Official Title: **A PHASE II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM INJECTION-CONTROLLED EXPOSURE-RESPONSE STUDY OF LAMPALIZUMAB INTRAVITREAL INJECTIONS ADMINISTERED EVERY TWO WEEKS OR EVERY FOUR WEEKS TO PATIENTS WITH GEOGRAPHIC ATROPHY**

NCT Number: NCT02288559

Document Date: Protocol/Version 3: 24-Dec-2015

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM INJECTION-CONTROLLED EXPOSURE-RESPONSE STUDY OF LAMPALIZUMAB INTRAVITREAL INJECTIONS ADMINISTERED EVERY TWO WEEKS OR EVERY FOUR WEEKS TO PATIENTS WITH GEOGRAPHIC ATROPHY**
PROTOCOL NUMBER:	GX29455/ NCT02288559
VERSION NUMBER:	3
EUDRACT NUMBER:	Not applicable
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 4 September 2014
DATES AMENDED:	Version 1: 4 September 2014 Version 2: 2 April 2015 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Dec-2015 01:16:32

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol GX29455 has been amended as follows:

- To expand enrollment sites from 23 sites to 25–30 sites in the United States
- To expand the screening window from 21 days to 28 days and also allow the screening period to be extended up to 5 days for exceptional circumstances (if approved by the Medical Monitor)
- The patient age restriction for inclusion in the study was revised from "Age 60–89 years" to "Age ≥60 years"
- To allow re-screening of patients who have failed screening for reasons other than complement factor I biomarker
- To allow provision to administer the first study treatment within 1 working day after the Day 1 visit in the event of unexpected issues that prevent drug administration on Day 1
- To revise the pregnancy and contraceptive requirements to align with a global update to the protocol template and international recommendations
- To allow a single intraoperative administration of a corticosteroid during cataract surgery within 3 months prior to screening in order to permit limited use of corticosteroids in this specific application which will not impact study results and may facilitate patient eligibility for the study
- To allow inclusion of patients with appropriately treated and resolved retinal tears (if approved by the Medical Monitor)
- To clarify the definition of diabetic retinopathy and potentially allow patients with mild non–proliferative diabetic retinopathy for inclusion in the study (if approved by the Medical Monitor)
- To clarify that the Medical Monitor must approve participation of patients who have participated in other studies with investigational drugs
- To clarify inclusion criteria for patients with a history of a previous malignancy
- To include restrictions for patients with hypersensitivity to a biologic agent, lampalizumab, or any component of the lampalizumab injection
- To allow use of intra–articular or intra–muscular corticosteroids if used in a limited fashion and if approved by the Medical Monitor
- To clarify active local or systemic infections in the dose interruption, treatment, and study discontinuation criteria
- To modify the adverse event causal attribution guidance
- To add treatment measures for patients who develop a reaction to povidone-iodine

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.3.4: Rationale for Study GX29455

… On the basis of the preclinical Study 09-1554 and CFD4870g Phase II results, ~~the proposed~~ Study GX29455 will further investigate the exposure-response and safety of lampalizumab in the CFI profile biomarker-positive patient population over multiple intravitreal injections and dose exposures.

SECTION 3: STUDY DESIGN

…. A Q2W safety run-in assessment will precede the randomized study. Approximately 90 patients will be enrolled at an estimated ~~23~~ *25–30* study sites in the United States.

SECTION 3.1.2: Four-Arm, Randomized Study

An estimated ~~23~~ *25–30* study sites in the United States will participate in the randomized study. Approximately 84 CFI profile biomarker-positive patients with GA secondary to AMD will be enrolled. Biomarker status will be determined using the investigational cobas® CFI Profile CTA that will be run at a designated study laboratory testing site. The study will consist of a screening period of up to ~~21~~*28* days (Days −~~21~~*28* to −1) and a treatment period of 24 weeks.

Patients who failed screening for reasons other than CFI biomarker status (e.g., GA lesion size, BCVA, or prohibited concomitant medication) may be eligible for rescreening up to two additional times during the enrollment period of the study. At rescreening, all screening visit assessments will be performed except CFI biomarker sample provided that a valid CFI result is available.

The first study treatment will be administered on the same day as randomization (Day 1 visit). If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), with the Medical Monitor's permission, the patient's first study treatment may be administered within 1 working day after the Day 1 visit. The following assessments will be repeated on the day of the study treatment: BCVA, slit–lamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurement (recorded on Day 1 electronic Case Report Form (eCRF) and dated accordingly). After the Day 1 visit, if a patient misses a study visit when ocular images are scheduled (see Appendix 1), the images must be obtained at the next scheduled visit.

SECTION 4.1: PATIENTS

Patient Selection and Sex Distribution

Written informed consent will be obtained prior to initiation of any study procedures. The screening evaluation will be performed within ~~21~~*28* days preceding the Day 1 visit (the day of the first study treatment).

NOTE: Some patients may require an extended screening period as a result of repeat acquisition or evaluation of images or other issues. After consultation with and approval by the Medical Monitor, the screening period may be extended for up to 5 days for exceptional circumstances.

SECTION 4.1.1.1: General Inclusion Criteria

- *Age ≥60 years*
- ~~Age 60–89 years~~
- For women ~~who are not postmenopausal (≥12 months of non therapy induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus):~~*childbearing potential:* agreement to remain abstinent ~~or~~ *(refrain from heterosexual intercourse) or* use ~~single or combined~~ contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 30 days after the last dose of study drug. ~~Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, (hormonal implants, established, proper use of combined oral or injected hormonal contraceptives), and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.~~

  A woman is considered to be of childbearing potential if she is postmenarchial, has not reached postmenopausal state (≥12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (absence of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent or use ~~a condom~~*contraceptive measures and agreement to refrain from donating sperm as defined below:*

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 30 days *plus 90 days (a spermatogenesis cycle)* after the last dose of study drug. ~~and agreement to refrain from donating sperm during this same period. Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.~~

SECTION 4.1.2.2: Ocular Exclusion Criteria: Study Eye

- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, biodegradable/non-biodegradable implants or formulations, device implant, or encapsulated cell technology). *NOTE: A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.*
- History of retinal tear. *NOTE: a retinal tear adequately treated with laser photocoagulation and determined to be stable by investigator may be permitted after consultation with and approval by the Medical Monitor.*

SECTION 4.1.2.3: Ocular Exclusion Criteria: Either Eye

- *Proliferative* diabetic retinopathy. *NOTE: mild non-proliferative diabetic retinopathy (occasional hemorrhage or microaneurysm) in either eye may be permitted after consultation with and approval by the Medical Monitor; moreover, a patient with onset of mild non-proliferative diabetic retinopathy in either eye during study participation may be permitted to continue study treatment after consultation with the Medical Monitor.*
- Previous participation in other studies of investigational drugs (excluding vitamin and mineral supplements; topical ocular agents ≥ 3 months preceding Day 1) may be permitted after consultation with *and approval by* the Medical Monitor

SECTION 4.1.2.4: Systemic Exclusion Criteria: Concurrent Conditions

- Treatment for *an* active *localized or* systemic infection

  Ongoing prophylactic use of antimicrobial therapy should be discussed with and approved by the Medical Monitor.
- Active malignancy ~~or history of malignancy~~ within the previous ~~5 years (~~*12 months* except ~~completely~~*for appropriately treated carcinoma in situ of the cervix,* resolved ~~cutaneous basal cell carcinoma)~~*non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen (PSA) for ≥12 months.*
- *History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lampalizumab injection*
- Requirement for continuous use of any medications/treatments indicated in the "~~Excluded Concomitant~~*Prohibited* Therapy" section of the protocol *(see Section 4.4.2)*
- Woman ~~who are not post menopausal (≥12 months of non therapy induced amenorrhea) or surgically sterile~~*childbearing potential* must have a negative serum pregnancy test result within ~~21~~*28* days prior to initiation of study treatment

SECTION 4.4.1: Permitted Therapy

Patients who use other maintenance therapies should continue their use.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF. Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

~~A patient with onset of mild non-proliferative diabetic retinopathy in either eye during study participation (e.g., an occasional hemorrhage~~*Intra-articular* or ~~microaneurysm)~~*intra-muscular corticosteroids* may be ~~permitted to continue on study treatment~~*used in a limited fashion* after consultation with *and approval by* the Medical Monitor.

SECTION 4.4.2: Prohibited Therapy

At the discretion of the investigator, patients may continue to receive all medications and standard treatments administered for other conditions. ~~The~~*However, the* following medications and treatments *will exclude patients from study eligibility and* are prohibited from use during the patient's participation in the study ~~and patients required to use medications described below will not be eligible for enrollment in the study~~:

- Intravitreal, subtenon, or *chronic* topical (ocular) corticosteroids in either eye; short-term use of topical corticosteroids is permitted after cataract surgery
- Oral corticosteroids (prednisone or equivalent) at doses > 10 mg/day *(prohibited at screening for eligibility; for occurrence during study enrollment, see Table 2, Dose–Interruption Criteria)*
- ~~Intra articular or intra muscular corticosteroids may be used in a limited fashion after consultation with the Medical Monitor~~
- Intravenous corticosteroids *(prohibited at screening for eligibility; for occurrence during study enrollment, see Table 2, Dose-Interruption Criteria)*

SECTION 4.5.6.3: Genotyping: CFI Profile Biomarker

Whole–blood samples ~~for CFI profile biomarker status determination~~ will be collected and forwarded directly from the sites to the Sponsor-selected laboratory for analysis *to determine CFI profile biomarker status* (see the Central Laboratory Manual for details).

~~Whole blood sample for determination of CFI profile biomarker status~~

Table 2: Dose Interruption, Treatment, and Study Discontinuation Criteria

Table 2 was modified to clarify active local or systemic infections in the dose interruption, treatment, and study discontinuation criteria.

Table 4: Causal Attribution Guidance

The causal attribution guidance was modified.

SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse

event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

~~There are some hospitalization scenarios that do not require reporting as a serious adverse event when there is no occurrence of an adverse event. These scenarios include a planned hospitalization or prolonged hospitalization to undergo a diagnostic or elective surgical procedure for a preexisting medical condition other than ocular that has not changed.~~

- *Hospitalization for a preexisting condition, provided that the following criteria are met:*

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

Appendix 1: Study Flowchart Safety Run-In Assessment: Screening, Day 1 through Hiatus and Early Termination

The study flowchart for safety run-in assessments has been revised to reflect the changes to the protocol.

Appendix 2: Study Flowchart for Randomized Study: Q2W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination

The study flowchart for the randomized study Q2W assessments has been revised to reflect the changes to the protocol.

Appendix 3: Study Flowchart for Randomized Study: Q4W Arms: Screening, Day 1, Week 4 through Week 24, and Early Termination

The study flowchart for the randomized study Q4W assessments has been revised to reflect the changes to the protocol.

Appendix 6: Pre Injection Procedures for All Patients

- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.

NOTE: For patients who develop adverse reaction to povidone-iodine, the following approaches are permitted: irrigate the eye with sterile saline after the study treatment (lampalizumab or sham) with the aim to rinse away any remaining povidone-iodine or use a limited amount of povidone-iodine by placing a swab directly on the treatment site after the lid speculum has been placed.

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM INJECTION-CONTROLLED EXPOSURE-RESPONSE STUDY OF LAMPALIZUMAB INTRAVITREAL INJECTIONS ADMINISTERED EVERY TWO WEEKS OR EVERY FOUR WEEKS TO PATIENTS WITH GEOGRAPHIC ATROPHY**
PROTOCOL NUMBER:	GX29455
VERSION NUMBER:	3
EUDRACT NUMBER:	Not applicable
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed copy of this form as instructed by your study monitor or the Sponsor. Please retain the original of this document in your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM INJECTION-CONTROLLED EXPOSURE-RESPONSE STUDY OF LAMPALIZUMAB INTRAVITREAL INJECTIONS ADMINISTERED EVERY TWO WEEKS OR EVERY FOUR WEEKS TO PATIENTS WITH GEOGRAPHIC ATROPHY**
PROTOCOL NUMBER:	GX29455
VERSION NUMBER:	3
EUDRACT NUMBER:	Not applicable
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab
PHASE:	II
INDICATION:	Geographic atrophy secondary to age-related macular degeneration
SPONSOR:	Genentech, Inc.

Objectives

Primary Objective

The primary objective for this study is as follows:

- To investigate exposure-response of lampalizumab administered intravitreally every 2 weeks (Q2W) or 4 weeks (Q4W) compared with sham control in complement factor I (CFI) profile biomarker-positive geographic atrophy (GA) patients; treatment response will be measured as change in GA area by FAF (fundus autofluorescence)

Secondary Objectives

The secondary objectives for this study are as follows:

- To characterize the serum pharmacokinetics of lampalizumab following multiple Q2W and Q4W intravitreal doses
- To characterize systemic immunogenicity of lampalizumab following multiple Q2W and Q4W intravitreal doses
- To evaluate the ocular and systemic safety of lampalizumab Q2W and Q4W intravitreal doses compared with sham control

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the pharmacokinetic-pharmacodynamic (PK–PD) relationship of lampalizumab in aqueous humor samples
- To evaluate the potential association of genetic variants in CFI, complement-pathway genes, and age related macular degeneration (AMD) associated genes with disease characteristics and response to administration of lampalizumab

Study Design

Description of Study

The GX29455 Phase II is a multicenter, randomized, single-masked, sham injection- controlled study of the exposure-response and safety of lampalizumab administered intravitreally Q2W or Q4W for 24 weeks to CFI profile biomarker-positive patients with GA secondary to AMD. Profile

biomarker-positive patients will be determined by the investigational cobas® CFI Profile Clinical Trial Assay (CTA). All outcome measures will be evaluated at 24 weeks. A Q2W safety run-in assessment will precede the randomized study. Approximately 90 patients will be enrolled at an estimated 25–30 study sites in the United States.

Number of Patients

Approximately 90 patients will be enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

- Willingness to provide signed Informed Consent and Health Insurance Portability and Accountability Act authorization
- *Age ≥60 years*
- CFI profile biomarker–positive result
- For women of *childbearing potential:* agreement to remain abstinent *(refrain from heterosexual intercourse) or* use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 30 days after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarchial, has not reached postmenopausal state (≥12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (absence of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent or use *contraceptive measures and agreement to refrain from donating sperm as defined below:*

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 30 days *plus 90 days (a spermatogenesis cycle)* after the last dose of study drug.
- Ability and willingness to undertake all scheduled visits and assessments

Ocular Inclusion Criteria: Study Eye

- Best Corrected Visual Acuity (BCVA) Early Treatment of Diabetic Retinopathy Study (ETDRS)

  For the safety run-in assessment: BCVA of 20/80 to 20/400 inclusive (Snellen equivalent) using ETDRS charts

  For the randomized study: BCVA of 20/50 to 20/400 inclusive (Snellen equivalent) using ETDRS charts
- Well demarcated area of GA secondary to AMD
- GA must be ≥ 1 disc area (DA) (2.54 mm^2) in the absence of CNV
- If GA is multifocal, at least one focal lesion must be ≥ 0.5 DA (1.27 mm^2)
- The total lesion size must be ≤ to 7 DA (17.78 mm^2) and must reside completely within the FAF imaging field
- Presence of hyperautofluorescence adjacent to the area of GA (banded or diffuse perilesional FAF patterns)

- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging

Ocular Inclusion Criteria: Fellow (Non-Study) Eye

- GA secondary to AMD in the absence of prior or active CNV

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry

Ocular Exclusion Criteria: Geographic Atrophy Characteristics

- GA in the study eye that extends beyond FAF imaging field or fails to meet single or multifocal lesion criteria
- Absence or minimal hyperfluorescence adjacent to GA in the study eye (e.g., focal or no perilesional FAF pattern)
- GA in either eye due to causes other than AMD (e.g., Stargardt disease, cone-rod dystrophy, chloroquine/hydroxychloroquine toxicity)

Ocular Exclusion Criteria: Study Eye

- History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD
- Previous subfoveal focal laser photocoagulation
- Laser photocoagulation (juxtafoveal or extrafoveal)
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, biodegradable/non-biodegradable implants or formulations, device implant, or encapsulated cell technology). *NOTE: A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.*
- Previous cell-based (e.g., regenerative or trophic) intraocular treatment
- RPE tear involving the macula
- History of retinal tear. *NOTE: a retinal tear adequately treated with laser photocoagulation and determined to be stable by investigator may be permitted after consultation with and approval by the Medical Monitor.*
- Any concurrent ocular or intraocular condition (e.g., cataract or epiretinal membrane) that, in the opinion of the investigator, could do either of the following:
- Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition; or
- If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of BCVA during the study period
- Active vitreous hemorrhage
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or absence of the posterior capsule
- Previous violation of the posterior capsule is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia
- Intraocular surgery (including cataract surgery) within 3 months preceding Day 1
- Glaucoma that is uncontrolled (defined as IOP $\geq$ 30 mmHg despite treatment with anti-glaucoma medication)
- History of glaucoma-filtering surgery

