD in either eye within 90 days of screening
    Note: Concomitant use of vitamins/supplements is not excluded
13. Any periocular or IVT injections in either eye within 90 days of baseline
14. Any of the following abnormal vital signs at screening: temperature > 100.5° F (38° C); heart rate> 100 bpm; systolic blood pressure <90 mmHg or > 160 mmHg, diastolic blood pressure > 95 mmHg.
    Note: Out of range vital signs may be repeated once. If the values are still out of range the visit must be rescheduled. If out of range vitals are observed again and persistent at re-measurement, the subject must be disqualified from the study. Subjects may be rescreened when values have stabilized.
15. Uncontrolled ocular hypertension or glaucoma in the study eye (IOP >25 mmHg despite current pharmacological or non-pharmacological treatment)
16. Participation in any interventional clinical trial within 12 weeks prior to screening
17. Any history of participation in interventional clinical trials involving gene therapy or extended release products, or any product with expected long term efficacy

5 Restrictions for study subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

In general, systemic medications are allowed; however, corticosteroids (ophthalmic or systemic) should only be used if necessary.

- For both eyes, topical ophthalmic corticosteroids are allowed, however, for the study eye, no IVT ophthalmic agents are allowed
- For the fellow eye, there is no restriction to the use of any topical or IVT ophthalmic agents, provided they are not investigational products

5.1 Contraception requirements

Please refer to the exclusion criteria (Section 4) for details of contraception requirements for the study.

5.2 Prohibited treatment

ELECTIVE intraocular surgeries are prohibited in both eyes.

Any IVT treatments, other than the study treatment, to the study eye are prohibited. If needed, the study ophthalmologist should administer the required IVT treatment (e.g. Lucentis for new onset choroidal neovascularization) to the study eye promptly. However, the study subject who receives the intervention MUST be discontinued from the study and undergo the follow up visit and end of study evaluation.

6 Treatment

6.1 Study treatment

Details on the storage and management of investigational product, randomization and instructions for preparing and administering study treatment are outlined in the MOP.

6.1.1 Investigational treatment

The investigational products CLG561 and LFG316 will be provided by the Sponsor and supplied to the Investigator. The Investigator will be responsible for the preparation of CLG561 injection and the co-administered dose of CLG561 and LFG316 injection.

Subjects assigned to sham injections are treated in the same manner as those assigned to the other two treatment arms, except instead of an IVT injection, the hub of an empty syringe (without a needle) is placed against the eye.

6.2 Treatment arms

Subjects are assigned to one of the following 3 treatment arms in a ratio of 1:1:1.

1. IVT CLG561 (10 mg/100 µL), administered every 28 days for total of 12 injections
2. IVT CLG561 5 mg + LFG316 5 mg co-injected in 100 µL total volume via a single injection, administered every 28 days for total of 12 injections
3. Sham injections, administered every 28 days for total of 12 sham injections

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted.

6.4 Treatment assignment

Subject numbers are assigned by the EDC in ascending, sequential order to all subjects who sign informed consent at each clinical site. The Investigator will enter the subject number in the IRT and EDC as required.

A randomization scheme is used to ensure that treatment assignment is unbiased and concealed from subjects and masked site staff. A randomization list is produced by or under the responsibility of the Sponsor using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Sponsor randomization group.

6.5 Treatment masking

This is a single masked study. Subjects, the CRC, and select investigational staff (technicians performing visual acuity and obtaining images) are masked to the identity of study treatments.

6.6 Emergency breaking of assigned treatment code

The Investigator will have access to the assigned treatment code throughout the study because the study design is single masked. No emergency breaking of assigned treatment code is necessary based on the single masked design.

6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) are determined in all subjects treated with CLG561 or the combination of CLG561 and LFG316, as detailed in Section 8.5.

6.8 Recommended treatment of adverse events

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

6.9 Rescue medication

Use of rescue medication is not allowed. Any IVT treatments, other than the study treatment, to the study eye are prohibited. If needed, the study ophthalmologist should administer the required IVT treatment to the study eye promptly. However, the study subject who receives the intervention will be discontinued from the study and undergo the follow up visit and end of study evaluation. The required IVT treatment must be recorded on the Concomitant medications/Significant non-drug therapies eCRF after start of study drug.

6.10 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies section of the eCRF.

In general, systemic medications are allowed; however, corticosteroids (ophthalmic or systemic) should only be used if necessary.

- For both eyes, topical ophthalmic corticosteroids are allowed, however, for the study eye, no IVT ophthalmic agents are allowed.
- For the fellow eye, there is no restriction to the use of any topical or IVT ophthalmic agents, provided they are not investigational products

Medication entries must be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

The Investigator must discontinue study treatment for a given subject if he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Any condition in the study eye requiring additional IVT treatment
- Any condition requiring intraocular surgery in the study eye
- Use of any ocular (in either eye) or systemic investigational treatments
- Use of prohibited treatment as per Section 5.2
- Any other protocol deviation that results in a significant risk to the subject's safety

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) must be made to contact them as specified in Section 7.2.1.

7.2 Study completion and post-study treatment

Each subject is required to complete the study in its entirety. No further study treatment will be made available to a subject after they have completed the study in its entirety.

