Official Title: **A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB (FCFD4514S) IN PATIENTS WITH GEOGRAPHIC ATROPHY WHO HAVE COMPLETED GENENTECH-SPONSORED LAMPALIZUMAB STUDIES**

NCT Number: NCT01602120

Document Date: Protocol/Version 4: 18-May-2017

PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB (FCFD4514S) IN PATIENTS WITH GEOGRAPHIC ATROPHY WHO HAVE COMPLETED GENENTECH-SPONSORED LAMPALIZUMAB STUDIES**
PROTOCOL NUMBER:	GX28198/ NCT01602120
VERSION NUMBER:	4
EUDRACT NUMBER:	2012-000578-41
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab (FCFD4514S; RO5490249)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	Version 1: 14 February 2012
DATES AMENDED	Version 2: 24 September 2013 Version 3: 25 June 2015 Version 4: See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	18-May-2017 16:33:32

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol GX28198 has been amended for the following reasons:

- The study duration has been extended an additional 30 months to provide study patients with access to treatment until potential commercialization of lampalizumab. Total study duration is now 96 months (Sections 3.1.3, 3.5, 4.3.1.2, 4.6, 4.6.4, 4.6.5, and 4.12.1 and Appendices1-A through 1-E).
- Table 1 (Dosing Schema) has been updated to clarify that no study treatment will be administered at the early termination visit.
- Clarifying language has been added to Section 3.1.3 regarding unscheduled safety assessment visits in the event of new ocular symptoms after injection.
- Section 3.1.3 has been updated to clarify procedures if study treatment cannot be administered at a scheduled visit.
- Language has been added to clarify the rationale for the crossover to monthly treatment in Study CFD4870g (Section 3.3).
- The safety plan has been updated to reflect the current safety information for lampalizumab (Section 3.5).
- Section 4.1.1 has been updated to include a notation regarding administration of the first ITV injection of lampalizumab.
- Formulation information for lampalizumab and ranibizumab has been removed as it is included in the pharmacy binder (Sections 4.3.1.1 and 4.4.1.1).
- Dose-holding or study discontinuation criteria language has been clarified (Table 2).
- Intravenous (IV) corticosteroids have been removed from the list of excluded concomitant therapies (Section 4.5.2) as study treatment interruption is expected only if patients are on IV corticosteroid therapy.
- The safety section (Section 5) language has been modified to reflect updates to the protocol template. Changes include:
  - Sections 5.2.2.2 and 5.5 have been revised regarding reporting in the event that the EDC system is unavailable.
  - Causal attribution guidance language has been updated in Table 4.
  - Section 5.3.5.7 has been modified to prohibit use of the term "sudden death" on the Adverse Event electronic Case Report Form (eCRF), unless it is combined with the presumed cause of death (e.g., "sudden cardiac death"), as use of the term "sudden death" will require the Sponsor to query the site for clarification on the cause of death.

  - Section 5.3.5.10 has been modified to clarify the reporting of adverse events leading to hospitalization.
  - Sections 5.3.6.1and 5.3.6.2 have been revised to indicate that pregnancies will no longer be reported using the Pregnancy Report eCRF, but will be reported on the paper Clinical Trial Pregnancy Reporting Form and submitted to the Sponsor 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.

- Appendices containing instructions regarding pre-injection preparation, administration of drug injection, and post-injection procedures have been removed as this information is referenced in the pharmacy binder (Appendices 3, 4, 5, 13, 14, and 15). Subsequent appendices have been renumbered accordingly.

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 4:
SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor has been changed from [redacted], M.D., to [redacted], M.D.

PROTOCOL SYNOPSIS

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

SECTION 3.1.3: <u>All Extension Study Patients</u>

At the scheduled monthly visits, patients will have safety ~~evaluations performed~~*assessments evaluated* by the investigator prior to receiving study drug injection. Patients will be contacted by site personnel 7 (±2) days after each injection to elicit reports of decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. *If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 1-F). Patients will be instructed to contact the investigator at any time if they have any health-related concern.* Patient self-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

The extension study is being extended by an additional ~~24~~*30* months to a total duration of ~~66~~*96* months *to provide study patients with access to treatment until potential commercialization of lampalizumab*. The monthly treatment arm patients enrolled from Study CFD4870g may receive up to ~~66~~*96* monthly ITV injections of study drug. The number of ITV injections of study drug for patients who enrolled from the every-other-month treatment arm will vary due to their later crossover to the monthly treatment arm, which was relative to their Day 1 visit date. The patients who enroll from study GX29455 may receive up to ~~24~~*54* monthly ITV injections of study drug.

All monthly visits will occur relative to the patient's Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug doses will ~~not~~ be made up *only in the following circumstance*:

- *If, during scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit, or other patient care issues), the patient's study treatment may be administered within 3 working days of that visit. The following assessments will be repeated on the day of the delayed study treatment: slit lamp examination, indirect ophthalmoscopy, and pre-treatment intraocular pressure (IOP) measurements. These assessments are to be recorded on the scheduled visit electronic Case Report Form [eCRF] and dated with the actual administration date.*

After the Day 1 visit, if a patient misses a study visit when ocular images are to be obtained (see Appendix 1-A through Appendix 1-E), the images must be obtained at the next scheduled visit that the patient attends.

Patients are expected to attend their scheduled visits unless there are extenuating circumstances justifying their inability to come to the clinic.

Patients who are prematurely discontinued from the study treatment in the extension study (prior to the Month ~~66~~*96* visit for patients enrolled from Study CFD4870g or prior to the Month ~~24~~*54* visit for patients enrolled from Study GX29455) will be also discontinued from the extension study and will be asked to return for an early termination (ET) visit ≥30 days following their last study drug treatment for monitoring of adverse events and the ET visit assessments (Appendix 1-A through Appendix 1-E).

The VA examiner role will remain masked to the patients' study eye assignment.

TABLE 1: Dosing Schema

Table 1 has been revised to reflect the extension of the study duration and to indicate that no study treatment will be administered at the early termination visit.

SECTION 3.2: TREATMENT FOR CHOROIDAL NEOVASCULARIZATION WITH RANIBIZUMAB

At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with CNV in either eye may receive treatment with 0.5 mg ranibizumab. For U.S. sites, the drug will be open-label ranibizumab for investigational use only supplied by Genentech (see *the pharmacy binder* ~~Section 4.4.1.1~~ for the drug formulation) and injected no more frequently than monthly.…

Please see *the pharmacy binder* for ranibizumab administration (~~Appendix 13~~ pre-injection procedure, ~~Appendix 14~~ preparation and administration, and ~~Appendix 15~~ post-injection procedure) at U.S. sites.

SECTION 3.3: RATIONALE FOR STUDY DESIGN

Patients from Study CFD4870g (including those in sham arms), initially received lampalizumab in the extension study at the same dosing frequency previously assigned in Study CFD4870g: patients in the monthly treatment arms continued receiving monthly treatment, and patients in the every-other-month treatment arm *continued receiving every-other-month treatment.*

After Study CFD4870g results demonstrated that monthly administration of lampalizumab had a clinically meaningful and statistically significant effect on reducing the GA area growth over the 18-month study treatment period (see Investigator Brochure for additional details), the every-other-month treatment arm patients were ~~later~~ crossed over to the monthly treatment arm for the remainder of their study participation, provided informed consent was obtained.

SECTION 3.5: SAFETY PLAN

~~Lampalizumab is not an approved drug and is currently in clinical development. Thus, the full safety profile is not completely known at this time. The safety plan for this study~~

~~is designed to minimize patient risk and will include specific eligibility criteria and monitoring assessments as detailed in Section 5 (Assessment of Safety).~~ *Lampalizumab is not approved and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with lampalizumab in completed and ongoing studies. The anticipated important safety risks for lampalizumab are outlined below. Please refer to the most current lampalizumab Investigator's Brochure for a complete summary of safety information.*

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at a higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessments of the nature, frequency, and severity of adverse events. Guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

Potential ocular safety issues currently thought to be associated with the route of administration or pharmacology of lampalizumab include decreased best corrected visual acuity (BCVA), conjunctival hemorrhage, ocular inflammation (see Section 5.1.3 for definition and Appendix 2 for anterior chamber and vitreous inflammation grading scales), intraocular infection (endophthalmitis), transient and/or sustained elevation of IOP, *transient vision loss,* cataract development or progression, retinal or vitreous hemorrhage, and retinal break or detachment. ~~The occurrence of all adverse events (serious and non serious) and pregnancies will be recorded on electronic Case Report Forms (eCRFs) for the duration of this study.~~

~~Please see the lampalizumab Investigator's Brochure for further details.~~

The incidence and characteristics of adverse events, serious adverse events, and laboratory abnormalities will be assessed….All adverse events *and pregnancies* will be recorded ~~on eCRFs~~ for the duration of this study.

Patients who are prematurely discontinued from the study treatment (prior to the Month ~~66~~*96* visit for CFD4870g patients and prior to the Month ~~24~~*54* visit for GX29455 patients) will be also discontinued from the extension study and will be asked to return for an ET evaluation ≥30 days following their last study drug treatment for monitoring of adverse events and the early study termination visit assessments (see Appendix 1-A through Appendix 1-E).

SECTION 4.1.1: Patient Selection

Note: All patients enrolled in the extension study will have the first ITV injection of lampalizumab administered by the investigator at the Day 1 visit, unless dose interruption is medically or otherwise justified by the investigator (see Section 4.3.1.2 and Table 2).

SECTION 4.3.1.1: Formulation

~~Lampalizumab will be supplied by the Sponsor as sterile, white to off white, lyophilized powder in a 6 cc USP/Ph. Eur. Type 1 glass vial intended for ITV administration. For information on the formulation and handling of lampalizumab, see the pharmacy manual and the lampalizumab Investigator's Brochure~~*See the pharmacy binder for details regarding formulation.*

SECTION 4.3.1.2: Dosage, Administration, and Storage

Dosage

Patients enrolled from Study CFD4870g:

The dose of 10 mg lampalizumab was administered monthly or every other month starting at the Day 1 visit for up to the 18-month of treatment period.…The study treatment period ~~has been~~*was again* extended by another 24 months *and now by 30 additional months* for a total treatment period of ~~66~~*96* months. Patients in the monthly treatment arm may receive up to ~~66~~*96* ITV injections of study drug. The number of ITV injections of study drug for patients who were in the every-other-month treatment arm prior to their crossover to the monthly treatment arm will vary and will depend on the date of their crossover relative to their Day 1 visit date.

Patients enrolled from Study GX29455:

All study GX29455 patients enrolled in the extension study will receive 10-mg ITV injections of lampalizumab. Dosing frequency for both treatment arms (Q2W and Q4W) of Study GX29455 changed to monthly dosing *upon entry to this study. Given that 30 months have been added to the original 24 month study duration for the patients from Study GX29455,* ~~thus~~ these patients may receive up to ~~24~~ *54* ITV injections of study drug.

All patients in Study GX29198 will have scheduled monthly visits and monthly study drug treatment for the duration of the study (see Table 1). The monthly visit will occur relative to the Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug treatments will not be made up *unless an extenuating circumstance applies (see Section 3.1.3).*

Administration

~~Lampalizumab reconstitution with Sterile Water for Injection (SWFI), USP/Ph. Eur., is required for preparation of the dose. The sites will supply the SWFI. Vials of lampalizumab are for single use only. Vials used for one patient may not be used for any other patient.~~ Detailed instructions for reconstitution of lampalizumab*, pre-injection preparation, administration of the study drug injection, and post-injection procedures for the study eye* are provided in the pharmacy binder.

~~Please refer to Appendix 3, Appendix 4, and Appendix 5 for detailed instructions on pre-injection preparation, administration of the study drug injection, and post-injection procedures for the study eye.~~

Storage

~~Upon receipt of lampalizumab, vials should be refrigerated at 2ºC-8ºC (36ºF-46ºF) until use. Lampalizumab vials should not be used beyond the expiration date provided by 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.~~

Detailed instruction for lampalizumab storage is provided in the pharmacy binder.

TABLE 2: Dose-Holding or Study Treatment and/or Study Discontinuation Criteria

Table 2 has been revised to clarify the criteria for dose-holding and study discontinuation.

SECTION 4.4.1.1: Formulation for Sites in the United States

Note: German sites will use commercially available Lucentis.

At U.S. sites, ranibizumab will be supplied by the Sponsor. ~~as a sterile solution aseptically filled in a sterile 2 mL stoppered glass vial.~~ For information on the formulation and handling of ranibizumab, see the *pharmacy binder* ~~manual~~ for ranibizumab.

Dosage, Administration, and Storage

At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with CNV in either eye may receive treatment with 0.5 mg ranibizumab. For U.S. sites, the drug will be open-label ranibizumab for investigational use only supplied by Genentech. The ranibizumab injection in the United States will be performed using the techniques as discussed in *the pharmacy binder* ~~Appendix 13, Appendix 14, and Appendix 15~~.

~~Ranibizumab vials must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until used. Each vial will be labeled as required by the relevant regulatory agencies.~~*Detailed instruction for ranibizumab storage is provided in the pharmacy binder.* Each vial will be labeled as required by the relevant regulatory agencies.

SECTION 4.5.2: Excluded Concomitant Therapy

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

- ~~Intravenous corticosteroids~~
- *Ocular or systemic* complement inhibitors, (e.g., eculizumab) except lampalizumab.
- Other experimental therapies (except ~~AMD related~~*those involving* vitamin and mineral supplements)

SECTION 4.6: STUDY ASSESSMENTS

Patients enrolled from Study CFD4870g will have up to ~~66~~*96* study visits (excluding the Day 1 visit). Patients enrolled from Study GX29455 will have up to ~~24~~*54* study visits (excluding the Day 1 visit). Any patient who discontinues the study prematurely (prior to the Month ~~66~~*96* visit for patients from Study CFD4870g and prior to the Month ~~24~~*54* visit for patients from Study GX29455) will have an ET visit completed $\geq$ 30 days after his or her last study drug treatment. Study visits will be scheduled every 30 ($\pm$ 7) days relative to the Day 1 visit.

SECTION 4.6.3: Assessments during Treatment

At all study visits the procedures and assessments should be performed prior to study drug administration unless otherwise indicated. All study visit assessments must be performed on the same day. *Note: see Section 3.1.3 for exception regarding delayed study treatment administration.*

SECTION 4.6.4: Study Completion/Early Termination Visit

For patients who withdraw early from the study (prior to the Month ~~66~~*96* visit for patients enrolled from CFD4870g and prior to the Month ~~24~~*54* visit for patients enrolled from GX29455) for any reason, these patients should complete the ET visit assessments $\geq$ 30 days following the last study treatment. Patients who discontinue from the study will not be allowed to re-enter the study. Please see the Study Flowcharts provided in Appendix 1-A through Appendix 1-E for the assessments to be performed at the study ET visit.