- History of corneal transplant

Ocular Exclusion Criteria: Either Eye

- *Proliferative* diabetic retinopathy. *NOTE: mild non-proliferative diabetic retinopathy (occasional hemorrhage or microaneurysm) in either eye may be permitted after consultation with and approval by the Medical Monitor; moreover, a patient with onset of mild non-proliferative diabetic retinopathy in either eye during study participation may be permitted to continue study treatment after consultation with the Medical Monitor.*
- Active or history of neovascular (wet) AMD
- History of idiopathic or autoimmune-associated uveitis
- Active uveitis and/or vitritis (see definitions and grading scales for iritis/anterior uveitis and vitritis in the full protocol)
- History of ocular or intraocular conditions that contraindicate the use of an investigational drug or may affect interpretation of study results or my render the patient at high risk for treatment complications
- Previous participation in other studies of investigational drugs (excluding vitamin and mineral supplements; topical ocular agents ≥ 3 months preceding Day 1 may be permitted after consultation with *and approval by* the Medical Monitor)
- Previous systemic treatment with a complement inhibitor
- Previous treatment with inhibitors/modulators of the visual cycle (e.g., fenretinide)
- Previous expression vector mediated intraocular treatments
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis
- History of infectious or inflammatory ocular disease

Systemic Exclusion Criteria: Concurrent Conditions

- Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 mmHg while patient is sitting)

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient can become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- Atrial fibrillation not managed by medication/cardioversion and the patient is under the care of a primary care physician or cardiologist
- Medical conditions that may be associated with a clinically significant risk for bleeding
- Active or history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or that renders the patient at high risk for treatment complications
- Treatment for *an* active *localized or* systemic infection

  Ongoing prophylactic use of antimicrobial therapy should be discussed with and approved by the Medical Monitor.
- Predisposition or history of increased risk for infection
- Active malignancy within the previous *12 months* except *for appropriately treated carcinoma in situ of the cervix,* resolved *non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen (PSA) for ≥12 months.*
- History of allergy to fluorescein, not amenable to treatment
- *History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lampalizumab injection*
- Inability to obtain FAF or near infrared images, fundus photographs, or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center

- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications/treatments indicated in the "*Prohibited* Therapy" section of the protocol
- Women who are pregnant or lactating or intending to become pregnant during the study
- Woman of *childbearing potential* must have a negative serum pregnancy test result within *28* days prior to initiation of study treatment

Length of Study

The approximate length of study is 24 weeks, not including the screening period.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected approximately 24 weeks after the last patient is randomized to the study.

Outcome Measures

Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Mean change in GA area from baseline to Week 24 as measured by FAF

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- The incidence of DLTs for Q2W multidose safety run-in assessment
- Incidence and severity of ocular and non-ocular (systemic) adverse events
- Mean change in BCVA from baseline to Week 24 using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart
- The incidence of changes and abnormalities in clinical ocular examinations
- The incidence of changes and abnormalities in clinical laboratory assessments
- The incidence of positive serum antibodies to lampalizumab

Pharmacokinetic Outcome Measures

The PK profile from the serum concentration–time data following administration of lampalizumab will be determined. Derived PK parameters may include the following:

- Maximum observed serum concentration (C_{max})
- Time of maximum observed serum concentration (t_{max})
- Observed steady-state trough concentration
- Accumulation ratio based on trough concentration

Optional anterior chamber (aqueous humor) paracentesis samples will be collected to assess PK and PD relationships. Additional PK analyses may be conducted as appropriate.

Exploratory Outcome Measures

The exploratory outcome measures for this study include the following:

- PK–PD relationship of lampalizumab in aqueous humor samples
- Evaluation of potential associations of genetic variants in CFI, complement-pathway genes, and AMD-associated genes with disease characteristics and response to administration of lampalizumab

Investigational Medicinal Products

Lampalizumab

Lampalizumab Drug Product is provided as a sterile, white to off-white, lyophilized powder in a 6-cc USP/European Pharmacopoeia Type 1 glass vial and is intended for intravitreal administration. Each glass vial contains a nominal 40 mg of lampalizumab. After reconstitution with Sterile Water for Injection, the Drug Product is formulated as 100 mg/mL lampalizumab in 40 mM L-histidine hydrochloride, 28 mM sodium chloride, 160 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.3.

Lampalizumab Intravitreal Injections

A 10-mg dose of lampalizumab will be used in this study and will be administered to patients randomized to lampalizumab treatment arms intravitreally Q2W or Q4W during the 24-week treatment period.

Comparator

Sham vials will be identical to vials of lampalizumab, but the sham vials will be empty.

A sham injection is a procedure that mimics an intravitreal injection of lampalizumab, except that the blunt end of an empty syringe is pressed against an anesthetized eye instead of a needle attached to a lampalizumab-filled syringe. Patients randomized to the control arms will receive sham injections Q2W or Q4W during the 24-week treatment period and will undergo the same assessments as the lampalizumab treatment arms.

Non-Investigational Medicinal Products

None.

Statistical Methods

Primary Analysis

Primary efficacy analyses will include all randomized patients with at least one post-baseline GA area measurement by FAF. Patients will be grouped according to the treatment assigned at randomization. Safety analyses will include all randomized patients who receive at least one dose of study treatment, with patients grouped according to the treatment actually received. Patients in the sham Q2W and sham Q4W groups will be pooled in the analyses.

The analysis of data for the 24-week treatment period will be performed when all randomized patients have either completed the 24-week treatment period or have discontinued from the study prior to Week 24, and all data from this period are in the database and have been cleaned and verified.

Determination of Sample Size

The GX29455 study is designed to evaluate the efficacy of lampalizumab administered intravitreally Q2W and Q4W to CFI profile biomarker-positive GA patients. The focus of the efficacy outcome analyses will be on estimation of the magnitude of the treatment effect.

The primary efficacy endpoint is the mean change in GA area from baseline to Week 24. The sample size was selected to provide adequate precision for the estimation of the treatment effect with respect to the primary endpoint. A total of approximately 90 patients will be enrolled in the study including the run-in and randomized components.

Approximately 84 patients will be randomized in a 3:1:2:1 ratio to one of four treatment groups: lampalizumab Q2W, sham Q2W, lampalizumab Q4W, or sham Q4W. With the assumption of a 15% drop-out rate by Week 24 and a standard deviation of 0.85 mm^2 for the change in GA area from baseline to Week 24 (estimated from the CFD4870g Phase II study with lampalizumab in GA), the 80% CI for the estimated difference in treatment effect for select hypothetical scenarios are presented in the full protocol. Assuming a GA area measurement error of $\pm$ 0.043 mm^2 (from CFD4870g image center technical report), the proposed sample size is considered sufficient for differentiating the treatment effect between lampalizumab Q2W and lampalizumab Q4W groups if the observed difference is 0.290 mm^2 (20% relative to sham) or larger.

These calculations are based on the following assumptions:

The standard deviation of the change in GA area from baseline to Week 24 is 0.85 mm^2.
The drop-out rate is 15% by Week 24 (estimated from the CFD4870g Phase II study with lampalizumab in GA).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACP	alternative complement pathway
AE	adverse event
ALT	alanine transaminase
AMD	age-related macular degeneration
AST	aspartate transaminase
ATA	anti-therapeutic antibody
BCVA	best corrected visual acuity
C3	complement component
C_{max}	maximum observed serum concentration
CFB	complement factor B
CFD	complement factor D
CFH	complement factor H
CFI	complement factor I
CFP	color fundus photograph
CNV	choroidal neovascularization
CRO	contract research organization
CTA	Clinical Trial Assay
DA	disc area
DLT	dose-limiting toxicity
ETDRS	Early Treatment of Diabetic Retinopathy Study
EC	Ethics Committee
eCRF	electronic Case Report Form
ECG	electrocardiogram
FAM	Fundus Autofluorescence in Age-Related Macular Degeneration
EDC	electronic data capture
FA	fluorescein angiography
FAF	fundus autofluorescence
FDA	U.S. Food and Drug Administration

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (cont.)

Abbreviation	Definition
GA	geographic atrophy
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
IxRS	interactive voice and Web response system
LPLV	last patient, last visit
MTD	maximum tolerated dose
NI	near-infrared
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
RCR	Roche Clinical Repository
RPE	retinal pigment epithelium
SAE	serious adverse event
SNP	single–nucleotide polymorphisms
T_{max}	time to maximum concentration
ULN	upper limit of normal
USP	United States Pharmacopeia
VA	visual acuity
VEGF	vascular endothelial growth factor
YAG	yttrium aluminum garnet

1. BACKGROUND

1.1 BACKGROUND ON GEOGRAPHIC ATROPHY

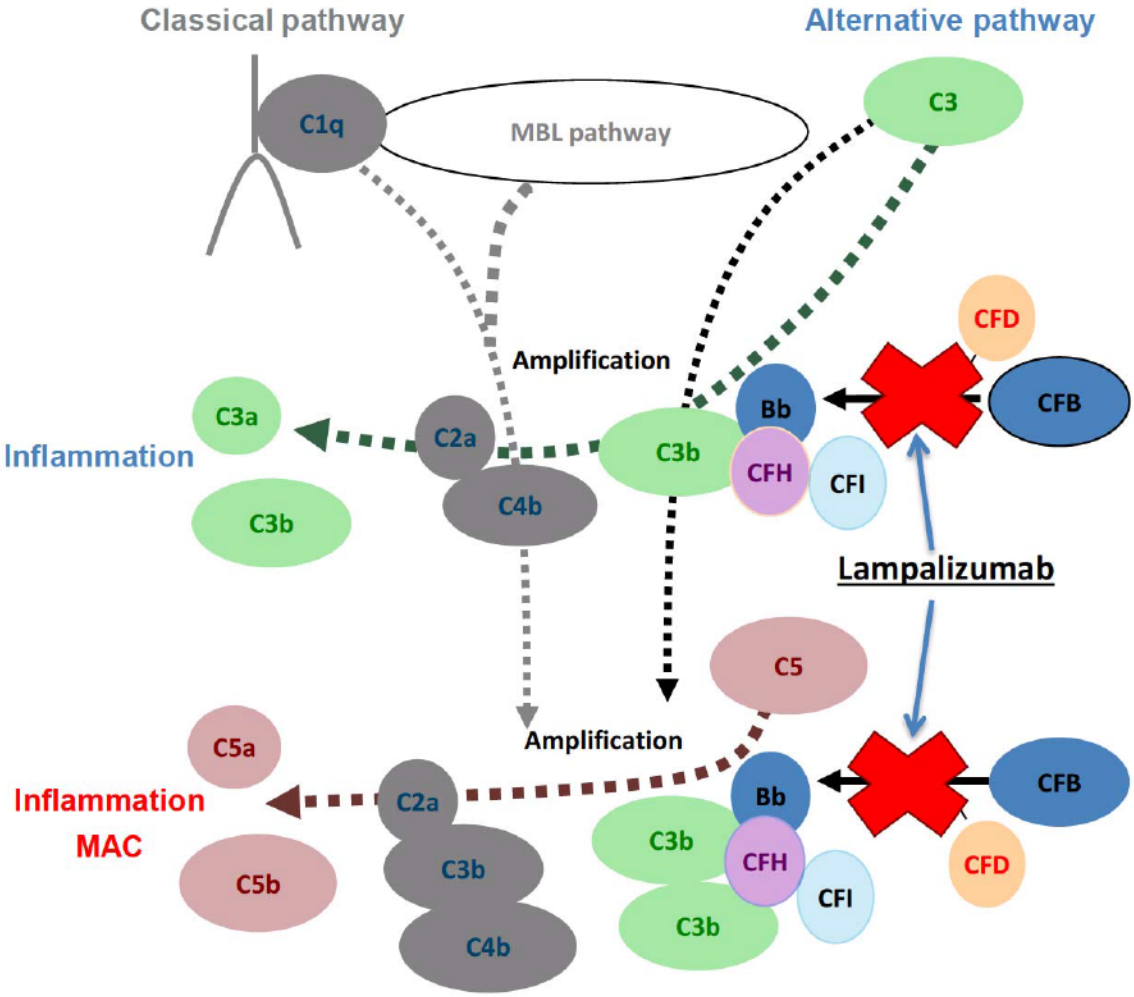
Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in industrial countries (Lim et al. 2012). Advanced AMD has been classified into two clinical forms: geographic atrophy (GA) characterized by loss of the choriocapillaris, retinal pigment epithelium (RPE) and photoreceptors, and exudative AMD characterized by choroidal neovascularization (CNV) (Holz et al. 2014a). The majority of severe vision loss in advanced disease has been associated with neovascular AMD; however, with available treatments for this form of AMD, visual impairment related to GA is increasing relative to neovascular AMD. GA represents a significant unmet medical need; there are no approved or efficacious treatments to prevent the onset or progression of this form of advanced AMD and associated visual loss.

1.2 BACKGROUND ON LAMPALIZUMAB

The pathogenesis of AMD is complex and remains to be established; however, genetics, hyperactivity of the alternative complement pathway (ACP), and environmental factors have been implicated in AMD pathophysiology (de Jong 2006; Loyet et al. 2012; Holz et al. 2014b). Increased activation of the ACP has been found in drusen, a hallmark clinical observation associated with AMD. Moreover, a role for ACP in AMD has been supported by human genetics (Yates et al. 2007; Scholl et al. 2008). At present, the largest study evaluating AMD genetics is a meta-analysis with 17,000 AMD cases and >60,000 controls that identified multiple genetic risk loci, including four genes (complement factor H [CFH], complement factor B [CFB], complement factor I [CFI], and complement component [C3]) in the ACP (Fritsche et al. 2013).

Complement factor D (CFD) is a highly specific chymotrypsin-like serine protease that plays a pivotal and rate-limiting role in the activation and amplification of the ACP (see Figure 1). The substrate for CFD is another alternative pathway serine protease, factor B. Following cleavage by CFD, CFB converts into the proteolytically active factor Bb and initiates the ACP.

Figure 1 Complement System Pathways and Site of Inhibition by Lampalizumab in the Alternative Complement Pathway



CFD = complement factor D; MAC = membrane attack complex; MBL = mannose-binding lectin.

Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody directed against CFD. Lampalizumab inhibits CFD-mediated cleavage of CFB, preventing activation of the ACP. Lampalizumab is specific for the ACP and shows no inhibitory effect on classic complement pathway activation. By inhibiting ACP activity, lampalizumab may impede the progression of GA and vision loss. Evidence for CFD in the pathogenesis of AMD includes protection against oxidative stress-mediated photoreceptor degeneration in a murine model with genetic deficiency of factor D (Rohrer et al. 2007) and detection of increased systemic activation of complement components, including CFD, in the serum of patients with AMD versus controls, which suggests that AMD may be a systemic disease with local manifestations in the aging macula (Scholl et al. 2008).

See the Lampalizumab Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The Phase Ia (Study CFD4711g) and Phase Ib/II (Study CFD4870g) studies provided preliminary evidence of a positive benefit-risk profile for the use of lampalizumab in patients with GA secondary to AMD and support further evaluation of lampalizumab in this study.

1.3.1 Study CFD4711g: Phase Ia

Study CFD4711g was a Phase Ia, first-in-human study of lampalizumab; it was an open-label, multicenter, single-dose, dose-escalation study designed to investigate the safety, tolerability, pharmacokinetics, and immunogenicity of six dose levels (0.1, 0.5, 1, 2, 5, and 10 mg) of lampalizumab administered as a single intravitreal injection to patients with GA (Do et al. 2014). Determination of the maximum tolerated dose (MTD) of lampalizumab was also an objective of this study. Study CFD4711g enrolled 18 patients in the United States. Lampalizumab was found to have an acceptable safety and tolerability profile at all six doses tested following a single intravitreal administration. The MTD for the study was considered to be 10 mg, the highest dose tested. All enrolled patients completed the study.

1.3.2 Study CFD4870g: Phase Ib/II

1.3.2.1 Phase Ib

The Phase Ib portion of Study CFD4870g served as the initial assessment of the safety and tolerability of multiple, monthly, intravitreal administrations with the 10-mg dose of lampalizumab. This safety run-in portion of Study CFD4870 was designed to obtain 10 evaluable GA patients exposed to a minimum of 3 monthly doses of lampalizumab at 10 mg to evaluate the safety and tolerability of lampalizumab administered by intravitreal injection prior to initiating the Phase II randomized component of this study. At the safety hiatus assessment for the run-in portion of the Phase Ib component of Study CFD4870g, the 10-mg dose was found to be well tolerated following multiple, monthly, intravitreal injections, and these results enabled enrollment into the Phase II component of Study CFD4870g.