Study completion is defined as:

- When the last subject completes the EOS visit

and

- Any repeat assessments or follow-up associated with the EOS are documented appropriately by the Investigator

or

- The date of an early study termination decision

At a minimum, subjects must be contacted for safety evaluations during the 28 days following the follow up visit. Documentation of attempts to contact the subject must be recorded in the source documentation.

The Investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include:

- Enrollment in an extension study
- Standard of care treatment as determined by the nature of their condition

The following are recommendations for initiating other treatment outside the study:

- Referral to another medical professional suitable to provide follow-up medical care
- Inform current medical provider on subject's current medical status

7.2.1 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject (e.g. dates of telephone calls, registered letters, etc.). A subject is not formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Subject withdrawal of consent includes the following conditions:

- Does not want to participate in the study
- Does not want any further visits or assessments
- Does not want any further study related contact
- Does not allow analysis of already obtained biologic material

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Study stopping rules

Under any of the following conditions, the current study/arm(s) are placed on temporary hold and potentially halted, pending full review of the clinical data by the Investigator and Sponsor:

- Two or more incidents of the same SAE that, in the opinion of the Investigator, are related to the study drug(s) and not the injection procedure
- The principal Investigator (or his/her designee) and the sponsor consider that the number and/or severity of AEs justify discontinuation of the study
- The Sponsor requests it

7.5 Early study termination

The study may be terminated at any time for any reason by Sponsor. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures as requested by the Sponsor in order to ensure that adequate consideration is given to the protection of the subject's interests.

The Investigator is responsible for informing IRBs/IECs of the early termination of the trial. In the case of representation by a central IRB, the Sponsor may be delegated this responsibility.

8 Procedures and assessments

Subjects must be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment window", and as specified in the MOP.

A single rescreening is permitted only for patients who failed screening under the original protocol but who would have qualified under the amendment 1 revised selection criteria. In addition to the criteria that were changed, the rescreened patients must fulfill the unchanged selection criteria at both screenings to be eligible. Since the inclusion criterion related to lesion size is now only relevant to a single eye (study eye), for lesion size, the rescreening is limited to eyes which qualified in the original screening. For example if the left eye qualified in the original screening, only the left eye can be rescreened as the study eye. If both eyes had qualified previously on the basis of the lesion size but the eyes had failed on the basis of the visual acuity both eyes are candidates for rescreening.

The subject number previously used will be retained in the database. A new subject number is not required. The original informed consent date is retained in the database. The new informed consent date is captured in the source. A new screening date with data for the assessments is captured in the database.

All data obtained from these assessments must be supported in the subject's source documentation. Source documentation must be available for all data collected during the study. IF it becomes necessary to repeat an evaluation, THEN the results of the repeat evaluation must be recorded in the source documents and the valid measurements and evaluation must be recorded on the eCRF.

All screening, baseline and pre-injection assessments must be completed prior to drug

Unscheduled Visits are allowed at the Investigator's discretion. During an unscheduled visit, the Investigator may perform any of the ocular and non-ocular protocol assessments as necessary to treat the subject (imaging is not required but may be obtained as needed by the investigator). Assessments performed during an unscheduled visit will be documented in the EDC. The Investigator may provide comments in the EDC to clarify unscheduled visit data as necessary.

For additional details of specific study procedures, please reference the MOP.

Table 8-1 Non-ocular assessment schedule

CCLG561X2201A	Screen	Treatment Period																FU	EOS[6]
Visit Numbers [1]	N/A	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 (V777)
Day	-30 to -1	BL/D1	D2	D8	D15	D29	D30	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337	D421
Visit Windows (Days)			+/- 1	+/- 1	+/- 1	- 2	+ 1	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 7
Injection		1				2		3	4	5	6	7	8	9	10	11	12		
Inclusion/exclusion criteria	X	X																	
Relevant medical history/current medical conditions	X	X																	
Ocular and AMD history	X																	X	
Demography	X																		
Dietary history	X																		
Hepatitis and HIV history	X																		
Alcohol and drug dependence history	X																		
Smoking history	X																		

CCLG561X2201A	Screen	Treatment Period																FU	EOS[6]
Visit Numbers [1]	N/A	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 (V777)
Day	-30 to -1	BL/D1	D2	D8	D15	D29	D30	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337	D421
Body height	X																		
Body weight	X	X																	X
Body temperature	X	X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X
Blood pressure / pulse rate	X	X[2]				X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X
Hematology, Blood chemistry, Urinalysis	X																	X	X
Drug administration		X				X		X	X	X	X	X	X	X	X	X	X		
Study completion information																			X
(Serious) Adverse events	as required																		
Concomitant meds/therapies	as required																		
Comments	as required																		

CCLG561X2201A	Screen	Treatment Period																FU	EOS[6]
Visit Numbers [1]	N/A	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 (V777)
Day	-30 to -1	BL/D1	D2	D8	D15	D29	D30	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337	D421
CLG561 and LFG316 concentration sample collection		X[3]	X	X	X	X[3]			X[3]			X[3]			X[3]		X[3]	X	X
IG sample collection		X[3]				X[3]			X[3]			X[3]			X[3]		X[3]	X	X