SECTION 4.6.5: Study Treatment Discontinuation /Early Termination Visit

Patients who prematurely discontinue the study treatment (prior to the Month ~~66~~*96* visit for patients enrolled from CFD4870g or prior to the Month ~~24~~*54* visit for patients enrolled from GX29455) will be also discontinued from the study, and they will be asked to return for an ET evaluation ≥30 days following their last study drug treatment for monitoring of adverse events and the study ET visit assessments.

SECTION 4.12.1: Safety Analysis

Safety will be assessed by adverse events, clinical laboratory evaluations, and immunogenicity as measured by ATA. Safety analyses will include all patients who enrolled into the extension study and received at least one lampalizumab injection ~~across Study CFD4870g or in Study GX29455 and~~ *in* the extension study. These patients will be grouped by the ~~first~~ treatment ~~regimen~~ received *(lampalizumab or sham)* when they were enrolled in the CFD4870 or GX29455for safety analyses.

The primary safety analysis is planned to occur at the time when patients enrolled from Study CFD4870g have reached approximately ~~66~~*96* months follow-up and when patients enrolled from Study GX29455 have reached approximately ~~24~~*54* months follow-up….

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to an adverse event severity grading scale (see Table 3).

SECTION 4.12.3: Exploratory Analyses

Mean GA lesion area growth and mean BCVA change from baseline over time will be summarized by treatment group. These patients will be grouped by *parent study and* the ~~first~~ treatment ~~regimen~~ received *(lampalizumab or sham)* when they were enrolled in Study CFD4870g or Study GX29455.

SECTION 5.1: 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, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

SECTION 5.1.3: ~~Protocol Defined Events of Special Interest/Serious/ Non Serious Adverse Events Subject to Expedited Reporting~~ *Adverse Events of Special Interest (Immediately Reportable to the Sponsor)*

This section heading has been revised.

SECTION 5.2: 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 study.…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~~*Adverse* events of special interest

SECTION 5.2.1: Emergency Medical Contacts

Medical Monitor Contact Information for sites in the United States and Germany:

United States

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted] (office)

Germany

Medical Monitor: [redacted], *M.D.*

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

or

Medical Monitor: [redacted] *MBChB, MFPM, MRCOphth*

Mobile Telephone No.: [redacted]

SECTION 5.2.2.2: 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 the last study visit.…

In the event that the EDC system is unavailable, ~~a~~*the* paper *Clinical Trial* Serious Adverse Event*/Adverse Event of Special Interest* Reporting Form ~~and fax cover sheet~~ *provided to investigators* should be completed and ~~faxed~~*submitted* to the Sponsor 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 ~~numbers~~*number or email address* provided to investigators ~~("Protocol Administrative and Contact Information and List of Investigators").~~. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.3.2: Eliciting Adverse Events

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

SECTION 5.3.3: Assessment of Severity ~~and Causality~~ of Adverse Events

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

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

SECTION 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).

- Course of the event, ~~considering especially~~*with special consideration of* the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)

TABLE 4: Causal Attribution Guidance

Table 4 has been revised to match current template language.

SECTION 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.

~~There is one eCRF page for recording adverse events or serious adverse events.~~

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

SECTION 5.3.5.7: Deaths

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 only be used 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 of 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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.5.

SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization ~~or Surgery~~

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 a serious adverse event in Section 5.1.2), except as outlined below.

~~The following hospitalizations are not considered to be adverse events:~~

~~Prolonged hospitalization to undergo a diagnostic or elective surgical procedure for a preexisting medical condition other than ocular that has not changed.~~

An event that leads to hospitalization under the following circumstance should not be reported as an adverse event or a serious adverse event:

- *Hospitalization for a preexisting condition, provided that all of 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.

SECTION 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. ~~as an adverse event of special interest~~ *If the associated adverse event meets the severity criteria, the event* should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

SECTION 5.3.6.1: 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 until the last study visit. ~~A Pregnancy Report eCRF should be completed by the investigator~~*A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor 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 with use of the fax number or e-mail address provided to investigators*~~and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management~~….

In addition, the investigator will submit a *paper* Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

~~In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor 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.~~

SECTION 5.3.6.1: 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 until the last study visit. ~~A Pregnancy Report eCRF should be completed by the investigator~~*A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor 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 with use of the fax number or e-mail address provided to investigators*~~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~~*After* the authorization has been signed, the investigator will ~~update the~~*will submit a paper Clinical Trial* Pregnancy ~~Report eCRF with additional~~*Reporting Form when updated* information on the course and outcome of the pregnancy *becomes available.* . 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 .~~

SECTION 5.5: ~~POST STUDY~~ ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the *paper Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the ~~below~~ fax number ~~and~~*or* email address~~:~~ *provided to investigators.*

~~For U.S. Sites:~~

~~Email Address: us_drug.safety@gene.com~~

~~Fax No.: 650-225-4682~~

~~Alternate Fax No.: 650-225-5288~~

~~For Germany Sites:~~

~~Email Address: grenzach.drug_safety@roche.com~~

~~Fax No.: 49 7624143183~~

SECTION 6.6: ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed *through use of a sponsor-designated EDC system*~~using the RAVE EDC system from Medidata Solutions Inc. (New York, NY)~~. 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.

APPENDIX 1: Schedule of Assessments

The schedules of assessments Appendix 1-A through Appendix 1-D have been revised to reflect the changes to the protocol. Appendices 1-E and 1-F have been added.

APPENDIX 3: ~~Pre Injection Procedures for All Patients Receiving the Study Drug (Lampalizumab)~~

Appendix 3 has been removed.

APPENDIX 4: ~~Preparation and Administration of Lampalizumab Injection~~

Appendix 4 has been removed.

APPENDIX 5: ~~Study Drug Post Injection Procedures for All Patients~~

Appendix 5 has been removed.

APPENDIX 13: ~~Ranibizumab Pre injection Procedure~~

Appendix 13 has been removed.

APPENDIX 14: ~~Preparation and Administration of Ranibizumab Injection~~

Appendix 14 has been removed.

APPENDIX 15: ~~Ranibizumab Post Injection Procedures~~

Appendix 15 has been removed.

SAMPLE INFORMED CONSENT FORMS

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB (FCFD4514S) IN PATIENTS WITH GEOGRAPHIC ATROPHY WHO HAVE COMPLETED GENENTECH-SPONSORED LAMPALIZUMAB STUDIES**
PROTOCOL NUMBER:	GX28198
VERSION NUMBER:	4
EUDRACT NUMBER:	2012-000578-41
IND NUMBER	104996
TEST PRODUCT:	Lampalizumab (RO5490249; FCFD4514S)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	14 February 2012
DATE AMENDED:	See electronic date stamp on protocol title page.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB (FCFD4514S) IN PATIENTS WITH GEOGRAPHIC ATROPHY WHO HAVE COMPLETED GENENTECH-SPONSORED LAMPALIZUMAB STUDIES**
PROTOCOL NUMBER:	GX28198
VERSION NUMBER:	4
EUDRACT NUMBER:	2012-000578-41
STUDY DRUG:	Lampalizumab (RO5490249; FCFD4514S)
PHASE:	Extension
INDICATION:	Geographic Atrophy
IND:	104996
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
DATE FINAL:	14 February 2012
DATE AMENDED:	See electronic date stamp on protocol title page.

Primary Objective

The primary objective of this study is to investigate the long-term ocular and systemic safety and tolerability of lampalizumab administered intravitreal (ITV) monthly.

Exploratory Objectives

The exploratory objectives of this study are the following:

- To assess long-term geographic atrophy (GA) area progression with fundus autofluorescence (FAF), color fundus photographs (CFP), and spectral domain-optical coherence tomography (SD-OCT)
- To evaluate potential anatomic biomarkers for earlier-stage GA progression and pharmacodynamic outcomes (e.g., retinal substructure analysis by SD-OCT)
- To assess the incidence of anti-therapeutic antibodies (ATA) to lampalizumab
- Clinical genotyping to assess relationships between genetic polymorphisms associated with age-related macular degeneration (AMD), disease characteristics, and response to administration of lampalizumab

Study Design

Study GX28198 is a multicenter, open-label extension study of safety and tolerability of lampalizumab administered by ITV injection to patients with GA who have completed the 18-month treatment in Study CFD4870g or the 24-week treatment in Study GX29455. As such, Study GX28198 is considered the extension for patients enrolled in these studies and is referred to as the extension study throughout the remainder of this protocol synopsis. CFD4870g patients who discontinued from study treatment early but remained on study for safety evaluation, or discontinued prior to completion of the 18-month treatment period, were not eligible for Study GX28198. Patients who participated in Study GX29455 and discontinued from study treatment prior to completion of the 24-week treatment period are not eligible for the extension study. Site investigators will be ophthalmologists with subspecialty expertise in virtreoretinal diseases.

The extension study enrolled 2 groups of patients from Study CFD4870g: patients previously exposed to lampalizumab and patients who were lampalizumab-naïve (i.e., received sham treatment). Eligible patients who consented to participate in the extension study were enrolled at the conclusion of the Month 18 visit for Study CFD4870g; the Month 18 visit served as the final visit for Study CFD4870g and the Day 1 visit for the extension study. Upon enrollment, all patients received 10-mg ITV injections of lampalizumab. Initially, patients continued on the same dosing frequency (monthly or every-other-month) assigned previously during their participation in Study CFD4870g. Patients in the every-other-month treatment arm were later crossed over to the monthly treatment arm for the remainder of their study participation period.

The extension study will enroll 2 groups of patients from Study GX29455: patients previously exposed to lampalizumab and patients who were lampalizumab-naïve (i.e., received sham). Eligible patients who consent to participate in the extension study will be enrolled at their conclusion of Study GX29455 (i.e., the Week 24 visit); the Week 24 visit will serve as the final visit for Study GX29455 and the Day 1 visit for the extension study.

All patients from Study GX29455 who enroll in the extension study will receive 10-mg ITV administrations of lampalizumab. The dosing frequency for both treatment arms (every 2 weeks [Q2W] and every 4 weeks [Q4W]) of Study GX29455 will change to monthly dosing to align with dosing in the extension study.

A patient must satisfy all eligibility criteria at Day 1 visit and will be enrolled using an interactive response system (IxRS). All patients enrolled in the extension study will have the first ITV injection of lampalizumab administered by the investigator at the Day 1 visit (unless dose-holding is medically justified by the investigator) which is scheduled on the same day and immediately following the conclusion of the Month 18 visit for Study CFD4870g or Week 24 visit for Study GX29455. Requisite Study CFD4870g Month 18 and Study GX29455 Week 24 assessment data will be extracted and incorporated into extension study Day 1 datasets.

All patients who enroll in Study GX28198 will have scheduled monthly visits with monthly study -drug treatment for the duration of their study participation.

At the scheduled monthly visits, patients will have safety *assessments evaluated* by the investigator prior to receiving study drug injection. Patients will be contacted by site personnel 7 (±2) days after each injection to elicit reports of decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. *If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit. Patients will be instructed to contact the investigator at any time if they have any health-related concern.* Patient self-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

The study eye for the extension study will be the same eye that received lampalizumab or sham administrations in Study CFD4870g or in Study GX29455. Only the study eye will receive administration of lampalizumab in the extension.

The extension study is being extended by an additional *30* months to a total duration of *96* months *to provide study patients with access to treatment until potential commercialization of lampalizumab*. The monthly treatment arm patients enrolled from Study CFD4870g may receive up to *96* monthly ITV injections of study drug. The number of ITV injections of study drug for patients who enrolled from the every-other-month treatment arm will vary due to their later crossover to the monthly treatment arm, which was relative to their Day 1 visit date. The patients who enroll from study GX29455 may receive up to *54* monthly ITV injections of study drug.

All monthly visits will occur relative to the patient's Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug doses will be made up *only in the following circumstance*:

- *If, during scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit, or other patient care issues), the patient's study treatment may be administered within 3 working days of that visit. The following assessments will be repeated on the day of the delayed study treatment: slit lamp examination, indirect ophthalmoscopy, and pre-treatment intraocular pressure (IOP) measurements. These assessments are to be recorded on the scheduled visit electronic Case Report Form [eCRF] and dated with the actual administration date.*

After the Day 1 visit, if a patient misses a study visit when ocular images are to be obtained, the images must be obtained at the next scheduled visit that the patient attends.

Patients are expected to attend their scheduled visits unless there are extenuating circumstances justifying their inability to come to the clinic

Patients who are prematurely discontinued from the study treatment in the extension study (prior to the Month *96* visit for patients enrolled from Study CFD4870g or prior to the Month *54* visit for patients enrolled from Study GX29455) will be also discontinued from the extension study; they will be asked to return for an early termination (ET) visit 30 days following their last study drug treatment for monitoring of adverse events and the ET visit assessments.

Patients will remain masked to their treatment assignment in Study CFD4870g or Study GX29455, and investigators are not permitted to provide treatment assignment in Study CFD4870g or Study 29455 until permitted by the Sponsor. The extension study is conducted in the United States and Germany.

The VA examiner role will remain masked to the patients' study eye assignment.

Outcome Measures

Primary Outcome Measure

- *Nature,* incidence and severity of ocular and non-ocular adverse events

Pharmacokinetic/Pharmacodynamic Outcome Measures

Scheduled pharmacokinetic assessments are not planned in the extension study. However, as necessary to assist in safety evaluations, serum lampalizumab concentration measurements will be performed.

Exploratory Outcome Measures

- Change in GA lesion area from baseline assessed by FAF, CFP, and SD-OCT
- Change from baseline in candidate anatomic biomarkers by SD-OCT
- The incidence of positive serum antibodies to lampalizumab
- Clinical genotyping to assess relationships between genetic polymorphisms associated with AMD, disease characteristics, and response to administration of lampalizumab

Safety Plan

Lampalizumab is not approved and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with lampalizumab in completed and ongoing studies. The anticipated important safety risks for lampalizumab are outlined below. Please refer to the most current lampalizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at a higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessments of the nature, frequency, and severity of adverse events. Guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

Potential ocular safety issues currently thought to be associated with the route of administration or pharmacology of lampalizumab include decreased best corrected visual acuity (BCVA), conjunctival hemorrhage, ocular inflammation, intraocular infection (endophthalmitis), transient and/or sustained elevation of IOP, *transient vision loss,* cataract development or progression, retinal or vitreous hemorrhage, and retinal break or detachment.