1.3.2.2 Phase II

The Phase II component of Study CFD4870g was a multicenter, randomized, single-masked, sham injection–controlled study of the safety, tolerability, and efficacy of lampalizumab (10-mg dose) intravitreal injections administered monthly or every other month to patients with GA. This study enrolled 129 patients at 26 sites in the United States and 6 sites in Germany.

Preliminary clinical evidence of lampalizumab's efficacy was demonstrated in the Phase II component of Study CFD4870g. The Phase II met its primary endpoint of mean change from baseline in GA area at 18 months as measured by fundus

autofluorescence (FAF) and met its secondary endpoint of mean change from baseline in GA area at 18 months as assessed by color fundus photographs (CFPs) in the lampalizumab monthly group. A positive treatment effect in slowing the progression of GA area growth was observed in the monthly group beginning at 6 months and extending through the study duration of 18 months. The mean difference in GA area between the monthly lampalizumab group compared with the pooled sham group at Month 18 was 0.595 mm^2 (80% CI: 0.109, 1.081; $p = 0.1170$, less than the prespecified type I error rate of 0.2). This difference corresponds to a reduction in GA area of 20.4% (80% CI: 4%, 37%) with monthly lampalizumab treatment; the reduction in GA area was calculated as $100\% \times$ [(mean GA area change in pooled sham – mean GA area change in lampalizumab)/mean GA area change in pooled sham].

The Phase II results demonstrated a clinically meaningful and statistically significant effect of lampalizumab administered monthly on reducing GA area growth over the 18-month study treatment period. There was no apparent treatment benefit observed in the lampalizumab every-other-month all-comer treatment group.

Results from Study CFD4870g demonstrated an acceptable safety and tolerability profile with lampalizumab administered as 10-mg intravitreal injections monthly or every other month over 18 months.

Exploratory Genetic Analysis Using Four Single- Nucleotide Polymorphisms in the Alternative Complement Pathway

Although AMD risk may involve multiple factors, it is well accepted that there is a strong genetic contribution. The largest study evaluating AMD genetics to date, a meta-analysis, identified AMD-associated single–nucleotide polymorphisms (SNPs) at multiple genetic loci, including five genes (CFH, CFB, CFI, C2, and C3) in the complement pathway (Fritsche et al. 2013). With the exception of C2, all of these proteins are associated with the ACP. The strong correlation of genetic variants in the ACP with the risk of AMD led to the hypothesis that patients with GA and with risk-associated variants at the ACP loci may have higher basal ACP complement activation and may derive greater potential treatment benefit from inhibition of the ACP with lampalizumab.

Four SNPs representing CFH, C2/CFB, C3, and CFI were selected and individually tested for an association with the observed efficacy of lampalizumab and for an association with the rate of GA progression in patients in the sham treatment group. The most statistically significant AMD risk SNPs in these ACP genes were chosen on the basis of a previously reported genomewide meta-analysis (Fritsche et al. 2013). C2 and CFB are tightly linked genetically and are represented by a single risk SNP. Patients who were heterozygous or homozygous for the risk alleles were grouped together for this analysis and were referred to as risk allele carriers. In patients who had genetic testing performed in the Phase II component of Study CFD4870g, approximately

96%, 98%, 47%, and 57% were carriers of CFH, C2/CFB, C3, and CFI risk alleles, respectively.

Phase II Exploratory Analyses with CFH, C2/CFB, C3, and CFI Single–Nucleotide Polymorphisms

Because very few patients in Study CFD4870g were non-carriers of the risk alleles for CFH and C2/CFB, these two SNPs could not be evaluated for an association with treatment response or for the rate of GA progression in patients receiving sham treatment.

Exploratory analysis of the C3 SNP did not show a significant association with treatment response or with the GA area progression in patients receiving sham treatment.

Exploratory analysis of the CFI SNPs indicated that there was greater efficacy in the subgroup of patients who were carriers of the CFI risk allele compared with patients who were non-carriers of the CFI risk allele. In CFI risk allele carriers, the mean difference in GA growth between the monthly group and the sham group at Month 18 was 1.839 mm^2, corresponding to a reduction in GA area of 44% (approximately 80% CI: 25%, 63%; $p=0.0037$). In CFI risk allele carriers, the mean difference in GA growth between the every-other-month group and the sham group at Month 18 was 0.734 mm^2, corresponding to a reduction in GA area of 18% (approximately 80% CI: – 1%, 36%; $p=0.2266$). In non-carriers of the CFI risk allele, there was no apparent lampalizumab treatment response in either the monthly or every-other-month group.

The prognostic effects of the CFI risk allele were also examined. In patients in the sham group, the change in GA area at Month 18 was 4.169 mm^2 (80% CI: 3.582, 4.756) in CFI risk allele carriers and 2.792 mm^2 (80% CI: 2.293, 3.292) in non-carriers of the CFI risk allele; the difference in the GA progression between CFI risk allele carriers and non-carriers at Month 18 was approximately 49%.

The results from the exploratory analysis suggest that the CFI risk allele may be both prognostic for more rapid progression of GA and predictive for treatment response to lampalizumab.

Definition of Complement Factor I Profile Biomarker

CFI profile biomarker-positive is defined as risk allele carriers of CFI that are also risk allele carriers at CFH and/or C2/CFB, and CFI profile biomarker-negative is defined as non-carriers of the CFI risk allele or carriers of the CFI risk allele who are non-carriers of the risk alleles at both CFH and C2/CFB (see Table 1). The CFI profile biomarker was defined using these three risk alleles on the basis of the association of the CFI risk allele with lampalizumab response, the high frequency of risk alleles at CFH and C2/CFB in Study CFD4870g, and the fact that the CFH and C2/CFB SNPs are highly significant in genomewide studies of AMD genetic risk ($p=1\times10^{434}$ and $p=4\times10^{89}$, respectively [Fritsche et al. 2013]). The inclusion of CFH and C2/CFB genotypes in the definition of

CFI profile biomarker-positive is intended to increase the likelihood of identifying patients with complement-driven GA disease. Of note, all CFI risk allele carriers in Study CFD4870g were also risk allele carriers at CFH and/or C2/CFB.

Table 1 Definition of Biomarker Status Using the CFI Profile Test

	CFI	CFH	C2/CFB
CFI profile biomarker-positive	+	+	+
	+	+	–
	+	–	+
CFI profile biomarker-negative	+	–	–
	–	+	+
	–	+	–
	–	–	+
	–	–	–

Note: "+" indicates that the patient is a risk allele carrier (i.e., heterozygous or homozygous for the risk allele) and "–" indicates that the patient is a non-carrier of the risk allele.

1.3.3 Study GX28198: Open-Label Extension

Study GX28198 is an ongoing, multicenter, open-label extension study of the safety and tolerability of lampalizumab administered by intravitreal injection to eligible patients with GA who have completed the 18-month treatment in Study CFD4870g.

For additional details on nonclinical and clinical studies, see the current Lampalizumab Investigator's Brochure.

1.3.4 Rationale for Study GX29455

Study CFD4870g Phase II results provided evidence that ACP inhibition with lampalizumab may reduce the progression of GA; moreover, lampalizumab administered as 10-mg intravitreal injections monthly over 18 months demonstrated an acceptable safety and tolerability profile in patients with GA secondary to AMD.

Exploratory genetic analyses from the Phase II Study CFD4870g suggest that in a biomarker-defined population (CFI profile biomarker-positive), GA lesions may progress more rapidly and potentially derive greater treatment benefit from lampalizumab than in patients negative for the biomarker (CFI profile biomarker-negative). On the basis of the preclinical Study 09-1554 and CFD4870g Phase II results, Study GX29455 will further investigate the exposure-response and safety of lampalizumab in the CFI profile biomarker-positive patient population over multiple intravitreal injections and dose exposures.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary efficacy objective for this study is as follows:

- To investigate exposure-response of lampalizumab administered intravitreally every 2 weeks (Q2W) or 4 weeks (Q4W) compared with sham control in CFI profile biomarker-positive GA patients; treatment response will be measured as change in GA area by FAF

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To characterize the serum pharmacokinetics of lampalizumab following multiple Q2W and Q4W intravitreal doses
- To characterize systemic immunogenicity of lampalizumab following multiple Q2W and Q4W intravitreal doses
- To evaluate the ocular and systemic safety of lampalizumab Q2W and Q4W intravitreal doses compared with sham control

2.3 EXPLORATORY OBJECTIVES

- To evaluate the pharmacokinetic-pharmacodynamic (PK–PD) relationship of lampalizumab in aqueous humor samples
- To evaluate the potential association of genetic variants in CFI, complement-pathway genes, and AMD–associated genes with disease characteristics and response to administration of lampalizumab

3. STUDY DESIGN

The GX29455 Phase II is a multicenter, randomized, single-masked, sham injection-controlled study of the exposure-response and safety of lampalizumab administered intravitreally Q2W or Q4W for 24 weeks to CFI profile biomarker-positive patients with GA secondary to AMD. Profile biomarker-positive patients will be determined by the investigational cobas® CFI Profile Clinical Trial Assay (CTA). All outcome measures will be evaluated at 24 weeks. A Q2W safety run-in assessment will precede the randomized study. Approximately 90 patients will be enrolled at an estimated 25–30 study sites in the United States.

3.1 DESCRIPTION OF STUDY

3.1.1 Safety Run-In Assessment

A safety run-in assessment with multiple 10-mg intravitreal administrations of lampalizumab at the Q2W frequency will be conducted at approximately 10 sites prior to initiating enrollment in the randomized study. This assessment is being performed to obtain an initial evaluation of the safety and tolerability of Q2W dosing. All patients in the safety run-in assessment will receive lampalizumab Q2W to obtain safety data from

3 evaluable patients (defined as a patient who has received ≥3 study drug injections). The safety run-in screening period is up to 21 days (Days–21 to–1), and the screening assessments may be completed over several separate days provided these days fall within the specified screening interval. Patient eligibility and enrollment for the safety run-in assessment will follow the same process and criteria described in Section 3.1.2 for the randomized study, with the exception of best corrected visual acuity (BCVA) inclusion criteria, the option of manual enrollment without interactive voice and Web response system (IxRS), and the option of receiving patient biomarker qualifying status directly from the laboratory versus contacting IxRS.

The safety run-in assessment will be open label; all patients will receive study drug. Each patient will receive study drug injection on Day 1 and will be contacted by study site personnel on Day 2 and Day 8 (±2 days) after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular signs or symptoms in the study eye (see Appendix 1). If warranted, patients will be asked to return to the clinic for an unscheduled safety assessment visit (see Appendix 4). All safety run-in patients will also return for safety assessment visits every 2 weeks (±2 days). After the third evaluable patient completes the Week 6 (±2 days) visit following the previous third study drug administration, a hiatus in treatment of approximately 3 days will ensue. During the hiatus, the Genentech Safety Review Committee (which consists of the Medical Monitor, Drug Safety Scientist, and Biostatistician) will review the safety results for the run-in assessment. If the results show acceptable safety in accordance with the dose-limiting toxicity (DLT) criteria (see Section 3.1.1.1), subsequently, the randomized study will be initiated.

Following the hiatus assessment and an initial acceptable safety profile for the Q2W dosing frequency, patients who participate in the safety run-in assessment will continue on the Q2W open-label study drug administration for the remainder of the 24-week treatment course, and study visit frequency and assessments will follow the same regimen as that of the Q2W arm of the randomized study (see Appendix 2). These patients will receive a maximum of 12 study drug treatments during the study.

Missed doses will not be replaced.

A schedule of assessments is provided in Appendix 1 and Appendix 2.

3.1.1.1 Dose-Limiting Toxicities Criteria for the Safety Run-In Assessment

If ≥2 patients experience the same DLT during the safety run-in assessment, all patients in that cohort will be discontinued from the study and follow the early termination process, and the study will be terminated. If a single DLT occurs during the safety run-in, the cohort will be expanded to obtain 3 additional patients. If ≥1 of the patients in the expanded cohort experiences a DLT, all patients will be discontinued from the study and follow the early termination process, and the study will be terminated. Successful

completion of the safety run-in will be required to subsequently initiate the randomized study.

3.1.1.2 Dose-Limiting Toxicities for the Safety Run-In Assessment

DLTs are any of the following adverse events that occur during the safety run-in assessment period and are believed by the investigator or the Sponsor to be study drug related:

- Intraocular inflammation (e.g., iritis, uveitis, or vitritis) defined as a change of two units on standard grading scales (see Appendix 5) after the study drug injection. In accordance with this definition, study exclusion criteria establish a baseline grade of 0, and an increase to 2+ or greater would constitute a DLT. Intraocular inflammation of Grade 4± would be considered a major toxicity requiring interruption of enrollment and further evaluation by the internal Safety Review Committee to determine whether further enrollment/treatment is appropriate.
- Endophthalmitis secondary to an encapsulated bacteria (i.e., *Streptococcus pneumonia, Haemophilus influenza,or Neisseria meningitidis)*
- Sustained elevation of intraocular pressure (IOP), defined as a measurement of ≥30 mmHg on three consecutive study treatment visits
- Sustained loss of BCVA ≥15 letters after the study drug injection that is not attributable to the injection procedure, progression of GA, or change in the ocular media (i.e., cornea, aqueous humor, lens, vitreous humor) as measured on the three consecutive study treatment visits

3.1.1.3 Dose-Limiting Toxicity Assessments Window for the Safety Run-In

The safety run-in patients will be assessed for DLTs every 2 weeks (± 2 days) after each study drug injection or during unscheduled visits, if prompted by the Day 2 or Day 8 follow-up calls. This regimen will continue for all safety run-in patients until the third evaluable patient receives the third study drug injection and completes the Week 6 (± 2 days) visit.

3.1.2 Four-Arm, Randomized Study

An estimated $25–30$ study sites in the United States will participate in the randomized study. Approximately 84 CFI profile biomarker-positive patients with GA secondary to AMD will be enrolled. Biomarker status will be determined using the investigational cobas® CFI Profile CTA that will be run at a designated study laboratory testing site. The study will consist of a screening period of up to 28 days (Days -28 to -1) and a treatment period of 24 weeks.

A patient must satisfy all eligibility criteria at both the screening and the Day 1 visits, including receipt of all screening visit images by the central reading center. Study sites will have to verify biomarker eligibility of a patient prior to the Day 1 visit by contacting IxRS.

Patients who failed screening for reasons other than CFI biomarker status (e.g., GA lesion size, BCVA, or prohibited concomitant medication) may be eligible for rescreening up to two additional times during the enrollment period of the study. At rescreening, all screening visit assessments will be performed except CFI biomarker sample provided that a valid CFI result is available.

Eligible patients will be enrolled on Day 1, the same day treatment is to be initiated, and randomized through an IxRS in a ratio of 3:1:2:1 so that approximately:

- 36 patients will receive study drug injections Q2W and 12 patients will receive sham injections Q2W for 24 weeks of treatment (12 total treatments)
- 24 patients will receive study drug injections Q4W and 12 patients will receive sham injections Q4W for 24 weeks (6 total treatments)

For additional details on dosing schema for Q2W and Q4QW treatment arms, see Figure 2a and Figure 2b, respectively.

Randomized patients will be stratified on the basis of baseline GA lesion size (<10 mm^2 versus ≥ 10 mm^2) and baseline BCVA (better than/equal to 20/100 versus worse than 20/100). Sham arms will be pooled for analyses. To obtain a similar distribution of patients in the randomized study with baseline BCVA better than/equal to 20/100 and worse than 20/100, a maximum of approximately 45 patients will be allotted to either of the baseline BCVA groups (i.e., better than/equal to 20/100 group or worse than 20/100 group). If the study enrolls the maximum allotted number of patients to either baseline BCVA group, additional screened patients who would have been enrolled in the baseline BCVA group that has been maximized will be screen-failed.

Figure 2a Dosing Schema for Q2W Treatment Arms

	Day Visit	Week Visit												
Treatment Arms	1	2	4	6	8	10	12	14	16	18	20	22	24 [a]	n
Lampalizumab [b]	x	x	x	x	x	x	x	x	x	x	x	x	–	48
Sham [c]	x	x	x	x	x	x	x	x	x	x	x	x	–	12

Q2W=every 2 weeks.

[a] Study treatment is not administered at Week 24 visit (final visit).

[b] Q2W intravitreal injections of 10 mg lampalizumab.

[c] Q2W sham injections.

Figure 2b Dosing Schema for Q4W Treatment Arms

	Day Visit	Week Visit						
Treatment Arms	1	4	8	12	16	20	24 [a]	n
Lampalizumab [b]	x	x	x	x	x	x	–	24
Sham [c]	x	x	x	x	x	x	–	12

Q4W = every 4 weeks.