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[1] Visit structure is given for internal programming purposes only

[2] Body temperature, blood pressure, and pulse rate must be measured prior to IVT injection

[3]

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Unscheduled visit assessments as needed and as determined by the investigator

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Table 8-2 Ocular assessments

CCLG561X2201A	Screen	Treatment Phase																FU	EOS[10]
Visit Number	N/A	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 (V777)
Day	-30 to -1	BL / D1	D2	D8	D15	D29	D30	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337	D421
Visit Window (Days)			+/- 1	+/- 1	+/- 1	- 2	+ 1	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 5	+/- 7
Injection		1				2		3	4	5	6	7	8	9	10	11	12		
Ocular examination[1,2,3]																			
Best corrected visual acuity	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Low luminance visual acuity		OU	OU			OU		OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Intraocular pressure	OU	OU[4]	SE	SE	SE	SE[4]	SE	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE[4]	SE	OU
Slit lamp biomicroscopy	OU	OU	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	OU
Dilated ophthalmoscopy	OU	OU[5]	SE	SE	SE	SE[5]	SE	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE[5]	SE	OU

Color fundus photo	OU	OU							OU			OU			OU			OU	OU
Fundus autofluorescence	OU	OU							OU			OU			OU			OU	OU
Fluorescein angiography	OU																		OU

CCLG561X2201A	Screen	Treatment Phase																FU	EOS[10]
Visit Number	N/A	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 (V777)
Day	-30 to -1	BL / D1	D2	D8	D15	D29	D30	D57	D85	D113	D141	D169	D197	D225	D253	D281	D309	D337	D421

All ocular examinations may be performed at the physician's discretion
[2] OU: both eyes
[3] SE: study eye
[4] For all visits requiring an IVT injection, IOP MUST be measured before and after the injection in the study eye
[5] For all visits requiring an IVT injection, dilated ophthalmoscopy MUST be performed before the injection and immediately after the injection in the study eye

[8] To be done at select sites only, see MOP for additional details
[9] Assessment at screening is for source documentation purposes only
[10] Unscheduled visit assessments as needed and as determined by the investigator, imaging not required

Table 8-3 Post-injection exams at injection visits

Visit	BL / V1					All injection visits				
Day	D1									
Injection	Inj 1									
Time point	Pre-Injection	Immediately Post-Inj	30 minutes Post-Inj	60 minutes Post-Inj, *if required*	Q 30 minute interval, *if required*	Pre-Injection	Immediately Post-Inj	30 minutes Post-Inj	60 minutes Post-Inj, *if required*	Q 30 minute interval, *if required*
Gross visual acuity		SE					SE			
IOP	OU	SE	SE	SE[1]	SE[2]	SE	SE	SE	SE[1]	SE[2]
Dilated Fundus	OU	SE				OU	SE			
Anterior Chamber Paracentesis, *if required* [3]		SE					SE			

[1] If the pressure is elevated >10 mmHg above pre-injection or above 30 mmHg when measured at 30 minutes post-injection it must be measured again at 60 minutes post-injection.

[2] If IOP still elevated at 60 min post-injection, repeat at 30 minute intervals until pressure is < 10 mmHg above pre-injection pressure or < 30 mmHg.

[3] Perform anterior chamber paracentesis if no retinal perfusion 2 or more minutes after injection.

8.1 Informed consent procedures

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Eligible subjects are included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. If incapable of doing so, in cases where the subject's representative gives consent, the subject will be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. The date of signing of informed consent (and withdrawal, if later withdrawn) must be documented in the eCRF.

The Sponsor will provide the Investigators with a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements. Any changes to the proposed informed consent form suggested by the Investigator must be agreed to by Sponsor before submission to the IRB/IEC.

A copy of the approved version of all consent forms must be provided to the Sponsor monitor after IRB/IEC approval.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data is collected on all subjects as stated in the MOP.

Relevant medical history/current medical conditions data includes data until signature of informed consent. When possible, diagnoses (not symptoms) must be recorded. Medical history/current medical conditions are confirmed at Visit 1 prior to drug administration.

Investigators have the discretion to record abnormal test findings that occurred prior to the informed consent signature on the medical history eCRF.

Ocular and AMD History

Past or current ocular history and history of AMD diagnosis, history of GA diagnosis, progression, and treatments must be captured on the appropriate eCRF. Ocular function questions must be reviewed as stated in the CLG561-2201 MOP.

Family History

First degree family history of ocular, renal and cardiovascular diseases must be gathered and captured on the appropriate eCRF as part of the medical history assessment.

Dietary History

Subjects must be asked to estimate their weekly consumption of fish (servings per week) and daily consumption of fruits and vegetables (servings per day). Subjects must be asked whether they use an AREDS-type supplement or omega-3 fatty acid supplement.

Alcohol and Drug Dependence History

All subjects must be asked to provide a verbal history of alcohol and drug dependence (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, etc.). The Investigator must use good clinical judgment based on the subject's verbal history in regard to the inclusion or exclusion of the subject.

Smoking History

Subjects must be asked to provide smoking history in during screening.