Systemic levels of lampalizumab following multiple ITV injections are anticipated to be low. Systemic side effects of lampalizumab are not anticipated based on nonclinical data and clinical studies conducted to date, but are possible. As part of the safety plan, masked aggregate adverse event reports will be reviewed periodically to identify potential systemic safety effects, such as cardiovascular events, neoplasms, or alteration in immune function (e.g., reports of infections with encapsulated bacteria such as Neisseria meningitidis, Streptococcus pneumonia, and Haemophilus influenza).

The incidence and characteristics of adverse events, serious adverse events, and laboratory abnormalities will be assessed. At the time of study enrollment, if a patient has an ongoing adverse event from Study CFD4870g or Study GX29455, the event will be continuously followed in the extension study. Any new adverse events will be collected from the time of Day 1 visit (the first study drug administration) in the extension study until a patient completes the study or discontinues prematurely. Safety will be assessed on an ongoing basis using expeditious reporting of serious adverse events and adverse events of special interest. All adverse events *and pregnancies* will be recorded for the duration of the study.

Periodic review of safety will be performed by an internal Genentech Safety Review Committee, composed of the Medical Monitor, Drug Safety Scientist, and Biostatistician. External experts may be consulted.

Starting with the Day 1 visit, all patients will be contacted by study site personnel 7 ($\pm$2) days after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Patient-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

Patients will be instructed to contact the investigator at any time if they have health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit.

A finger-counting test will be conducted for each patient within 15 minutes following study treatment by the investigator; hand motion or light perception will be tested when necessary. Intraocular pressure will be measured bilaterally prior to study treatment and at 60 ($\pm$10) minutes after study treatment for the study eye only. If there are no safety concerns at 60 (±10) minutes post treatment, the patient will be discharged from the clinic. If the IOP is increased by $\geq$10 mmHg from the pre-injection measurement at 60 (±10) minutes the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed.

Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, will be performed throughout the study. Routine hematology, serum chemistry, coagulation, and urinalysis profiles, as well as blood samples for antibodies to lampalizumab, will be obtained from all patients.

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

Patients who are prematurely discontinued from the study treatment (prior to the Month *96* visit for CFD4870g patients and prior to the Month *54* visit for GX29455 patients) will be also discontinued from the extension study and will be asked to return for an ET evaluation ≥30 days following their last study drug treatment for monitoring of adverse events and the early study termination visit assessments.

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

Refer to the main body of the protocol for dose-holding and study discontinuation criteria for adverse events.

Study Treatment for Patients Enrolled from Study CFD4870g

The dose of 10 mg lampalizumab was administered monthly or every other month starting at the Day 1 visit for up to the 18-month of treatment period. Later, the treatment period duration was extended by 24 months and patients in the every-other-month treatment arm were crossed over to the monthly treatment arm to receive monthly study drug treatment for the remainder of their study treatment period, provided that their informed consent has been obtained. The study treatment period *was again* extended by another 24 months *and now by 30 additional months* for a total treatment period of *96* months. Patients in the monthly treatment arm may receive up to *96* ITV injections of study drug. The number of ITV injections of study drug for patients who were in the every-other-month treatment arm prior to their crossover to the monthly treatment arm will vary and will depend on the date of their crossover relative to their Day 1 visit date.

Study Treatment for Patients Enrolled from Study GX29455

The extension study will enroll 2 groups of patients from Study GX29455: patients previously exposed to lampalizumab and patients who were lampalizumab-naïve (sham arm). Eligible patients who consented to participate in the extension study will be enrolled at the conclusion of the Week 24 visit for Study GX29455; the Week 24 visit will serve as the final visit for Study GX29455 and the Day 1 visit for the extension study.

All study GX29455 patients enrolled in the extension study will receive 10-mg ITV injections of lampalizumab. Dosing frequency for both treatment arms (Q2W and Q4W) of Study GX29455 changed to the monthly dosing *upon entry to this study. Given that 30 months have been added to the original 24 month study duration for the patients from Study GX29455,* these patients may receive up to *54* ITV injections of study drug.

All patients in Study GX29198 will have scheduled monthly visits and monthly study-drug treatment for the duration of the study. The monthly visit will occur relative to Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug treatments will not be made up *unless an extenuating circumstance applies*.

Permitted Concomitant Therapy and Clinical Practice

Permitted concomitant medications are any prescription drugs or over-the-counter preparations other than protocol-specified procedural treatments (e.g., dilating drops, fluorescein dyes) and pre- and post-injection medications (e.g., proparacaine, investigator-applied antimicrobials [if applicable] pre and post injection) used by a patient at the time of study enrollment on the Day 1 visit and through study completion or the ET visit.

Patients who use other maintenance therapies should continue their use. Patients required to use medications described in Excluded Concomitant Therapy will not be eligible for enrollment or continuation in the study. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

The onset of glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.

Of note, the following are some common therapies that are permitted:

- Short-term use of topical corticosteroids after cataract surgery, yttrium aluminum garnet capsulotomy, or peripheral iridotomy.
- Oral corticosteroids at doses ≤10 mg/day prednisone or equivalent
- Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.

- Onset of cataract or posterior capsular opacification in either eye during the patient's study participation may be treated as clinically indicated. Dose-interruption criteria may apply with cataract surgery.
- At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with choroidal neovascularization (CNV) may be treated with ranibizumab if they are diagnosed in either eye with CNV.

NOTE: If treatment with ranibizumab is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab, the treatment with ranibizumab must be administered first. The safety assessments (including IOP check) required to proceed to the study eye treatment with lampalizumab must be assessed prior to calling IxRS for the study drug kit assignment. Individual trays and sterile prep must be separately prepared for each treatment.

Excluded Concomitant Therapy

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

- Systemic anti-vascular endothelial growth factor (VEGF) agents
- ITV anti-VEGF agents (other than ranibizumab) in either eye
- ITV, subtenon, or chronic topical (ocular) corticosteroids in the study eye
- Systemic or IV immunomodulatory therapy (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, anti-tumor necrosis factor α agents)
- *Ocular or systemic* complement inhibitors, (e.g., eculizumab) except lampalizumab
- Treatment with Visudyne® in either eye
- Other experimental therapies (except *those involving* vitamin and mineral supplements)

Excluded Concomitant Conditions

Medical or surgical conditions or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, or that might affect interpretation of the study results, or that may render a study patient at high risk for treatment complications; when such a condition is identified, consultation with the Medical Monitor will be required to determine a patient's eligibility to continue in the extension study.

Statistical Methods

Safety Analysis

Safety will be assessed by adverse events, clinical laboratory evaluations, and immunogenicity as measured by ATA. Safety analyses will include all patients who enrolled into the extension study and received at least 1 lampalizumab injection *in* the extension study. These patients will be grouped by the treatment received *(lampalizumab or sham)* when they were enrolled in Study CFD4870g or Study GX29455 for safety analyses.

The primary safety analysis is planned to occur at the time when patients enrolled from Study CFD4870g have reached approximately *96* months follow up and when patients enrolled from Study GX29455 have reached approximately *54* months follow- up. The timing of the primary analysis may be adjusted according to the start of the open-label extension for Studies GX29176 and GX29185, to which patients from the extension study may have the opportunity to enroll. Earlier safety analyses of this study may be performed on an ad hoc basis.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to an adverse event severity grading scale.

Missing Data

All efforts will be made to minimize missing data; no imputation will be performed for the safety analysis.

Determination of Sample Size

This study is open to all patients who complete Study CFD4870g and Study GX29455 and who meet eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation.

Interim Analysis

The primary analysis time will occur after all patients enrolled from Study CFD4870g have reached approximately 96 months follow up and when patients enrolled from Study GX29455 have reached approximately 54 months follow-up. Earlier analyses may be performed on an ad hoc basis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACP	alternative complement pathway
AE	adverse event
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
ATA	anti-therapeutic antibody
BCVA	best corrected visual acuity
CFB	complement factor B
CFD	complement factor D
CFP	color fundus photographs
C_{max}	maximum observed serum concentration
CNV	choroidal neovascularization
CRO	contract research organization
DA	disk area
DAP	Data Analysis Plan
DLC	dose-limiting criteria
DLT	dose-limiting toxicity
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	fluorescein angiogram
Fab	antigen-binding fragment
FAF	fundus autofluorescence
FDA	Food and Drug Administration
FP	fundus photography
GA	geographic atrophy
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IOP	intraocular pressure
ITV	intravitreal
IxRS	interactive response system
MTD	maximum tolerated dose

Abbreviation	Definition
NI	near infrared
PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
RPE	retinal pigment epithelial
SAE	serious adverse event
SD-OCT	spectral domain–optical coherence tomography
TAE	targeted adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
YAG	yttrium aluminum garnet

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

1.1.1 Epidemiology

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people 50 years of age or older in the developed world (Friedman et al. 2004). The overall prevalence of AMD is projected to increase by more than 50% by the year 2020. Advanced AMD is classified into two clinical forms: geographic atrophy (GA) and exudative disease characterized by choroidal neovascularization (CNV) (Age-Related Eye Disease Study [AREDS] Research Group 2003). Progression of GA may be associated with a significant decrease in visual function with approximately 40% of a subset of GA patients losing at least 3 Snellen equivalent lines of vision over a 2 year period (Sunness et al. 2007).

1.1.2 Pathophysiology

The pathogenesis of AMD is not well understood; however, environmental factors and the alternative complement pathway (ACP) have been implicated in AMD (de Jong 2006). Increased activation of the ACP has been found in drusen, lipoproteinous depositions in the space between the retinal pigment epithelial (RPE) and Bruch's membrane, which are a hallmark of AMD. Moreover, a role for ACP activation in AMD has been supported by human genetics (Yates et al. 2007). Complement factor D (CFD) is a rate-limiting enzyme that plays a pivotal role in the activation and amplification of ACP activity. Evidence for CFD in the pathogenesis of AMD includes protection against oxidative-stress-mediated photoreceptor degeneration in a murine model with genetic deficiency of CFD (Rohrer et al. 2007), and detection of increased systemic activation of complement, including CFD, in the serum of AMD patients versus controls, suggesting that AMD may be a systemic disease with local manifestations in the aging macula (Scholl et al. 2008).

1.1.3 Management of Geographic Atrophy

Currently, intravitreal (ITV) anti-VEGF (vascular endothelial growth factor) therapy is the standard of care for the wet form of advanced AMD; however, there is no treatment that definitively halts or reduces the progression of GA and vision function loss. Although the AREDS Research Group has shown that antioxidant vitamin and mineral supplementation had a statistically significant but modest effect on reducing the progression of AMD, it was the reduction in progression to neovascular AMD rather than progression to central GA that was principally responsible for this observation (AREDS Research Group 2001). Currently, there is no approved treatment to prevent *or reduce* progression of GA, creating a significant unmet need for these patients. By inhibiting ACP activity, lampalizumab may offer the potential to impede or arrest the progression of GA and visual function loss.

1.2 BACKGROUND ON THE MOLECULE

Lampalizumab is an antigen-binding fragment (Fab) of a humanized monoclonal antibody directed against the complement component factor D (CFD). Lampalizumab binds human factor D with a dissociation equilibrium constant of approximately 20 pM. Factor D is a highly specific serine protease that is a rate-limiting enzyme of the ACP. The substrate for factor D is another alternative pathway serine protease, complement factor B (CFB). Following cleavage by CFD, CFB converts into the proteolytically active complement factor Bb and initiates the ACP. Lampalizumab inhibits ACP activity by preventing CFD–mediated cleavage of CFB. Lampalizumab activity is specific for the ACP and shows no inhibitory effect on the classical or mannose-binding lectin complement pathways.

Through inhibition of ACP activity, lampalizumab may offer the potential to impede or arrest the progression of GA and visual function 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 CFD (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 RATIONALE FOR DOING THIS STUDY

The open-label extension study will provide data to investigate the long-term safety and tolerability of lampalizumab in patients with GA. At present, there is no approved treatment to prevent the progression of GA and vision loss; lampalizumab is being studied as a potential treatment for this indication. For patients who complete the18-month treatment assignment in Study CFD4870g or 24-week treatment assignment in Study GX29455, Study GX28198 will permit the evaluation of long-term safety and tolerability of lampalizumab in participants continuing from the active treatment arms. In addition, Study GX28198 will provide the opportunity for eligible patients from the sham treatment arms in Study CFD4870g or Study GX29455 to receive lampalizumab.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is as follows:

- To investigate the long-term ocular and systemic safety and tolerability of lampalizumab administered ITV monthly

2.2 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- To assess long-term GA area progression with fundus autofluorescence (FAF), color fundus photographs (CFP), and spectral domain-optical coherence tomography (SD-OCT)
- To evaluate potential anatomic biomarkers for earlier-stage GA progression and pharmacodynamic outcomes (e.g., retinal substructure analysis by SD-OCT)
- To assess the incidence of anti-therapeutic antibodies (ATA) to lampalizumab
- Clinical genotyping to assess relationships between genetic polymorphisms associated with AMD, disease characteristics, and response to administration of lampalizumab

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study GX28198 is a multicenter, open-label extension study of safety and tolerability of lampalizumab administered by ITV injection to patients with GA who have completed the 18-month treatment in Study CFD4870g or 24-week treatment in Study GX29455. As such, Study GX28198 is considered the extension for patients enrolled in these studies and is referred to as the extension study throughout the remainder of this protocol. CFD4870g patients who discontinued from study treatment early but remained in the study for safety evaluation, or discontinued prior to completion of the 18-month treatment period, were not eligible for Study GX28198. Patients who participated in Study GX29455 and discontinued from study treatment prior to completion of the 24-week treatment period are not eligible for the extension study. Site investigators will be ophthalmologists with subspecialty expertise in vitreoretinal diseases.

3.1.1 Patients Enrolled from Study CFD4870g

The extension study enrolled 2 groups of patients from Study CFD4870g: patients previously exposed to lampalizumab and patients who were lampalizumab-naïve (i.e., received sham treatment). Eligible patients who consented to participate in the extension study were enrolled at the conclusion of the Month 18 visit for Study CFD4870g; the Month 18 visit served as the final visit for Study CFD4870g and the Day 1 visit for the extension study. Upon enrollment, all patients received 10-mg ITV injections of lampalizumab. Initially, patients continued on the same dosing frequency (monthly or every-other month) assigned previously during their participation in Study CFD4870g. Patients in the every-other-month treatment arm were later crossed over to the monthly treatment arm for the remainder of their study participation period (see Section 3.3).