[a] Study treatment is not administered at Week 24 visit (final visit).

[b] Q4W intravitreal injections of 10 mg lampalizumab.

[c] Q4W sham injections.

Only one eye will be chosen as the study eye. If both eyes are eligible, the eye with the worse visual function (as determined by the investigator and the patient) will be the study eye; if both eyes have the same visual function, the eye with the larger GA area will be selected as the study eye. Investigators and other site staff members will not be masked to patient treatment assignment (drug vs. sham). The BCVA examiner will be masked to the study eye and treatment assigned (drug vs. sham) and will perform only the BCVA assessment. The BCVA examiner is not allowed to perform any other tasks involving direct patient care. Patients will be masked to their treatment assignment (study drug vs. sham). Randomized patients will receive the first study drug or sham treatment administered by the investigator on Day 1. All patients will have scheduled safety and ocular assessment at the Q2W or Q4W treatment visits during the 24-week study (see Figure 2a and Figure 2b). Safety assessments will be evaluated by the investigator prior to study drug or sham administration. Missed doses will not be replaced. Patients who are discontinued from study treatment prematurely will be discontinued from the study as well. Patients withdrawn from the study prior to completion will be asked to return for an early termination visit 30 (+7) days following their last study treatment.

The first study treatment will be administered on the same day as randomization (Day 1 visit). If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), with the Medical Monitor's permission, the patient's first study treatment may be administered within 1 working day after the Day 1 visit. The following assessments will be repeated on the day of the study treatment: BCVA, slit–lamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurement (recorded on Day 1 electronic Case Report Form (eCRF) and dated accordingly). After the Day 1 visit, if a patient misses a study visit when ocular images are scheduled (see Appendix 1), the images must be obtained at the next scheduled visit.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected approximately 24 weeks after the last patient is randomized to the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Lampalizumab Dose and Schedule

To provide a more extensive characterization of lampalizumab in patients with GA secondary to AMD, Study GX29455 will further investigate the exposure-response relationship with a 10-mg dose of study drug administered intravitreally at Q2W and Q4W intervals. The 10-mg monthly dosing regimen was found to be the most efficacious in the Phase II component of Study CFD4870g; moreover, the 10-mg dose was observed to have an acceptable safety profile in Study CFD4870g. Data to support the Q2W dosing frequency are provided by the preclinical cynomolgus monkey Study 09-1554. For additional details on nonclinical and clinical studies, see the current Lampalizumab Investigator's Brochure.

3.3.2 Rationale for Patient Population and Analysis Groups

3.3.2.1 Rationale for Evaluating Lampalizumab in Patients with Geographic Atrophy

Currently, there are no approved treatments to prevent the progression of GA secondary to AMD and the associated decrease in visual function. Consequently, a significant unmet medical need exists for treatment of this serious vision-impairing disease. Study GX29455 will enroll patients with the diagnosis of GA secondary to AMD. On the basis of the results from Study CFD4870g, patients in Study GX29455 will be stratified by baseline GA lesion size and baseline BCVA. Moreover, consistent with Study CFD4870g results, select clinical and genetic eligibility criteria have been chosen to enrich the Study GX29455 study population for patients at increased risk for rapid expansion of GA area to maximize the opportunity of detecting disease progression and treatment response over the planned 24-week study duration. The select clinical eligibility criteria and rationale for these criteria are presented below.

Presence of Hyperautofluorescence (i.e., Banded or Diffuse Junctional Fundus Autofluorescence Patterns) Adjacent to the Geographic Atrophy Lesion in the Study Eye

Holz et al. (2007) previously described four major perilesional FAF patterns (none, focal, banded, and diffuse) that were correlated with the rate of GA lesion growth in the longitudinal natural history investigation of patients with GA secondary to AMD in the multicenter Fundus Autofluorescence in Age-Related Macular Degeneration (FAM)-study. This study reported that GA lesions with banded or diffuse junctional patterns showed a significantly increased rate of GA lesion progression versus lesions with focal or no hyperautofluorescence patterns. Moreover, approximately 70% of the FAM study patients exhibited banded or diffuse junctional perilesional FAF patterns.

Geographic Atrophy in Both Study Eye and Non-Study (Fellow) Eye

In patients with GA, bilateral disease represents the majority of the population (approximately 60%–67%) with this form of advanced AMD as reported in two natural history studies (Holz et al. 2007; Sunness et al. 2007); moreover, bilateral

GA has been associated with an increased rate of lesion progression compared with unilateral GA lesions (Sunness et al. 2007).

Complement Factor I Profile Biomarker-Positive Selection

Exploratory analyses of the Phase II CFD4870g study suggest that the CFI profile biomarker-positive population may progress more rapidly and have a significantly greater treatment benefit with lampalizumab than the CFI profile biomarker-negative population; therefore, the objectives of Study GX29455 will be investigated in CFI profile biomarker-positive patients. Furthermore, based on the exploratory lampalizumab treatment results at 6 months in Study CFD4870g with the CFI biomarker-positive patient population, the objectives of Study GX29455 are expected to be completed in the proposed 24-week study.

The cobas® CFI Profile Clinical Trial Assay

A valid CFI biomarker result will be determined at a designated study laboratory testing site using the cobas CFI Profile CTA, which is a real-time polymerase chain reaction (PCR) test developed by Roche Molecular Systems to identify genotypes of three SNPs associated with CFH, CFI, and C2/CFB in DNA extracted from whole-blood samples from patients with GA secondary to AMD. The cobas CFI Profile CTA is intended to be used as an Investigational Use Only assay to characterize the complement factor profile of study participants. The cobas CFI Profile CTA biomarker status results will then be used to determine eligibility for enrollment.

The cobas CFI Profile CTA consists of two kits and will use the cobas 4800 platform. The cobas DNA Sample Preparation Kit (DNA isolation kit) provides the necessary components to manually extract genomic DNA from whole blood samples. The cobas CFI Profile CTA contains the necessary PCR master mix, oligonucleotides, cofactor, and controls to detect three SNPs associated with CFI, CFH, and C2/CFB.

3.3.3 Rationale for Control Group

A sham control group will be used as a comparator for the exposure-response and safety of lampalizumab administered Q2W or Q4W. Patients randomized to the sham control group will undergo the same assessments as patients randomized to the lampalizumab intravitreal injection groups.

Sham injections, rather than placebo intravitreal injections, were selected to minimize the known risk of intravitreal injection-related adverse events (e.g., endophthalmitis), and no potential patient value would be derived from an intravitreal injection of placebo.

3.3.4 Rationale for Biomarker Assessments

On the basis of the results of the Phase II Study CFD4870g, lampalizumab is hypothesized to be most effective in CFI Profile biomarker-positive patients. To further assess the exposure-response of lampalizumab, Study GX29455 will enroll only CFI Profile–positive patients. The response to lampalizumab treatment will be evaluated in a

prespecified population defined by the genetic biomarker test (cobas® CFI Profile CTA) on the basis of the common genetic variants of CFI, CFH, and C2/CFB. The whole blood sample CFI profile results will be determined by utilizing an investigational cobas CFI Profile CTA (see Appendix 16). Although the CFI profile test is based on the common genetic variants of CFI, CFH, and C2/CFB test, recent studies have identified rare variants in CFI that have been associated with increased AMD risk (van de Ven et al. 2013). Given the potential for rare variants in CFI and other complement pathway genes to affect disease characteristics including progression and the response to lampalizumab treatment, additional exploratory genetic analysis may be conducted using the biomarker clinical genotyping sample including sequencing of CFI, other complement-pathway genes, and AMD associated genes.

3.4 OUTCOME MEASURES

3.4.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- Mean change in GA area from baseline to Week 24 as measured by FAF

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- The incidence of DLTs for Q2W multidose safety run-in assessment
- Incidence and severity of ocular and non-ocular (systemic) adverse events
- Mean change in BCVA from baseline to Week 24 using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart
- The incidence of changes and abnormalities in clinical ocular examinations
- The incidence of changes and abnormalities in clinical laboratory assessments
- The incidence of positive serum antibodies to lampalizumab

3.4.3 Pharmacokinetic Outcome Measures

The PK profile from the serum concentration–time data following administration of lampalizumab will be determined. Derived PK parameters may include the following:

- Maximum observed serum concentration (C_{max})
- Time of maximum observed serum concentration (t_{max})
- Observed steady-state trough concentration
- Accumulation ratio based on trough concentration

Optional anterior chamber (aqueous humor) paracentesis samples will be collected to assess PK and PD relationships. Additional PK analyses may be conducted as appropriate.

3.4.4 Exploratory Outcome Measures

Exploratory outcome measures for this study include the following:

- PK-PD relationship of lampalizumab in aqueous humor samples
- Evaluation of potential associations of genetic variants in CFI, complement-pathway genes, and AMD-associated genes with disease characteristics and response to administration of lampalizumab

4. MATERIALS AND METHODS

4.1 PATIENTS

Patient Selection and Sex Distribution

Written informed consent will be obtained prior to initiation of any study procedures. The screening evaluation will be performed within *28* days preceding the Day 1 visit (the day of the first study treatment).

> *NOTE: Some patients may require an extended screening period as a result of repeat acquisition or evaluation of images or other issues. After consultation with and approval by the Medical Monitor, the screening period may be extended for up to 5 days for exceptional circumstances.*

Only one eye will be chosen as the study eye. If both eyes are eligible, the eye with the worse visual function (as determined by the investigator and patient) will be the study eye. If both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye.

The protocol allows enrollment of both men and women, provided the entry criteria are met. However, women who are pregnant or breastfeeding will be excluded from the study. The remaining inclusion/exclusion criteria apply to both male and female patients and pertain to issues of patient health performance and safety.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry.

4.1.1.1 General Inclusion Criteria

- Willingness to provide signed Informed Consent and Health Insurance Portability and Accountability Act authorization
- *Age ≥60 years*
- CFI profile biomarker–positive result
- For women of *childbearing potential:* agreement to remain abstinent *(refrain from heterosexual intercourse) or* use contraceptive methods that result in a failure rate of<1% per year during the treatment period and for at least 30 days after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarchial, has not reached postmenopausal state (≥12 months of amenorrhea with no identified

cause other than menopause), and has not undergone surgical sterilization (absence of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent or use *contraceptive measures and agreement to refrain from donating sperm as defined below:*

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 30 days *plus 90 days (a spermatogenesis cycle)* after the last dose of study drug.

- Ability and willingness to undertake all scheduled visits and assessments

4.1.1.2 Ocular Inclusion Criteria: Study Eye

- BCVA ETDRS

  For the safety run-in assessment: BCVA of 20/80 to 20/400 inclusive (Snellen equivalent) using ETDRS charts

  For the randomized study: BCVA of 20/50 to 20/400 inclusive (Snellen equivalent) using ETDRS charts

- Well–demarcated area of GA secondary to AMD
- GA must be ≥ 1 disc area (DA) (2.54 mm^2) in the absence of CNV
- If GA is multifocal, at least one focal lesion must be ≥0.5 DA (1.27 mm^2)
- The total lesion size must be ≤ to 7 DA (17.78 mm^2) and must reside completely within the FAF imaging field
- Presence of hyperautofluorescence adjacent to the area of GA (banded or diffuse perilesional FAF patterns)
- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging

4.1.1.3 Ocular Inclusion Criteria: Fellow (Non-Study) Eye

- GA secondary to AMD in the absence of prior or active CNV

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

4.1.2.1 Ocular Exclusion Criteria: Geographic Atrophy Characteristics

- GA in the study eye that extends beyond FAF imaging field or fails to meet single or multifocal lesion criteria
- Absence or minimal hyperfluorescence adjacent to GA in the study eye (e.g., focal or no perilesional FAF pattern)
- GA in either eye due to causes other than AMD (e.g., Stargardt disease, cone-rod dystrophy, chloroquine/hydroxychloroquine toxicity)

4.1.2.2 Ocular Exclusion Criteria: Study Eye

- History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD
- Previous subfoveal focal laser photocoagulation
- Laser photocoagulation (juxtafoveal or extrafoveal)
- Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, biodegradable/non-biodegradable implants or formulations, device implant, or encapsulated cell technology). *NOTE: A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.*
- Previous cell-based (e.g., regenerative or trophic) intraocular treatment
- RPE tear involving the macula
- History of retinal tear. *NOTE: a retinal tear adequately treated with laser photocoagulation and determined to be stable by investigator may be permitted after consultation with and approval by the Medical Monitor.*
- Any concurrent ocular or intraocular condition (e.g., cataract or epiretinal membrane) that, in the opinion of the investigator, could do either of the following:

  Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition; or

  If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of BCVA during the study period
- Active vitreous hemorrhage
- History of retinal detachment or macular hole (Stage 3 or 4)
- Aphakia or absence of the posterior capsule

  Previous violation of the posterior capsule is also excluded unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia

- For patients who have undergone prior refractive or cataract surgery, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia
- Intraocular surgery (including cataract surgery) within 3 months preceding Day 1
- Glaucoma that is uncontrolled (defined as IOP ≥ 30 mmHg despite treatment with anti-glaucoma medication)
- History of glaucoma-filtering surgery
- History of corneal transplant

4.1.2.3 Ocular Exclusion Criteria: Either Eye

- *Proliferative* diabetic retinopathy. *NOTE: mild non-proliferative diabetic retinopathy (occasional hemorrhage or microaneurysm) in either eye may be permitted after consultation with and approval by the Medical Monitor; moreover, a patient with onset of mild non-proliferative diabetic retinopathy in either eye during study participation may be permitted to continue study treatment after consultation with the Medical Monitor.*
- Active or history of neovascular (wet) AMD
- History of idiopathic or autoimmune-associated uveitis
- Active uveitis and/or vitritis (see definitions and grading scales for iritis/anterior uveitis and vitritis in Appendix 5)
- History of ocular or intraocular conditions that contraindicate the use of an investigational drug or may affect interpretation of study results or my render the patient at high risk for treatment complications
- Previous participation in other studies of investigational drugs (excluding vitamin and mineral supplements; topical ocular agents ≥ 3 months preceding Day 1) may be permitted after consultation with *and approval by* the Medical Monitor
- Previous systemic treatment with a complement inhibitor
- Previous treatment with inhibitors/modulators of the visual cycle (e.g., fenretinide)
- Previous expression vector mediated intraocular treatments
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis
- History of infectious or inflammatory ocular disease

4.1.2.4 Systemic Exclusion Criteria: Concurrent Conditions

- Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 mmHg while patient is sitting)

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient can become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- Atrial fibrillation not managed by medication/cardioversion and the patient is under the care of a primary care physician or cardiologist

- Medical conditions that may be associated with a clinically significant risk for bleeding
- Active or history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or that renders the patient at high risk for treatment complications
- Treatment for *an* active *localized or* systemic infection

  Ongoing prophylactic use of antimicrobial therapy should be discussed with and approved by the Medical Monitor.
- Predisposition or history of increased risk for infection
- Active malignancy within the previous *12 months* except *for appropriately treated carcinoma in situ of the cervix,* resolved *non-melanoma skin carcinoma, and prostate cancer with a Gleason score of ≤6 and a stable prostate-specific antigen (PSA) for ≥12 months.*
- History of allergy to fluorescein, not amenable to treatment
- *History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lampalizumab injection*
- Inability to obtain FAF or near infrared images, fundus photographs, or fluorescein angiograms of sufficient quality to be analyzed and graded by the central reading center
- Inability to comply with study or follow-up procedures
- Requirement for continuous use of any medications/treatments indicated in the "*Prohibited* Therapy" section of the protocol *(see Section 4.4.2)*
- Women who are pregnant or lactating or intending to become pregnant during the study
- Woman of *childbearing potential* must have a negative serum pregnancy test result within *28* days prior to initiation of study treatment

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Safety Run-In Assessment Treatment Assignment and Masking

The safety run-in assessment is open label; all patients will receive study drug. After written informed consent has been obtained, all patients will receive a screening number assigned through the IxRS. A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) at both the screening and the Day 1 visit (first study treatment) prior to enrollment. As part of the screening process, the central reading center will evaluate FAF images, CFP, and fluorescein angiography (FA) to provide an objective, assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IxRS on the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). The study treatment kit will be also assigned by IxRS at that time. All patients enrolled in the safety

run-in assessment will receive a 10-mg dose of lampalizumab Q2W for the duration of their study participation.

The site study staff, vendors, and Sponsor study personnel will not be masked to the patients' treatment arm assignment (study drug vs. sham). The BCVA examiner will be masked to the study eye and treatment assigned (study drug vs. sham) and will perform only the refraction and BCVA assessment. The BCVA examiner will be also masked to the BCVA scores of a patient's previous visits and may only know patient's refraction data from previous visits. The BCVA examiner is not allowed to perform any other tasks involving direct patient care. Patients will be masked to their treatment assignment.

4.2.2 Randomized Study Treatment Assignment and Masking

The randomized study is single masked. After written informed consent has been obtained, all patients will receive a screening number assigned through the IxRS. A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) at both the screening and the Day 1 visit (first study treatment) prior to randomization. As part of the screening process, the central reading center (masked to patient treatment assignment) will evaluate FAF images, CFP, and FA to provide an objective, masked assessment of patient eligibility. Patient biomarker eligibility criteria will be verified by contacting IxRS prior to the Day 1 visit. After all patient eligibility requirements are confirmed and Day 1 visit assessments performed, site personnel will contact the IxRS on the Day 1 visit for assignment of a patient identification number (a separate number from the screening number). The study treatment kit number will be also assigned by IxRS at that time. Patients will be randomized in a 3:1:2:1 ratio to one of four treatment groups: lampalizumab Q2W, sham Q2W, lampalizumab Q4W, or sham Q4W. Patients will be randomized on the same day the study treatment is to be initiated (Day 1 visit).

The site study staff, vendors, and Sponsor study personnel will not be masked to the patients' treatment arm assignment (study drug vs sham). The BCVA examiner will be masked to the study eye and treatment assigned (study drug versus sham) and will only perform the refraction and BCVA assessment. The BCVA examiner will be also masked to the BCVA scores of a patient's previous visits and may only know patient's refraction data from previous visits. The BCVA examiner is not allowed to perform any other tasks involving direct patient care. Patients will be masked to their treatment assignment.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Lampalizumab

Lampalizumab vials will be supplied by the Sponsor.

Formulation

Lampalizumab Drug Product is provided as a sterile, white to off-white, lyophilized powder in a 6-cc USP/European Pharmacopoeia Type 1 glass vial and is intended for intravitreal administration. Each glass vial contains a nominal 40 mg of lampalizumab.

After reconstitution with Sterile Water for Injection, the drug product is formulated as 100 mg/mL lampalizumab in 40 mM L-histidine hydrochloride, 28 mM sodium chloride, 160 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.3.

4.3.1.2 Sham

Sham vials will be supplied by the Sponsor.

Sham vials will be identical to vials of lampalizumab, but the sham vials will be empty.

Storage

Upon receipt of lampalizumab and sham, vials should be refrigerated at 2°C–8°C (36°F–46°F) until use. Lampalizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in lampalizumab drug product; therefore, the vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight. Within 2 hours following dose preparation (reconstitution), lampalizumab should be administered; the prepared dose may be maintained at room temperature prior to administration.

For further details, see the Lampalizumab Investigator's Brochure and/or Pharmacy Binder.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Lampalizumab and Sham

Dosage

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.1.1. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Safety Run-In Assessment: A safety run-in assessment with multiple 10-mg intravitreal administrations of lampalizumab at the Q2W frequency will be conducted prior to initiating enrollment in the randomized study. A schedule of assessments is provided in Appendix 1. Patients in the safety run-in assessment will receive lampalizumab injections Q2W to obtain safety data from 3 evaluable patients (defined as a patient who has received ≥3 study drug injections). Each patient will receive study drug on Day 1 and will be contacted by study site personnel on Day 2 and Day 8 (± 2 days) after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular signs or symptoms in the study eye; if warranted, patients will be asked to return to the clinic for an unscheduled safety assessment visit (see Appendix 4). All safety run-in patients will also return for safety assessment visits every 2 weeks (± 2 days). After the third evaluable patient completes the Week 6 (± 2 days) visit following the third study drug administration, a hiatus in treatment of approximately 3 days will ensue. During the hiatus, the Genentech Safety Review Committee consisting of the Medical Monitor, Drug Safety Scientist, and Biostatistician will review the safety results for the run-in assessment. If the results show

acceptable safety in accordance with the DLT criteria (see Section 3.1.1.1), subsequently, the randomized study will be initiated.

Following the hiatus assessment and an initial acceptable safety profile for the Q2W dosing frequency, patients who participate in the safety run-in assessment will continue on the Q2W study drug administration for the remainder of the 24-week treatment course. The study treatment visit frequency and assessments (see Appendix 2) will follow the same regimen as the Q2W arm of the randomized study. These patients will receive a maximum of 12 study drug treatments during the study.

Missed doses will not be made up.

Randomized Study

Lampalizumab Intravitreal Injections: A 10-mg dose of lampalizumab will be used in this study and will be administered intravitreally during the 24-week treatment period starting at the Day 1 visit for a total of 12 injections to patients randomized to the Q2W treatment arm and a total of 6 injections to patients randomized to the Q4W treatment arm.

Missed doses will not be made up.

A schedule of assessments is provided in Appendix 2 and Appendix 3.

Sham Injections: Patients randomized to the control arms will receive sham injections. A total of 12 sham injections will be administered in the Q2W arm, and 6 sham injections will be administered in the Q4W arm during the 24-week treatment period. Sham arms will undergo the same assessments as the lampalizumab treatment arms (see Appendix 2 and Appendix 3).

A sham injection is a procedure that mimics an intravitreal injection of lampalizumab, except that the blunt end of an empty syringe is pressed against an anesthetized eye instead of a needle attached to a lampalizumab-filled syringe.

Missed doses will not be made up.

A schedule of assessments is provided in Appendix 2 and Appendix 3.

4.3.2.2 Administration

See Appendix 6 for the pre-injection procedures of lampalizumab and sham treatments for all patients, Appendix 7 for the injection procedures of the study drug, Appendix 8 for the injection procedures of the sham treatment, and Appendix 9 for the post-injection procedures for all treated patients.

4.3.2.3 Compliance

This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations; the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice; and applicable local, state, and federal laws, as well as other applicable country laws.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (lampalizumab and sham) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Lampalizumab

The Sponsor (Genentech) is a member of the Roche group and is subject to Roche's global policies. The Sponsor will offer post-trial access to the study drug (lampalizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a sight-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for GA.

- The Sponsor has reasonable safety concerns regarding the study drug as treatment for GA.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant medications are any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops; fluorescein dyes; etc.) and pre- and post-injection medications (e.g., proparacaine, etc.) used by a patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit.

4.4.1 Permitted Therapy

Patients who use other maintenance therapies should continue their use.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF. Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Intra-articular or *intra-muscular corticosteroids* may be *used in a limited fashion* after consultation with *and approval by* the Medical Monitor. The onset of glaucoma in the study eye during a patient's study participation should be treated as clinically indicated

4.4.2 Prohibited Therapy

At the discretion of the investigator, patients may continue to receive all medications and standard treatments administered for other conditions. *However, the* following medications and treatments *will exclude patients from study eligibility and* are prohibited from use during the patient's participation in the study:

- Systemic anti-vascular endothelial growth factor (VEGF) agents
- Intravitreal anti-VEGF agents in either eye
- Intravitreal, subtenon, or *chronic* topical (ocular) corticosteroids in either eye; short-term use of topical corticosteroids is permitted after cataract surgery
- Oral corticosteroids (prednisone or equivalent) at doses > 10 mg/day *(prohibited at screening for eligibility; for occurrence during study enrollment, see Table 2 , Dose–Interruption Criteria)*
- Intravenous corticosteroids *(prohibited at screening for eligibility; for occurrence during study enrollment, see Table 2, Dose-Interruption Criteria)*

- Systemic or intravenous immunomodulatory therapy (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, tocilizumab, eculizumab, or an anti-tumor necrosis factor agent)
- Treatment with Visudyne in either eye
- Other experimental therapies (except vitamins and minerals)

4.5 STUDY ASSESSMENTS

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and Day 1 visits evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment (safety run-in patients and randomized patients). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, including chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, and ophthalmic history); tobacco use; surgeries; cancer history; reproductive status; and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Day 1 visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. Height and weight will be collected. If any abnormalities are noted during the study, the patient may be referred to another physician with specialty expertise. The investigator should use his or her clinical judgment for appropriate treatment and/or medical referral. Should any clinically significant abnormalities be found at screening or Day 1 prior to study treatment, the condition should be noted in the patient's medical history, and the investigator must perform (or refer the patient for) a directed physical examination prior to patient enrollment. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of systolic and diastolic blood pressure, pulse, respiration rate, and temperature while the patient is in a seated position after resting for at least 5 minutes. Vital signs should be taken before the study treatment as indicated (see Appendix 1, Appendix 2, and Appendix 3).

4.5.5 Other Disease-Specific Assessments

Ocular Assessments

- BCVA at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 10)
- IOP measurement (perform prior to dilating eyes; the method used for a patient must remain consistent throughout the study)
- Slit-lamp examination (for grading scales for cells, see Appendix 5)
- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger counting test, or hand motion or light perception tests (when necessary) performed within 15 minutes post-treatment for the study eye only by physician
- IOP measurement 60 (±10) minutes post-treatment for the study eye only; the method used for a patient must remain consistent throughout the study

Ocular Imaging

- FAF and NI images of both eyes (see Appendix 13 and Appendix 14)
- Stereoscopic, digital CFPs of both eyes (see Appendix 11)
- FAs of both eyes (perform after laboratory samples are obtained) (see Appendix 12)

Except as noted, all ocular assessments should be performed for both eyes.

4.5.6 Laboratory Assessments, Other Biological Assessments, and Genotyping for the CFI Profile Biomarker

4.5.6.1 Laboratory Assessments

Specimens in this section will be forwarded to the central laboratory where the following tests will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBCs, WBCs, and differentials including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), alkaline phosphatase, and uric acid
- Urinalysis: Specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, microscopic examination (if any of the preceding urinalysis tests, other that glucose and ketones, are abnormal)

- Coagulation: aPTT and PT
- Screening visit serum pregnancy test (β-human chorionic gonadotropin): for women of childbearing potential, including those who have had tubal ligation. If positive, study drug will not be administered.

Instructions for obtaining, processing, storing, and shipping all specimens for central laboratory evaluations are provided in the Laboratory Manual.

4.5.6.2 Other Biological Assessments

Samples in this section will be forwarded from the central laboratory to designated laboratories for analysis.

- Serum samples will be obtained to measure lampalizumab concentration; drug concentration will be determined in serum using an ELISA method.
- Serum samples will be obtained for measurement of anti-lampalizumab antibodies; anti-therapeutic antibodies will be detected in serum using a bridging ELISA.
- Optional anterior chamber (aqueous humor) paracentesis samples will be obtained to assess lampalizumab and CFD levels, and PK-PD relationships.
- Systemic alternative complement pathway activity assay (AH50)
- Whole blood sample to evaluate the potential association of genetic variants in CFI, complement-pathway genes, and AMD-associated genes with disease characteristics and response to administration of lampalizumab

4.5.6.3 Genotyping: CFI Profile Biomarker

Whole–blood samples will be collected and forwarded directly from the sites to the Sponsor-selected laboratory for analysis *to determine CFI profile biomarker status* (see the Central Laboratory Manual for details).

The cobas® CFI Profile Clinical Trial Assay

A valid CFI biomarker result will be determined at a designated study laboratory testing site using the cobas CFI Profile CTA, which is a real-time PCR test developed by Roche Molecular Systems to identify genotypes of three SNPs associated with CFH, CFI, and C2/CFB in DNA extracted from whole blood samples from patients with GA secondary to AMD. The cobas CFI Profile CTA is intended to be used as an Investigational Use Only assay to characterize the complement factor profile of study participants. The cobas CFI Profile CTA biomarker status results will be used in Study GX29455 to determine the eligibility of patients for enrollment.

The cobas CFI Profile CTA consists of two kits and will use the cobas 4800 platform. The cobas DNA Sample Preparation Kit (DNA isolation kit) provides the necessary components to manually extract genomic DNA from whole blood samples. The cobas CFI Profile CTA contains the necessary PCR master mix, oligonucleotides, cofactor, and controls to detect three SNPs associated with CFI, CFH, and C2/CFB.

4.5.6.4 Storage

The samples (except for hematology, serum chemistry, urinalysis, coagulation, and serum and urine pregnancy tests that will be destroyed after their analysis during the study) will be stored for up to 5 years after the date of final closure of the associated clinical database.

In addition, residuals of serum pharmacokinetics, serum anti-therapeutic antibodies (ATAs), biomarker whole blood clinical genotyping samples, and aqueous humor samples will be stored for up to 15 years after the date of the final closure of the associated clinical database provided the patient has given specific Roche Clinical Repository (RCR) consent for residual samples to be stored for the optional research.

See Appendix 16 and the Central Lab Manual for detailed instructions.

4.5.7 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the RCR. Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.7.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.7.2 Sample Collection

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

- Residual aqueous humor sample
- Residual serum PK sample
- Residual serum ATA sample
- Residual biomarker whole blood clinical genotyping sample

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

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.7.3 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.7.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.7.5 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GX29455 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GX29455.

4.5.7.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the

Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

Patients withdrawn from the study prior to completion will be asked to return for an early termination evaluation 30 (+7) days following their last study treatment for monitoring of adverse events and assessments listed for the early termination visit (see Appendix 1, Appendix 2, and Appendix 3). The reason for the study discontinuation should be recorded on the appropriate eCRF. Discontinued patients will not be replaced or allowed to re-enter the study.

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who are discontinued from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

The investigator has the right to discontinue a patient from the study treatment for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study treatment, for reasons of non-compliance (e.g., missed doses, visits), if the patient becomes pregnant, or if the investigator determines it is in the best interest of the patient. The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced or allowed to re-start the study treatment.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.

- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

At present, lampalizumab is in clinical development and is not an approved drug. Consequently, an extensive safety profile for lampalizumab remains to be established. The safety plan for this study is designed to help minimize patient risk and will include specific eligibility criteria and monitoring assessments as detailed below.

Safety considerations associated with the intravitreal route of administration or pharmacology of lampalizumab include endophthalmitis, traumatic complications (i.e., conjunctival hemorrhage, conjunctival edema, eye irritation, eye pain or ocular foreign body sensation), and post-injection transient increase in IOP.

There is a potential risk for retinal edema/inflammation or sterile inflammatory reactions, traumatic cataracts or retinal detachments related to the administration of lampalizumab. As lampalizumab is a biologic agent, there is also a risk of developing ATAs; however, there have been no reported adverse events associated with the development of ATAs in patients receiving lampalizumab in the completed Studies CFD4711g and CFD4870g.

Multiple lampalizumab administrations in Study CFD4870g showed no apparent adverse systemic effects associated with inhibition of the alternative complement pathway; nevertheless, monitoring for potential systemic adverse events, such as lowered infection threshold to encapsulated bacteria (i.e., *Streptococcus pneumonia, Haemophilus influenza or Neisseria meningitides)*, will be performed (AH50 assay).

The incidence and characteristics of adverse events, serious adverse events, and laboratory abnormalities will be assessed. Ongoing review of safety will be performed by an internal Genentech Safety Review Committee consisting of the Medical Monitor, Drug Safety Scientist, and Biostatistician. External experts may be consulted. All adverse events will be recorded on eCRFs for the duration of the study.

For the patients in the safety run-in assessment, safety monitoring and review of safety data after each study drug treatment will be performed to determine whether the DLT criteria are met. All DLTs occurring within the pre-specified window of study drug administration should be reported to Genentech within 24 hours of becoming aware of the event. DLTs will be reviewed expeditiously by the Genentech Safety Review Committee.

After each study drug injection, all safety run-in patients will be contacted by study site personnel on post-injection Day 2 and Day 8 (±2 days) to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular sign or symptom in the study eye; if warranted, patients will be asked to return to the clinic for an unscheduled safety assessment visit (see Appendix 4). All safety run-in patients will also return for safety assessment visits every 2 weeks (± 2 days) (see Appendix 1). Subsequently, safety run-in patients will follow the same visits schedule as the Q2W arms of the randomized study (see Appendix 2) until study completion at the Week 24 visit.

The randomized study patients will have safety assessments performed at each scheduled study visit according to their treatment arm assignment (Q2W or Q4W) (see Appendix 2 and Appendix 3). The study patients will be contacted by study site personnel 3 (± 1) days after each study treatment to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular signs or symptoms in the study eye. If warranted, patients will be asked to return to the clinic for an unscheduled safety assessment visit (Appendix 4) and will receive instructions to contact the investigator at any time should they have any health-related concerns.