Hepatitis and HIV History

All subjects are screened for history of Hepatitis B, Hepatitis C, and HIV. Screening will be based on a verbal history and confirmed by central lab analysis. Results are available as source data only. In the event of a positive case, the subject must be informed of the result. The Investigator must instruct the subject to seek appropriate medical care and provide physician referrals as necessary.

8.3 Efficacy / pharmacodynamics

Pharmacodynamic assessments are specified below. Assessments are performed and samples and images are collected at the time point(s) defined in the assessment schedule.

8.3.1 Pharmacodynamic sample collection

Concentrations of total C5 concentrations of total properdin, and Corporate Confidential Information Corporate Confidential Information All samples are given a unique sample number as indicated in the log that is included in the MOP. Further details on sample collection, numbering, processing and shipment can be found in the MOP.

8.3.2 Pharmacodynamic analytical methods

Determination of the concentration of total properdin and total C5 in serum is performed using either an immunoassay or Liquid Chromatography – Tandem Mass Spectrometry (LC/MS/MS) method. A detailed description of the methods used to quantify the concentration of total properdin and total C5 is included in the bioanalytical raw data of the study and in the bioanalytical data report. The LLOQ is documented in the bioanalytical data reports.

8.3.3 Ocular pharmacodynamic assessments

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The methods for assessment and recording are specified in the IAG for the sites and in the IRC and Reviewer Training Manual for the CRC.

Certification of the equipment and examiners at each investigative site will occur prior to the evaluation of study subjects. The methods for assessment and recording are specified in the IAG for the sites and in the IRC and Reviewer Training Manual for the CRC.

8.3.3.2 Fluorescein angiography (FA)

FA is performed using a standardized technique. FA is performed for each subject according to the assessment schedule. The methods for assessment and recording are specified in the IAG for the sites and in the IRC and Reviewer Training Manual for the CRC.

Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects.

8.3.3.3 Fundus autofluorescence (FAF)

FAF is performed on each subject according to the assessment schedule. The methods for assessment and recording are specified in the IAG for the sites and in the IRC and Reviewer Training Manual for the CRC.

Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects.

8.3.3.4 Color fundus photography (CFP)

CFP will be performed on each subject according to the assessment schedule. The methods for assessment and recording are specified in the IAG for the sites and in the IRC and Reviewer Training Manual for the CRC.

Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. Color fundus photography is undertaken for assessment of safety if needed. The sponsor may request reading of the color fundus photos if needed or may not assess these if not needed.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the MOP, with the assessment schedule detailing when each assessment is performed.

8.4.1 Vital signs and body measurements

Vital signs measured include:

- Body temperature
- BP
- Pulse Rate

Body measurements include:

- Height
- Body weight
- BMI will be calculated (Body weight (kg) / [Height (m)]^2)

8.4.2 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Sponsor personnel. The results must be evaluated for criteria defining an AE and reported if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Sponsor personnel must be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count are measured.

Clinical chemistry/blood chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, aPTT, PT/INR, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin is differentiated.

Urinalysis

Urine test by dipstick: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample must be sent for microscopic analysis of WBC, RBC and casts.

8.4.3 Post-injection safety assessments

Post-injection safety assessments are described in Table 8-3 Post-Injection Exams at Injection visits. Within 0-5 minutes after an IVT injection, perfusion of the central retinal artery must be verified by indirect ophthalmoscopy; in case of non-perfusion, treat with anterior chamber

paracentesis 2 or more minutes after injection. Normalization of intraocular pressure must be verified within 30 minutes of the injection. Intraocular pressure must be re-measured again at 60 minutes post injection if the pressure is elevated > 10 mmHg above the pre-dose value or if the pressure is above 30 mmHg.

8.4.4 Pregnancy

Women of childbearing potential are excluded from participation in this study.

8.5 Other assessments

8.5.1 Immunogenicity

IG samples will be collected at the time points defined in the assessment schedule. All samples will be given a unique sample number as indicated in the log that is included in the MOP. Further details on sample collection, numbering, processing and shipment can be found in the MOP.

Validated immunoassays are used for the detection of anti-CLG561 and anti-LFG316 antibodies. Corporate Confidential Information

8.5.2 Pharmacokinetics

PK samples must be collected at the time points defined in the assessment schedule.

All samples are given a unique sample number as indicated in the log that is included in the MOP. Further details on sample collection, numbering, processing and shipment can be found in the MOP. Total CLG561 and total LFG316 is determined by a validated immunoassay method. A detailed description of the methods used to quantify the concentration of total CLG561 and total LFG316 will be included in the bioanalytical raw data of the study and in the bioanalytical data report. The LLOQ will be documented in the bioanalytical data reports.

Samples from the sham group is not analyzed for total CLG561 or total LFG316. Concentrations below the LLOQ is reported as “zero” and missing data is labeled as such in the Bioanalytical Data Report.

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8.5.3 Drug administration

IVT or Sham Injections will be administered as described in the assessment schedule and in the MOP.

8.5.4 Ocular examination

In addition to ocular efficacy endpoint assessments, the following must be conducted as part of the ocular examination:

- Best Corrected Visual Acuity
- Low Luminance Visual Acuity
- Intraocular Pressure
- Slit-lamp Biomicroscopy
- Dilated Ophthalmoscopy (Dilated Fundus Exam)

Immediately post-injection, gross visual acuity must be performed.