3.1.2 Patients Enrolled from Study GX29455

The extension study will enroll 2 groups of patients from Study GX29455: patients previously exposed to lampalizumab and patients who were lampalizumab-naïve (i.e., received sham). Eligible patients who consent to participate in the extension study will be enrolled at their conclusion of Study GX29455 (i.e., the Week 24 visit); the Week 24 visit will serve as the final visit for Study GX29455 and the Day 1 visit for the extension study.

All patients from Study GX29455 who enroll in the extension study will receive 10-mg ITV administrations of lampalizumab. The dosing frequency for both treatment arms (every 2 weeks [Q2W] and every 4 weeks [Q4W]) of Study GX29455 will change to monthly dosing to align with dosing in the extension study.

3.1.3 All Extension Study Patients

A patient must satisfy all eligibility criteria at Day 1 visit and will be enrolled using an interactive response system (IxRS). All patients enrolled in the extension study will have the first ITV injection of lampalizumab administered by the investigator at the Day 1 visit (unless dose holding is medically justified by the investigator) which is scheduled on the same day and immediately following the conclusion of the Month 18 visit for Study CFD4870g or Week 24 visit for Study GX29455. Requisite Study CFD4870g Month 18 and Study GX29455 Week 24 assessment data will be extracted and incorporated into extension study Day 1 datasets.

All patients who enroll in Study GX28198 will have scheduled monthly visits with monthly study-drug treatment for the duration of their study participation (see *Table 1*).

Table 1 Dosing Schema

Treatment	Day 1[a]	Monthly Lampalizumab Dosing Visit Month 1 through Visit Month *95*[b] or Visit Month 1 through Visit Month *53*[c]	*ET*[e] *or Final visit* Month *96*[d] or Month *54*[d]
Lampalizumab 10-mg ITV injections	x	x	

ET = early termination; ITV =intravitreal.

[a] Day 1 visit will occur at the conclusion of the Month 18 visit for Study CFD4870g or Week 24 visit for Study GX29455; the first study drug administration for the extension study is at the Day 1 visit.

[b] Patients enrolled from Study CFD4870g in the monthly treatment arm continue to receive monthly lampalizumab treatment (Months 1–*95*) without change; patients in the every-other-month treatment arm were crossed over to the monthly treatment arm and are receiving monthly lampalizumab treatment for the remainder of their *95*-month study treatment period.

[c] Patients enrolled from Study GX29455 will receive monthly treatment (visit Months 1–*53*) with lampalizumab irrespective of the treatment arm (Q2W or Q4W) they were randomized to in Study GX29455.

[d] Month *96* visit is a final study visit for patients enrolled from Study CFD4870g and Month *54* visit is the final study visit for patients enrolled from Study GX29455; no study treatment will be administered at the final visit.

[e] *Patients may undergo an ET visit as per protocol section 4.7 through 4.9; no study treatment will be administered at this visit.*

At the scheduled monthly visits, patients will have safety *assessments evaluated* by the investigator prior to receiving study drug injection. Patients will be contacted by site personnel 7 (±2) days after each injection to elicit reports of decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. *If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 1-F). Patients will be instructed to contact the investigator at any time if they have any health-related concern.* Patient self-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

The study eye for the extension study will be the same eye that received lampalizumab or sham administrations in Study CFD4870g or in Study GX29455. Only the study eye will receive administration of lampalizumab in the extension.

The extension study is being extended by an additional *30* months to a total duration of *96* months *to provide study patients with access to treatment until potential commercialization of lampalizumab*. The monthly treatment arm patients enrolled from Study CFD4870g may receive up to *96* monthly ITV injections of study drug. The number of ITV injections of study drug for patients who enrolled from the every-other-month treatment arm will vary due to their later crossover to the monthly

treatment arm, which was relative to their Day 1 visit date. The patients who enroll from study GX29455 may receive up to *54* monthly ITV injections of study drug.

All monthly visits will occur relative to the patient's Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug doses will be made up *only in the following circumstance*:

- *If, during scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit, or other patient care issues), the patient's study treatment may be administered within 3 working days of that visit. The following assessments will be repeated on the day of the delayed study treatment: slit lamp examination, indirect ophthalmoscopy, and pre-treatment intraocular pressure (IOP) measurements. These assessments are to be recorded on the scheduled visit electronic Case Report Form [eCRF] and dated with the actual administration date.*

After the Day 1 visit, if a patient misses a study visit when ocular images are to be obtained (see Appendix 1-A through Appendix 1-E), the images must be obtained at the next scheduled visit that the patient attends.

Patients are expected to attend their scheduled visits unless there are extenuating circumstances justifying their inability to come to the clinic.

Patients who are prematurely discontinued from the study treatment in the extension study (prior to the Month *96* visit for patients enrolled from Study CFD4870g or prior to the Month *54* visit for patients enrolled from Study GX29455) will be also discontinued from the extension study and will be asked to return for an early termination (ET) visit ≥30 days following their last study drug treatment for monitoring of adverse events and the ET visit assessments (Appendix 1-A through Appendix 1-E).

Patients will remain masked to their treatment assignment in Study CFD4870g or Study GX29455, and investigators are not permitted to provide treatment assignment in Study CFD4870g or Study GX29455 until permitted by the Sponsor. The extension study is being conducted in the United States and Germany.

The VA examiner role will remain masked to the patients' study eye assignment.

3.2 TREATMENT FOR CHOROIDAL NEOVASCULARIZATION WITH RANIBIZUMAB

At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with CNV in either eye may receive treatment with 0.5 mg ranibizumab. For U.S. sites, the drug will be open-label ranibizumab for investigational use only supplied by Genentech (see *the pharmacy binder* for the drug formulation) and injected no more frequently than monthly. Sites in Germany will use commercially available ranibizumab (Lucentis®) in Germany and consult with the region-specific Lucentis Prescribing Information for the recommended dose, frequency, and administration of treatment.

Please see *the pharmacy binder* for ranibizumab administration (pre-injection procedure, preparation and administration, and post-injection procedure) at U.S. sites.

3.3 RATIONALE FOR STUDY DESIGN

The primary objective of the extension study is to assess the long-term ocular and systemic safety and tolerability of lampalizumab in GA patients.

Patients from Study CFD4870g (including those in sham arms), initially received lampalizumab in the extension study at the same dosing frequency previously assigned in Study CFD4870g: patients in the monthly treatment arms continued receiving monthly treatment, and patients in the every-other-month treatment arm *continued receiving every-other-month treatment.*

After Study CFD4870g results demonstrated that monthly administration of lampalizumab had a clinically meaningful and statistically significant effect on reducing the GA area growth over the 18-month study treatment period (see Investigator Brochure for additional details), the every-other-month treatment arm patients were crossed over to the monthly treatment arm for the remainder of their study participation, provided informed consent was obtained.

All patients, regardless of treatment arm in the 6-month GX29455 exposure-response study (including those in sham arms) who are subsequently enrolled in the extension study will be assigned to the 10-mg lampalizumab monthly dosing frequency.

The extension study design will permit an assessment of several exploratory outcomes (see Section 3.4.3) that may offer a better understanding of disease progression and treatment effects.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measure

- *Nature,* incidence, and severity of ocular and non-ocular adverse events

3.4.2 Pharmacokinetic/Pharmacodynamic Outcome Measures

Scheduled pharmacokinetic assessments are not planned in the extension study. However, as necessary to assist in safety evaluations, serum lampalizumab concentration measurements will be performed.

3.4.3 Exploratory Outcome Measures

- Change in GA lesion area from baseline assessed by FAF, CFP, and SD-OCT
- Change from baseline in candidate anatomic biomarkers by SD-OCT
- The incidence of positive serum antibodies to lampalizumab
- Clinical genotyping to assess relationships between genetic polymorphisms associated with AMD, disease characteristics, and response to administration of lampalizumab

3.5 SAFETY PLAN

Lampalizumab is not approved and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with lampalizumab in completed and ongoing studies. The anticipated important safety risks for lampalizumab are outlined below. Please refer to the most current lampalizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at a higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessments of the nature, frequency, and severity of adverse events. Guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

Potential ocular safety issues currently thought to be associated with the route of administration or pharmacology of lampalizumab include decreased best corrected visual acuity (BCVA), conjunctival hemorrhage, ocular inflammation (see Section 5.1.3 for definition and Appendix 2 for anterior chamber and vitreous inflammation grading scales), intraocular infection (endophthalmitis), transient and/or sustained elevation of IOP, *transient vision loss,* cataract development or progression, retinal or vitreous hemorrhage, and retinal break or detachment.

Systemic levels of lampalizumab following multiple ITV injections are anticipated to be low. Systemic side effects of lampalizumab are not anticipated based on nonclinical data and clinical studies conducted to date, but are possible. As part of the safety plan, masked aggregate adverse event reports will be reviewed periodically to identify potential systemic safety effects, such as cardiovascular events, neoplasms, or alteration in immune function (e.g., reports of infections with encapsulated bacteria such as Neisseria meningitidis, Streptococcus pneumonia, and Haemophilus influenza).

The incidence and characteristics of adverse events, serious adverse events, and laboratory abnormalities will be assessed. At the time of study enrollment, if a patient has an ongoing adverse event from Study CFD4870g or Study GX29455, the event will be continuously followed in the extension study. Any new adverse events will be collected from the time of Day 1 visit (the first study drug administration) in the extension study until a patient completes the study or discontinues prematurely. Safety will be assessed on an ongoing basis using expeditious reporting of serious adverse events and adverse events of special interest. All adverse events *and pregnancies* will be recorded for the duration of this study.

Periodic review of safety will be performed by an internal Genentech Safety Review Committee, composed of the Medical Monitor, Drug Safety Scientist, and Biostatistician. External experts may be consulted.

Starting with the Day 1 visit, all patients will be contacted by study site personnel 7 (±2) days after each injection to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. Patient-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

Patients will be instructed to contact the investigator at any time if they have health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (Appendix 1-F).

A finger-counting test will be conducted for each patient within 15 minutes following study treatment by the investigator; hand motion or light perception will be tested when necessary. IOP will be measured bilaterally prior to study treatment and at 60 (±10) minutes after study treatment for the study eye only. If there are no safety concerns at 60 (±10) minutes post treatment, the patient will be discharged from the clinic. If the IOP is increased by≥10 mmHg from the pre-injection measurement at 60 (±10) minutes the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.3.5).

Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, will be performed throughout the study. Routine hematology, serum chemistry, coagulation, and urinalysis profiles, as well as blood samples for antibodies to lampalizumab, will be obtained from all patients (see Appendix 1-A through Appendix 1-E).

The VA examiner will be masked to the patient's treated (study) eye and will perform only the VA (including refraction). The VA examiner is not allowed to perform any other tasks involving direct patient care.

Patients who are prematurely discontinued from the study treatment (prior to the Month *96* visit for CFD4870g patients and prior to the Month *54* visit for GX29455 patients) will be also discontinued from the extension study and will be asked to return for an ET evaluation ≥30 days following their last study drug treatment for monitoring of adverse events and the early study termination visit assessments (see Appendix 1-A through Appendix 1-E).

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

See Section 4.8 for dose-holding and study discontinuation criteria for adverse events.

If a patient's eye is injected with ranibizumab, the same post-dose safety assessments (finger counting, IOP measurement, and follow-up call) should be followed as for the study treatment. Treatment (dose) holding and/or treatment discontinuation for adverse events will be determined using the criteria in *Table 2* in Section 4.3.1.2. Associated adverse events should be recorded on the Adverse Event eCRF.

3.6 STUDY PATIENTS

All patients who complete Study CFD4870g or Study GX29455 and who satisfy eligibility criteria are offered the opportunity to participate in the extension study.

3.7 CONTROL GROUPS

This is an open-label extension study. There is no control group for this study.

3.8 ETHICAL CONSIDERATIONS

The patient population to be enrolled in this study must meet eligibility criteria and agree to participate in the extension study following an informed consent process. This study will comply with laws and guidelines as discussed in Compliance with Laws and Regulations (see Section 3.10), Informed Consent (see Section 6.3), Disclosure of Data (see Section 6.11), and Institutional Review Board Approval (see Section 6.4).

3.9 ADMINISTRATIVE STRUCTURE

This study will be sponsored by Genentech, which is the U.S.-based global affiliate of F. Hoffmann-La Roche; F. Hoffmann-La Roche will serve as the legal sponsor in Germany. Genentech will perform study management, oversight of data management, and statistical programming. A contract research organization (CRO) will be responsible for project management, monitoring, vendor management, and data management (including quality checking of the data). An IxRS will be used for patient enrollment 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 Genentech for analysis). Data will be recorded by an electronic data capture (EDC) system using eCRFs (see Section 6.6). A central reading center will be used for ocular imaging analyses (FAF, near infrared [NI], CFP, FA and SD-OCT).

3.10 COMPLIANCE WITH LAWS AND REGULATIONS

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. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Patients who have completed study treatment and the Month 18 visit of Study CFD4870g or Week 24 visit of Study GX29455 will be eligible to participate in the extension study.

Patients who discontinued from study treatment early but remained on study for safety evaluation, or discontinued from Study CFD4870g prior to completion of the 18 month treatment period, will not be eligible for the extension study.

Patients who discontinued from study treatment prior to completion of the 24-week treatment period in Study GX29455 will not be eligible for the extension study.

Written informed consent will be obtained prior to enrollment and the initiation of any study procedures. On the same day, patients will be enrolled in the extension study at the conclusion of the Month 18 completion visit for Study CFD4870g or of the Week 24 completion visit for Study GX29455 provided inclusion/exclusion criteria are met; the Month 18 CFD4870g visit data or Week 24 GX29455 visit data will serve as the Day 1 visit data for the extension study. In the case where a patient misses the final

Month 18 visit for Study CFD4870g or final Week 24 visit for Study GX29455, eligibility for the extension study will be determined by the Sponsor.

Note: All patients enrolled in the extension study will have the first ITV injection of lampalizumab administered by the investigator at the Day 1 visit, unless dose interruption is medically or otherwise justified by the investigator (see Section 4.3.1.2 and Table 2).

4.1.2 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

4.1.2.1 General Inclusion Criteria

- Willingness and ability to provide signed Informed Consent; in addition, at U.S. sites, Health Insurance Portability and Accountability Act (HIPPA) authorization, in other countries as applicable according to national laws
- Ability and willingness to undertake all scheduled visits and assessments
- For CFD4870g patients: Previous enrollment and completion (Month 18 visit) of Study CFD4870g without early treatment discontinuation (lampalizumab or sham)
- For GX29455 patients: Previous enrollment and completion (Week 24 visit) of Study GX29455 without early treatment discontinuation (lampalizumab or sham)
- 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 post-menarcheal, has not reached a post-menopausal state ($\geq$12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal 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 (refrain from heterosexual intercourse) 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. Men must refrain from donating sperm during this same period.