Following the study treatment, patients will remain in the clinic for 60 (±10) minutes. A finger counting will be tested for each patient within 15 minutes following study treatment by the physician; hand motion or light perception will be tested when necessary. IOP will be measured bilaterally prior to dosing; IOP will be measured again 60 (±10) minutes after study treatment for the study eye only. All IOP measurements will be performed by qualified site personnel. If there are no safety concerns at 60 (±10) minutes, the patient may be discharged from the clinic. If the IOP is increased by ≥10 mmHg from the pre-treatment measurement at 60 (±10) minutes and is of concern to the investigator, the patient will remain in the clinic to be treated in accordance with the investigator's clinical judgment prior to discharge. If applicable, the Adverse Event CRF page will be completed.

Detailed ocular examinations, including slit-lamp and indirect ophthalmoscopy, will be performed throughout the study. Laboratory testing will include hematology, serum chemistry, coagulation, AH50, and urinalysis; blood samples for serum study drug concentrations, antibodies to lampalizumab; biomarker whole blood samples will also be obtained from all patients (see Appendix 1, Appendix 2, and Appendix 3). Optional aqueous humor samples will be obtained from patients who consent to this procedure and sample collection.

Treatment interruption and/or treatment discontinuation for adverse events will be determined using the criteria in Table 2.

Patients withdrawn from the study prior to completion will be asked to return for early termination visit assessments 30 (+7) days following the last study treatment visit (see Appendix 1, Appendix 2, and Appendix 3). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular).

Serious adverse events will be collected and reported in compliance with Good Clinical Practice guidelines.

5.1.1 Management of Specific Adverse Events

5.1.1.1 Dose-Interruption, Treatment and Study Discontinuation Criteria

Treatment interruption and patient discontinuation from the study treatment and the study for adverse events will be determined using the criteria listed in Table 2. If the criteria are met, treatment will either be interrupted or discontinued. The reason for treatment interruption should be recorded on the Dose Interruption eCRF; study discontinuation should be reported on Study Discontinuation eCRF. If applicable, report an adverse events on the Adverse Event eCRF.

Table 2 Dose-Interruption, Treatment, and Study-Discontinuation Criteria

Event	Dose-Interruption Criteria
Intraocular inflammation	Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥ 1+ in the study eye. Patients with ≥ 2+ intraocular inflammation will be discontinued from the study.
VA loss	Interrupt study treatment if there is a treatment-related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of VA prior to the most recent treatment. Study-drug treatment may be permitted subsequently as determined by the Sponsor and investigator.
IOP	Interrupt study treatment if IOP in the study eye is ≥ 30 mmHg. Treatment may be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the Sponsor and investigator.
Vitreous hemorrhage	Interrupt study treatment in the event of a vitreous hemorrhage in the study eye; study drug treatment may be permitted subsequently as determined by the Sponsor and investigator.
Rhegmatogenous retinal break	Interrupt study treatment if a retinal break is present in the study eye. Following successful repair, study drug treatment may be permitted subsequently as determined by the Sponsor and investigator.
Rhegmatogenous retinal detachment or macular hole	Patients with a rhegmatogenous retinal detachment or Stage 3 or 4 macular holes will be discontinued from treatment and the study.
Active local or systemic infection	Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye, or if the patient is currently receiving treatment for *an active local or* systemic infection. Patients with endophthalmitis in either eye will be discontinued from the study. For other conditions, study drug treatment may be permitted subsequently as determined by the Sponsor and investigator.
Cataract surgery and YAG laser treatment	If cataract surgery or YAG laser is required, consultation with the Sponsor is required. Cataract surgery and YAG laser for posterior capsular opacification may be permitted in either eye; however, dose interruption may be required for the study eye and will be determined by the Sponsor and investigator; uncomplicated cataract surgery or YAG laser therapy will be required to resume study treatment.
Laser photocoagulation for CNV	A single treatment of CNV with laser photocoagulation may be permitted in either eye; if permitted, dose interruption may be required for the study eye and will be determined by the Sponsor and investigator.
Oral corticosteroids (prednisone or equivalent) >10–mg/day	Interrupt study treatment. Study treatment may be resumed when oral corticosteroid dosing (prednisone or equivalent) is ≤ 10 mg/day.
IV corticosteroids	Interrupt study treatment. Study treatment may be resumed when the patient has completed IV corticosteroid treatment and oral corticosteroid dosing (prednisone or equivalent) is ≤10 mg/day.

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; IOP = intraocular pressure; IV = intravenous; VA = visual acuity; YAG = yttrium aluminum garnet.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g.,ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious or serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated alanine transaminase (ALT) or aspartate transaminase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Adverse events resulting from medication error

  Examples of medication errors include, but are not limited to, overdose, incorrect dose, incorrect route, incorrect drug, incorrect administration, or incorrect kit.

  If the medication error did result in an adverse event, the primary event term should reflect the adverse event that occurred as a result of the medication error and identify it in "other suspected causes of SAE/AE" data field as a medication error.

- Sight-threatening adverse events

An adverse event is considered to be sight threatening and should be reported expeditiously if it meets one or more of the following criteria:

- It causes a decrease of ≥30 letters in visual acuity (VA) score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour.
- It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+anterior chamber cell/flare or 4+vitritis; see Appendix 5 for intraocular inflammation grading scales).
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight.

All of the above-listed, sight-threatening adverse events should be reported as serious events.

5.2.3.1 Safety Run-in Assessment Period: Targeted Dose-Limiting Toxicities Adverse Events

DLTs are any of the following adverse events that occur during the safety run-in assessment period (prior to hiatus) and are believed by the investigator or the sponsor to be study drug related:

- Intraocular inflammation (e.g., iritis, uveitis, or vitritis) defined as a change of two units on standard grading scales (see Appendix 5) after the study drug injection. In accordance with this definition, study exclusion criteria establish a baseline grade of 0, and an increase to 2+ or greater would constitute a DLT. Intraocular inflammation of Grade 4+ would be considered a major toxicity requiring interruption of enrollment and further evaluation by the internal Safety Review Committee to determine if further enrollment/treatment is appropriate.
- Endophthalmitis secondary to an encapsulated bacteria (i.e., *Streptococcus pneumonia, Haemophilus influenza or Neisseria meningitidis)*
- Sustained elevation of IOP defined as a measurement of ≥30 mmHg on three consecutive study treatment visits
- Sustained loss of BCVA ≥15 letters after the study drug injection that is not attributable to the injection procedure, progression of GA, or change in the ocular media (i.e., cornea, aqueous humor, lens, vitreous humor) as measured on the three consecutive study treatment visits

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 30 (+7) days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale in Table 3 will be used for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Notes: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	*There is a plausible* temporal relationship *between the onset* of the *adverse event and* administration *of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness,* or *concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug and, if applicable, reappears upon re-challenge.*
NO	*An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible* temporal relationship to administration *of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).*

AE = adverse event; SAE = serious adverse event.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

For the purposes of reporting events of infection and inflammation, the following terms and definitions should be used:

- Iritis: the presence of inflammatory cells in the anterior chamber
- The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)
- Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause. A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis. Results of bacterial or fungal cultures, treatment given, and final ophthalmologic outcome must be provided in the details section of the Adverse Event eCRF.

Please note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by the dilation process and are not red blood cells or white blood cells or the result of any ocular disorder should not be recorded as an adverse event.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF with us of the “AE Most Extreme Intensity” eCRF field. Details regarding any increases in severity will be captured on the Adverse Event Intensity Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious"

to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory assessments (hematology, coagulation, serum chemistry, urinalysis, and pregnancy tests). Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5×ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ upper limit of normal [ULN]) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a serious or non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in

the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Worsening of Geographic Atrophy in Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of the progression of GA in the study eye should be recorded as an adverse event only if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of GA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated GA").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

- *Hospitalization for a preexisting condition, provided that the following criteria are met:*

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills

seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of lampalizumab are available.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D.

Telephone Nos.: [redacted] (office) (U.S.A.)

[redacted] (mobile) (U.S.A.)

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 30 (+7) days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 30 (+7) days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event

eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 (+7) days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (because the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period, defined as 30 (+7) days after the last dose of study drug, if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Lampalizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS METHODS

Primary efficacy analyses will include all randomized patients with at least one post-baseline GA area measurement by FAF. Patients will be grouped according to the treatment assigned at randomization. Safety analyses will include all randomized patients who receive at least one dose of study treatment, with patients grouped according to the treatment actually received. Patients in the sham Q2W and sham Q4W groups will be pooled in the analyses.

The analysis of data for the 24-week treatment period will be performed when all randomized patients have either completed the 24-week treatment period or have discontinued from the study prior to Week 24, and all data from this period are in the database and have been cleaned and verified.

6.1 DETERMINATION OF SAMPLE SIZE

The GX29455 study is designed to evaluate the efficacy of lampalizumab administered intravitreally Q2W and Q4W to CFI profile biomarker-positive GA patients. The focus of the efficacy outcome analyses will be on estimation of the magnitude of the treatment effect.

The primary efficacy endpoint is the mean change in GA area from baseline to Week 24. The sample size was selected to provide adequate precision for the estimation of the treatment effect with respect to the primary endpoint. A total of approximately 90 patients will be enrolled in the study including the run-in and randomized components.

Approximately 84 patients will be randomized in a 3:1:2:1 ratio to one of four treatment groups: lampalizumab Q2W, sham Q2W, lampalizumab Q4W, or sham Q4W. With the assumption of a 15% drop-out rate by Week 24 and a standard deviation of 0.85 mm^2 for the change in GA area from baseline to Week 24 (estimated from the Phase II Study CFD4870g with lampalizumab in GA), the 80% CI for the estimated difference in treatment effect for select hypothetical scenarios are presented in Table 5 . Assuming a GA area measurement error of +/- 0.043 mm^2 (from CFD4870g image center technical report), the proposed sample size is considered sufficient for

differentiating the treatment effect between lampalizumab Q2W and lampalizumab Q4W groups if the observed difference is 0.290 mm^2 (20% relative to sham) or larger (see Table 5)

Table 5 Scenario Analysis: Observed Mean Change in Geographic Atrophy Area and 80% Confidence Intervals for Difference between Lampalizumab Q2W and Q4W Groups

Scenario	Observed Relative Reduction [a] in ΔGA at 24 Weeks (Q4W, Q2W)	ΔGA (mm^2) at 24 Weeks in Sham (n=24)	ΔGA (mm^2) at 24 Weeks in Q4W (n=24)	ΔGA (mm^2) at 24 Weeks in Q2W (n=36)	Q4W–Q2W 80% CI
1	40%, 60%	1.448	0.869	0.579	0.290 (–0.024, 0.604) (–2% a, 42% a)
2	40%, 58%	1.448	0.869	0.608	0.261 (–0.053, 0.575) (–4% a, 40% a)
3	40%, 55%	1.448	0.869	0.652	0.217 (–0.097, 0.531) (–7% a, 37% a)

Δ=change; GA=geographic atrophy; Q2W=every 2 weeks; Q4W=every 4 weeks.

[a] The reduction is relative to GA area (ΔGA area at 6M) in sham and calculated as 100% × [(mean GA area change in pooled sham – mean GA area change in lampalizumab)/mean GA area change in pooled sham].

These calculations are based on the following assumptions:

The SD of the change in GA area from baseline to Week 24 is 0.85 mm^2. The drop-out rate is 15% by Week 24 (estimated from the Phase II Study CFD4870g with lampalizumab in GA).

6.2 EFFICACY ANALYSES

The primary efficacy endpoint is mean change in GA area from baseline to Week 24. If not otherwise specified, analyses of efficacy outcome measures will be stratified by baseline GA lesion size (<10 mm^2 versus ≥ 10 mm^2) and baseline BCVA (better than or equal to 20/100 versus worse than 20/100). A data–as-observed approach with the mixed-effect model will be used to handle missing data in the primary analysis. Sensitivity analyses based on imputed data may be performed to evaluate the impact of missing data on the results. Two-sided 80% CI will be provided for the estimated treatment effects. Hypothesis testing will be conducted at the two-sided significance level of 0.2; no multiple testing adjustment is planned. Additional exploratory analyses may be conducted if deemed appropriate.

6.3 SAFETY ANALYSES

Safety will be assessed by adverse events, ocular assessments (e.g., inflammation, IOP, BCVA), clinical laboratory evaluation, immunogenicity as measured by ATAs directed against lampalizumab. Patients will be analyzed according to actual treatment received.

Adverse events will be collected from the time of the first study treatment administration until a patient has completed the study or discontinued prematurely. Adverse events reported during the safety run-in and the randomized study may be summarized separately.

Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade (if applicable).

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study treatment. Treatment-emergent adverse events will be summarized by treatment group.

Clinical laboratory data and vital signs will be summarized by descriptive statistics by treatment group. The number and percentage of patients with confirmed positive ATA levels will be reported for each treatment group.

6.4 PHARMACOKINETIC ANALYSES

Individual and mean serum lampalizumab concentration–time data will be tabulated and plotted by dose level. The serum pharmacokinetics of lampalizumab may be summarized by parameters estimates of maximum observed serum concentration (C_{max}), time of maximum observed serum concentration (t_{max}), and time to steady-state and

accumulation ratio. Estimates for these parameters will be tabulated and summarized by descriptive statistics. Additional PK analyses maybe conducted as appropriate.

6.5 HANDLING OF MISSING DATA

All efforts will be made to avoid missing data. In the primary analysis, missing data will not be imputed. Sensitivity analyses based on imputed data may be performed to evaluate the impact of missing data on the results.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and Central Reading Center data will be sent directly to the Sponsor using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples and the collection of the optional aqueous humor samples from the randomized study patients for exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens and the collection of the optional aqueous humor samples to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This research study is being sponsored by Genentech Inc, South San Francisco California. Genentech will perform vendor management, data management, statistical programming, data analysis, safety and regulatory activities. A CRO will be responsible for study management and will assist with data management. An IxRS will be used for patient randomization and for management of study drug requests and shipments. A central laboratory will be used for most laboratory assessments and for storage of other laboratory samples (i.e., anti-lampalizumab antibody serum samples) prior to being shipped to Sponsor or its designee for analysis. Data will be recorded by an EDC system using eCRFs (see Section 5.4.2.2) or forwarded to the Sponsor electronically (e.g., central laboratory data). A central reading center will be used for ocular imaging analyses (e.g., FAF, near infrared, CFP, FA) which will be forwarded to the Sponsor electronically.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Study Flowchart Safety Run-In Assessment: Screening, Day 1 through Hiatus [a] and Early Termination

Note: After completion of baseline visits, safety run-in assessment patients will have study visits every 2 weeks according to the Week X schedule shown below (i.e., Week 2, Week 4, Week 6, etc.) until notification by the Sponsor that the hiatus has begun. Thereafter, the safety run-in patients will continue Q2W visits according to Appendix 2 **with the exception of the optional anterior chamber (aqueous humor) sampling (i.e., patients in the safety run-in will not participate in the optional anterior chamber sampling).**

Visits	Screening	Baseline			Week X			Early Term [b]
		Day 1	+1 Day	+ 7 Days	Week X	+ 1 Day	+7 Days	
Assessment Window (Days)	–21 to –1	NA	(±0)	(±2)	(+4)	(±0)	(±2)	(+7)
Written informed consent	x							
Review of inclusion and exclusion criteria	x	x						
Site to contact IxRS (as applicable) [c]	x	x			x			x
Medical and surgical history including tobacco history [d]	x							
Demographic information	x							
Physical examination [e]	x							x
Vital signs [e]	x	x						x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) [f]	x							x
Serum anti-lampalizumab antibody sample PRE-treatment [f]		x			x [f]			x
Serum PK sample for lampalizumab concentration PRE-treatment [f]		x			x [f]			x
Serum PK sample for lampalizumab concentration POST-treatment [f]		x						
AH50 samples PRE-treatment [f]		x			x [f]			x
Serum pregnancy test [f, g]	x							x

Appendix 1
Study Flowchart Safety Run-In Assessment: Screening, Day 1 through Hiatus [a] and Early Termination (cont.)

Visits	Screening	Baseline			Week X			Early Term [b]
		Day 1	+1 Day	+ 7 Days	Week X	+ 1 Day	+7 Days	
Assessment Window (Days)	–21 to –1	NA	(±0)	(±2)	(+4)	(±0)	(±2)	(+7)
Urine pregnancy test [f, g]		x			x			
CFI biomarker whole blood sample [f]	x							
Biomarker whole blood clinical genotyping sample [f]		x						
BCVA testing (starting at 4 m) [h]	x	x			x			x
Intraocular pressure	x	x			x			x
Slit-lamp examination	x	x			x			x
Dilated binocular indirect ophthalmoscopy	x	x			x			x
FAF and NI [j]	x							x
Fundus photography [j]	x							x
Fluorescein angiography [j]	x							x
Pre- and post-treatment antimicrobials (if applicable) [k]		x			x			
Administration of study drug		x			x			
Post-treatment finger counting and IOP measurement [l]		x			x			
Follow-up call [m]			x	x		x	x	
Concomitant medications [n]	x	x			x			x
Adverse events [o]		x			x			x
Concurrent ocular procedures [p]		x			x			x

BCVA=best corrected visual acuity; FAF=fundus autofluorescence; IOP=intraocular pressure; IxRS = Interactive Voice and Web System;

Appendix 1
Study Flowchart Safety Run-In Assessment: Screening, Day 1 through Hiatus [a] and Early Termination (cont.)

NA=not applicable; NI=near infrared; PK = pharmacokinetic; Term = termination.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening.

[a] Genentech will inform the sites when the third evaluable patient has cleared the follow-up visit after the third study drug injection and the initiation and termination dates for the hiatus in the study drug treatment. Patients will not receive any study treatment during the hiatus; after the hiatus, safety run-in assessment patients will follow the same treatment and scheduled visits as randomized study patients in the Q2W treatment arm (Appendix 2) for the remainder of their participation in the study (until the Week 24 visit).

[b] Patients who withdraw early from the study will have early termination visit 30 (+7) days after the last study treatment.

[c] At screening, contact the IxRS (or if not available, contact the study team) to obtain patient screening number prior to assessments. Prior to Day 1 visit, contact IxRS (if not available, you will receive confirmation directly from the study site monitor) to verify a patient's biomarker eligibility. On Day 1, contact IxRS for patient study number and study treatment kit assignment after all assessments are performed; at the remaining scheduled study treatment visits, obtain study treatment kit assignment after all visit assessments were performed. At the early termination visit, contact the IxRS to request that patient's status be changed to "early termination." At the final study visit, contact IxRS to request to change patient status to "completed."

[d] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history); tobacco use.

[e] A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. Vital signs consist of blood pressure, pulse, respiration, and temperature; perform pre-treatment.

[f] Obtain prior to fluorescein angiography (if applicable). Collect PRE-treatment serum antibody at Weeks 4, 8, 16, and 24; PRE-treatment serum PK at Weeks 2, 4, 8, 16, and 24; and PRE-treatment AH50 samples at Weeks 2, 4, 8, 16, and 24. Consult the Central Laboratory Manual for detailed description of the laboratory assessments.

[g] Collect serum sample at screening visit from women of childbearing potential. If positive, do not enroll the patient in the study. Perform urine pregnancy test prior to each study treatment starting at Day 1 visit for women of childbearing potential. If positive, collect a sample for the serum pregnancy test and forward to the central laboratory for analysis. If the serum pregnancy test is positive, discontinue the patient from study treatment.

[h] The VA examiner will be masked to the patient's treated (study) eye and treatment assignment and will perform only the visual acuity (including refraction) assessments. VA examiner is not allowed to perform any other tasks involving direct patient care.

[i] Pre-injection IOP and IOP measurement at non-treatment visits will be measured prior to dilation.

[j] FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center (refer to the Central Reading Center Manual).

[k] If applicable, before and after treatment, ensure that the patient self-administered antimicrobials as per the investigator's discretion.

Appendix 1
Study Flowchart Safety Run-In Assessment: Screening, Day 1 through Hiatus [a] and Early Termination (cont.)

[l] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes post-study treatment. At study treatment visits, IOP measurement will be obtained 60 (±10) minutes post-treatment in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If the IOP is increased ≥10 mmHg from pre-treatment measurement, the patient will remain in the clinic and will be treated in accordance with the investigator's clinical judgment prior to the patient's discharge.

[m] Subsequent to the initial treatment visit, patients will receive a telephone call 1 day and 7 (± 2) days after each treatment visit to solicit adverse events. If warranted, patients will be asked to return for unscheduled visit to assess possible adverse events.

[n] Record any concomitant medications used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit (i.e., any prescription medications or over–the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine).

[o] Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to study drug should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if the patient's participation in the study has been terminated.

[p] Record all concurrent ocular procedures performed on the study or non-study eye.

Appendix 2
Study Flowchart for Randomized Study: Q2W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination

Visits	Screening	Day	Week											Early Term [a]
		1	2	4	6	8	10	12	14	16	18	20	22	24	+ 7
Assessment Windows (Days)	−28 to −1	NA	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	
Written informed consent	x														
Review of inclusion and exclusion criteria	x	x													
Site to contact IxRS (as applicable) [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medical and surgical history including tobacco history [c]	x														
Demographic information	x														
Physical examination [d]	x													x	x
Vital signs [d]	x	x												x	x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) [e]	x													x	x
Serum anti-lampalizumab antibody sample PRE-treatment [e]		x		x		x				x				x	x
Serum PK sample for lampalizumab concentration PRE-treatment [e]		x	x	x		x				x				x	x
Serum PK sample for lampalizumab concentration POST-treatment [e]		x													
Optional anterior chamber (aqueous humor) sample PRE-treatment [e]		x		x		x									
AH50 samples PRE-treatment [e]		x	x	x		x				x				x	x
Serum pregnancy test [e, f]	x													x	x

Appendix 2
Study Flowchart for Randomized Study: Q2W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination (cont.)

Visits	Screening	Day	Week											Early Term [a] + 7
		1	2	4	6	8	10	12	14	16	18	20	22	24	
Assessment Windows (Days)	*–28* to –1	NA	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	+4	
Urine pregnancy test [e, f]		x	x	x	x	x	x	x	x	x	x	x	x		
CFI biomarker whole blood sample [e]	x														
Biomarker whole blood clinical genotyping sample [e]		x													
BCVA testing (starting at 4 m) [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Intraocular pressure [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slit-lamp examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF and NI [i]	x							x						x	x
Fundus photography [i]	x							x						x	x
Fluorescein angiography [i]	x													x	x
Pre- and post-treatment topical antimicrobials (if applicable) [j]		x	x	x	x	x	x	x	x	x	x	x	x		
Administration of study drug or sham injection		x	x	x	x	x	x	x	x	x	x	x	x		
Post-treatment finger counting and IOP measurement [k]		x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call (if applicable) [o]		x	x	x	x	x	x	x	x	x	x	x	x		

Appendix 2
Study Flowchart for Randomized Study: Q2W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination (cont.)

BCVA=best corrected visual acuity; FAF=fundus autofluorescence; IOP=intraocular pressure; IxRS = Interactive Voice and Web System; NA=not applicable; NI=near infrared; PK = pharmacokinetic.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening.

[a] For patients who withdraw early from the study, early termination visit assessments will be performed 30 (+7) days after the last study treatment.

[b] At screening, contact the IxRS to obtain patient screening number prior to assessments. Prior to Day 1 visit, contact IxRS to verify a patient's biomarker eligibility. On Day 1, contact IxRS for patient study number and study treatment kit assignment after all assessments are performed; at the remaining scheduled study treatment visits, obtain study treatment kit assignment after all visit assessments were performed. At the early termination visit, contact the IxRS to request that patient's status be changed to "early termination." At the final study visit, contact IxRS to request to change patient status to "completed."

[c] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history); tobacco use.

[d] A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. Vital signs consist of blood pressure, pulse, respiration, and temperature; perform pre-injection.

[e] Obtain prior fluorescein angiography (if applicable). Consult the Central Laboratory Manual for detailed description of the laboratory assessments.

[f] Collect serum sample at screening visit from women of childbearing potential, including those who have had a tubal ligation. If positive, do not enroll the patient in the study. Perform urine pregnancy test prior to each study treatment starting at Day 1 visit for women of childbearing potential, including those who have had tubal ligation. If positive, collect a sample for the serum pregnancy test and forward to the central laboratory for analysis. If the serum pregnancy test is positive, discontinue the patient from study treatment.

[g] The VA examiner will be masked to the patients' treated (study) eye and treatment arm (drug vs. sham) assignment and will perform only the VA (including refraction) assessments. VA examiner is not allowed to perform any other tasks involving direct patient care.

[h] Pre-injection IOP and IOP measurement at non-treatment visits will be measured prior to dilation.

[i] FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center (refer to the Central Reading Center Manual).

[j] If applicable, before and after study treatment, ensure that the patient self-administered antimicrobials as per the investigator's discretion.

[k] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes post-study treatment. At study treatment visits, IOP measurement will be obtained 60 ($\pm$10) minutes post-study treatment in the study eye only. If there are no safety concerns at 60 ($\pm$10) minutes, the patient will be discharged from the clinic. If the IOP is increased $\geq$10 mmHg from pre-treatment measurement, the patient will remain in the clinic and will be treated in accordance with the investigator's clinical judgment prior to the patient's discharge.

[l] Record any concomitant medications used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine).

Appendix 2
Study Flowchart for Randomized Study: Q2W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination (cont.)

[m] Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to study drug should be followed until event resolves or the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has been terminated.

[n] Record all concurrent ocular procedures performed on the study or non-study eye.

[o] Subsequent to the initial treatment visit, patients treated with study drug or sham will receive a telephone call 3 (±1) days after each treatment visit to solicit adverse events.

Appendix 3
Study Flowchart for Randomized Study: Q4W Arms: Screening, Day 1, Week 4 through Week 24, and Early Termination

Visits	Screening	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Term [a] + 7
Assessment Windows (Days)	−28 to −1	NA	+4	+4	+4	+4	+4	+4	
Written informed consent	x								
Review of inclusion and exclusion criteria	x	x							
Site to contact IxRS (as applicable) b	x	x	x	x	x	x	x	x	x
Medical and surgical history including tobacco history [c]	x								
Demographic information	x								
Physical examination [d]	x							x	x
Vital signs [d]	x	x						x	x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis)[e]	x							x	x
Serum anti-lampalizumab antibody sample PRE-treatment [e]		x	x	x		x		x	x
Serum PK sample for lampalizumab concentration PRE-treatment [e]		x	x	x		x		x	x
Serum PK sample for lampalizumab concentration POST-treatment [e]		x							
Optional anterior chamber (aqueous humor) sample PRE-treatment [e]		x	x	x					
AH50 samples PRE-treatment [e]		x		x		x		x	x
Serum pregnancy test [e, f]	x							x	x
Urine pregnancy test [e,f]		x	x	x	x	x	x		
CFI biomarker whole blood sample [e]	x								
Biomarker whole blood clinical genotyping sample [e]		x							
BCVA testing (starting at 4 m) [g]	x	x	x	x	x	x	x	x	x
Intraocular pressure[h]	x	x	x	x	x	x	x	x	x

Appendix 3
Study Flowchart for Randomized Study: Q4W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination (cont.)

Visits	Screening	Day	Week						Early Term [a]
		1	4	8	12	16	20	24	
Assessment Windows (Days)	*–28* to –1	NA	+4	+4	+4	+4	+4	+4	+ 7
Slit-lamp examination	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x
FAF and NI [i]	x				x			x	x
Fundus photography [i]	x				x			x	x
Fluorescein angiography [i]	x							x	x
Pre- and post-treatment antimicrobials (if applicable) [j]		x	x	x	x	x	x		
Administration of study drug or sham injection		x	x	x	x	x	x		
Post-treatment finger counting and IOP measurement [k]		x	x	x	x	x	x		
Concomitant medications [l]	x	x	x	x	x	x	x	x	x
Adverse events [m]		x	x	x	x	x	x	x	x
Concurrent ocular procedures [n]		x	x	x	x	x	x	x	x
Follow-up call (if applicable) [o]		x	x	x	x	x	x		

BCVA=best corrected visual acuity; FAF= fundus autofluorescence; IOP=intraocular pressure; IxRS = Interactive Voice and Web System; NA=not applicable; NI=near infrared; PK=pharmacokinetic.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except those at screening.

[a] For patients who withdraw early from the study, early termination assessments will be performed 30 (+7) days after the last study treatment.

[b] At screening, contact the IxRS to obtain patient screening number prior to assessments. Prior to the Day 1 visit, contact IxRS to verify a patient's biomarker eligibility. On Day 1, contact IxRS for patient study number and study treatment kit assignment after all assessments are performed; at the remaining scheduled study treatment visits, obtain study treatment kit assignment after all visit assessments were performed. At the early termination visit, contact the IxRS to request patient's status be changed to "early termination". At the final study visit, contact IxRS to request to change patient status to "completed".

[c] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history); tobacco use.

Appendix 3
Study Flowchart for Randomized Study: Q4W Arms: Screening, Day 1, Week 2 through Week 24, and Early Termination (cont.)

Visits	Screening	Day	Week						Early Term [a]
		1	4	8	12	16	20	24	
Assessment Windows (Days)	–28 to –1	NA	+4	+4	+4	+4	+4	+4	+ 7

[d] A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. Vital signs consist of blood pressure, pulse, respiration, and temperature at all study visits; on days of study treatment administration, perform pre-treatment.

[e] Obtain prior to fluorescein angiography (if applicable). Consult the Central Laboratory Manual for a detailed description of the laboratory assessments.

[f] Collect serum sample at screening visit from women of childbearing potential, including those who have had a tubal ligation. If positive, do not enroll the patient in the study. Perform urine pregnancy test prior to each study treatment starting at Day 1 visit for women of childbearing potential, including those who have had tubal ligation. If positive, collect a sample for the serum pregnancy test and forward to the central laboratory for analysis. If the serum pregnancy test is positive, discontinue the patient from study treatment.

[g] The VA examiner will be masked to patients' treated (study) eye and treatment arm (drug vs. sham) assignment and will perform only the VA (including refraction) assessments. VA examiner is not allowed to perform any other tasks involving direct patient care.

[h] Pre-treatment IOP and IOP measurement at non-treatment visits (as applicable) will be measured prior to dilation.

[i] FAF and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center (refer to the Central Reading Center Manual).

[j] If applicable, before and after treatment, ensure that the patient self-administered antimicrobials as per the investigator's discretion

[k] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes after study treatment injection. At study treatment visits, IOP measurement will be obtained 60 (±10) minutes post-treatment in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If the IOP is increased ≥10 mmHg from pre-treatment measurement, the patient will remain in the clinic and will be treated in accordance with the investigator's clinical judgment prior to the patient's discharge.

[l] Record any concomitant medications used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit (i.e., any prescription medications or over–the-counter preparations other than protocol-specified procedural medications, and pre-treatment and post-treatment medications, such as proparacaine).

[m] Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to study drug should be followed until event resolves or the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has been terminated.

[n] Record all concurrent ocular procedures performed on the study or non-study eye.

[o] Subsequent to the initial treatment visit, patients treated with study drug or sham will receive a telephone call 3 (±1) days after each treatment visit to solicit adverse events.

Appendix 4
Study Flowchart: Unscheduled Safety Visit Assessments

Assessment [a]	
Vital signs (blood pressure, respiration rate, temperature, and pulse)	x
Physical exam	x
Best corrected visual acuity (4-meter starting distance) [b]	x
Slit-lamp examination	x
Dilated binocular indirect high-magnification ophthalmoscopy	x
Intraocular pressure [c]	x
Adverse events [d]	x
Concurrent ocular procedures	x
Concomitant medications	x

[a] If determined to be necessary by the physician, perform listed assessments. All ocular assessments should be performed on both eyes.

[b] Perform finger-counting test followed by hand motion and light perception tests, when necessary.

[c] The method used for the IOP measurement for a patient must remain consistent throughout the study.

[d] Adverse events causality to be evaluated by the qualified ophthalmologist.

Appendix 5
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells

Grading Scale for Anterior Chamber Flare or Cells

	Flare
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein is detectable in the anterior chamber: this protein is visible only with careful scrutiny by an experienced observer using slit-lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Slight amount of protein is detectable in the anterior chamber: the presence of protein in the anterior chamber is immediately apparent to an experienced observer using slit-lamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2–3+	Moderate amount of protein is detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light. This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large amount of protein is detectable in the anterior chamber. This grade is similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It should be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood–aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).
	Cells
0	No cells are seen in any optical section when a large slit-lamp beam is swept across the anterior chamber.
Trace	Few (1–3) cells are observed when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, not every optical section contains circulating cells.
1+	3–10 cells/optical section are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
2+	10–25 cells are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells.
3+	25–50 cells are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

Modified from: Hogan MH, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. Am J Ophthalmol 1959;47(5, Part 2):155–70.

Appendix 5
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells (cont.)

Grading Scale for Vitreous Cells

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

Modified from: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis*: fundamentals and clinical practice*; 2nd ed. St Louis: Mosby, 1996; 64.

Appendix 6
Pre-Injection Procedures for All Patients

The pre-injection procedure, lampalizumab reconstitution and injection and sham injection procedures and post-injection procedures are also described in details in the Pharmacy Binder.

While reconstituting lampalizumab, a sterile field must be used, and any personnel must wear a surgical face mask. Lampalizumab should be administered within 2 hours following reconstitution; the prepared dose may be maintained at room temperature prior to administration.