8.5.8 General comments

The Investigator may record general comments as deemed necessary in the source and eCRF to document important and scientifically notable details throughout the trial.

9 Safety monitoring

9.1 Adverse events - general information

An AE is any untoward medical occurrence in a subject who is administered a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The determination of clinical relevance is based upon the medical judgment of the Investigator.

9.2 Monitoring for adverse events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs must be reported for any clinically relevant change in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes in any protocol-specific parameters and questionnaires (if applicable) evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

9.3 Procedures for recording and reporting AEs and SAEs

Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF). A separate AEF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology must be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (e.g., severity), any action with study treatment taken as a result of the event, and an assessment of the AE's relationship to the study

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects that are already known about the investigational drug can be found in the IB or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and must be discussed with the subject during the study as needed.

The Investigator should also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Sponsor.

Non-serious Adverse Events

A non-serious AE is defined as any untoward change in a subject's medical health that does not meet serious criteria noted below (e.g., is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.). All AEs must be reported regardless of whether or not they are related to the study treatment. For non-serious AEs, an AEF containing all available information will be collected on a routine basis according to instructions provided by the study sponsor.

Serious Adverse Events

A SAE is defined as any adverse experience that meets any of the following criteria:

- Results in death
- Is life-threatening
- Note: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event must be considered serious.

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
- Is a congenital anomaly/birth defect
- Is an important medical event. An important medical event is an event that may not result in death, be life- threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in a subject's hospitalization, or the development of drug dependency or drug abuse

All available information on a SAE(s) must be forwarded to the study Sponsor immediately (i.e., within 24 hours of the Investigator's or site's knowledge of the event) as follows:

- In studies utilizing EDC (electronic data capture), all available information for the SAE must be entered immediately into the EDC system. Note: Should the Electronic Data Capture (EDC) system become non-operational, the site must complete the appropriate paper SAE Form. The completed form is faxed to the study Sponsor at 1-817-302-1927 within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes operational.
- Sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.
- Additional information for any applicable event is to be reported as soon as it becomes available.

In addition to the reporting of SAEs to the study sponsor, the SAE must be reported to the IRB / IEC according to their requirements.

If the SAE was due to a hospitalization of the subject, a copy of the discharge summary is to be forwarded to the study Sponsor as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, the Sponsor may request copies of applicable portions of the subject's medical records.

An assessment of seriousness will also be performed for all AEs by a study Sponsor physician utilizing the same criteria. If an AE reported for an Investigator's subject is upgraded to a SAE by a study Sponsor physician, the Investigator will receive a notification by the study Sponsor.

Adverse Events of Special Interest

An AE of special interest is one of scientific and medical concern specific to the sponsor's product, route of administration or program where ongoing monitoring and rapid communication by the Investigator to the sponsor may be appropriate. These AEs may be serious or non-serious. Applicable AEs may require further investigation in order to characterize and understand, and depending upon the nature of the event, rapid communication by the trial sponsor to other parties may also be required. These AEs of special interest must be reported using the same mechanism (EDC or fax) and timeframe (i.e., within 24 hours of the Investigator's or site's knowledge of the event) as described previously for SAEs.

The AEs of special interest include the following:

- Endophthalmitis
- Grade ≥ 3 aqueous flare and/or Grade 4 aqueous cells (see MOP for grading scale)
- Grade 2 aqueous flare and/or Grade 2 or 3 aqueous cells that fail to decrease to 1 or less within 30 days of the onset of the event (see MOP for grading scale)
- Grade ≥ 2 vitreous haze and/or Grade ≥3 vitreous cells (see MOP for grading scale)
- ≥ 30 letter decrease in BCVA compared with Baseline visual acuity
- Sustained (> 15 minutes) loss of light perception due to elevated IOP
- IOP > 30 mmHg at/past 60 minutes post injection
- New retinal tear or detachment
- New vitreous hemorrhage > 2+ severity that does not resolve within 30 days of the onset of the event (see MOP for grading scale)

If an ESI occurs in a study subject, a decision will be made by the Sponsor concerning further exposure to study treatment. The study subject will be followed for resolution of the ESI and a decision will be made by the Sponsor concerning further participation in the study.

9.4 Intensity and causality assessments

For every AE, the Investigator must assess the intensity (severity) and causality (relationship to study treatment). Specifically, events must be classified as mild, moderate, or severe. The assessment of causality will be based upon the categories of related and not related. These classifications must be based on the following definitions:

Intensity (Severity)

Mild	An event is mild if the subject is aware of, but can easily tolerate the sign or symptom.
Moderate	An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

Causality

Related — AEs classified as related may be either definitely related or possibly related where a direct cause and effect relationship between the study treatment and the event has not been demonstrated but there is a reasonable possibility that the event was caused by the study treatment.

Not Related — AEs classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the AE).

An assessment of causality will also be performed by a study sponsor physician utilizing the same definitions. For a serious AE reported by an Investigator as not related that upon review of the available data by the study sponsor physician is assessed (upgraded) to be related, the Investigator will receive a notification.

9.5 Unmasking of study treatment

Not applicable; this study is single masked (subject masked).