  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.

4.1.2.2 Ocular Inclusion Criterion

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

4.1.3 Exclusion Criteria

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

4.1.3.1 Ocular Exclusion Criteria

- Vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye
- Subfoveal focal laser photocoagulation in the study eye
- Treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
- ITV drug delivery (e.g., ITV corticosteroid injection, anti-angiogenic drugs, anti-complement drugs, or device implantation) in the study eye. Lampalizumab in study eye and ranibizumab in either eye are permitted.
- Any concurrent ocular or intraocular condition in the study eye that contraindicates the use of an investigational drug or may affect interpretation of the study results or may render the patient at high risk for treatment complications
- Idiopathic or autoimmune-associated uveitis/vitritis in either eye
- RPE tear involving the macula in the study eye
- Retinal detachment or macular hole (Stage 3 or 4) in the study eye
- Aphakia or absence of the posterior capsule in the study eye
- Violation of the posterior capsule in the study eye 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

- Uncontrolled glaucoma in the study eye (defined as IOP ≥30 mmHg despite treatment with anti-glaucoma medication)
- Planned or anticipated glaucoma-filtering surgery in the study eye
- Planned or anticipated corneal transplant in the study eye
- Diabetic retinopathy in either eye
- Scleritis, keratitis, or endophthalmitis in either eye

4.1.3.2 Concurrent Systemic Conditions

- Uncontrolled blood pressure (defined as systolic greater than 180 mmHg and/or diastolic greater than 110 mmHg while the patient is sitting)
- Medical conditions that may be associated with a clinically significant risk for bleeding
- Metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or that renders the patient at high risk for treatment complications
- Predisposition to increased risk for infection
- Active malignancy within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for > 12 months.
- Allergy to fluorescein, not amenable to treatment
- Inability to obtain study images 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 "Excluded Concomitant Therapy" Section 4.5.2

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

This is an open-label extension study. All patients enrolled in the extension study will receive 10-mg ITV administrations of lampalizumab.

Dosing frequency in the extension study was either monthly or every other month in accordance with the Study CFD4870g treatment frequency assignment. Patients in the every-other-month treatment arm were later crossed over to the monthly treatment arm for the remainder of their study participation, provided that their informed consents have been obtained. The patients who joined the extension study from Study GX29455 will receive 10-mg ITV administration of lampalizumab monthly.

The patients will remain masked to their previous lampalizumab or sham treatment assignments in Study CFD4870g or Study GX29455 until the Sponsor permits investigators to release this information. The VA examiner will remain masked to patients' study eye assignment and will perform only the VA (including refraction). The VA examiner is not allowed to perform any other tasks involving direct patient care.

4.3 STUDY TREATMENT

4.3.1 Lampalizumab

4.3.1.1 Formulation

See the pharmacy binder for details regarding formulation.

4.3.1.2 Dosage, Administration, and Storage

Dosage

Patients enrolled from Study CFD4870g:

The dose of 10 mg lampalizumab was administered monthly or every other month starting at the Day 1 visit for up to the 18-month of treatment period. Later, the treatment period duration was extended by 24 months and patients in the every-other-month treatment arm were crossed over to the monthly treatment arm to receive monthly study drug treatment for the remainder of their study treatment period, provided that their informed consent has been obtained. The study treatment period *was again* extended by another 24 months *and now by 30 additional months* for a total treatment period of *96* months. Patients in the monthly treatment arm may receive up to *96* ITV injections of study drug. The number of ITV injections of study drug for patients who were in the every-other-month treatment arm prior to their crossover to the monthly treatment arm will vary and will depend on the date of their crossover relative to their Day 1 visit date.

Patients enrolled from Study GX29455:

The extension study will enroll 2 groups of patients from Study GX29455: patients previously exposed to lampalizumab and patients who are lampalizumab-naïve (sham arm). Eligible patients who consent to participate in the extension study will be enrolled at the conclusion of the Week 24 visit for Study GX29455; the Week 24 visit will serve as the final visit for Study GX29455 and the Day 1 visit for the extension study.

All study GX29455 patients enrolled in the extension study will receive 10-mg ITV injections of lampalizumab. Dosing frequency for both treatment arms (Q2W and Q4W) of Study GX29455 changed to monthly dosing *upon entry to this study. Given that 30 months have been added to the original 24 month study duration for the patients from Study GX29455,* these patients may receive up to *54* ITV injections of study drug.

All patients in Study GX29198 will have scheduled monthly visits and monthly study drug treatment for the duration of the study (see Table 1). The monthly visit will occur relative to the Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing. Missed study drug treatments will not be made up *unless an extenuating circumstance applies (see Section 3.1.3)*.

Administration

Detailed instructions for reconstitution of lampalizumab*, pre-injection preparation, administration of the study drug injection, and post-injection procedures for the study eye* are provided in the pharmacy binder.

Storage

Detailed instruction for lampalizumab storage is provided in the pharmacy binder.

Lampalizumab Dose-Holding and Study Discontinuation Criteria

Study treatment interruption and/or patient discontinuation from the study (if applicable) due to adverse events will be determined using the criteria listed in Table 2. If any of these criteria are met, treatment will be held and will not be resumed earlier than the next scheduled study visit; with select adverse events, patients may be discontinued from the study. The reason for holding treatment should be recorded on the Dose Holding eCRF and, if applicable, on the Adverse Event eCRF.

Table 2 Dose-Holding or Study Discontinuation Criteria

Event	Dose-Holding or Study Discontinuation Criteria
Intraocular inflammation	Hold dose if intraocular inflammation (iritis, iridocyclitis or vitritis) is ≥ 1+ in the study eye (see definitions of intraocular inflammation in Section 5.1.3 and inflammation grading scales in Appendix 2); study drug treatment may be permitted subsequently as determined by the investigator. *Patients with ≥ 3+ intraocular inflammation will be discontinued from the study treatment.*
VA *decrease*	Hold dose 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 investigator.
IOP	Hold dose if IOP in the study eye is ≥30 mmHg. Study drug may be permitted when IOP has been controlled either spontaneously or by treatment as determined by the investigator.
Vitreous hemorrhage	Hold dose in the event of a vitreous hemorrhage in the study eye; study drug treatment may be permitted subsequently as determined by the investigator.
Rhegmatogenous retinal break	Hold dose if a retinal break is present in the study eye. *Study treatment may be resumed no earlier than 30 days after successful laser retinopexy as determined by the investigator.*
Rhegmatogenous retinal detachment *or* macular hole	Patients with a rhegmatogenous retinal detachment or Stage 3 or Stage 4 macular holes will be discontinued from the study.
Active infection	Hold dose 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 *systemic* treatment for an active infection. *Patients with endophthalmitis in the study eye will be discontinued from the study.*
Cataract surgery *in study eye*	*Interrupt study treatment after cataract surgery in study eye. Study treatment may be resumed no earlier than 30 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation. For cataract surgery with complications, study treatment may be permitted as determined by the investigator and Sponsor.*
Oral corticosteroids (prednisone >10 mg/day or equivalent)	Hold dose. Study treatment may be resumed when oral corticosteroids dosing is prednisone ≤10 mg/day or equivalent.
IV corticosteroids	Hold dose. Study treatment may be resumed when the patient has finished IV corticosteroid course *and oral corticosteroid dosing is prednisone ≤ 10 mg/day or equivalent.*

BCVA =best corrected visual acuity; IOP =intraocular pressure; IV =intravenous; VA =visual acuity.

If a patient misses more than three consecutive doses of study treatment within any 6-month treatment period, the investigator and the Sponsor may consider withdrawing the patient from the study.

4.4 TREATMENT FOR CHOROIDAL NEOVASCULARIZATION WITH RANIBIZUMAB

4.4.1 Ranibizumab

4.4.1.1 Formulation for Sites in the United States

Note: German sites will use commercially available Lucentis.

At U.S. sites, ranibizumab will be supplied by the Sponsor. For information on the formulation and handling of ranibizumab, see the *pharmacy binder* for ranibizumab.

Dosage, Administration, and Storage

At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with CNV in either eye may receive treatment with 0.5 mg ranibizumab. For U.S. sites, the drug will be open-label ranibizumab for investigational use only supplied by Genentech. The ranibizumab injection in the United States will be performed using the techniques as discussed in *the pharmacy binder*. Sites in Germany will use commercially available ranibizumab (Lucentis) and consult with the region-specific Lucentis Prescribing Information for the recommended dose, frequency, and administration of treatment.

NOTE: If treatment with ranibizumab is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab, the treatment with ranibizumab must be administered first. The safety assessments (including IOP check) to proceed to the study eye treatment with lampalizumab must be assessed prior to calling the IxRS for the study treatment kit assignment. Individual trays and sterile prep must be separately prepared for each treatment.

Note: Sites will contact the IxRS to report the treatment with the Genentech-supplied ranibizumab and record this information on the specific eCRF page. For German sites, ranibizumab will be recorded on the concomitant medications eCRF.

Detailed instruction for ranibizumab storage is provided in the pharmacy binder. Each vial will be labeled as required by the relevant regulatory agencies.

4.5 CONCOMITANT AND EXCLUDED THERAPIES

4.5.1 Permitted Concomitant Therapy

Permitted concomitant medications are any prescription drugs or over-the-counter preparations other than protocol-specified procedural treatments (e.g., dilating drops, fluorescein dyes, etc.) and pre- and post-injection medications (e.g., proparacaine, investigator-applied antimicrobials (if applicable) pre and post injection, etc.) used by a patient at the time of study enrollment on the Day 1 visit and through study completion or the ET visit.

Patients who use other maintenance therapies should continue their use. Patients required to use medications described in Excluded Concomitant Therapy (see Section 4.5.2 will not be eligible for enrollment or continuation in the study.
All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

The onset of glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.

Of note, the following are some common therapies that are permitted:

- Short-term use of topical corticosteroids after cataract surgery, YAG capsulotomy, or peripheral iridotomy.
- Oral corticosteroids at doses $\leq$10 mg/day prednisone or equivalent
- Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated.
- Onset of cataract or posterior capsular opacification in either eye during the patient's study participation may be treated as clinically indicated. Dose-interruption criteria (see *Table 2*) may apply with cataract surgery.
- At the discretion of the investigator, enrolled patients who are receiving study treatment and are diagnosed with CNV may be treated with ranibizumab if they are diagnosed in either eye with CNV.

  NOTE: If treatment with ranibizumab is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab, the treatment with ranibizumab must be administered first. The safety assessments (including IOP check) required to proceed to the study eye treatment with lampalizumab must be assessed prior to calling IxRS for the study drug kit assignment. Individual trays and sterile prep must be separately prepared for each treatment.

4.5.2 Excluded Concomitant Therapy

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

- Systemic anti-VEGF agents
- ITV anti-VEGF agents (other than ranibizumab) in either eye
- ITV, subtenon, or chronic topical (ocular) corticosteroids in the study eye
- Systemic or IV immunomodulatory therapy (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, anti-tumor necrosis factor α agents)
- $Ocular\ or\ systemic$ complement inhibitors, (e.g., eculizumab) except lampalizumab
- Treatment with Visudyne® in either eye
- Other experimental therapies (except $those\ involving$ vitamin and mineral supplements)

4.5.3 Excluded Concomitant Conditions

- Medical or surgical conditions or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, or that might affect interpretation of the study results, or that may render a study patient at high risk for treatment complications; when such a condition is identified, consultation with the Medical Monitor will be required to determine a patient's eligibility to continue on the extension study

4.6 STUDY ASSESSMENTS

Please refer to the detailed schedules of assessments provided in Appendix 1-A through Appendix 1-F.

Patients enrolled from Study CFD4870g will have up to 96 study visits (excluding the Day 1 visit). Patients enrolled from Study GX29455 will have up to 54 study visits (excluding the Day 1 visit). Any patient who discontinues the study prematurely (prior to the Month 96 visit for patients from Study CFD4870g and prior to the Month 54 visit for patients from Study GX29455) will have an ET visit completed $\geq$ 30 days after his or her last study drug treatment. Study visits will be scheduled every 30 ($\pm$ 7) days relative to the Day 1 visit.

4.6.1 Definitions of Study Assessments

4.6.1.1 Clinical Evaluations

- **Demographic Data:** date of birth and sex will be collected; the patient's race/ethnicity data will also be entered. At a minimum, year of birth and sex will be retrieved.
- **Vital Signs:** will include measurements of pulse, temperature, respiration rate, and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs should be obtained before injection of lampalizumab.
- **Physical Examination:** should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. 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. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Height and weight will be collected for patients enrolling from CFD4870g study.
- **Medical History (including surgeries, procedures and ocular therapy history):** the patient's data will be retrieved from the CFD4870g and GX29455 databases.

4.6.1.2 Ocular Assessments

- BCVA on ETDRS chart at a starting distance of 4 meters (perform prior to dilating eyes; see Appendix 3)
- Pre-injection IOP measurement for both eyes (perform prior to dilating eyes; the method used for this assessment must remain consistent throughout the study)
- Slit-lamp examination (see definition of ocular inflammation see Section 5.1.3; for inflammation grading scales, see Appendix 2)
- Dilated binocular indirect ophthalmoscopy
- Finger-counting test, or hand motion, or light perception tests performed by the investigator within 15 minutes post-injection for the study eye only
- IOP measurement at 60 (±10) minutes post-injection for the study eye only; if IOP increased ≥10 mmHg from pre-injection, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.2.2). The method of IOP measurement used for a patient must remain consistent throughout the study

  Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post-ranibizumab treatment IOP value on the appropriate eCRF.

4.6.1.3 Ocular Imaging

An independent review of digital color fundus photographs, fluorescein angiograms, FAF, NI, and SD-OCT images (including exploratory anatomic biomarker studies) will be performed at a central reading center to provide an objective analysis of these assessments. The central reading center evaluation will be performed by graders and retinal specialists experienced in the conduct of AMD clinical trials.

The central reading center will provide sites with a study manual and training material for specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software (where applicable) will be certified/validated by the reading center as specified in the study manual. "Grandfathering" certifications for personnel and equipment from CFD4870g or GX29455 will be allowed as per reading center guidelines. All ocular images will be obtained by trained site personnel at the study sites and forwarded to the central reading center for independent analysis and/or storage.

Ocular images obtained include the following:

- Stereoscopic, digital color fundus photographs of both eyes (see Appendix 4)
- Fluorescein angiograms of both eyes (perform after laboratory samples are obtained; see Appendix 5)
- FAF, SD-OCT, and NI images of both eyes;(see Appendix 6, Appendix 7, and Appendix 8, respectively)

  Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken (see Appendix 1-A through Appendix 1-E), the images should be obtained at the next scheduled visit.

Additional details on obtaining these images are included in the central reading center manual.

4.6.1.4 Laboratory Assessments

At the scheduled visit, specimens should be collected prior to study eye treatment and FA assessments (if applicable). Fasting is not required prior to specimen collection. All specimens will be forwarded to the central laboratory for processing. The central laboratory will either perform the analysis or forward to Genentech for analysis. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the Laboratory Manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1-A through Appendix 1-E for the collection timepoints of samples.

The following assessments will be performed:

- Hematology: hemoglobin, hematocrit, quantitative platelet count, RBC, WBC, and differentials including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute and percent)
- Coagulation: aPTT and PT
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, AST, ALT, 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 than glucose and ketones, are abnormal)
- Serum sample to measure anti-lampalizumab antibodies (ATA) and drug concentration at ATA sample timepoint collections

Optional Clinical Genotyping Samples:

- An optional, single, whole-blood sample will be collected for genotyping analysis at any time during the study from German study site patients; of note, blood samples for genotyping analysis from the U.S. study site patients were collected previously in Study CFD4870g and Study GX29455. The genotyping samples will be used to evaluate relationships between genetic polymorphisms associated with AMD, baseline disease characteristics, and response to administration of lampalizumab.

4.6.2 Screening and Pretreatment Assessments

After a patient has signed the extension study informed consent form and has completed all Month 18 visit assessments for Study CFD4870g or completed all Week 24 assessments for Study GX29455, he or she will be offered the opportunity to enroll in this extension study on the same day (Day 1) if they satisfy all eligibility criteria. The patient's study CFD4870g Month 18 visit assessments or Study GX29455 Week 24 visit assessment will be utilized for a patient's eligibility to enter this study. If applicable as per investigator discretion, the patient will confirm administration of antimicrobials prior to the Day 1 visit.

Please see the Study Flowchart provided in Appendix 1-A (for patients from Study CFD4870g) and Appendix 1-D (for patients from Study GX29455) for the schedule of screening and pretreatment assessments on the Day 1 visit.

4.6.3 Assessments during Treatment

After a patient has signed the informed consent form, the site will contact the IxRS to obtain a patient enrollment ID number assignment and to report the study drug distribution on the Day 1 visit (at conclusion of Month 18 visit in study CFD4870g or Week 24 visit in study GX29455). Patient self-administered antimicrobials in the pre- and post-injection period may be used at the investigator's discretion.

At all study visits the procedures and assessments should be performed prior to study drug administration unless otherwise indicated. All study visit assessments must be performed on the same day. *Note: see Section 3.1.3 for exception regarding delayed study treatment administration.*

The study scheduled visits should occur every 30 (±7) days relative to the Day 1 visit date. Dosing should not occur earlier than 23 days after the previous dosing.

Please see the Study Flowcharts provided in Appendix 1-A through Appendix 1-E for the schedule of treatment period assessments.

4.6.4 Study Completion/Early Termination Visit

For patients who withdraw early from the study (prior to the Month *96* visit for patients enrolled from CFD4870g and prior to the Month *54* visit for patients enrolled from GX29455) for any reason, these patients should complete the ET visit assessments $\geq$ 30 days following the last study treatment. Patients who discontinue from the study will not be allowed to re-enter the study. Please see the Study Flowcharts provided in Appendix 1-A through Appendix 1-E for the assessments to be performed at the study ET visit.

4.6.5 Study Treatment Discontinuation/Early Termination Visit

Patients who prematurely discontinue the study treatment (prior to the Month *96* visit for patients enrolled from CFD4870g or prior to the Month *54* visit for patients enrolled from GX29455) will be also discontinued from the study, and they will be asked to return for an ET evaluation ≥30 days following their last study drug treatment for monitoring of adverse events and the study ET visit assessments.

Please see the Study Flowcharts provided in Appendix 1-A through Appendix 1-E for the assessments to be performed at the ET visit.

4.6.6 Unscheduled Safety Assessment Visit

If a patient experiences eye pain, a decrease in vision, unusual redness, or any other new ocular symptoms in the study eye, the investigator will determine whether the patient should return to the clinic for a safety assessment as soon as possible. If a visit is required, the assessments listed in Appendix 1-F will be performed.

4.7 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
- Patient non-compliance, defined as e.g., missed doses, visits

Every effort should be made to obtain information on patients who withdraw 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.

4.8 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 reason for the treatment discontinuation should be recorded on the appropriate eCRF.

Treatment discontinued patients will be also discontinued from the study and will not be replaced or allowed to re-enter the study.

4.9 STUDY 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 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 International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

4.10 POST-TRIAL ACCESS TO LAMPALIZUMAB

The Sponsor will offer post-study access to the study drug lampalizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to IMPs 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 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 would not 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 IMPs is available at the following Web site:

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

4.11 ASSAY METHODS

Drug concentration will be determined in serum using a validated ELISA method. ATA will be detected in serum using a validated ELISA.

4.12 STATISTICAL METHODS

4.12.1 Safety Analysis

Safety will be assessed by adverse events, clinical laboratory evaluations, and immunogenicity as measured by ATA. Safety analyses will include all patients who enrolled into the extension study and received at least one lampalizumab injection *in* the extension study. These patients will be grouped by the treatment received *(lampalizumab or sham)* when they were enrolled in the CFD4870 or GX29455 for safety analyses.

The primary safety analysis is planned to occur at the time when patients enrolled from Study CFD4870g have reached approximately *96* months follow-up and when patients enrolled from Study GX29455 have reached approximately *54* months follow-up. The timing of the primary analysis may be adjusted according to the start of the open-label extension for Studies GX29176 and GX29185, to which patients from the extension study may have the opportunity to enroll. Earlier safety analyses of this study may be performed on an ad hoc basis.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to an adverse event severity grading scale (see Table 3).

4.12.2 Pharmacokinetic and Pharmacodynamic Analyses

Scheduled pharmacokinetic and pharmacodynamic assessments are not planned in the extension study. However, to assist in safety evaluations, serum lampalizumab concentration measurements *may* be performed.

4.12.3 Exploratory Analyses

Mean GA lesion area growth and mean BCVA change from baseline over time will be summarized by treatment group. These patients will be grouped by *parent study and* the treatment received *(lampalizumab or sham)* when they were enrolled in Study CFD4870g or Study GX29455.

4.12.4 Handling of Missing Data

All efforts will be made to minimize missing data; no imputation will be performed for the safety analysis.

4.12.5 Determination of Sample Size

This study is open to all patients who complete Study CFD4870g or Study GX29455 and who meet eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation.

4.12.6 Interim Analysis

The primary analysis time will occur as specified in Section 4.12.1. Earlier analyses may be performed on an ad hoc basis.

4.13 DATA QUALITY ASSURANCE

The data will be collected via Electronic Data Capture (EDC) using eCRFs. The site 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 CRO will be responsible for the data management of this trial, including quality checking of the data.

Genentech will perform oversight of the data management of this trial. Genentech 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 Genentech, using Genentech'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 at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of adverse events require immediate reporting to the Sponsor, as outlined in Section 5.2.

5.1.1 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)

5.1.2 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 5.2.2 for reporting instructions).

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

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 5.2.2 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 ALT or 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 indicating an infection in a patient exposed to a medicinal product. This term only applies 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 serious adverse event/ adverse event" 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 $\geq$30 letters in 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 Section 5.1.3 for definition and Appendix 2 for intraocular inflammation grading scales)

  – In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight

All above listed sight-threatening adverse events should be reported as serious events, listing the underlying cause (if known) of the event as primary event term.

5.2 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 study. 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
- *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.

5.2.1 Emergency Medical Contacts

Medical Monitor Contact Information for sites in the United States and Germany:

United States

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted] (office)

Germany

Medical Monitor: [redacted], *M.D.*

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

or

Medical Monitor: [redacted], *MBChB, MFPM, MRCOphth*

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Sponsor Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.2.2 Reporting Requirements for All Serious Adverse Events and Adverse Events of Special Interest

5.2.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to the Day 1 visit in the extension study, all adverse events will be reported to either Study CFD4870g or Study GX29455 databases. If the events are ongoing at the Day 1 visit in the extension study they will also be transcribed to this study database.

5.2.2.2 Events that Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the last study visit. 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 Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, *the* paper *Clinical Trial* Serious Adverse Event*/Adverse Event of Special Interest* Reporting Form *provided to investigators* should be completed and *submitted* to the Sponsor 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 5.5.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.1 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 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 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.

At the time of enrollment, any adverse events or serious adverse events that are ongoing from Study CFD4870g or study GX29455 should be recorded on the GX29198 eCRF.

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

5.3.2 Eliciting Adverse Events

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 will be used for assessing adverse event severity. *Table 3* provides guidance 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

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

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 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, *with special consideration of* 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 or dose reduction 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).*

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

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by dilation and are not RBCs or WBCs 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 intensity should also be recorded on the Adverse Event 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 5.2.2 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 findings. 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 $\times$ 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 elevated ALT or AST (>3×ULN) in combination with either elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST>3×ULN in combination with total bilirubin>2×ULN
- Treatment-emergent ALT or AST>3×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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an serious adverse event or as a non-serious adverse event of special interest (see Section 5.2.2).

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 5.2.2).

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. 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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.5.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for Study CFD4870g or Study GX29455. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF of these 2 studies databases. In a case where the site identifies a preexisting condition after Study CFD4870g or Study GX29455 closes the condition should be entered to the extension study medical history eCRF page.

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., worsening, exacerbation, or 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 normal 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 study eye 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”). The expedited reporting requirements for sight-threatening events (listed in Section 5.2) apply to these unexpected changes in the study eye GA.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events.

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 a serious adverse event in Section 5.1.2), except as outlined below.

An event that leads to hospitalization under the following circumstance should not be reported as an adverse event or a serious adverse event:

- *Hospitalization for a preexisting condition, provided that all of 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 meets the severity criteria, the event* should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

No safety data related to overdosing of lampalizumab are available.

5.3.6 Reporting Requirements for Pregnancies

5.3.6.1 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 until the last study visit. *A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor 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 with use of the fax number or e-mail address provided to investigators*. 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 addition, the investigator will submit a *paper* Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.3.6.2 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 until the last study visit. *A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor 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 with use of the fax number or e-mail address provided to investigators.* 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. *After* the authorization has been signed, the investigator will *submit a paper Clinical Trial* Pregnancy *Reporting Form when updated* information on the course and outcome of the pregnancy *becomes available.* . 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.

5.3.6.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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 5.2.2).

5.3.6.4 Congenital Anomalies/Birth Defects

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 5.2.2).

5.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.4.1 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.

5.4.2 Sponsor Follow-Up

For serious adverse events, 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.

5.5 ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

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 the last study visit), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the *paper Clinical Trial* Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number *or* email address *provided to investigators.*

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

The Sponsor will promptly evaluate all serious adverse events and 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. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator
- The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations
- Current curricula vitae and evidence of licensure of the Principal Investigator and all sub-investigators
- Complete financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572
- Federal-wide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form
- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator

- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- For global studies, list documents as appropriate for additional countries

6.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and sub-investigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s)[if applicable]
- Updated financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Home Nursing 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. 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.

For sites in the United States, 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.

6.4 COMMUNICATION WITH THE 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 for review and approval 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 regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 6.13).

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 regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's study file.

6.5 STUDY MONITORING REQUIREMENTS

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.

6.6 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.

6.7 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.

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 6.12.

To facilitate source data verification, the investigator(s) and institution(s) 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.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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.

6.9 STUDY MEDICATION ACCOUNTABILITY

All IMPs required for completion of this study (lampalizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP by returning the appropriate documentation to confirm 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 study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

6.10. Genentech-Provided Ranibizumab Accountability

Ranibizumab for U.S. sites will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all ranibizumab vials received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Ranibizumab Inventory Log.

Ranibizumab is supplied in single-use vials. Partially used vials of ranibizumab will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy ranibizumab, the method of destruction must be documented.

Genentech must evaluate and approve the study site's ranibizumab destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.11 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or 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 regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.12 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, 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.

6.13 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).

7. REFERENCES

Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS Report 8. Arch Ophthalmol 2001;119:1417–36.

Age-Related Eye Disease Study Research Group. Potential public health impact of Age-Related Eye Disease Study results: AREDS Report 11. Arch Ophthalmol 2003;121:1621–24.

de Jong PTVM. Age-related macular degeneration. New Engl J Med 2006;355:1474–85.

Friedman DS, O'Colmain BJ, Munoz B, et al. Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–72.

Rohrer B, Guo Y, Kunchithapautham K, et al. Eliminating complement factor D reduces photoreceptor susceptibility to light-induced damage. Invest Ophthalmol Vis Sci 2007;48:5282–89.

Scholl HPN, Issa PC, Walier M, et al. Systemic complement activation in age-related macular degeneration. PLoS ONE 2008;3:e2593.

Sunness JS, Applegate CA, Bressler NM, et al. Designing clinical trials for age-related geographic atrophy of the macula: enrollment data from the geographic atrophy natural history study. Retina 2007;7:204–10.

Yates JRW, Sepp T, Matharu BK, et al. Complement C3 variant and the risk of age-related macular degeneration New Engl J Med 2007;357:553–61.

Appendix 1
Schedule of Assessments

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination

	CFD4870g Month 17	Day		Visit Month										
		Day 1[a]		1–5	6	7–11	12	13–17	18	19–23	24	25–29	30	ET[b]
Assessment windows (days) between monthly visits		Extracted from CFD4870g Month 18		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[b]
Written informed consent signed	x													
Review of inclusion and exclusion criteria			x											
Demographic information[c]			x											
Site to contact IxRS (as applicable)[d]			x	x	x	x	x	x	x	x	x	x	x	x
Physical examination		x												x
Vital signs[e]		x												x
Central laboratory samples (hematology, coagulation, serum chemistry, urinalysis)[f]		x												x
Urine sample for pregnancy testing (if applicable)[f]			x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination (cont.)

	CFD4870g Month 17	Day	Visit Month										
		Day 1[a]	1–5	6	7–11	12	13–17	18	19–23	24	25–29	30	ET[b]
Assessment windows (days) between monthly visits		Extracted from CFD4870g Month 18	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[b]
Serum sample for anti-lampalizumab antibody and corresponding drug concentration[f]		x		x		x				*x*			x
Optional single, whole-blood sample for genotyping[f]			Collect 1 sample at any timepoint from study patients at German sites										
Patient-reported weight and height			Collect patient-reported weight and height once during the study										
BCVA testing (starting at 4 pm)[g]		x	x	x	x	x	x	x	x	x	x	x	x
IOP[h]		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
Dilated binocular indirect ophthalmoscopy		x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination (cont.)

	CFD4870g Month 17	Day		Visit Month										
		Day 1[a]		1–5	6	7–11	12	13–17	18	19–23	24	25–29	30	ET[b]
Assessment windows (days) between monthly visits		Extracted from CFD4870g Month 18		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[b]
SD-OCT[i]			x	Perform every 3 months starting at Month 3 visit (6, 9, 12, 15, 18, 21, 24, 27, 30)										x
FAF and NI[i]		x			x				x				x	x
Fundus photography[i]		x			x				x				x	x
Fluorescein angiography[i]		x			x				x				x	x
Patient-administered pre- and post-study drug injection antimicrobials (if applicable)[j]			x	x	x	x	x	x	x	x	x	x	x	
Administration of study drug injections			x	x	x	x	x	x	x	x	x	x	x	
Post-injection finger counting and IOP measurement[k]			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

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination (cont.)

	CFD4870g Month 17	Day		Visit Month										
		Day 1[a]		1–5	6	7–11	12	13–17	18	19–23	24	25–29	30	ET[b]
Assessment windows (days) between monthly visits		Extracted from CFD4870g Month 18		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	[b]
Adverse events[m]			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
Follow-up call (if applicable)[o]			x	x	x	x	x	x	x	x	x	x	x	

BCVA =best corrected visual acuity; ET =early termination; FAF =fundus autofluorescence; IOP =intraocular pressure; IxRS =interactive response system; NA =not applicable; NI =near infrared; SD OCT =spectral domain optical coherence tomography.

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

[a] Day 1 visit will occur at the study CFD4870g Month 18 visit conclusion. The Study CFD4870g Month 18 visit assessments will be extracted from that study's database and will be used for the extension study Day 1 visit. All study patients will receive their first study drug injection in the extension study at the Day 1 visit (unless dose holding is medically justified by the investigator). Study drug treatment related data will be entered into the extension study database. Written informed consent will be obtained prior to enrollment and the initiation of any study procedures and treatment.

[b] For patients who withdraw early from the study, ET assessments will be performed ≥ 30 days after the last study treatment injection.

[c] Demographics data will be re-entered into the extension study database on a Demographics eCRF.

[d] At each visit starting at Day 1 contact IxRS to obtain study drug kit assignment (if applicable). At the ET 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."

[e] Vital signs consist of blood pressure, respiration, pulse, and temperature.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination (cont.)

[f] Obtain prior to study drug treatments and prior to fluorescein angiography (if applicable). ATA samples may be also used to measure lampalizumab concentration to assist in safety evaluation. For patients at German sites, the optional, single, whole-blood sample for genotyping analysis may be collected at any study visit. For women of childbearing potential perform urine pregnancy test prior to every study treatment. If positive, collect the serum sample for pregnancy test to be performed by the central lab and do not administer the study treatment. For detailed description of the laboratory assessments to be performed, see separate Laboratory Manual.

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

[h] At Day 1, pre study drug administration IOP (performed prior to dilating eyes) data will be extracted from CFD4870g study (as applicable) while post study drug administration IOP will be obtained after the study drug treatment in the extension study and entered into the study database.

[i] SD-OCT, FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center. Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit.

[j] Patient self-administered antimicrobials may be used at the investigator's discretion. If applicable inform the patient to self-administer them prior to the Month 18 (CFD 4870g) visit.

[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 drug treatment injection. At study treatment injection visits, IOP measurement will be obtained bilaterally prior to study treatment and then at 60 (±10) minutes post-injection in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If at 60 (±10) minutes the post-injection IOP remains elevated by ≥10 mmHg from the pre-injection measurement, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.3.1). Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post- ranibizumab treatment IOP value on the eCRF irrespective of the study treatment administration later.

[l] At enrollment, any concomitant medications that are ongoing from Study CFD4870g should be entered into the eCRF for the extension study. Record any concomitant medications currently used by the patient and through the conclusion of the patient's study participation or ET visit (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-injection and post-injection medications, such as proparacaine, investigator applied pre- and post-injection antimicrobials (if applicable)).

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-A: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Day 1, Months 1–30, and Early Termination (cont.)

[m] Adverse events will be recorded starting on Day 1 after the study treatment injection through the last study visit. At the time of study enrollment, if the patient has any ongoing adverse events from Study CFD4870g, these events will also be entered into the extension study eCRF. 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.

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

[o] Subsequent to the initial study treatment visit, patients treated with study drug will receive a telephone call 7 (±2) days after each treatment visit to solicit adverse events.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-B: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Months 31–66 and Early Termination

	Visit Month[a]											
	31–35	36	37–41	42	43–47	48	49–53	54	55–59	60	61–65	66	ET[b]
Assessment windows (days) between monthly visits	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	≥30
Site to contact IxRS (as applicable)[b]	x	x	x	x	x	X	x	x	x	x	x	x	x
Physical examination													x
Vital signs[c]													x
Central laboratory samples (hematology, coagulation, serum chemistry, urinalysis)[d]													x
Urine pregnancy test (if applicable)[d]	x	x	x	x	x	x	x	x	x	x	x	*x*	x
Serum sample for anti-lampalizumab antibody and corresponding drug concentration[d]		x		x				x				x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-B: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Months 31–66 and Early Termination (cont.)

	Visit Month[a]											
	31–35	36	37–41	42	43–47	48	49–53	54	55–59	60	61–65	66	ET[b]
Assessment windows (days) between monthly visits	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	≥30
Optional single whole-blood sample for genotyping[d]	Collect 1 sample at any timepoint from study patients at German site												
Patient-reported weight and height	Collect patient-reported weight and height once during the study												
BCVA testing (starting at 4 pm)[e]	x	x	x	x	x	x	x	x	x	x	x	x	x
IOP[f]	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
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x	x
SD-OCT[g]	Perform at Months 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63 and 66												
FAF and NI[g]				x				x				x	x
Fundus photography[g]				x				x				x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-B: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Months 31–66 and Early Termination (cont.)

	Visit Month[a]											
	31–35	36	37–41	42	43–47	48	49–53	54	55–59	60	61–65	66	ET[b]
Assessment windows (days) between monthly visits	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	≥30
Fluorescein angiography[g]				x				x				x	x
Patient-administered pre- and post-study drug injection antimicrobials (if applicable)[h]	x	x	x	x	x	x	x	x	x	x	x	*x*	
Administration of study drug injections	x	x	x	x	x	x	x	x	x	x	x	*x*	
Post-injection finger counting and IOP measurement[i]	x	x	x	x	x	x	x	x	x	x	x	*x*	
Concomitant medications[j]	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events[k]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures[l]	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-B: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Months 31–66 and Early Termination (cont.)

	Visit Month[a]											
	31–35	36	37–41	42	43–47	48	49–53	54	55–59	60	61–65	66	ET[b]
Assessment windows (days) between monthly visits	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	≥30
Follow-up call (if applicable)[m]	x	x	x	x	x	x	x	x	x	x	x	x	

BCVA =best corrected visual acuity; ET =early termination; FAF =fundus autofluorescence; IOP =intraocular pressure; IxRS =interactive response system; NA =not applicable; NI =near infrared; SD OCT =spectral domain optical coherence tomography.

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

[a] At each visit starting at Day 1, contact IxRS to obtain study drug kit assignment (if applicable). At the ET 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."

[b] For patients who withdraw early from the study, ET assessments will be performed ≥ 30 days after the last study treatment injection.

[c] Vital signs consist of blood pressure, respiration, pulse, and temperature.

[d] Obtain prior to study drug treatments and prior to fluorescein angiography (if applicable). ATA samples may be also used to measure lampalizumab concentration to assist in safety evaluation. For patients at German sites, the optional, single, whole-blood sample for genotyping analysis may be collected at any study visit. For women of childbearing potential perform urine pregnancy test prior to every study treatment. If positive, collect the serum sample for pregnancy test to be performed by the central lab and do not administer the study treatment. For detailed description of the laboratory assessments to be performed, see separate Laboratory Manual.

[e] The VA examiner will be masked to patients' treated (study) eye and will perform only the VA (including refraction). The VA examiner is not allowed to perform any other tasks involving direct patient care.

[f] At Day 1, pre study drug administration IOP (performed prior to dilating eyes) data will be extracted from CFD4870g study (as applicable) while post study drug administration IOP will be entered into the extension study database.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-B: Schedule of Assessments for Patients Enrolled from Study CFD4870g: Months 31–66 and Early Termination (cont.)

[g] SD-OCT, FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center. Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit.

[h] Patient self-administered antimicrobials may be used at the investigator's discretion. If applicable inform the patient to self-administer them prior to the Month 18 (CFD 4870g) visit.

[i] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes post-study drug treatment injection. At study treatment injection visits, IOP measurement will be obtained bilaterally prior to study treatment and then at 60 (±10) minutes post-injection in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If at 60 (±10) minutes the post-injection IOP remains elevated by ≥10 mmHg from the pre-injection measurement, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.2.2). Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post- ranibizumab treatment IOP value on the eCRF irrespective of the study treatment administration later.

[j] At enrollment, any concomitant medications that are ongoing from Study CFD4870g should be entered into the eCRF for the extension study. Record any concomitant medications currently used by the patient and through the conclusion of the patient's study participation or ET visit (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-injection and post-injection medications, such as proparacaine, investigator applied pre- and post-injection antimicrobials (if applicable)).

[k] Adverse events will be recorded starting on Day 1 after the study treatment injection through the last study visit. At the time of study enrollment, if the patient has any ongoing adverse events from Study CFD4870g, these events will also be entered into the extension study eCRF. 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.

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

[m] Subsequent to the initial treatment visit, patients treated with study drug will receive a telephone call 7 (±2) days after each treatment visit to solicit adverse events.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-C: Schedule of Assessments for *Patients Enrolled from Study CFD4870g*: *Months 67–96 and Early Termination*

	Visit Month[a]										*ET*[,b]
	67–71	*72*	*73–77*	*78*	*79–83*	*84*	*85–89*	*90*	*91–95*	*96*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
Site to contact IxRS (as applicable)[b]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Physical examination											*x*
Vital signs[c]											*x*
Central laboratory samples (hematology, coagulation, serum chemistry, urinalysis)[d]											*x*
Urine pregnancy test (if applicable)[d]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Serum sample for anti-lampalizumab antibody and corresponding drug concentration[d]										*x*	*x*
Optional single whole-blood sample for genotyping[d]	*Collect 1 sample at any timepoint from study patients at German site*										
Patient-reported weight and height	*Collect patient-reported weight and height once during the study*										
BCVA testing (starting at 4 pm)[e]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-C: Schedule of Assessments for *Patients Enrolled from Study CFD4870g: Months 67–96 and Early Termination (cont.)*

	Visit Month[a]										*ET*[,b]
	67–71	*72*	*73–77*	*78*	*79–83*	*84*	*85–89*	*90*	*91–95*	*96*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
IOP[f]	*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*
Dilated binocular indirect ophthalmoscopy	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SD-OCT[g]	*Perform at Months 69, 72, 75, 78, 81, 84, 87, 90, 93 and 96*										*x*
FAF and NI[g]				*x*				*x*		*x*	*x*
Fundus photography[g]				*x*				*x*		*x*	*x*
Fluorescein angiography[g]				*x*				*x*		*x*	*x*
Patient-administered pre- and post-study drug injection antimicrobials (if applicable)[h]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Administration of study drug injections	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Post-injection finger counting and IOP measurement[i]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Concomitant medications[j]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-C: Schedule of Assessments for *Patients Enrolled from Study CFD4870g: Months 67–96 and Early Termination (cont.)*

	Visit Month[a]										*ET*[,b]
	67–71	*72*	*73–77*	*78*	*79–83*	*84*	*85–89*	*90*	*91–95*	*96*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
Adverse events[k]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Concurrent ocular procedures[l]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Follow-up call (if applicable)[m]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		

BCVA =best corrected visual acuity; ET =early termination; FAF =fundus autofluorescence; IOP =intraocular pressure; IxRS =interactive response system; NA =not applicable; NI =near infrared; SD OCT =spectral domain optical coherence tomography.

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

[a] *At each visit starting at Day 1, contact IxRS to obtain study drug kit assignment (if applicable). At the ET 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."*

[b] *For patients who withdraw early from the study, ET assessments will be performed ≥ 30 days after the last study treatment injection.*

[c] *Vital signs consist of blood pressure, respiration, pulse, and temperature.*

[d] *Obtain prior to study drug treatments and prior to fluorescein angiography (if applicable). ATA samples may be also used to measure lampalizumab concentration to assist in safety evaluation. For patients at German sites, the optional, single, whole-blood sample for genotyping analysis may be collected at any study visit. For women of childbearing potential perform urine pregnancy test prior to every study treatment. If positive, collect the serum sample for pregnancy test to be performed by the central lab and do not administer the study treatment. For detailed description of the laboratory assessments to be performed, see separate Laboratory Manual.*

[e] *The VA examiner will be masked to patients' treated (study) eye and will perform only the VA (including refraction). The VA examiner is not allowed to perform any other tasks involving direct patient care.*

[f] *At Day 1, pre study drug administration IOP (performed prior to dilating eyes) data will be extracted from Study CFD4870g (as applicable) while post study drug administration IOP will be entered into the extension study database.*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-C: Schedule of Assessments for *Patients Enrolled from Study CFD4870g: Months 67–96 and Early Termination (cont.)*

[g] *SD-OCT, FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center. Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit.*

[h] *Patient self-administered antimicrobials may be used at the investigator's discretion. If applicable inform the patient to self-administer them prior to the Month 18 (CFD4870g) visit.*

[i] *Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes post-study drug treatment injection. At study treatment injection visits, IOP measurement will be obtained bilaterally prior to study treatment and then at 60 (±10) minutes post-injection in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If at 60 (±10) minutes the post-injection IOP remains elevated by ≥10 mmHg from the pre-injection measurement, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.2.2). Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post- ranibizumab treatment IOP value on the eCRF irrespective of the study treatment administration later.*

[j] *At enrollment, any concomitant medications that are ongoing from Study CFD4870g should be entered into the eCRF for the extension study. Record any concomitant medications currently used by the patient and through the conclusion of the patient's study participation or ET visit (i.e., any prescription medications or over-the-counter preparations **other than** protocol-specified procedural medications, and pre-injection and post-injection medications, such as proparacaine, investigator applied pre- and post-injection antimicrobials (if applicable)).*

[k] *Adverse events will be recorded starting on Day 1 after the study treatment injection through the last study visit. At the time of study enrollment, if the patient has any ongoing adverse events from Study CFD4870g, these events will also be entered into the extension study eCRF. 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.*

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

[m] *Subsequent to the initial treatment visit, patients treated with study drug will receive a telephone call 7 (±2) days after each treatment visit to solicit adverse events.*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-D: *Schedule of Assessments for Patients Enrolled from Study GX29455: Day 1, Months 1–24 and Early Termination*

		Day		Visit Month								ET [b]
		Day 1 [a]		1–5	6	7–11	12	13–17	18	19–23	24	
Assessment window (days) between monthly visits	GX29455 Week 23 or Week 24 Visit	Extracted from GX29455 Week 24 Visit		±7	±7	±7	±7	±7	±7	±7	±7	≥30
Written informed consent signed	x											
Review of inclusion and exclusion criteria			x									
Demographic information [c]			x									
Site to contact IxRS (as applicable) [d]			x	x	x	x	x	x	x	x	x	x
Physical examination		x										x
Vital signs [e]		x										x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) [f]		x										x
Urine sample for pregnancy testing (if applicable) [f]			x	x	x	x	x	x	x	x	x	x
Serum sample for anti-lampalizumab antibody and corresponding drug concentration [f]		x			x		x				x	x
BCVA testing (starting at 4 m) [g]		x		x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-D: *Schedule of Assessments for Patients Enrolled from Study GX29455: Day 1, Months 1–24 and Early Termination (cont.)*

		Day		Visit Month								ET [b]
		Day 1 [a]		1–5	6	7–11	12	13–17	18	19–23	24	
Assessment window (days) between monthly visits	GX29455 Week 23 or Week 24 Visit	Extracted from GX29455 Week 24 Visit		±7	±7	±7	±7	±7	±7	±7	±7	≥30
IOP [h]		x		x	x	x	x	x	x	x	x	x
Slit-lamp examination		x		x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy		x		x	x	x	x	x	x	x	x	x
SD-OCT [i]			x	Perform at visits Month 3, 6, 9, 12, 15, 18, 21 and 24								x
FAF and NI [i]		x			x				x		x	x
Fundus photography [i]		x			x				x		x	x
Fluorescein angiography [i]		x			x				x		x	x
Patient self-administered pre- and post-study drug injection antimicrobials (if applicable) [j]			x	x	x	x	x	x	x	x	x	
Administration of study drug injections			x	x	x	x	x	x	x	x	x	
Post-injection finger counting and IOP measurement [k]			x	x	x	x	x	x	x	x	x	
Concomitant medications [l]			x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-D: *Schedule of Assessments for Patients Enrolled from Study GX29455: Day 1, Months 1–24 and Early Termination (cont.)*

		Day		Visit Month								ET [b]
		Day 1 [a]		1–5	6	7–11	12	13–17	18	19–23	24	
Assessment window (days) between monthly visits	GX29455 Week 23 or Week 24 Visit	Extracted from GX29455 Week 24 Visit		±7	±7	±7	±7	±7	±7	±7	±7	≥30
Adverse events [m]			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	

BCVA =best corrected visual acuity; ET =early termination; FAF =fundus autofluorescence; IOP =intraocular pressure; IxRS =interactive response system; NA =not applicable; NI =near infrared; SD-OCT =spectral domain optical coherence tomography.

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

[a] Day 1 visit will occur at the study GX29455 Week 24 visit conclusion. The Study GX29455 Week 24 visit assessments will be extracted from that study's database and will be used for Study GX28198 Day 1 visit. All study patients will receive their first study drug injection in Study GX28198 at the Day 1 visit (unless dose holding is medically justified by the investigator). Study drug treatment related data will be entered into the Study GX28198 database. Written informed consent will be obtained prior to enrollment and the initiation of any study procedures and treatment.

[b] For patients who withdraw early from the study, ET assessments will be performed ≥ 30 days after the last study treatment injection.

[c] Demographics data will be re-entered into the Study GX28198 database on a Demographics eCRF.

[d] At each visit starting at Day 1 contact IxRS to obtain study drug kit assignment (if applicable). At the ET 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."

[e] Vital signs consist of blood pressure, respiration, pulse, and temperature.

[f] Obtain prior to study drug treatments and prior to fluorescein angiography (if applicable). ATA samples may be also used to measure lampalizumab concentration to assist in safety evaluation. For women of childbearing potential perform urine pregnancy test prior to every study treatment. If positive, collect the serum sample for pregnancy test to be performed by the central lab and do not administer the study treatment. For detailed description of the laboratory assessments to be performed, see separate Laboratory Manual.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-D: *Schedule of Assessments for Patients Enrolled from Study GX29455: Day 1, Months 1–24 and Early Termination (cont.)*

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

[h] At Day 1, pre study drug administration IOP (performed prior to dilating eyes) data will be extracted from GX29455 study (as applicable) while post study drug administration IOP will be obtained after the study drug treatment in study GX28198 and entered into the Study GX28198 database.

[i] SD-OCT, FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center. Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit.

[j] Patient self-administered antimicrobials may be used at the investigator's discretion. If applicable inform the patient to self-administer them prior to the Week 24 (GX29455) visit.

[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 drug treatment injection. At study treatment injection visits, IOP measurement will be obtained bilaterally prior to study treatment and then at 60 (±10) minutes post-injection in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If at 60 (±10) minutes the post-injection IOP remains elevated by ≥10 mmHg from the pre-injection measurement, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.2.2). Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post-ranibizumab treatment IOP value on the eCRF irrespective of the study treatment administration later.

[l] At enrollment, any concomitant medications that are ongoing from Study GX29455 should be entered into the eCRF for Study GX28198. Record any concomitant medications currently used by the patient and through the conclusion of the patient's study participation or ET visit (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications, and pre-injection and post-injection medications, such as proparacaine, investigator applied pre- and post-injection antimicrobials if applicable).

[m] Adverse events will be recorded starting on Day 1 after the study treatment injection through the last study visit. At the time of study enrollment, if the patient has any ongoing adverse events from Study GX29455, these events will also be entered into the Study GX28198 eCRF. 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.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-D: *Schedule of Assessments for Patients Enrolled from Study GX29455: Day 1, Months 1–24 and Early Termination (cont.)*

[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 will receive a telephone call 7 (±2) days after each treatment visit to solicit adverse events.

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-*E*: ***Schedule of Assessments for Patients Enrolled from Study GX29455: Months 25–54 and Early Termination***

	Visit Month[a]										*ET*[,b]
	25–29	*30*	*31–35*	*36*	*37–41*	*42*	*43–47*	*48*	*49–53*	*54*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
Site to contact IxRS (as applicable)[b]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Physical examination											*x*
Vital signs[c]											*x*
Central laboratory samples (hematology, coagulation, serum chemistry, urinalysis)[d]											*x*
Urine pregnancy test (if applicable)[d]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Serum sample for anti-lampalizumab antibody and corresponding drug concentration[d]										*x*	*x*
BCVA testing (starting at 4 pm)[e]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
IOP[f]	*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*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-*E*: ***Schedule of Assessments for Patients Enrolled from Study GX29455: Months 25–54 and Early Termination (cont.)***

	Visit Month[a]										*ET*[,b]
	25–29	*30*	*31–35*	*36*	*37–41*	*42*	*43–47*	*48*	*49–53*	*54*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
Dilated binocular indirect ophthalmoscopy	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
SD-OCT[g]	*Perform at Months 27, 30, 33, 36, 39, 42, 45, 48, 51 and 54*										*x*
FAF and NI[g]				*x*				*x*		*x*	*x*
Fundus photography[g]				*x*				*x*		*x*	*x*
Fluorescein angiography[g]				*x*				*x*		*x*	*x*
Patient-administered pre- and post-study drug injection antimicrobials (if applicable)[h]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Administration of study drug injections	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Post-injection finger counting and IOP measurement[i]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		
Concomitant medications[j]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse events[k]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-*E*: ***Schedule of Assessments for Patients Enrolled from Study GX29455: Months 25–54 and Early Termination (cont.)***

	Visit Month[a]										*ET*[,b]
	25–29	*30*	*31–35*	*36*	*37–41*	*42*	*43–47*	*48*	*49–53*	*54*	
Assessment windows (days) between monthly visits	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*±7*	*≥30*
Concurrent ocular procedures[l]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Follow-up call (if applicable)[m]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*		

BCVA =best corrected visual acuity; ET =early termination; FAF =fundus autofluorescence; IOP =intraocular pressure; IxRS =interactive response system; NA =not applicable; NI =near infrared; SD OCT =spectral domain optical coherence tomography.

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

[a] *At each visit starting at Day 1, contact IxRS to obtain study drug kit assignment (if applicable). At the ET 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."*

[b] *For patients who withdraw early from the study, ET assessments will be performed ≥ 30 days after the last study treatment injection.*

[c] *Vital signs consist of blood pressure, respiration, pulse, and temperature.*

[d] *Obtain prior to study drug treatments and prior to fluorescein angiography (if applicable). ATA samples may be also used to measure lampalizumab concentration to assist in safety evaluation. For patients at German sites, the optional, single, whole-blood sample for genotyping analysis may be collected at any study visit. For women of childbearing potential perform urine pregnancy test prior to every study treatment. If positive, collect the serum sample for pregnancy test to be performed by the central lab and do not administer the study treatment. For detailed description of the laboratory assessments to be performed, see separate Laboratory Manual.*

[e] *The VA examiner will be masked to patients' treated (study) eye and will perform only the VA (including refraction). The VA examiner is not allowed to perform any other tasks involving direct patient care.*

[f] *At Day 1, pre study drug administration IOP (performed prior to dilating eyes) data will be extracted from GX29455 study (as applicable) while post study drug administration IOP will be entered into the extension study database.*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-*E*: *Schedule of Assessments for Patients Enrolled from Study GX29455: Months 25–54 and Early Termination (cont.)*

[g] *SD-OCT, FAF, and NI images, fluorescein angiograms, and fundus photographs (as applicable) will be forwarded to the central reading center. Note: after enrollment, if a patient misses a study visit during which ocular images were scheduled to be taken, the images should be obtained at the next scheduled visit.*

[h] *Patient self-administered antimicrobials may be used at the investigator's discretion. If applicable inform the patient to self-administer them prior to the Month 18 (GX29455) visit.*

[i] *Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the investigator within 15 minutes post-study drug treatment injection. At study treatment injection visits, IOP measurement will be obtained bilaterally prior to study treatment and then at 60 (±10) minutes post-injection in the study eye only. If there are no safety concerns at 60 (±10) minutes, the patient will be discharged from the clinic. If at 60 (±10) minutes the post-injection IOP remains elevated by ≥10 mmHg from the pre-injection measurement, the patient will remain in the clinic and will be treated according to the investigator's clinical judgment prior to the patient's discharge; if applicable, an Adverse Event eCRF page will be completed (see Section 5.2.2. Note: if the study eye is treated with a ranibizumab injection during the same visit as the study treatment with lampalizumab, the treatment with ranibizumab has to be performed first. Please measure and record the post- ranibizumab treatment IOP value on the eCRF irrespective of the study treatment administration later.*

[j] *At enrollment, any concomitant medications that are ongoing from Study GX29455 should be entered into the eCRF for the extension study. Record any concomitant medications currently used by the patient and through the conclusion of the patient's study participation or ET visit (i.e., any prescription medications or over-the-counter preparations **other than** protocol-specified procedural medications, and pre-injection and post-injection medications, such as proparacaine, investigator applied pre- and post-injection antimicrobials (if applicable)).*

[k] *Adverse events will be recorded starting on Day 1 after the study treatment injection through the last study visit. At the time of study enrollment, if the patient has any ongoing adverse events from Study GX29455g, these events will also be entered into the extension study eCRF. 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.*

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

[m] *Subsequent to the initial treatment visit, patients treated with study drug will receive a telephone call 7 (±2) days after each treatment visit to solicit adverse events.*

Appendix 1
Schedule of Assessments (cont.)

Appendix 1-*F*: Unscheduled Safety Visit Assessments for All Study Patients

Assessments [a]	
Vital signs (blood pressure, respiration rate, temperature, pulse)	x
Physical examination	x
Best corrected visual acuity (4-m 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 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 2
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 2
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells (cont.)

Grading Scale for Vitreous Cells

Cells in Retroilluminated 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

Note: The grading will be performed using a Hruby lens.

Modified from: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis. Fundamentals and clinical practice. 2nd rev. ed. New York: Mosby, 1996, p. 64.

Appendix 3
Best Corrected Visual Acuity Testing

Scope

Best corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites. The VA examiner must be masked to the treated (study) eye. The VA examiner is not allowed to perform any other tasks involving direct patient care which may unmask him/her to patient's study eye. VA will be measured at the intervals specified in the protocol (see Section 4.5 and Appendix 1-A through Appendix 1-F).

Equipment

The following is 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 1, 2, and R)
- Retro-illuminated box
- Trial frame
- Trial 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 4
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.

Analysis 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 material. 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 5
Fluorescein Angiography

Scope

Fluorescein angiography (FA) will be performed at the study sites by trained personnel who are certified by the central reading center. The fluorescein angiograms will be obtained at the intervals specified in the protocol (see Section 4.5 and Appendix 1-A through Appendix 1-E).

Equipment

- Digitally based 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 material. Photographers, systems, and software will be certified prior to obtaining angiograms of patients.

Appendix 6
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 Section 4.5 and Appendix 1-A through Appendix 1-E).

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

Equipment

Equipment utilized during this trial is described in the Central Reading Center Manual. The ability to transfer images to electronically export 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 7
Spectral Domain-Optical Coherence Tomography

Scope

Spectral domain-optical coherence tomography (SD-OCT) will be performed at the study sites by trained personnel who are certified by the central reading center. SD OCT imaging will be performed for each patient at the intervals specified in the protocol (see Section 4.5 and Appendix 1-A through Appendix 1-E).

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

Equipment

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

Procedures and Certification

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

Appendix 8
Near-Infrared Imaging

Note: near infrared images are taken to complement the central reading center evaluation of FAF images.

Scope

Near Infrared (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 Section 4.5 and Appendix 1-A through Appendix 1-E).

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

Equipment

Equipment utilized during this trial is described in the Central Reading Center Manual. The ability to transfer images to electronically export 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 9
Biological Sample Collection and Shipping Instructions

Biological Samples

Patient samples for assessment of anti-lampalizumab antibodies, laboratory assessment samples (hematology, serum chemistry, coagulation, and urinalysis), and the optional, single, whole-blood sample for genotyping analysis (German sites only), will be collected at the timepoints specified in Section 4.5 of the protocol, Appendix 1-A through Appendix 1-E, and in the Laboratory Manual.

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