The following procedures will be used to minimize the risk of potential adverse events associated with intravitreal (ITV) injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug (lampalizumab) preparation and administration. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with ITV injections will be observed.

As per individual site investigator decision, patients may self-administer antimicrobial drops prior to treatment and after treatment following each injection (study drug or sham).

The following procedures will be conducted by the physician performing the ITV injection of study drug:

- Prepare a sterile field with supplies that include the following:
  - 10% povidone iodine swabs, sterile surgical gloves
  - 4 × 4 sterile pads
  - a pack of sterile cotton-tipped applicators
  - eyelid speculum
  - sterile ophthalmic drape
  - 0.5% proparacaine hydrochloride
  - 5% povidone iodine ophthalmic solution
  - 1% or 2% lidocaine for the anesthesia, ophthalmic antimicrobial solution (per individual investigator decision), and injection supplies
- Instill two drops of 0.5% proparacaine hydrochloride into the study eye
- Wait 90 seconds
- As per individual investigator decision, instill two drops of antimicrobial drops (e.g., ofloxacin ophthalmic solution [Ocuflox®], trimethoprim-polymyxin B ophthalmic solution [Polytrim®], moxifloxacin ophthalmic solution [Vigamox®], or gatifloxacin ophthalmic solution [Zymar®] single-use vial)

Appendix 6
Pre-Injection Procedures for All Patients (cont.)

- Wait 5 minutes
- Instill two more drops of 0.5% proparacaine hydrochloride into the study eye
- Wait 90 seconds
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.

NOTE: For patients who develop adverse reaction to povidone-iodine, the following approaches are permitted: irrigate the eye with sterile saline after the study treatment (lampalizumab or sham) with the aim to rinse away any remaining povidone-iodine or use a limited amount of povidone-iodine by placing a swab directly on the treatment site after the lid speculum has been placed.

Appendix 7
Preparation and Administration of Lampalizumab Injection

The drug must be reconstituted using a sterile field while personnel are wearing a surgical face mask. Within 2 hours following dose preparation (reconstitution), lampalizumab should be administered; the prepared dose may be maintained at room temperature prior to administration.

Reconstitute the for 10-mg lampalizumab dose as follows:

1. Remove the plastic flip-off seal from one vial of lampalizumab lyophilized powder (6-cc vial), and swab the top of the vial with an alcohol swab.
2. Remove the plastic flip-off seal from one vial of Sterile Water for Injection (SWFI) (10-cc vial), and swab the top of the vial with an alcohol swab.
3. Using a 1-cc tuberculin syringe, withdraw 0.50 mL of SWFI (10-cc vial) from a vial, expel any air bubbles, insert the syringe into the lampalizumab vial, and add.
4. Swirl the lampalizumab vial gently until the lyophilized powder dissolves; **do not shake or vortex the vial vigorously.** Let stand for approximately 5 minutes until bubbles dissolve.

Filter the lampalizumab as follows:

1. Withdraw 0.2 mL of lampalizumab dose solution through a 19-gauge, 1.5 TW, 5-μm filter needle attached to a 1-cc tuberculin syringe.
2. After withdrawing lampalizumab in through the filter, **remove filter needle; replace it with a 30-gauge, 0.5-inch Precision Glide® needle** and expel excess of lampalizumab so that the syringe contains 0.1 mL of lampalizumab solution for dosing.

Appendix 7
Preparation and Administration of Lampalizumab Injection (cont.)

Table 1 Lampalizumab Reconstitution

Step	Procedure	Materials	Methods
1	**Reconstitute the lyophilized lampalizumab** Note: Vials of lampalizumab should remain refrigerated (2°C-8°C or 36°F–46°F) until just prior to reconstitution with SWFI.	• One vial of lyophilized lampalizumab • 1-cc tuberculin syringes • 10-cc vial of SWFI • Alcohol swabs	Swab the top of lampalizumab vial with an alcohol swab after removing the flip-top seal. Swab the top of SWFI vial with an alcohol swab after removing the flip-top seal. Expel any air bubbles from the syringe prior to injecting 0.50 mL SWFI into lampalizumab vial. Swirl the lampalizumab vial containing the SWFI gently until the lyophilized powder dissolves. **Do not shake vigorously or vortex the vials.** Let stand for approximately 5 minutes until bubbles dissolve.
2	**Filter the lampalizumab**	• 5-μm filter needle (needle is 19-gauge, 1.5 TW) • 1-cc tuberculin syringe • 30 gauge, 0.5-inch Precision Glide needle	Withdraw 0.2 mL of lampalizumab dose solution through a 5-μm filter needle attached to a 1-cc tuberculin syringe. After withdrawing lampalizumab in through the filter, **remove filter needle, replace it with a 30-gauge, 0.5-inch Precision Glide needle**, expel excess lampalizumab so that the syringe contains 0.1 mL of lampalizumab solution.

SWFI = Sterile Water for Injection.

ADMINISTRATION OF LAMPALIZUMAB

To administer intravitreal lampalizumab, the treating physician will conduct the following procedures:

- Put on gloves, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.

Appendix 7
Preparation and Administration of Lampalizumab Injection (cont.)

- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% or 2% lidocaine hydrochloride solution for injection (without epinephrine).
- Inject 1% or 2% lidocaine (without epinephrine) subconjunctivally. For the patients intolerant of lidocaine as evidenced by an associated adverse event, topical proparacaine may be permitted after consultation with the Medical Monitor.
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct the patient to direct gaze away from syringe prior to lampalizumab injection.
- **Physician will wear surgical face mask and refrain from talking, coughing, or sneezing during the injection.**

Administer lampalizumab as follows:

- Insert the needle through an area 3.5–4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe. Rotate the injection site at every treatment visit.
- **Inject the dose solution slowly.**
- Remove the needle slowly to ensure that all drug solution is in the eye.
- Refer to Appendix 9 for detailed post-injection procedures

Appendix 8
Preparation and Administration of Sham Injection

Genentech will supply all materials for the sham injections.

The designated physician (a qualified ophthalmologist administering the intravitreal or sham injection) will prepare the sham injection as outlined below.

SHAM PREPARATION

The preparation process for the sham injection will be identical to the study drug injection (see Appendix 6). A sterile tray will be assembled by study personnel. The tray assembly will be identical for both lampalizumab and sham injections.

Refer to Appendix 6 for detailed instructions for pre-injection procedures.

The treating physician will **not** use a needle for the sham injection (except of lidocaine injection given subconjunctivally); the treating physician will discard the lidocaine needle and syringes from the sterile tray in the sharps container immediately following each sham injection and will return the sham vial in the kit box.

SHAM ADMINISTRATION

Patients receiving sham injections do not receive an actual injection. The procedures for cleansing and anesthetizing the study eye will be performed as outlined in Appendix 6. The patient should be instructed to direct his or her gaze away from the syringe prior to administration of the sham injection. The treating physician will withdraw the tuberculin syringe plunger to the 0.1-mL mark on the syringe, then place the hub of the syringe – without the needle – against the pre-anesthetized conjunctival surface. The treating physician will then press the syringe hub firmly against the globe and then slowly depress the plunger, mimicking the action of an injection.

It is essential that the procedures of the sham injection, including preparation and the sham injection itself, mimic as much as possible those used for the administration of lampalizumab. For subsequent sham injections, follow the same procedure of rotating the location of the injection site, as is done with the lampalizumab injections (see Appendix 6).

The treating physician or unmasked technician (if applicable) will discard all injection materials (i.e., syringes and needles) in a sharps container immediately following each sham injection, and the empty vial will be placed in the kit box. Refer to Appendix 9 for detailed post-injection procedures.

Appendix 9
Post-Injection Procedures for All Patients

As per individual investigator decision, immediately following the lampalizumab or sham injection, instill two drops of antimicrobial drops (e.g., ofloxacin ophthalmic solution [Ocuflox®], trimethoprim-polymyxin B ophthalmic solution [Polytrim®], moxifloxacin ophthalmic solution [Vigamox®], or gatifloxacin ophthalmic solution [Zymar®] single-use vial).

The patient will be monitored with a finger-counting test within 15 minutes of the study drug or sham treatment by the treating physician.

Discard the supplies in order to preserve patient's masking. Discard all syringes and needles in the sharps container.

The used study drug/sham kit, including the used vial should be stored until Genentech representative conducts the study drug accountability and the site is instructed to discard or ship to Genentech.

Any materials that could disclose the identity of study drug or patient treatment assignment should be removed from the tray.

A measurement of IOP in the study eye only will be obtained 60 ($\pm$10) minutes after study treatment. If there are no safety concerns at the 60 ($\pm$10) minute measurement, the patient may be discharged from the clinic. If the IOP is increased by $\geq$10 mmHg from the pre-treatment measurement at 60 ($\pm$10) minutes and is of concern to the investigator, the patient will remain in the clinic to be treated in accordance with the investigator's clinical judgment prior to discharge. If applicable, the Adverse Event CRF page will be completed.

As per individual site investigator decision, patients may self-administer antimicrobial drops after treatment following each injection (study drug or sham).

Appendix 10
Best Corrected Visual Acuity Testing

SCOPE

Best corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites. The visual acuity (VA) examiner must be masked to each patient's study (treated) eye, treatment arm (study drug vs. sham) assignment. BCVA will be measured at the intervals specified in the protocol (see Section 4.5 of the protocol and Appendix 1, Appendix 2, and Appendix 3).

EQUIPMENT

The following are needed to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts (modified Early Treatment Diabetic Retinopathy Study Charts R, 1, and 2 in the United States)
- Retro-Illuminated box
- Study frame
- Study lens set

TRAINING AND CERTIFICATION

A VA specifications document, procedure manual, and training materials will be provided to the investigational sites, and examiner certification will be obtained. The VA examination room also must be certified before any VA examinations are performed.

Appendix 11
Color Fundus Photography

SCOPE

Stereo color fundus photographs will be taken by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the protocol (see Appendix 1, Appendix 2, and Appendix 3). Analysis (if applicable) of fundus photographs will be performed by the central reading center.

EQUIPMENT

See the Central Reading Center Manual.

PROCEDURE

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

Appendix 12
Fluorescein Angiography

SCOPE

Fluorescein angiography will be performed at the study sites by trained personnel who are certified by the central reading center. The fluorescein angiograms (FAs) will be obtained at the intervals specified in the protocol (see Appendix 1, Appendix 2, and Appendix 3). Analysis (if applicable) of FAs will be performed by the central reading center.

EQUIPMENT

Digital angiograms must be used while conducting an angiographic evaluation for the study.

Film-based angiography is not acceptable.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES

The central reading center will provide a study manual and training materials. Photographers, systems, and software will be certified prior to obtaining angiograms of patients.

Appendix 13
Fundus Autofluorescence

SCOPE

Fundus autofluorescence (FAF) will be performed at the study sites by trained personnel who are certified by the central reading center. FAF imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1, Appendix 2, and Appendix 3) and will be forwarded to the central reading center. Analysis (if applicable) of FAF images will be performed by the central reading center.

EQUIPMENT

Equipment utilized during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed FAF images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials.
FAF operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 14
Near-Infrared Imaging

Note: Near infrared (NI) images are taken to complement the central reading center evaluation of fundus autofluorescence images.

SCOPE

NI imaging will be performed at the study sites by trained personnel who are certified by the central reading center. NI imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1, Appendix 2, and Appendix 3).

The NI images of both eyes will be obtained at protocol-specified visits and will be forwarded to the central reading center.

EQUIPMENT

Equipment utilized during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed NI images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. NI operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 15
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLES

Biological samples for the assessment of lampalizumab concentrations (pharmacokinetics), anti-lampalizumab antibodies, systemic alternative complement pathway activity assay, complement factor I whole blood sample, biomarker whole blood clinical genotyping sample and laboratory assessment (hematology, serum chemistry, coagulation, and urinalysis) samples will be collected at the timepoints specified in Appendix 1, Appendix 2, and Appendix 3.

Refer to the Central Laboratory Manual for detailed sample collection, storage, and shipping instructions. All necessary transfer tubes, Vacutainers™, labels, shipping boxes, and forms will be provided by the central laboratory.

OPTIONAL ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

The optional aqueous humor paracentesis samples will be collected from patients who consent to the procedure and sample acquisition. An aqueous humor sample will be collected before the patient's study eye treatment visits as indicated in Appendix 1, Appendix 2, and Appendix 3. The aqueous humor sample collection consists of an anterior chamber paracentesis (removing approximately 0.1 mL of fluid from the anterior chamber of the eye).

The anterior chamber paracentesis will be performed by a qualified physician by placing a drop of topical anesthetic on the cornea, passing a 30-gauge needle through the limbus into the anterior chamber and removing 0.1 mL of aqueous fluid.

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

For administration of study treatment following the collection of the aqueous humor sample, the subconjunctival lidocaine anesthetic must be injected into the eye prior to study drug/sham injection.

Appendix 16
The cobas® CFI Profile Clinical Trial Assay (CTA)

The cobas complement factor I (CFI) Profile Clinical Trial Assay (CTA) is a real-time polymerase chain reaction (PCR) test developed by Roche Molecular Systems (RMS) to identify genotypes of three single–nucleotide polymorphisms (SNPs) associated with CFI, complement factor H (CFH), and C2/complement factor B (CFB) in DNA extracted from whole blood samples from patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The cobas CFI Profile CTA is intended to be used as an Investigational-Use-Only assay to characterize the complement factor profile of study participants. It may also be used to stratify research participants for randomization or to enrich the study population with CFI biomarker-positive participants in specific type clinical studies.

The cobas CFI Profile CTA consists of two kits and will use the cobas 4800 platform. The cobas DNA Sample Preparation Kit (DNA isolation kit) provides the necessary components to manually extract genomic DNA from whole blood samples. The cobas CFI Profile CTA contains the necessary PCR master mix, oligonucleotides, cofactor, and controls to detect three SNPs associated with CFI, CFH, and C2/CFB.

	AMD Gene	chr. No.	Tagging SNP	Tagging SNP Location	Risk Allele	Major Allele	Valid cobas Test Results		
							Risk Hmzy	Het	Non-Risk Hmzy
MMx1	*CFI*	4	rs4698775	*CCDC*	G	T	rs4698775 GG	rs4698775 TG	rs4698775 TT
MMx2	*C2/ CFB*	6	rs429608	*SKIV2L*	G	G	rs429608 GG	rs429608 GA	rs429608 AA
MMx3	*CFH*	1	rs1329428	*CFH*	C	C	rs1329428 CC	rs1329428 CT	rs1329428 TT

AMD = age-related macular degeneration; C = complement component; CF = complement factor; chr = chromosome; het = heterozygous; hmzy = homozygous; SNP = single nucleotide polymorphism.

Appendix 16
The cobas® CFI Profile Clinical Trial Assay (CTA) (cont.)

MMx1	MMx2	MMx3	
CFI	*C2/CFB*	*CFH*	*Biomarker Status*
rs4698775 GG	rs429608 GG	rs1329428 CC	+
rs4698775 GG	rs429608 GG	rs1329428 CT	+
rs4698775 GG	rs429608 GG	rs1329428 TT	+
rs4698775 GG	rs429608 GA	rs1329428 CC	+
rs4698775 GG	rs429608 GA	rs1329428 CT	+
rs4698775 GG	rs429608 GA	rs1329428 TT	+
rs4698775 GG	rs429608 AA	rs1329428 CC	+
rs4698775 GG	rs429608 AA	rs1329428 CT	+
rs4698775 GG	rs429608 AA	rs1329428 TT	–
rs4698775 TG	rs429608 GG	rs1329428 CC	+
rs4698775 TG	rs429608 GG	rs1329428 CT	+
rs4698775 TG	rs429608 GG	rs1329428 TT	+
rs4698775 TG	rs429608 GA	rs1329428 CC	+
rs4698775 TG	rs429608 GA	rs1329428 CT	+
rs4698775 TG	rs429608 GA	rs1329428 TT	+
rs4698775 TG	rs429608 AA	rs1329428 CC	+
rs4698775 TG	rs429608 AA	rs1329428 CT	+
rs4698775 TG	rs429608 AA	rs1329428 TT	–
rs4698775 TT	rs429608 GG	rs1329428 CC	–
rs4698775 TT	rs429608 GG	rs1329428 CT	–
rs4698775 TT	rs429608 GG	rs1329428 TT	–
rs4698775 TT	rs429608 GA	rs1329428 CC	–
rs4698775 TT	rs429608 GA	rs1329428 CT	–
rs4698775 TT	rs429608 GA	rs1329428 TT	–
rs4698775 TT	rs429608 AA	rs1329428 CC	–
rs4698775 TT	rs429608 AA	rs1329428 CT	–
rs4698775 TT	rs429608 AA	rs1329428 TT	–