9.6 Follow-up of subjects with adverse events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. Any additional data from these follow-up procedures must be documented and available to the Sponsor who will determine when the data need to be documented on the case report forms.

Pregnancy reporting

Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Women of childbearing potential are excluded from this study.

Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case by case basis. A Sponsor specific pregnancy form is utilized to capture all pregnancy-related information until birth of the child or termination of pregnancy.

10 Data review and database management

10.1 Site monitoring

Before study initiation, the Sponsor representative will review the protocol and other study documentation with the Investigators and their staff. Training may occur at a site initiation visit or at an Investigator's meeting.

During the study Sponsor employs several methods of ensuring protocol compliance, GCP compliance, and the quality and integrity of the sites' data. The Clinical Site Manager (CSM) will visit the site to review:

- Completeness of subject records
- Accuracy of entries on the eCRFs
- Adherence to the protocol and to Good Clinical Practice
- Progress of enrollment
- Ensure that study drug is being stored, dispensed, and accounted for according to specifications

Key study personnel must be available to assist the CSM during the study monitoring visits.

Continuous remote monitoring of each site's data may be performed by the Sponsor. A central analytics team may analyze data, identify risks, identify trends for site operational parameters, and provide reports to Sponsor Clinical Teams to assist with trial oversight.

The nature and location of all source documents will be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the site manager. If electronic records are maintained, the method of verification must be determined in advance of starting the study. The Investigator must maintain source documents for each subject in the study. Source documents consist of case and visit notes (e.g. hospital or clinic medical records) that may include demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on eCRFs must be traceable to the source documents. It is required that all entries in the source documents are identified by the author. The Investigator must also keep the original informed consent form signed by the subject. The Investigator must provide a signed copy is to the subject.

The Investigator must give the clinical site manager access to all relevant source documents to confirm their consistency with the eCRF entries. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that is used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects, beyond subject number and demographic information, is disclosed.

10.2 Data collection

The EDC uses fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff are required to enter the data specified by the protocol into the eCRFs. Designated Investigator site staff must not be given access to the EDC system until they have been trained.

The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive electronic files of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic) with the eCRF not considered as source.

All data must be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Sponsor staff will review the data entered into the eCRFs by investigational staff for completeness and accuracy. Sponsor staff may instruct the site personnel to make required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff are required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database are coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Laboratory samples are processed centrally or at an external laboratory. The results are sent electronically to the Sponsor.

The Interactive Response Technology (IRT) is used to:

- Store randomization codes
- Store data in reference to dispensing of study products to the subject

The system is supplied by a vendor that manages the IRT database. The IRT database is sent electronically to the Sponsor.

The occurrence of any protocol deviations must be determined prior to database lock. Once the database is declared to be complete and accurate, it is locked and the data becomes available for data analysis. Any changes to the database after that database lock can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

10.3 Data monitoring committee

Not required.

10.4 Adjudication committee

Not required.

10.5 Safety committee

The study team, consisting of Investigators and a Sponsor internal clinical team, MUST provide rigorous AE monitoring oversight of each individual subject following their first dose, and prior to their second and third doses. If the number or severity of drug-related AEs are of concern, the safety committee may put a treatment arm or the whole study on hold until further review of the available safety data.

10.6 Regulatory documentation and records retention

The Investigator is required to maintain updated and complete regulatory documentation. The Investigator's files are reviewed as part of ongoing study monitoring. Financial information is not subject to regulatory inspection and MUST be kept separately.

Additionally, the Investigator MUST keep study records and source documents until the Sponsor provides written approval for their destruction. IF the Investigator retires, relocates, or withdraws from responsibility of the study records, THEN study record custody MUST be transferred to the Sponsor or a designee.

11 Data analysis

11.1 Analysis sets

The final subject evaluability will be determined prior to locking the database.

The full analysis set will be used for assessment of efficacy and the data from both the study eye and fellow eye (fellow eye as reference for the within subject comparison) will be used for analysis. The full analysis set will include all subjects who receive any study treatment and have at least one follow-up visit with an assessment of the GA lesion size. The full analysis set will use the treatment as randomized.

The per-protocol (PP) set will be used for assessment of efficacy and the data from both the study eye and fellow eye will be used for analysis. The PP set will be comprised of all full analysis set subjects who have no critical protocol deviations, and have a valid assessment of the primary efficacy endpoint (change in geographic atrophy lesion size from baseline to Day 337 as assessed by FAF). Key per protocol criteria are compliance regarding the monthly injection schedule up to Day 337 (not missing greater than 1 in any 6 months period or not missing 2 consecutive doses) and in addition to baseline lesion size assessment the corresponding assessment on Day 337 and/or Day 253. Protocol deviations will be identified and classified before database lock. The PP analysis set will use the treatment as randomized. The PP set is the primary efficacy analysis set.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

Summary statistics will be provided for demographic and baseline characteristics by treatment group and overall. Baseline characteristics will be presented for both the study and fellow eye. Number and percentage will be presented for categorical variables and descriptive statistics, including mean, standard deviation, quartiles, minimum and maximum will be presented for continuous variables.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be summarized by treatment group. Ocular parameters will be presented separately for study and fellow eye.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration, concomitant therapies, and compliance will be summarized by treatment group with separate presentation for study and fellow eye.

11.4 Analysis of the primary variable(s)

The primary objective aim of this study is to evaluate, in the study eye, the efficacy of 12 (every 28 days) IVT injections of CLG561 as a monotherapy and in combination with LFG316 as compared to sham on the growth of GA lesion as assessed by FAF.

11.4.1 Variable(s)

The primary endpoint of this study is the change in geographic atrophy lesion size [mm^2] in the study eye between Day 337 and Baseline as measured by FAF.

11.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy hypotheses are that the change in geographic atrophy lesion size in the study eye under CLG561 as a monotherapy and/or in combination with LFG316 is lower than the sham arm. The null and alternative hypotheses are:

$$\mathbf{H_{01}}: \mu_{CLG} - \mu_{Sham} \geq 0 \text{ mm}^2 \text{ vs } \mathbf{H_{A1}}: \mu_{CLG} - \mu_{Sham} < 0 \text{ mm}^2$$

$$\mathbf{H_{02}}: \mu_{CLG+LFG} - \mu_{Sham} \geq 0 \text{ mm}^2 \text{ vs } \mathbf{H_{A2}}: \mu_{CLG+LFG} - \mu_{Sham} < 0 \text{ mm}^2$$

μ_{CLG}, $\mu_{CLF+LFG}$ and μ_{Sham} being the corresponding unknown true treatment specific mean changes from Baseline to Day 337.

The comparison of the two active arms will be done descriptively.

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The lesion size change from baseline to Day 337 will be analyzed by an analysis of variance model including, but not limited to, the class variables representing categories of baseline lesion size (edge length) and categories of lesion location.

The primary efficacy analysis set will be the PP set.

11.4.3 Handling of missing values/censoring/discontinuations

In the primary efficacy analysis which is based on the PP set, a subject will have in the study a baseline lesion size assessment and a corresponding assessment on Day 337 and/or Day 253. For subjects with missing values of lesion size in the study eye on Day 337, the missing value will be imputed based on linear regression/extrapolation (which at minimum will be based on the Day 253 assessment).

11.4.4 Supportive analyses

The primary efficacy analysis will be performed using the PP set with treatment as randomized. Sensitivity analysis regarding major protocol deviations will be performed on the primary efficacy endpoint sing the full analysis set as randomized. In case of deviations from the treatment allocation as randomized the full analysis set will also be analyzed on an as 'as treated' basis.

An additional sensitivity analysis will be performed assuming linear lesion growth in the study for all treatment for the one year observation period using a Mixed-Effect Model Repeated Measure (MMRM) model with random slops and including class-variables as specified for the primary analysis.

11.4.5 Subgroup analyses

The following subgroups will be analyzed for the primary efficacy endpoint using the same approach:

- Age category (< 75 years and ≥ 75 years)
- Gender (male and female)
- Baseline BCVA categories (<60 letters, 60 – 73 letters, and > 73 letters)
- Baseline lesion size (edge-length)
- Baseline lesion location
- Baseline lesion type: uni-focal vs multi-focal
- Corporate Confidential Information

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy endpoints

Analyses will be performed for both the PP set and the FAS.

Potential treatment effects will primarily be assessed based on the difference in change from baseline in the study eye between active treatment and sham treatment. In addition, the corresponding difference between study and fellow eye will be explored within the active treatment arms.

At time points assessed, each efficacy endpoint will be presented graphically and by descriptive statistics provided for observed absolute values and changes from baseline. Changes from baseline will be compared between treatment arms using ANOVA models and/or stratified/unstratified Cochran-Mantel-Haenszel Tests.

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For treatment differences and differences between study and fellow eye 80% confidence intervals will be provided.

The following secondary endpoints will be evaluated:

- Change in geographic atrophy lesion size from baseline to Days 85, 169, 253, 337 and 421 as measured by fundus auto-fluorescence
- Change in BCVA, low luminance visual acuity and low luminance visual acuity deficit from baseline by visit up to Day 337 as measured by ETDRS in the overall population and in subsets of patients with baseline visual acuity < 73 letters
- Subject status regarding ≥15 letters, ≥10 letters, and ≥5 letters change from baseline in BCVA by visit up to Day 337
- Average change in BCVA/low luminance visual acuity/low luminance visual acuity deficit from baseline to the period Day 281 to Day 337

For the changes in geographic atrophy lesion size from baseline between either of the active arms and sham as measured by FAF, the same analysis model used for the primary hypothesis (Section 11.4.2) will be used.

11.5.2 Pharmacodynamic endpoints

Total properdin, total C5 concentrations Corporate Confidential Information (% change from baseline) data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

11.5.3 Immunogenicity endpoints

A positive or negative result will be generated from the immunogenicity assay indicating the presence or lack of presence of anti-CLG561 or anti-LFG316 antibodies. Results from immunogenicity assay will be listed by treatment group, subjects and visit/time. Summary statistics (n, % of subjects with positive/negative results) will be provided by treatment group and visit/time.

11.5.4 Pharmacokinetic endpoints

Total CLG561 and total LFG316 serum concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

11.5.6 Safety

Adverse events

All information obtained on AEs will be displayed by treatment and subject.

The number and percentage of subjects with AEs will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple AEs within a body system is only counted once towards the total of this body system.

Vital signs

All vital signs data will be listed by treatment, subject, and visit and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

Ocular assessments

Ocular assessments for safety analyses will include slit lamp examination, dilated fundus examination, best corrected visual acuity and intraocular pressure. All data will be listed by treatment group and subjects. Summary statistics will be provided by treatment group and visit.

For each continuous variable, observed values will be presented descriptively (N, mean, standard deviation, median, minimum and maximum) at each visit by treatment group. Change from Screening (Day -30 to Day -1) will be summarized similarly. Also, categorical summaries depending on the parameter will be presented. These reports will be supported by individual subject listings. Details will be described in the statistical analysis plan.

11.5.7 Other assessments

11.6 Sample size calculation

A sample size of 30 PP evaluable subjects per treatment arm will allow identification of a treatment difference of 0.67 mm^2 in lesion size change from baseline to Day 337 (representing a 33% reduction in lesion growth rate, assuming an average natural disease progression of 2.0 mm^2 per year) at a one-sided alpha level of 0.1 with a power of 80% assuming a standard deviation of 1.2 mm^2.

In anticipation of a drop-out /protocol deviation rate of 20%, a total sample size of ~114 randomized subjects (~38 subjects /arm) is planned for the current study to ensure sufficient study completers for the above described PP analysis. Depending on ongoing monitoring of the drop-out / protocol deviation rate the need for additional recruitment will be assessed to ensure 90 PP evaluable subjects are available for the Day 337 analysis.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable.

12.2 Responsibilities of the Investigator and IRB/IEC

The Investigator and all clinical study staff MUST conduct the clinical study in compliance with the protocol. The Investigator must make sure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Investigator is required to:

- Sign a protocol signature page confirming his/her agreement to conduct the study in accordance all of the instructions and procedures found in this protocol
- Give access to all relevant data and records to the Sponsor including:
  - Monitors
  - Auditors
  - Sponsor Quality Assurance representatives
  - Designated agents of Sponsor
  - IRBs/IECs
  - Regulatory authorities

    NOTE: If an inspection of the clinical site is requested by a regulatory authority, the Investigator MUST inform the Sponsor immediately.
- Obtain approval/favorable opinion from the IRB/IEC and provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must include:
  - The clinical trial protocol
  - Written informed consent form
  - Consent form updates, if applicable
  - Subject recruitment procedures (e.g. advertisements)
  - Written information to be provided to subjects
  - Subject compensation programs
- Provide the IEC/IRB with a copy of the IB, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB.
- Notify the IEC/IRB that the study is complete or if the study is terminated prematurely
- Report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB

Voluntary informed consent MUST be obtained from every subject (and/or legal representative, as applicable) prior to any study-related procedures.

The Investigator MUST:

- Have a defined process for obtaining consent
- Explain the clinical study to each potential subject
- Provide the subject with a copy of the consent form written in a language the subject understands
- Keep the original, signed copy of the consent and must provide a duplicate copy to each subject

The Subject MUST:

- Indicate voluntary consent by signing and dating the approved informed consent form
- Be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel

The consent document MUST meet all applicable local laws and MUST provide subjects with information regarding:

- Purpose of the study
- Procedures of the study
- Requirements of the study
- Restrictions of the study
- Known risks and potential benefits
- Available compensation
- Established provisions to maintain confidentiality of protected health information
- Explain the voluntary nature of participation in the study
- Provided with contact information for questions or concerns during the study
- Explain that the records may be accessed by appropriate authorities and Sponsor-designated personnel

12.3 Publication of study protocol and results

The Sponsor assures that the key design elements of this protocol is posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results. For multi-center trials, a Coordinating Investigator will be selected by the Sponsor around the time of Last Subject Last Visit to be a reviewer and signatory for the clinical study report.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. IF additional assessments are required to ensure safety of subjects, Then the Investigator must administer the appropriate care as deemed necessary on a case by case basis. The Investigator is not allowed under any circumstance to collect additional data or conduct additional procedures for research related purposes outside of the protocol.

Investigators must apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the CSR. The Investigator MUST NOT implement any protocol deviations, even if the Investigator believes it is warranted to improved conduct of the study.

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments are created by the Sponsor and must be approved by the IEC/IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor must be informed and (serious) AE reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request

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Novartis Institutes for BioMedical Research

CLG561

Protocol CCLG561X2201A
(Alcon Protocol CLG561-2201)

A randomized, multi-center, single masked, sham controlled, proof-of-concept study of intravitreal CLG561 as a monotherapy and in combination with LFG316 in subjects with geographic atrophy

Document type:	Amended Protocol Version 01 Signature Page
Referring to:	Amended Protocol Version No. 01 released on 13-Jan-2016

Novartis approval signatures for:

Amended Protocol Version 01

Corporate Confidential Information

Investigator approval signatures for:

Amended Protocol Version 01

Investigator signature

I have read the amended protocol version and agree to conduct this trial in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the ethical principles laid down in the Declaration of Helsinki.

Investigator	Signature	Date

Center name and address: