Official Title: **A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Lampalizumab in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration Who Have Completed a Roche-Sponsored Study**

NCT Number: **NCT02745119**

Document Date: Protocol/Version 2: 11-July-2017

PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION WHO HAVE COMPLETED A ROCHE-SPONSORED STUDY**
PROTOCOL NUMBER:	GX30191/ NCT02745119
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-000423-13
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab (RO5490249)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 07 March 2016 Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	11-Jul-2017 05:00:43

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 3.1.3, Independent Data Monitoring Committee (iDMC), was added to monitor patients' long-term safety. This open-label study data will be reviewed by the iDMC along with data from the ongoing double-masked parent studies (i.e., GX29176 and GX29185). This change was made following a recommendation to have an iDMC from an Ethics Committee and the Sponsor's position that having all lampalizumab studies under a single iDMC would aid safety data interpretation. This information was also added to Section 5.1.
- Information regarding lampalizumab's formulation, packaging, storage, and handling as well as reconstitution and study treatment administration instructions were moved from Section 4.3.1 and Appendices 4–6 to the Pharmacy Manual to assist sites in locating necessary information promptly.
- The Medical Monitor was changed for administrative reasons.
- Additional changes listed below have been incorporated for clarity and consistency, and to aid the transition of patients from the parent studies to this open-label extension study.
  - Section 3.1.1 and Section 4.1 were updated to clarify procedures if images cannot be conducted at the Week 96 visit of the parent study.
  - In Section 4.4.1, prophylactic antibiotics were added to the permitted therapy list.
  - In Section 4.6.2, the study treatment discontinuation criteria were reorganized.
  - Section 5.1 was updated to clarify procedures if study treatment cannot be administered at a scheduled visit.
  - In Section 5.1.1, Table 1 was updated to clarify the dose-interruption, treatment-discontinuation, and study-withdrawal criteria language.
  - In Section 5.4.2, the reporting requirements for serious adverse events and adverse events of special interest during the transition period between the parent study and this extension study were clarified.
  - In Section 8.2, the phrase "patient's legally authorized representative" was removed to clarify that the patient is required to sign the informed consent.
- Revisions were made to update selected sections to match the Sponsor's current model document text.

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

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

GLOBAL CHANGES

The abbreviation "ITV" has been spelled out as "intravitreal" and the Medical Monitor was changed from [redacted], M.D. to [redacted], M.D. throughout the protocol. The original Appendices 4–6 were removed, thus the numbering of appendices thereafter was updated.

PROTOCOL SYNOPSIS

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

SECTION 1.3.3: Phase II Study GX29455

Study GX29455 is *a completed*,~~an ongoing~~ multicenter, randomized, single-masked, sham injection-controlled, Phase II study investigating the exposure response and safety of lampalizumab administered *intravitreally*~~ITV~~ every 2 weeks or every 4 weeks (Q4W) for 24 weeks in patients with GA secondary to AMD. *The results of this study are pending.*

SECTION 1.4: STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The OLE study, Study GX30191, will evaluate the long-term safety and tolerability of 10 mg lampalizumab administered by *intravitreal* injection ~~every 4 weeks~~*Q4W* or every 6 weeks (Q6W) to patients with GA secondary to AMD who have completed study treatment and the Week 96 visit in one of the parent studies (Study GX29176 or GX29815).

SECTION 3.1.1: Overview of Study Design

If a site is not able to collect images during the Week 96 visit of the parent study, then the Day 1 visit study treatment will be interrupted, and the images will be collected as soon as possible and prior to the study treatment administration at the next study treatment visit (e.g., Week 4 or Week 6). The reason for the study treatment interruption at the Day 1 visit will be recorded on the study treatment interruption electronic case report form (eCRF).

All patients enrolled in the extension study will have the first *intravitreal* ~~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 5.1.1 and Table 1)~~.~~ *by the investigator.* The lampalizumab injections should not be repeated earlier than 22 days from previous dosing~~;~~. *M*~~m~~issed doses of study drug will not be made up~~.~~ *unless the missed dose is due to an unexpected issue, such as those listed in the following paragraph.* Patients' self-administered anti-microbials pre- and post-injection may be used at the investigator's discretion.

All subsequent study treatment visits will be scheduled Q4W or Q6W (±5 days), relative to Day 1 visit date, at which patients will have safety evaluations performed prior to receiving the study drug injection (see Appendix 1). Patients will be contacted by site personnel 4 (± 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 2). Patients will be instructed to contact the investigator at any time if they have any health-related concerns. ~~If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).~~ If, during *a* scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit *or there are any issues with a patient's care*),~~with the Medical Monitor's permission,~~ 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 study treatment: slit lamp examination, indirect ophthalmoscopy, and pre~~- and post~~-treatment intraocular pressure (IOP) measurements (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), the images must be obtained at the next scheduled *study* visit*, if a patient attends it.*

SECTION 3.1.3: *Data Monitoring Committee*

An independent Data Monitoring Committee (iDMC) which is monitoring parent study will monitor safety and study conduct of this extension study on an ongoing basis as well. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate the benefit-risk profile of lampalizumab treatment through reviewing both safety and efficacy data. No formal interim efficacy/futility analysis is planned to be conducted by iDMC. The iDMC may recommend stopping the study early for safety reasons.

Further details can be found in the iDMC charter.

SECTION 4.1: PATIENTS

If a site is not able to collect images during the Week 96 visit of the parent study, then the Day 1 visit study treatment will be interrupted, and the images will be collected as soon as possible and prior to the study treatment administration at the next study treatment visit (e.g., Week 4 or Week 6). The reason for the study treatment interruption at the Day 1 visit will be recorded on the study treatment interruption eCRF.

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods ~~that result in~~*with* a failure rate of $<1\%$ per year during the treatment period and for at least 30 days after the last dose of lampalizumab.

SECTION 4.3.1: *Lampalizumab* Formulation, Packaging, Storage, and Handling

~~4.3.1.1 Lampalizumab Formulation~~

~~Lampalizumab drug product is provided as a sterile, white to off-white, lyophilized powder in a 6-cc USP/European Pharmacopoeia (Ph. Eur.) Type 1 glass vial and is intended for ITV administration. For the Phase III clinical studies, each glass vial contains a nominal 40 mg lampalizumab. After reconstitution with Sterile Water for Injection (SWFI), the drug product is formulated as 100 mg/mL lampalizumab in 40 mM L-histidine hydrochloride, 28 mM sodium chloride, 160 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.3.~~

~~Storage~~

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

~~For further details,~~*Please* see the Lampalizumab Investigator's Brochure ~~and/or~~ *for the lampalizumab clinical formulation. See the* Pharmacy ~~Binder~~*Manual for additional specifics regarding the lampalizumab formulation, product packaging, storage, and handling.*

SECTION 4.3.2: *Lampalizumab* Dosage, Administration, and Compliance

SECTION 4.3.2.1: ~~Lampalizumab~~ Dosage

A 10-mg dose of lampalizumab will be used in the extension study and will be administered by *intravitreal*~~ITV~~ injection to all enrolled patients either Q4W or Q6W during the treatment period (see Appendix 1 for the study flowchart).

The lampalizumab injections should not be repeated earlier than 22 days from previous dosing~~;~~. *M*~~m~~issed doses of study drug will not be made up *unless the missed dose is due to an unexpected issue, such as those listed in Section3.1.1.*

SECTION 4.3.2.2: Administration

The detailed instructions for lampalizumab reconstitution ~~with SWFI, USP/Ph. Eur., is required for preparation of the dose. 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 are provided in the Pharmacy Binder.~~

~~Please refer to Appendix 4, Appendix 5, and Appendix 6 for detailed instructions on~~*, for the* pre-injection procedure~~s~~, ~~preparation and~~ *intravitreal* ~~I~~TV administration ~~of the study drug injection~~, and post-injection procedure~~s~~ for the study eye~~, respectively~~ *are provided in the Pharmacy Manual.*

SECTION 4.4.1: Permitted Therapy

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

- *Prophylactic use of systemic antibiotics (e.g., for prevention of urinary tract infection [UTI]) should be discussed with Medical Monitor.*

SECTION 4.5.2: Medical History and Demographic Data

Medical history and demographic data were collected during the parent studies and will not need to be ~~reobtained~~*obtained again* during the OLE *study*.

SECTION 4.5.4.2: Ocular Imaging and Microperimetry

- FAF, SD-OCT, and NI images of both eyes (see Appendix 7, Appendix 8, and Appendix 9, respectively)

  Note: After enrollment, if a patient misses a study visit during which ocular images are scheduled to be taken, the images should be obtained at the next scheduled visit~~.~~*, if a patient attends it.*

SECTION 4.6.1: Patient Discontinuation *from Study*

Only the section title was revised.

SECTION 4.6.2: Study Treatment Discontinuation

~~The investigator has the right to~~*Patients must permanently* discontinue ~~a patient from the~~ study treatment ~~for~~*if they experience* any *of the following:*

- *Any* medical condition that the investigator *or Sponsor* determines may jeopardize the patient's safety if he or she continues ~~in the~~*to receive* study treatment
- Pregnancy~~,~~

The investigator has the right to discontinue a patient for reasons of non-compliance (e.g., missed doses and/or visits~~), if the patient becomes pregnant,~~*)* or if the investigator *or Sponsor* determines it is in the best interest of the patient. The *primary* reason for the treatment discontinuation should be recorded on the appropriate eCRF.

~~Treatment discontinued patients~~*Patients who must discontinue treatment* will not be replaced or allowed to restart the study treatment. Any patient discontinued from study treatment will also be discontinued from the study and will not be allowed to re-enter the study; the patient will be encouraged to undergo a study early termination visit.

SECTION 5.1: SAFETY PLAN

The incidence and characteristics of adverse events, serious adverse events, and laboratory abnormalities will be assessed as described within this protocol. *An iDMC will monitor patient safety and study conduct on an ongoing basis (see Section 3.1.3). The iDMC shares with the Sponsor the responsibility to monitor overall patient safety in relation to the IMP, lampalizumab.*

SECTION 5.1.1: Safety Procedures

Subheading was added.

SECTION 5.1.2: Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria

The following rows of Table 1 were revised as follows:

Table 1 Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria

Event	Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria
VA ~~loss~~*decrease*	Interrupt study treatment if there is a *study* treatment-related decrease of ≥30 letters in BCVA in the study eye compared with the last assessment of BCVA prior to the most recent treatment. Study treatment may be permitted subsequently as determined by the ~~Sponsor and~~ investigator.
Vitreous hemorrhage	Interrupt study treatment in the event of a vitreous hemorrhage in the study eye. Study treatment may be permitted subsequently as determined by the ~~Sponsor and~~ investigator.
Active ~~local or systemic~~ infection	Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye; or if the patient is currently receiving *systemic* treatment for an active ~~local or systemic~~ infection. Patients with endophthalmitis in the study eye will **discontinue** the study treatment and be **withdrawn** from the study.

SECTION 5.2: 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, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

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

SECTION 5.3.1: Adverse Events Reporting Period

After ~~informed consent has been obtained but prior to initiation~~*completion* of ~~study drug in~~*the Week 96 visit of the parent study and informed consent for* the extension study~~, adverse events should be reported in the parent study. Any adverse events or serious~~ *has been obtained, any* adverse events that are ongoing ~~from~~ *or started after the Week 96 visit of* the parent study ~~when study drug is initiated in~~*should be reported on* the extension study ~~should also be reported on the GX30191~~*Adverse Event* eCRF.

~~After initiation of study drug,~~ *A*ll adverse events will be reported until *at least* 30 days after the last dose of study drug *or the last study visit, whichever is later*. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

SECTION 5.3.5.7: Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of "GA secondary to AMD progression," geographic atrophy secondary to advanced macular degeneration progression should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

SECTION 5.3.5.9: ~~Lack of Efficacy or~~ Worsening of Geographic Atrophy *in Study Eye*

Events that are clearly consistent with the expected pattern of progression of the underlying disease *in the study eye* should not be recorded as adverse events. The expedited reporting requirements for sight-threatening events (listed in the Section 5.2.3) *still* apply to these unexpected changes in the study eye GA.

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor Contact Information for Sites in North and South America

Medical Monitor/Roche Medical Responsible: [redacted], M.D. (Primary)

~~Telephone No.:~~ [redacted]

Mobile Telephone No.: [redacted]

SECTION 5.4.2.1: ~~Events That Occur prior to Study Drug Initiation~~

~~After informed consent has been obtained but prior to initiation of study drug in the extension study,~~ ~~s~~*S*erious adverse events and adverse events of special interest *with onset prior to completion of* ~~the parent study~~ *the Week 96 visit of the parent study* should be reported in the parent study. ~~Any serious adverse events or adverse events of special interest that are ongoing from the parent study when study drug is initiated in the extension study should also be reported on the OLE eCRF.~~ *After completion of the Week 96 visit of the parent study* ~~the parent study Week 96 visit~~ *and an informed consent for the extension study has been obtained, the serious adverse events and adverse events of special interest that are ongoing or started after the Week 96 visit of the parent study* ~~the parent study Week 96 visit~~ *should be reported on the extension study eCRF.*

SECTION 5.4.2.2: ~~Events That Occur after Study Drug Initiation~~

~~After initiation of study drug, s~~*S*erious adverse events and adverse events of special interest will be reported until *at least* 30 days after administration of *the* last dose *of study drug or the last study visit, whichever is later*. 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.

SECTION 5.6: ~~POST STUDY~~ ADVERSE EVENTS *THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD*

Only the section title was revised.

SECTION 6.2: SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS AND CONDUCT OF THE STUDY

Demographic and disease characteristics (such as GA area, BCVA, and VA under low-luminance conditions prior to enrollment) for patients enrolled in the extension study will be summarized *in all patients and* by treatment group in the parent study (Study GX29176 or Study GX29185). Patient disposition and exposure to study drug (number of study treatments and duration of treatment) will be summarized *in all patients and* by treatment group in the parent study.

SECTION 6.3: SAFETY ANALYSES

The safety analyses will include patients enrolled in this study who receive at least 1 dose of study drug *in all* ~~with~~ patients *and* ~~grouped~~ according to treatment received in the parent study.

SECTION 6.4: ANATOMIC AND CLINICAL OUTCOME ANALYSES

The anatomic and clinical outcome analyses will include *all* patients enrolled in this study who *have received at least one dose of study drug. The analyses will be summarized in all patients and by treatment group in the parent study* ~~had at least one assessment after the first dose of study drug, with patients grouped according to treatment received in the parent study~~.

SECTION 6.5: PHARMACOKINETIC ANALYSES

The PK analyses will include all enrolled patients who have *received at least one dose of study drug and have* at least one serum sample. *The analyses will be summarized by treatment group in the parent study.* ~~with patients grouped according to treatment actually received and treatment received before being rolled to the study.~~ Serum concentrations of lampalizumab will be summarized descriptively.

SECTION 6.6: IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose *(defined as prior to the first dose in the extension study for the prior sham patients, and prior to the first dose in the parent study for the prior lampalizumab patients)* and one postdose ATA assessment. *The analysis will be summarized by treatment group in the parent study.* ~~with patients grouped according to treatment received (Q4W or Q6W) and to the treatment received in the parent study.~~

The number and proportion of ATA-positive and ATA-negative patients during this study will be summarized by treatment group. The relationship between ATA status and the safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively in subgroup analyses. Patients are considered to be ATA--positive if they are ATA-negative at baseline *(defined as the last measurement prior to the first dose in the extension study for the prior sham patients, and the last measurement prior to the first dose in the Parent study for the prior lampalizumab patients)* but develop an ATA response following study drug administration (i.e., treatment-induced ATA response) or if

they are ATA-positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (i.e., treatment-enhanced ATA response).

SECTION 6.7: *HANDLING OF MISSING DATA*

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

SECTION 6.8: OPTIONAL INTERIM ANALYSIS

~~No formal interim efficacy analysis is planned since all patients on this study will receive active lampalizumab treatment.~~*Interim safety analyses will be conducted periodically by independent Data Monitoring Committee (iDMC) to monitor safety and study conduct of this extension study. No formal interim efficacy/futility analyses are planned.*
Exploratory efficacy and/or safety analyses may be performed with interim data (e.g., to support regulatory submissions).

SECTION 8.2: INFORMED CONSENT

The Consent Forms must be signed and dated by the patient ~~or the patient's legally authorized representative~~ 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.

A copy of each signed ICF must be provided to the patient~~ or the patient's legally authorized representative~~. 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.

APPENDIX 1: Schedule of Activities

The schedule of activities has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM

None of the protocol revisions affected the Informed Consent Form; therefore, it was not updated.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION WHO HAVE COMPLETED A ROCHE-SPONSORED STUDY**
PROTOCOL NUMBER:	GX30191
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-000423-13
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab (RO5490249)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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 of this form to the local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF LAMPALIZUMAB IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION WHO HAVE COMPLETED A ROCHE-SPONSORED STUDY**
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VERSION NUMBER:	2
EUDRACT NUMBER:	2016-000423-13
IND NUMBER:	104996
TEST PRODUCT:	Lampalizumab (RO5490249)
PHASE:	IIIb
INDICATION:	Geographic atrophy
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of intravitreal injections of 10 mg lampalizumab administered to patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) as assessed by the *following*:

- Incidence and severity of ocular adverse events
- Incidence and severity of systemic (non-ocular) adverse events

Exploratory Objectives

The exploratory objective of this study is to investigate the long-term efficacy of *intravitreal* injections of 10 mg lampalizumab as assessed by:

- GA area progression (as measured by fundus autofluorescence)
- Change in clinical outcomes (as outlined below)
- Correlation between GA area progression and change in clinical outcomes

The clinical and patient-reported outcomes included in this study are the following:

- Best corrected visual acuity (BCVA) score, as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (at a starting distance of 4 meters)
- BCVA score, as measured using ETDRS chart at a starting distance of 4 meters under low-luminance conditions
- Binocular and monocular reading speed, critical print size, and reading acuity, as assessed using the Minnesota Low-Vision Reading Test or by Radner Reading Charts
- Patient-reported visual function, as assessed using the National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25), particularly the NEI VFQ-25 composite score, the near activity subscale score, and the distance activity subscale score

- Patient-reported functional reading independence, as assessed using the Functional Reading Independence Index score
- In a selected subset of patients, macular functional response, as assessed by mesopic microperimetry and measured by the number of scotomatous points and change in macular sensitivity

At the discretion of the Sponsor, additional assessments may be included in this open-label extension (OLE) study (Study GX30191), in which case a supplemental assessment protocol will be provided.

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to observe the systemic trough concentrations of 10 mg lampalizumab administered by *intravitreal* injections through the analysis of the serum lampalizumab concentrations.

The exploratory PK objectives for this study are to observe the aqueous humor concentrations of lampalizumab and to explore possible relationships between lampalizumab PK, biomarkers, and clinically related endpoints.

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to lampalizumab through the analysis of the incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ATAs on the efficacy, safety, biomarker or PK endpoints.

Biomarker Objective

The biomarker objective of this study is to explore the relationship of biomarkers to each other and to the endpoints in the study. These biomarkers include genetic variants identified in patients who completed the Phase III studies GX29176 and GX29185, candidate anatomic biomarkers identified by spectral domain–optical coherence tomography, levels in the blood of proteins in the complement pathway, and molecular biomarkers measured in the optional aqueous humor sample.

Study Design

Description of Study

Study GX30191 is a multicenter, *open-label extension (*OLE*)* study designed to evaluate the safety and tolerability of a 10-mg dose of lampalizumab administered by *intravitreal* injection to patients with GA secondary to AMD who have completed Study GX29176 or GX29185 (henceforth referred to as the parent studies). Patients in the parent studies who discontinued from study treatment prior to completion of the 96-week treatment period are not eligible for enrollment in this extension study.

The extension study will enroll two groups of patients from the parent studies: patients previously exposed to lampalizumab as well as patients who are lampalizumab-naive (i.e., received sham during a parent study). Although this extension study is open-label, patients will remain masked to their previous treatment assignment in the parent study, unless unmasking is permitted by the Sponsor. In addition, the visual acuity (VA) examiner role will remain masked to the patients' study eye assignment.

Eligible patients who consent to participate in this extension study will be enrolled upon completion of the parent study (i.e., at the Week 96 visit) and study treatment. The Week 96 visit will serve as the final visit for the parent study and the Day 1 visit for the extension study (i.e., the two visits will be conducted on the same day). Patients must satisfy all eligibility criteria at the Day 1 visit; eligible patients will be enrolled using an interactive response system (IxRS).

If a site is not able to collect images during the Week 96 visit of the parent study, then the Day 1 visit study treatment will be interrupted, and the images will be collected as soon as possible and prior to the study treatment administration at the next study treatment visit (e.g., Week 4 or Week 6). The reason for the study treatment interruption at the Day 1 visit will be recorded on the study treatment interruption electronic case report form (eCRF).

All patients from the parent studies who enroll in the OLE study will receive 10-mg *intravitreal* injections of lampalizumab. The study eye for the extension study will be the same eye that received lampalizumab or sham administrations in the parent study; only the study eye will receive administration of lampalizumab in this extension study. Dosing frequency in this extension study will remain consistent with the original dosing schedule in the parent study. That is, if a patient was originally randomized to the every 4 weeks (Q4W) arm in the parent study, the patient will remain on a Q4W schedule in the extension study. Similarly, if a patient was originally randomized to the every 6 weeks (Q6W) arm in the parent study, the patient will remain on a Q6W schedule.

All patients enrolled in the extension study will have the first *intravitreal* injection of lampalizumab administered by the investigator at the Day 1 visit, unless dose interruption is medically *or otherwise* justified by the investigator. The lampalizumab injections should not be repeated earlier than 22 days from previous dosing. *M*issed doses of study drug will not be made up *unless the missed dose is due to an unexpected issue, such as those listed in the following paragraph*. Patients' self-administered anti-microbials pre- and post-injection may be used at the investigator's discretion.

All subsequent study treatment visits will be scheduled Q4W or Q6W (±5 days), relative to Day 1 visit date, at which patients will have safety evaluations performed prior to receiving the study drug injection. Patients will be contacted by site personnel 4 (± 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 concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit. If, during *a* scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit *or there are any issues with a patient's care*), with the Medical Monitor's permission, 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 study treatment: slit lamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurements (recorded on the scheduled visit electronic Case Report Form 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 *study* visit*, if a patient attends it*.

Patients are not expected to attend their scheduled visits if there are extenuating circumstances justifying their inability to come to the clinic.

Patients who discontinue from the study will be asked to return for an early termination visit after a minimum of 30 days has elapsed following their last study treatment for monitoring of adverse events and the early termination visit assessments.

A subset of the patients at selected sites may participate in a mesopic microperimetry assessment in order to evaluate macular functional response.

An independent Data Monitoring Committee (iDMC), which is monitoring the parent studies, will monitor safety and study conduct of this extension study on an ongoing basis as well.

Number of Patients

Up to 1800 patients may be enrolled in the study at up to 300 sites located globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Willingness and ability to provide signed informed consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act authorization, and in other countries, as applicable according to national laws.
- Willingness and ability to undertake all scheduled visits and assessments

- Previous enrollment in and completion of study treatment and the Week 96 visit of either Study GX29185 or Study GX29176, without early treatment discontinuation (lampalizumab or sham)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods $with$ a failure rate of $<1\%$ per year during the treatment period and for at least 30 days after the last dose of lampalizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous 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 120 days after the last dose of study drug. Men must refrain from donating sperm during this same time period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 120 days after the last dose of study drug to avoid exposing the embryo.

  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 patients participating in microperimetry (at selected sites only): must have participated in the microperimetry testing during the parent study

<u>Exclusion Criteria</u>

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

- Concurrent ocular conditions exclusion criterion

  History of other ocular diseases that give reasonable suspicion of a disease or condition that contraindicates the use of lampalizumab or that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications
- Concurrent systemic conditions exclusion criteria

  History of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or condition that contraindicates the use of lampalizumab or that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications

  Predisposition to or history of increased risk of infection (e.g., history of splenectomy or chronic immunosuppression)

  Requirement for continuous use of any medications or treatments indicated in the "Excluded Therapy" section of the protocol

  Pregnancy or lactation, or intention to become pregnant during the study

    Women of childbearing potential must have a negative urine pregnancy test result at the Day 1 visit prior to initiation of study drug.

End of Study

The end of the study is defined as the date when the last patient, last visit occurs.

Length of Study

The duration of the OLE study in each participating country will depend upon the health authority approval of lampalizumab in that country as well as the Sponsor's discretion. After completion of the phase III OLE study, patients will have access to post trial lampalizumab.

Investigational Medicinal Products

Test Product (Investigational Drug)

A 10 mg dose of lampalizumab will be used in the extension study and will be administered by injection to all enrolled patients either Q4W or Q6W during the treatment period.

The lampalizumab injections should not be repeated earlier than 22 days from previous dosing; missed doses of study drug will not be made up.

Statistical Methods

Safety Analyses

The safety analyses will include patients enrolled in this study who receive at least 1 dose of study drug *in all* patients *and* according to treatment received in the parent study.

Verbatim descriptions of treatment-emergent adverse events will be coded, and their incidence will be summarized, as appropriate. Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events judged to be related to lampalizumab. In addition, separate summaries will be prepared for systemic (non-ocular) and ocular adverse events. Descriptive summaries will be generated for VA and IOP. All patients will receive lampalizumab treatment in this study; therefore, caution must be taken when interpreting safety results as there is no inactive/sham treatment group for comparison.

Determination of Sample Size

This study is open to all patients who complete study treatment and the Week 96 visit in parent Studies GX29176 and GX29185 and who meet the eligibility criteria.

Optional Interim Analysis

No formal interim efficacy analysis is planned since all patients on this study will receive active lampalizumab treatment. Exploratory efficacy and/or safety analyses may be performed with interim data (e.g., to support regulatory submissions).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACP	alternative complement pathway
ALT	alanine aminotransferase
AMD	age-related macular degeneration
anti-VEGF	anti-vascular endothelial growth factor
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
BCVA	best corrected visual acuity
C3	complement component 3
CFB	complement factor B
CFD	complement factor D
CFH	complement factor H
CFI	complement factor I
CFP	color fundus photograph
CNV	choroidal neovascularization
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAF	fundus autofluorescence
FDA	Food and Drug Administration
FRI	Functional Reading Independence
GA	geographic atrophy
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iDMC	*independent Data Monitoring Committee*
IMP	investigational medicinal product
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board

Abbreviation	Definition
IxRS	interactive response system
logMAR	logarithm of the minimum angle of resolution
LPLV	last patient, last visit
LL BCVA	low-luminance best corrected visual acuity
MNRead	Minnesota Low-Vision Reading Test
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25-item Version
NI	near-infrared
OLE	open-label extension
PD	pharmacodynamic
PK	pharmacokinetic(s)
PRO	patient-reported outcome
Q4W	every 4 weeks
Q6W	every 6 weeks
RCR	Roche Clinical Repository
RPE	retinal pigment epithelium
SD-OCT	spectral domain–optical coherence tomography
ULN	upper limit of normal
UTI	*urinary tract infection*
VA	visual acuity
VEGF	vascular endothelial growth factor

1. BACKGROUND

1.1 BACKGROUND ON GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 50 years or older in the developed world (Friedman et al. 2004). The majority of the visual loss occurs in the advanced stage of AMD, which has two clinical forms: a non-exudative form, geographic atrophy (GA), which is characterized by loss of choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors; and an exudative or wet form, which is characterized by choroidal neovascularization (CNV) (Sunness et al. 1999b; Lindblad et al. 2009). The prevalence of GA increases exponentially with age and approximately quadruples per decade beyond 50 years of age. The estimated prevalence of GA in populations of European ancestry and those 70 years of age is 0.70% and rises to 2.91% and 11.29% for those 80 years of age and 90 years of age, respectively (Rudnicka et al. 2012).

In the early stages of GA, patients typically show minimal changes in central visual acuity (VA). However, while central VA may not yet be affected, patients often still experience significant symptoms from visual dysfunction, such as dense parafoveal scotomas (e.g., leading to difficulties with face recognition), delayed dark adaptation, reduced contrast sensitivity, and a decrease in reading rate (Sunness et al. 1995, 1996, 1999a). In the later stages, as the GA lesion expands into the fovea, a profound decrease in central VA occurs leading to a decline in activities of daily living (Lindblad and Clemons 2005). Moreover, GA is bilateral in most patients with advanced AMD (Sunness et al. 1999b; Lindblad et al. 2009). As such, GA is a significant cause of both moderate and severe central visual loss.

Currently, there are no approved treatments to prevent the worsening of GA or the associated declines in visual function. Consequently, a significant unmet need exists for the treatment of this serious condition.

1.2 BACKGROUND ON LAMPALIZUMAB

The pathogenesis of AMD is complex and not well understood; however, genetics and environmental factors (such as smoking) as well as the alternative complement pathway (ACP) have all been implicated in AMD pathophysiology (de Jong 2006). Increased activation of the ACP has been found in drusen, which are lipoproteinous depositions in the space between the RPE and Bruch's membrane and a hallmark clinical observation associated with AMD. Moreover, a role for ACP in AMD has been supported by human genetics (Yates et al. 2007; Scholl et al. 2008). The largest study evaluating AMD genetics to date is a meta-analysis of 17,000 AMD cases and more than 60,000 controls that identified multiple genetic-risk loci, including four genes (complement factor H [CFH], complement factor B [CFB], complement factor I [CFI], and complement component 3 [C3]) in the ACP as confirmed genetic risk factors (Fritsche et al. 2013).

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

Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody directed against CFD. Lampalizumab inhibits CFD-mediated cleavage of CFB, preventing activation of the ACP. Lampalizumab is specific for the ACP and shows no inhibitory effect on classical complement pathway activation.

By inhibiting ACP activity, lampalizumab may offer the potential to impede or arrest the progression of GA and vision loss. Evidence for CFD in the pathogenesis of AMD include protection against oxidative-stress–mediated photoreceptor degeneration in a murine model with genetic deficiency of factor D (Rohrer et al. 2007) and detection of increased systemic activation of complement components, including CFD, in the serum of patients with AMD compared with controls, suggesting 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 ONGOING CLINICAL STUDIES

The safety and efficacy profile of lampalizumab as well as the natural history of GA have been and are continuing to be investigated in multiple trials. A brief description of these ongoing studies is provided below.

For more details about the safety and efficacy of lampalizumab in all clinical trials to date, please refer to the Lampalizumab Investigator's Brochure.

1.3.1 Phase III Studies GX29176 and GX29185 (Chroma and Spectri)

Studies GX29176 and GX29185 are Phase III, multicenter, randomized, double-masked, sham-controlled studies evaluating the efficacy and safety of lampalizumab administered by intravitreal injections to patients with GA. The studies are 96 weeks in duration and are ongoing. Provided they meet the eligibility criteria, patients from either study who complete both study treatment and the study will be allowed to enroll in this open-label extension (OLE) study (GX30191).

1.3.2 Phase II Open-Label Extension Study GX28198 (MAHALO OLE)

Study GX28198 is a multicenter, OLE study of the safety and tolerability of lampalizumab administered by *intravitreal* injection to patients with GA who have completed Study CFD4870g (a Phase Ib/II, randomized, single-masked, sham injection–controlled study of safety, tolerability, and evidence of activity of lampalizumab *intravitreal* injections in patients with GA) or Study GX29455 (a Phase II,

randomized, single-masked, sham injection-controlled exposure-response study of *intravitreal* lampalizumab). Study GX28198 is ongoing.

1.3.3 Phase II Study GX29455

Study GX29455 is *a completed*, multicenter, randomized, single-masked, sham injection-controlled, Phase II study investigating the exposure response and safety of lampalizumab administered *intravitreally* every 2 weeks or every 4 weeks (Q4W) for 24 weeks in patients with GA secondary to AMD. *The results of this study are pending.*

1.3.4 Prospective Epidemiological Studies GX29633 and GX29639 (Proxima A and Proxima B)

Studies GX29633 and GX29639 are ongoing multicenter, prospective, epidemiologic studies of the progression of GA secondary to AMD. Study GX29633 includes patients with bilateral GA secondary to AMD. Study GX29639 includes patients with unilateral GA secondary to AMD or patients with GA secondary to AMD in one eye and CNV (active or treated) secondary to AMD in the contralateral eye. No study drug is administered in these studies.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Results from the Phase II Study CFD4870g provide evidence that inhibition of the ACP by lampalizumab may slow the progression of GA and that lampalizumab administered as 10-mg *intravitreal* injections monthly over 18 months demonstrates an acceptable safety and tolerability profile in patients with GA secondary to AMD (see Lampalizumab Investigator's Brochure for further details on Study CFD4870g). In addition, exploratory genetic analyses suggest that there may be a biomarker-defined population (CFI profile biomarker positive) that may have a more rapid progression of disease and potentially derive a greater efficacy benefit from lampalizumab than a group that is negative for the biomarker (CFI profile biomarker negative).

The OLE study, Study GX30191, will evaluate the long-term safety and tolerability of 10 mg lampalizumab administered by *intravitreal* injection *Q4W* or every 6 weeks (Q6W) to patients with GA secondary to AMD who have completed study treatment and the Week 96 visit in one of the parent studies (Study GX29176 or GX29815). Study GX30191 will permit the evaluation of long-term safety and tolerability of lampalizumab in participants continuing from the active treatment arms. In addition, this study will provide the opportunity for eligible patients from the sham treatment arms to receive lampalizumab.

Specific objectives and corresponding endpoints for the study are outlined below.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the long-term safety and tolerability of *intravitreal* injections of 10 mg lampalizumab administered to patients with GA secondary to AMD as assessed by the *following*:

- Incidence and severity of ocular adverse events
- Incidence and severity of systemic (non-ocular) adverse events

2.2 EXPLORATORY OBJECTIVES

The exploratory objective of this study is to investigate the long-term efficacy of *intravitreal* injections of 10 mg lampalizumab as assessed by:

- GA area progression (as measured by fundus autofluorescence [FAF])
- Change in clinical outcomes (as outlined below)
- Correlation between GA area progression and change in clinical outcomes

The clinical and patient-reported outcomes (PROs) included in this study are the following:

- Best corrected visual acuity (BCVA) score, as measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (at a starting distance of 4 meters)
- BCVA score, as measured using ETDRS chart at a starting distance of 4 meters under low-luminance conditions
- Binocular and monocular reading speed, critical print size, and reading acuity, as assessed using the Minnesota Low-Vision Reading Test (MNRead) or by Radner Reading Charts
- Patient-reported visual function, as assessed using the National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25), particularly the NEI VFQ-25 composite score, the near activity subscale score, and the distance activity subscale score
- Patient-reported functional reading independence, as assessed using the Functional Reading Independence (FRI) Index score
- In a selected subset of patients, macular functional response, as assessed by mesopic microperimetry and measured by the number of scotomatous points and change in macular sensitivity

At the discretion of the Sponsor, additional assessments may be included in this OLE study (Study GX30191), in which case a supplemental assessment protocol will be provided.

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to observe the systemic trough concentrations of 10 mg lampalizumab administered by *intravitreal* injections through the analysis of the serum lampalizumab concentrations.

The exploratory PK objectives for this study are to observe the aqueous humor concentrations of lampalizumab and to explore possible relationships between lampalizumab PK, biomarkers, and clinically related endpoints.

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to lampalizumab through the analysis of the incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ATAs on the efficacy, safety, biomarker, or PK endpoints.

2.5 BIOMARKER OBJECTIVE

The biomarker objective of this study is to explore the relationship of biomarkers to each other and to the endpoints in the study. These biomarkers include genetic variants identified in patients who completed the Phase III studies GX29176 and GX29185, candidate anatomic biomarkers identified by spectral domain–optical coherence tomography (SD-OCT), levels in the blood of proteins in the complement pathway, and molecular biomarkers measured in the optional aqueous humor sample.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study GX30191 is a multicenter, *open-label extension (*OLE*)* study designed to evaluate the safety and tolerability of a 10-mg dose of lampalizumab administered by *intravitreal* injection to patients with GA secondary to AMD who have completed Study GX29176 or GX29185 (henceforth referred to as the parent studies). Patients in the parent studies who discontinued from study treatment prior to completion of the 96-week treatment period are not eligible for enrollment in this extension study.

The extension study will enroll two groups of patients from the parent studies: patients previously exposed to lampalizumab as well as patients who are lampalizumab-naive (i.e., received sham during a parent study). Although this extension study is open-label, patients will remain masked to their previous treatment assignment in the parent study, unless unmasking is permitted by the Sponsor. In addition, the VA examiner role will remain masked to the patients' study eye assignment.

Eligible patients who consent to participate in this extension study will be enrolled upon completion of the parent study (i.e., at the Week 96 visit) and study treatment. The Week 96 visit will serve as the final visit for the parent study and the Day 1 visit for the extension study (i.e., the two visits will be conducted on the same day). Patients must satisfy all eligibility criteria at the Day 1 visit (see Sections 4.1.1 and 4.1.2); eligible patients will be enrolled using an interactive response system (IxRS).

If a site is not able to collect images during the Week 96 visit of the parent study, then the Day 1 visit study treatment will be interrupted, and the images will be collected as soon as possible and prior to the study treatment administration at the next study treatment visit (e.g., Week 4 or Week 6). The reason for the study treatment interruption at the Day 1 visit will be recorded on the study treatment interruption electronic case report form (eCRF).

All patients from the parent studies who enroll in the OLE study will receive 10-mg *intravitreal* injections of lampalizumab. The study eye for the extension study will be the same eye that received lampalizumab or sham administrations in the parent study; only the study eye will receive administration of lampalizumab in this extension study. Dosing frequency in this extension study will remain consistent with the original dosing schedule in the parent study. That is, if a patient was originally randomized to the Q4W arm in the parent study, the patient will remain on a Q4W schedule in the extension study. Similarly, if a patient was originally randomized to the Q6W arm in the parent study, the patient will remain on a Q6W schedule.

All patients enrolled in the extension study will have the first *intravitreal* injection of lampalizumab administered by the investigator at the Day 1 visit, unless dose interruption is medically *or otherwise* justified (see Section 5.1.2 and Table 1) *by the investigator.* The lampalizumab injections should not be repeated earlier than 22 days from previous dosing. *M*issed doses of study drug will not be made up *unless the missed dose is due to an unexpected issue, such as those listed in the following paragraph.* Patients' self-administered anti-microbials pre- and post-injection may be used at the investigator's discretion.

All subsequent study treatment visits will be scheduled Q4W or Q6W (±5 days), relative to Day 1 visit date, at which patients will have safety evaluations performed prior to receiving the study drug injection (see Appendix 1). Patients will be contacted by site personnel 4 (± 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 2). Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If, during *a* scheduled visit, a site encounters an unexpected issue (e.g., the IxRS is not able to assign the study kit *or there are any issues with a patient's care*), 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 study treatment: slit lamp examination, indirect ophthalmoscopy, and pre-treatment intraocular pressure (IOP) measurements (recorded on the scheduled visit 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), the images must be obtained at the next scheduled *study* visit*, if a patient attends it.*

Patients are not expected to attend their scheduled visits if there are extenuating circumstances justifying their inability to come to the clinic.

Patients who discontinue from the study will be asked to return for an early termination visit after a minimum of 30 days has elapsed following their last study treatment for monitoring of adverse events and the early termination visit assessments (see Appendix 1).

A subset of the patients at selected sites may participate in a mesopic microperimetry assessment in order to evaluate macular functional response.

3.1.2 Planned Total Sample Size

Up to 1800 patients may be enrolled in the study at up to 300 sites located globally.

3.1.3 *Data Monitoring Committee*

An independent Data Monitoring Committee (iDMC), which is monitoring the parent studies, will monitor safety and study conduct of this extension study on an ongoing basis as well. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate the benefit-risk profile of lampalizumab treatment through reviewing both safety and efficacy data. No formal interim efficacy/futility analysis is planned to be conducted by iDMC. The iDMC may recommend stopping the study early for safety reasons.

Further details can be found in the iDMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs.

The duration of the OLE study in each participating country will depend upon the health authority approval of lampalizumab in that country as well as the Sponsor's discretion. After completion of the Phase III OLE study, patients will have access to post-trial lampalizumab as outlined in the guidance in Section 4.3.4.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Lampalizumab Dose and Schedule

The 10 mg lampalizumab monthly dosage was the dosing regimen that was found to be the most efficacious and was also well tolerated in the Phase II component of Study CFD4870g (see the Lampalizumab Investigator's Brochure).

In the ongoing Phase III studies GX29176 and GX29185, both the 10 mg Q4W and 10 mg Q6W dosing regimens are being evaluated.

This OLE study, Study GX30191, will evaluate the long-term safety and tolerability of 10 mg lampalizumab in patients who have completed study treatment and the Week 96 visit in one of the parent studies (i.e., Studies GX29176 and GX29185). Patients will continue on the same dosing regimen as they were assigned in the parent study.

3.3.2 Rationale for Biomarker Assessments

A biomarker plasma sample will be collected at the Day 1 visit of the study. This sample will allow comparison of plasma biomarkers of the complement-pathway between the baseline sample collected in the parent study and a sample collected 2 years later (at entry into Study GX30191). Evaluation of the longitudinal stability of plasma biomarkers will aid the understanding of relationships between these biomarkers and other biomarkers and endpoints in the study.

4. MATERIALS AND METHODS

4.1 PATIENTS

All patients who have completed study treatment and the Week 96 visit of either parent study (Study GX29176 or GX29185) will be eligible to participate in this extension study. Patients who discontinued from study treatment early in the parent study, but remained in the study for safety evaluations, will not be eligible for this extension study.

Written informed consent will be obtained prior to enrollment and the initiation of any study procedures for the extension study. Day 1 of the extension study will occur on the same day as the Week 96 completion visit of the parent study, provided that the following inclusion and exclusion criteria are met. If a patient misses the final Week 96 visit in the parent study, participation in the extension study will be at the discretion of the Sponsor (and subject eligibility criteria).

Note: Refer to Section 5.1.2 and Table 1 for the dose interruption and treatment discontinuation criteria. The criteria need to be reviewed on Day 1 of the extension study to ascertain whether injection on Day 1 can proceed or needs to be interrupted.

If a site is not able to collect images during the Week 96 visit of the parent study, then the Day 1 visit study treatment will be interrupted, and the images will be collected as soon as possible and prior to the study treatment administration at the next study

treatment visit (e.g., Week 4 or Week 6). The reason for the study treatment interruption at the Day 1 visit will be recorded on the study treatment interruption eCRF.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Willingness and ability to provide signed informed consent

  Additionally, at U.S. sites, patients must provide Health Insurance Portability and Accountability Act (HIPAA) authorization, and in other countries, as applicable according to national laws.

- Willingness and ability to undertake all scheduled visits and assessments
- Previous enrollment in and completion of study treatment and the Week 96 visit of either Study GX29185 or Study GX29176, without early treatment discontinuation (lampalizumab or sham)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods *with* a failure rate of $<1\%$ per year during the treatment period and for at least 30 days after the last dose of lampalizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous 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 120 days after the last dose of study drug. Men must refrain from donating sperm during this same time period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 120 days after the last dose of study drug to avoid exposing the embryo.

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 patients participating in microperimetry (at selected sites only): must have participated in the microperimetry testing during the parent study

4.1.2 Exclusion Criteria

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

- Concurrent ocular conditions exclusion criterion

  History of other ocular diseases that give reasonable suspicion of a disease or condition that contraindicates the use of lampalizumab or that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications

- Concurrent systemic conditions exclusion criteria

  History of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or condition that contraindicates the use of lampalizumab or that might affect interpretation of the results of the study or that renders the patient at high risk of treatment complications

  Predisposition to or history of increased risk of infection (e.g., history of splenectomy or chronic immunosuppression)

  Requirement for continuous use of any medications or treatments indicated in the "Excluded Therapy" section of the protocol (see Section 4.4.2)

  Pregnancy or lactation, or intention to become pregnant during the study

    Women of childbearing potential must have a negative urine pregnancy test result at the Day 1 visit prior to initiation of study drug.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. All patients enrolled in the extension study will receive 10 mg *intravitreal* injections of lampalizumab Q4W or Q6W.

A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) at the Day 1 visit (first study treatment) and sign informed consent for enrollment. All patients enrolled will receive lampalizumab treatment at the same dosing frequency as their originally assigned dosing frequency in the parent study.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is lampalizumab.

4.3.1 *Lampalizumab* Formulation, Packaging, Storage, and Handling

Please see the Lampalizumab Investigator's Brochure *for the lampalizumab clinical formulation. See the* Pharmacy *Manual for additional specifics regarding the lampalizumab formulation, product packaging, storage, and handling.*

4.3.2 *Lampalizumab* Dosage, Administration, and Compliance

4.3.2.1 Dosage

A 10-mg dose of lampalizumab will be used in the extension study and will be administered by *intravitreal* injection to all enrolled patients either Q4W or Q6W during the treatment period (see Appendix 1 for the study flowchart).

The lampalizumab injections should not be repeated earlier than 22 days from previous dosing. *M*issed doses of study drug will not be made up *unless the missed dose is due to an unexpected issue, such as those listed in Section 3.1.1.*

4.3.2.2 Administration

The detailed instructions for lampalizumab reconstitution *for the* pre-injection procedure, *intravitreal* administration, and post-injection procedure for the study eye *are provided in the Pharmacy Manual.*

Guidelines for treatment interruption or discontinuation are provided in Section 5.1 and Table 1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.3 Compliance

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (lampalizumab) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to Lampalizumab

The Sponsor will offer post-trial access to the study drug (lampalizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

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

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

A patient will not be eligible to receive study drug after completing 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 Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Patients who use other maintenance therapies should continue their use. Patients required to use medications that are prohibited will not be eligible for enrollment or continuation in the study (see Section 4.4.2).

Concomitant therapy includes any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops) and pre- and post-study treatment medications (e.g., proparacaine or anti-microbials [if applicable]) used by a patient from the time of study enrollment at the Day 1 visit through the conclusion of the patient's study participation or early termination visit. All concomitant

medications should be reported to the investigator and recorded on the Concomitant Medications eCRF log except for Lucentis® for treatment of either eye (if applicable), which will have a separate eCRF log.

4.4.1 Permitted Therapy

Patients required to use medications that are prohibited (see Section 4.4.2) will not be eligible for the study or continuation of the study. Of note, the following are examples of some common therapies that are permitted:

- Onset of ocular hypertension or glaucoma in either 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 Section 5.1.2 and Table 1) may apply with cataract surgery.
- Short-term use of topical corticosteroids may be administered (e.g., after cataract surgery, yttrium aluminum garnet capsulotomy, or peripheral iridotomy).
- At the discretion of the investigator, patients may be treated with Lucentis if they are diagnosed with an ocular condition in either eye for which Lucentis is approved in the patient's country. Consult the region-specific Lucentis prescribing information for dosing, frequency, and administration guidance.

  Note: If, in the opinion of the investigator, treatment with Lucentis should be given (in either eye) at the same visit during which study treatment will be administered, treatment with Lucentis must be administered first. Following this, the safety assessments (including IOP check) must be performed prior to calling IxRS for the study treatment kit assignment and prior to lampalizumab injections. Individual trays and separate sterile preparation must be prepared and separately performed for each treatment.
- Oral corticosteroids at doses $\leq$ 10 mg/day of prednisone or equivalent may be administered. The dose-holding criteria apply to doses $>$ 10 mg/day (see Section 5.1.2 and Table 1).
- *Prophylactic use of systemic antibiotics (e.g., for prevention of urinary tract infection [UTI]) should be discussed with Medical Monitor.*

4.4.2 Excluded Therapy

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions. However, the following medications and treatments are prohibited from use during a patient's study treatment, and patients discontinue the study drug and the study to receive these therapies:

- Investigational therapy other than study drug
- Systemic anti-vascular endothelial growth factor (anti-VEGF) agents
- *Intravitreal* anti-VEGF agents (other than Lucentis) in either eye
- *Intravitreal*, subtenon, or chronic topical (ocular) corticosteroids in study eye

- Systemic or intravenous immunomodulatory therapy (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, antitumor necrosis factors, eculizumab)
- Treatment with Visudyne® in study eye
- Other experimental therapies (except those with vitamins and minerals)

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms (ICFs) for enrolled patients will be maintained at the study site.

At the sites where investigator intends to ask his/*her* patients to self-administer antimicrobials pre- and post-injection, the ICF needs to be signed at an earlier date (e.g., Week 90 or 92 visit in parent study) in order to allow the ICF to be in place prior to the patient receiving pre-injection antimicrobials. In addition, during the Week 96 visit, if the ICF is signed prior to completion of the Week 96 assessments of the parent study, then the Week 96 parent study blood draws and the Day 1 OLE blood draw can be performed at the same time.

All parent-study Week 96 evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria prior to enrollment at the Day 1 visit in this extension study. The investigator will maintain a log to record details of all patients who sign the ICF to confirm patient's eligibility or ineligibility to be enrolled in the study as applicable.

4.5.2 Medical History and Demographic Data

Medical history and demographic data were collected during the parent studies and will not need to be *obtained again* during the OLE *study*.

4.5.3 Vital Signs

Vital signs will be collected at the early termination visits and will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for 5 minutes.

4.5.4 Other Disease-Specific Assessments

4.5.4.1 Ocular Assessments

Ocular assessments include the following:

- BCVA on ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes; see Appendix 4)
- BCVA assessed by ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes; see Appendix 5) under low luminance conditions

- MNRead charts (see Appendix 14 for details on specific countries where test will be administered) or Radner Reading Charts (see Appendix 15 for details on specific countries where test will be administered; perform prior to dilating eyes). The test will be administered first monocularly (right/left eye) and then binocularly (both eyes).
- 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 (for the definition of ocular inflammation, see Section 5.3.5; for inflammation grading scales, see Appendix 3)
- Dilated binocular indirect ophthalmoscopy
- Finger-counting, hand-motion, or light-perception tests performed by the investigator within 15 minutes post-injection for the study eye only. A finger-counting test will be conducted for each patient by the physician within 15 minutes following study treatment; hand-motion and light-perception tests will be performed when necessary.
- Following the study treatment, IOP will be measured between 30 and 50 minutes after study treatment by qualified site staff (except for the VA examiner) for the study eye only; if the IOP is increased by ≥10 mmHg from the pre-injection IOP value, IOP will be measured again at 60–80 minutes post-injection. If there are no safety concerns, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. Both the last post-injection IOP measured prior to any intervention for increased IOP (if applicable) and the last post-intervention IOP value (if applicable) will be recorded on the appropriate eCRF. If applicable, an Adverse Event eCRF should also be completed (see Section 5.2.1).

  Note: If the study eye is treated with a Lucentis injection during the same visit that study treatment is administered, the treatment with Lucentis must be performed first. The post-Lucentis treatment IOP is to be measured and recorded on the eCRF, irrespective of the subsequent study treatment administration.

4.5.4.2 Ocular Imaging and Microperimetry

The central reading center will provide sites with the central reading center's manual and training materials for specified study ocular images and microperimetry (at selected sites). Before any study images and microperimetry are obtained, site personnel, test images, systems, and software (where applicable) will be certified/validated by the reading center as specified in the central reading center manual.

"Grandfathering" certifications for personnel and equipment from the parent studies will be allowed according to central reading center's guidelines.

All ocular images and microperimetry results will be obtained by trained site personnel at the study sites and forwarded to the central reading center for independent analysis and/or storage (see Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10, and Appendix 11).

An independent review of digital color fundus photographs (CFPs); FAF, near-infrared (NI), and SD-OCT images (including exploratory anatomic biomarker studies); and fluorescein angiography (FA) 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. For further details, please refer to the central reading center's manual.

Ocular images obtained include the following:

- Stereoscopic, digital CFPs of both eyes (see Appendix 6)
- FAs of both eyes (performed after laboratory samples are obtained; see Appendix 7)
- FAF, SD-OCT, and NI images of both eyes (see Appendix 8, Appendix 9, and Appendix 10, respectively)

  Note: After enrollment, if a patient misses a study visit during which ocular images are scheduled to be taken, the images should be obtained at the next scheduled visit*, if a patient attends it.*

Additional details on obtaining these images are included in the Central Reading Center manual.

4.5.5 Laboratory and Other Biological Samples

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. Specimens will be forwarded to the central laboratory, where they will be analyzed or forwarded to the Sponsor or its designee for analysis and/or storage.

The following assessments will be performed:

- Urine pregnancy test (performed at the site) prior to each study treatment for women of childbearing potential, including those who have had tubal ligation

  If positive, collect blood sample for the serum pregnancy test and forward to central lab for analysis. If the serum pregnancy test is positive, discontinue the patient from study treatment.
- Measurement of anti-lampalizumab antibodies in serum samples
- Measurement of lampalizumab concentration in serum samples
- Measurement of lampalizumab and CFD levels in optional anterior chamber (aqueous humor) paracentesis samples in order to assess PK and pharmacodynamic (PD) relationships
- Assessment of measures of the complement pathway in plasma samples

The following assessments will be performed only at the early termination visit:

- Urinalysis: specific gravity, pH, blood, protein, ketones, glucose, bilirubin, urobilinogen, and microscopic examination (if any of the preceding urinalysis tests, other than glucose and ketones, are abnormal)

- Hematology: hemoglobin, hematocrit, quantitative platelet count, red blood cell counts, white blood cell counts, and differentials, including neutrophils, bands, lymphocytes, basophils, eosinophils, and monocytes (absolute)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, alkaline phosphatase, and uric acid
- Coagulation: activated partial thromboplastin time and prothrombin time

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

In addition, remainders of serum PK, serum ATAs, biomarker plasma, and aqueous humor samples will be stored for up to 15 years after the date of the final closure of the associated clinical database if the patient gave specific Roche Clinical Repository (RCR) consent for them to be stored for optional research (see Appendix 16).

Drug concentration will be determined in serum using an enzyme-linked immunosorbent assay (ELISA) method. ATAs will be detected in serum using a bridging ELISA.

4.5.6 Patient-Reported Outcomes

PROs (i.e., the NEI VFQ-25 and the FRI Index) will be collected via interviewer-administered questionnaires to help characterize the clinical profile of lampalizumab from the patient's perspective.

The questionnaires will be translated as required to different languages. The questionnaires will be administered by the site staff (except for the VA examiner) prior to any other study visit assessments being performed on that day.

The National Eye Institute Visual Functioning Questionnaire 25-Item Version

The NEI VFQ-25 is a 25-item, interviewer-administered assessment of visual functioning (see Appendix 12). The appendix items for the near and distance domains will also be included (an additional three items for each domain). It is scored on a scale of 0–100, with higher scores indicating better visual function. It has a composite score and 12 domains: general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. It does not have a specified recall period.

The Functional Reading Independence Index

The FRI Index is an interviewer-administered assessment of functional reading independence containing seven items on performance of activities of daily living that require reading and follow-up items on compensating mechanisms, adjustments, and assistance required for each activity (see Appendix 13). The mean FRI Index score is a continuous score ranging from 1 to 4, with a higher score representing higher functional reading independence. A categorical FRI level score may also be computed, with scores of 1 = unable to do, 2 = help some or most of the time, 3 = moderately independent, and 4 = totally independent. The FRI Index has a specified recall period of 7 days.

4.5.7 Reading Speed Assessments

Reading function will be assessed using one of two validated and widely used tests prior to eye dilation: the MNREAD or the Radner Reading Charts. Test selection is based on language availability (see Appendix 14 and Appendix 15, respectively, for details on specific countries where each test will be administered). The test will be administered to patients first monocularly (right/left eye) and then binocularly (both eyes), prior to dilation. From each test, scores will be derived for maximum reading speed (words per minute), critical print size (logarithm of the minimum angle of resolution [logMAR]), and reading acuity (logMAR). For maximum reading speed, a higher score indicates better reading function. For critical print size and reading acuity, a lower score indicates better reading function.

4.5.7.1 Minnesota Low-Vision Reading Test

The MNRead acuity cards are continuous-text reading cards, with 19 highly comparable sentences in terms of number of words, word length, position of words, and reading level. The print sizes are scaled logarithmically. The test is performed under standardized conditions, and speed and accuracy are recorded on a worksheet.

4.5.7.2 Radner Reading Charts

Radner Reading Charts are also continuous-text reading cards available in numerous languages. Each card has 24 highly comparable sentences in terms of number of words, word length, position of words, and reading level. The print sizes are scaled logarithmically. The test is performed under standardized conditions, and speed and accuracy are recorded on a worksheet.

4.5.8 Optional Samples for Roche Clinical Repository

4.5.8.1 Overview of the Roche Clinical Repository

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

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

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

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the ICF by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

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

- Residual aqueous humor sample
- Residual biomarker plasma sample
- Residual serum PK sample
- Residual serum ATA sample

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

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

4.5.8.4 Confidentiality

Confidentiality for All RCR Specimens

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

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

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

Additional Confidentiality for Specimens Used for Genetic Research

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

4.5.8.5 Consent to Participate in the Roche Clinical Repository

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

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

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

4.5.8.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GX30191 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GX30191.

4.5.8.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with GCP by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the ICF. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

Patients withdrawn from the study will be asked to return for an early termination evaluation after a minimum of 30 days has elapsed following their last study treatment for monitoring of adverse events and assessments listed for the early termination visit (see Appendix 1). The reason for the patient's discontinuation from the study should be recorded on the appropriate eCRF. Discontinued patients will not be replaced or allowed to re-enter the study.

4.6.1 Patient Discontinuation *from Study*

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 missed doses and visits

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.

Every effort should be made to obtain information on patients who are discontinued from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF.

If a patient discontinues from the study but has not withdrawn informed consent, the site should make every effort to continue to follow-up on serious adverse events, deaths, and adverse events of special interest in these patients. In order to avoid loss to follow-up, the investigator should ask the patient at the study start for the contact details of a relative or friend who may be contacted in case the patient cannot be reached. However, patients will not be followed for any reason after consent has been withdrawn. Patients who discontinue from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must permanently discontinue study treatment *if they experience* any *of the following:*

- *Any* medical condition that the investigator *or Sponsor* determines may jeopardize the patient's safety if he or she continues *to receive* study treatment
- Pregnancy

The investigator has the right to discontinue a patient for reasons of non-compliance (e.g., missed doses and/or visits*)* or if the investigator *or Sponsor* determines it is in the best interest of the patient. The *primary* reason for the treatment discontinuation should be recorded on the appropriate eCRF.

Patients who must discontinue treatment will not be replaced or allowed to restart the study treatment. Any patient discontinued from study treatment will also be discontinued from the study and will not be allowed to re-enter the study; the patient will be encouraged to undergo a study early termination visit.

4.6.3 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

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

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

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

5. ASSESSMENT OF SAFETY

5.1 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 patients in this study is based on clinical experience with lampalizumab in completed and ongoing studies. The safety plan for this study is designed to help minimize patient risk and will include specific monitoring assessments as detailed below. The incidence and characteristics of adverse events and serious adverse events will be assessed as described in this protocol. Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, will be performed throughout the study.

Potential ocular safety issues currently thought to be associated with the route of administration or pharmacology of lampalizumab include decreased BCVA, conjunctival hemorrhage, ocular inflammation (see Section 5.3.5 and Appendix 3 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 for the duration of this study.

Systemic levels of lampalizumab following multiple *intravitreal* administrations 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, aggregate adverse event reports will be reviewed periodically to assess for potential systemic safety effects, such as cardiovascular events, neoplasms, or alteration in immune function (e.g., reports of infections to 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 as described within this protocol. *An iDMC will monitor patient safety and study conduct on an ongoing basis (see Section 3.1.3). The iDMC shares with the Sponsor the responsibility to monitor overall patient safety in relation to the IMP, lampalizumab.*

Patients will be contacted by study site personnel 4 (±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. At the sites where the investigator's decision is for the patients to take pre- and post-injection anti-microbials, the patients will also be asked whether they have taken the prescribed, self-administered, pre- and post-injection anti-microbials. Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 2).

5.1.1 *Safety Procedures*

A finger-counting test will be conducted for each patient by the physician within 15 minutes following study treatment; hand-motion and light-perception tests will be performed when necessary. Following the study treatment, IOP will be measured between 30 and 50 minutes after study treatment by the site staff for the study eye only; if the IOP is increased by ≥10 mmHg from the pre-injection IOP value, IOP will be measured again at 60–80 minutes post-injection. If there are no safety concerns, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. Both the last post-injection IOP measured prior to any intervention for increased IOP (if applicable) and the last post-intervention IOP value (if applicable) will be recorded on the appropriate eCRF. If applicable, an Adverse Event eCRF should also be completed (see Section 5.2.1).

If the study eye is treated with a Lucentis injection during the same visit that study treatment is administered, the treatment with Lucentis has to be performed first. Please measure and record the post-Lucentis treatment IOP value on the eCRF, irrespective of the subsequent study treatment administration.

Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, will be performed throughout the study. Blood samples will be obtained from all patients at selected timepoints in order to measure serum lampalizumab concentrations and levels of antibodies to lampalizumab and other biomarkers (see Appendix 1). The optional aqueous humor samples will be obtained from the patients who consent to this procedure and sample collection.

Patients discontinued from the study will be asked to return for early termination visit assessments after a minimum of 30 days has elapsed following the last study treatment visit (see Appendix 1). The visit will include assessment of all adverse events (serious and non-serious; ocular and non-ocular). Serious adverse events will be reported in compliance with GCP guidelines.

5.1.2 Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria

Study-treatment interruption, discontinuation of study treatment, and patient withdrawal from the study due to adverse events will be determined using the criteria listed in Table 1. If any of these criteria are met, treatment will be interrupted (or discontinued, if applicable) and will not be resumed earlier than the next scheduled study visit. The reason for study-treatment interruption or discontinuation should be recorded on the Study Drug Interruption eCRF and, if applicable, on the Adverse Event eCRF.

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.

Table 1 Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria

Event	Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria
Intraocular inflammation	Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis, or vitritis) is ≥ 1+ in the study eye (see the grading scales of intraocular inflammation in Section 5.3.5 and Appendix 3). Patients with > 3+ intraocular inflammation will **discontinue** study treatment and will be **withdrawn** from the study.
VA *decrease*	Interrupt study treatment if there is a *study* treatment-related decrease of ≥ 30 letters in BCVA in the study eye compared with the last assessment of BCVA prior to the most recent treatment. Study treatment may be permitted subsequently as determined by the investigator.
Elevated IOP	Interrupt study treatment if IOP in the study eye is ≥ 30 mmHg. Treatment may be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, or as determined by the investigator.
Vitreous hemorrhage	Interrupt study treatment in the event of a vitreous hemorrhage in the study eye. Study treatment may be permitted subsequently as determined by the investigator.
Rhegmatogenous retinal break	Interrupt study treatment 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	**Discontinue** study treatment and **withdraw** the patient from the study if rhegmatogenous retinal detachment or Stage 3 or 4 macular hole is observed.
Central serous retinopathy	Interrupt study treatment if serous retinopathy is present in the study eye. Study treatment may be resumed upon resolution.

Table 1 Dose-Interruption, Treatment-Discontinuation, and Study-Withdrawal Criteria (cont.)

Event	Dose-Interruption, Treatment-Discontinuation, Study-Withdrawal Criteria
Active infection	Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye; or if the patient is currently receiving *systemic* treatment for an active infection. Patients with endophthalmitis in the study eye will **discontinue** the study treatment and be **withdrawn** 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 Sponsor and investigator.
Oral corticosteroids (prednisone >10 mg/day or equivalent)	Interrupt study treatment. Study treatment may be resumed when oral corticosteroids dosing is prednisone ≤ 10 mg/day or equivalent.
IV corticosteroids	Interrupt study treatment. 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.

5.2 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,* and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical, investigational, patient-administered 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., electrocardiogram, 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 study drug administration (e.g., screening invasive procedures, such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated 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 that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Adverse events resulting from medication error

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

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

- Sight-threatening adverse events: An adverse event is considered to be *serious and* 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-infective agents, 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 5.3.5 and Appendix 3 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 the primary event term.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After *completion* of *the Week 96 visit of the parent study and informed consent for* the extension study *has been obtained, any* adverse events that are ongoing *or started after the Week 96 visit of* the parent study *should be reported on* the extension study *Adverse Event* eCRF.

*A*ll adverse events will be reported until *at least* 30 days after the last dose of study drug *or the last study visit, whichever is later*. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale in Table 2 will be used for assessing adverse event severity.

Table 2 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 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether 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 3):

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

Table 3 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., pre-existing 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: defined as 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: defined as the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: defined as 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: defined as diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause. A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis. Results of bacterial or fungal cultures, treatment given, and final ophthalmologic outcome should also be provided in the details section of the Adverse Event eCRF.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious and completing all data fields related to serious adverse events.

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

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory 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 × the upper limit of normal [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 whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (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 $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value 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 a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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

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").*

If the death is attributed to progression of "GA secondary to AMD progression," geographic atrophy secondary to advanced macular degeneration progression should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Worsening of Geographic Atrophy *in Study Eye*

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

Events that are clearly consistent with the expected pattern of progression of the underlying disease *in the study eye* should not be recorded as adverse events. The expedited reporting requirements for sight-threatening events (listed in the Section 5.2.3) *still* apply to these unexpected changes in the study eye GA.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

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

No safety data related to overdosing of lampalizumab are available.

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for Sites in North and South America

Medical Monitor/Roche Medical Responsible: [redacted], M.D. (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for Rest of World

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), 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, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

*S*erious adverse events and adverse events of special interest *with onset prior to completion of the Week 96 visit of the parent study* should be reported in the parent study. *After completion of the Week 96 visit of the parent study and an informed consent for the extension study has been obtained, the serious adverse events and adverse events of special interest that are ongoing or started after the Week 96 visit of the parent study should be reported on the extension study eCRF.*

The 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.

*S*erious adverse events and adverse events of special interest will be reported until *at least* 30 days after administration of *the* last dose *of study drug or the last study visit, whichever is later*. 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 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 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or until 30 days after the last dose of study drug. A 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 using the fax number or email 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 Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or until 120 days after the last dose of study drug. A 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 using the fax number or email 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 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.

5.4.3.3 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 5.4.2).

5.4.3.4 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 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 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.

5.6 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.

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

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

The Sponsor will promptly evaluate all serious adverse events and 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 adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Lampalizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

This study is open to all patients who complete study treatment and the Week 96 visit in parent Studies GX29176 and GX29185 and who meet the eligibility criteria (see Sections 4.1.1 and 4.1.2).

6.2 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS AND CONDUCT OF THE STUDY

Demographic and disease characteristics (such as GA area, BCVA, and VA under low-luminance conditions prior to enrollment) for patients enrolled in the extension study will be summarized *in all patients and* by treatment group in the parent study (Study GX29176 or Study GX29185). Patient disposition and exposure to study drug (number of study treatments and duration of treatment) will be summarized *in all patients and* by treatment group in the parent study.

6.3 SAFETY ANALYSES

The safety analyses will include patients enrolled in this study who receive at least 1 dose of study drug *in all* patients *and* according to treatment received in the parent study.

Verbatim descriptions of treatment-emergent adverse events will be coded, and their incidence will be summarized, as appropriate. Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events judged to be related to lampalizumab. In addition, separate

summaries will be prepared for systemic (non-ocular) and ocular adverse events. Descriptive summaries will be generated for VA and IOP. All patients will receive lampalizumab treatment in this study; therefore, caution must be taken when interpreting safety results as there is no inactive/sham treatment group for comparison.

6.4 ANATOMIC AND CLINICAL OUTCOME ANALYSES

The anatomic and clinical outcome analyses will include *all* patients enrolled in this study who *have received at least one dose of study drug. The analyses will be summarized in all patients and by treatment group in the parent study.*

Descriptive summaries will be generated for all anatomic and clinical outcomes, including PROs, over time. Correlation between anatomic and clinical outcomes will be summarized. Additional details of analysis will be included in the Data Analysis Plan.

6.5 PHARMACOKINETIC ANALYSES

The PK analyses will include all enrolled patients who have *received at least one dose of study drug and have* at least one serum sample. *The analyses will be summarized by treatment group in the parent study.* Serum concentrations of lampalizumab will be summarized descriptively.

Concentrations of lampalizumab from the optional collection of aqueous humor may be reported and/or summarized as appropriate. Additional PK/PD and exposure–response analyses may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the Clinical Study Report.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose *(defined as prior to the first dose in the extension study for the prior sham patients, and prior to the first dose in the parent study for the prior lampalizumab patients)* and one postdose ATA assessment. *The analysis will be summarized by treatment group in the parent study.*

The number and proportion of ATA-positive and ATA-negative patients during this study will be summarized by treatment group. The relationship between ATA status and the safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively in subgroup analyses. Patients are considered to be ATA--positive if they are ATA-negative at baseline *(defined as the last measurement prior to the first dose in the extension study for the prior sham patients, and the last measurement prior to the first dose in the Parent study for the prior lampalizumab patients)* but develop an ATA response following study drug administration (i.e., treatment-induced ATA response) or if they are ATA-positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$ 0.60 titer units) than the titer of the baseline sample (i.e.,

treatment-enhanced ATA response). Patients are considered to be ATA-negative if they are ATA-negative at baseline and all post-baseline samples are negative or if they are ATA-positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (i.e., treatment unaffected).

The relationship between ATA status and the safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.7 *HANDLING OF MISSING DATA*

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

6.8 OPTIONAL INTERIM ANALYSIS

Interim safety analyses will be conducted periodically by independent Data Monitoring Committee (iDMC) to monitor safety and study conduct of this extension study. No formal interim efficacy/futility analyses are planned. Exploratory efficacy and/or safety analyses may be performed with interim data (e.g., to support regulatory submissions).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via the EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

The Sponsor will supply eCRF specifications for this study.

Data from PRO questionnaires will be recorded on worksheets, and the data will be entered into the EDC by sites.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion.

eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry

of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample ICF (and ancillary sample ICFs, 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 ICFs 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 ICF 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 ICF 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 ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and

data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This research study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland and may be implemented in individual countries by Roche's local affiliates. The Sponsor will perform project management, study management, monitoring, vendor management, and statistical programming. An IxRS will be used for patient randomization and for management of study drug requests and shipments.

A central laboratory will be used for most laboratory assessments and for storage of other laboratory samples (i.e., anti-lampalizumab antibody serum samples) prior to being shipped to Sponsor or its designee for analysis. Data will be recorded by an EDC system using eCRFs (see Section 7.1) or forwarded to Sponsor electronically. A central reading center will be used for ocular imaging analyses (i.e., FAF, NI, CFP, FA, and SD-OCT) and microperimetry data, which will be forwarded to the Sponsor electronically.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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Appendix 1
Schedule of Assessments

Table 1 Study Flowchart for Q4W Arm: Day 1, Week 4 through Week 52, and Early Termination

	Day 1 [a]		Week												ET [b]
Assessment Window (Days)	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	4 ±5	8 ±5	12 ±5	16 ±5	20 ±5	24 ±5	28 ±5	32 ±5	36 ±5	40 ±5	44 ±5	48 ±5	52 ±5	≥30
Written informed consent		x [c]														
Review of inclusion and exclusion criteria		x														
Demographic information (age, sex, and self-reported race/ethnicity) [d]	x															
NEI VFQ-25 [e] (as applicable)	x							x						x		x
FRI Index [e] (as applicable)	x							x						x		x
Vital signs [f]																x
Central laboratory samples (hematology, coagulation, chemistry panel, and urinalysis) [g]																x
Biomarker plasma sample [g]		x														
Urine pregnancy test [g, h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum ATA sample [g]	x													x		x

Appendix 1
Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arm: Day 1, Week 4 through Week 52, and Early Termination (cont.)

	Day 1 [a]		Week												ET [b]
Assessment Window(Days)	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	4 ±5	8 ±5	12 ±5	16 ±5	20 ±5	24 ±5	28 ±5	32 ±5	36 ±5	40 ±5	44 ±5	48 ±5	52 ±5	≥30
Serum PK sample for lampalizumab concentration [g]	x													x		x
Optional aqueous sample [g, i]														x		
BCVA testing (starting at 4 m) [j]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
LL BCVA testing (starting at 4 m) [j]	x		x		x									x		x
MNRead or Radner Reading Charts [j, k] (as applicable)	x													x		x
Pretreatment IOP measurement [j]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mesopic microperimetry at selected sites (study eye only) [l]	x													x		x
Slit lamp examination	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [m]	x							x			x			x		x
SD-OCT [m]	x							x						x		x
Near-infrared imaging [m]	x							x			x			x		x

Appendix 1
Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arm: Day 1, Week 4 through Week 52, and Early Termination (cont.)

	Day 1 [a]		Week												ET [b]
	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	4	8	12	16	20	24	28	32	36	40	44	48	52	
Assessment Window(Days)			±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	≥30
Color fundus photography [m]	x													x		x
Fluorescein angiography [m]	x															x
Administration of lampalizumab injection to study eye		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Post-treatment finger-counting and IOP measurement [n]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	

ATA = anti-therapeutic antibody; BCVA = best corrected visual acuity; eCRF = electronic Case Report Form; ET = early termination; FAF = fundus autofluorescence; FRI = Functional Reading Independence; ICF = informed consent form; IOP = intraocular pressure; LL BCVA = low-luminance BCVA; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; OLE = open-label extension; PK = pharmacokinetic; Q4W = every 4 weeks; SD-OCT = spectral domain–optical coherence tomography; VA = visual acuity.

Note: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day except for study laboratory sample collections, which can be collected up to 7 days before or after scheduled visit. *The study drug injection may be delayed for reasons specified in the Section 3.1.1.* All study visits will be scheduled relative to date of Day 1 visit.

Appendix 1
Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arm: Day 1, Week 4 through Week 52, and Early Termination (cont.)

[a] The Day 1 visit will be performed on the same day as the Week 96 visit in the parent study. *If a site is not able to collect images at the Week 96 visit of the parent study, the Day 1 visit study treatment will be interrupted and the images will be collected as soon as possible and prior to study treatment administration at the next study treatment visit (e.g., Week 4 or Week 6). The reason for study treatment interruption at Day 1 visit will be recorded on the study treatment interruption eCRF.*

[b] For patients who discontinue from the study, early termination assessments will be performed after a minimum of 30 days has elapsed following the last study drug treatment.

[c] At the sites where investigator intends to ask his patients to self-administer antimicrobials pre and post injection, the ICF needs to be signed at an earlier date (e.g., Week 90 or 92 visit in parent study) in order to allow the ICF to be in place prior to the patient receiving pre-injection antimicrobials. In addition, during the Week 96 visit, if the ICF is signed prior to completion of the Week 96 assessments of the parent study, then the Week 96 parent study blood draws and the Day 1 OLE blood draw can be performed at the same time.

[d] The sites will transcribe demographics data from the parent study to OLE RAVE eCRF.

[e] To be administered by the site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

[f] Vital signs include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for 5 minutes.

[g] If laboratory sample is being obtained on study visit day, it must obtained prior to fluorescein angiography (if applicable) and prior to study drug treatment.

[h] Starting on Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study drug treatment visit. If positive, collect the serum pregnancy sample and forward to central laboratory for testing, do not administer study drug, and if positive, withdraw the patient from the study.

[i] Optional aqueous sample will be collected from the patients who consented to it.

[j] Perform prior to dilating the eyes.

[k] Either MNRead charts or Radner Reading Charts will be performed during the study visit prior to dilating the eyes (see the tables in Appendix 14 and Appendix 15, respectively, for which chart to use according to country of the site). The test will be administered first monocularly (right/left eye) and then binocularly (both eyes).

[l] To be performed post-dilation on the study eye only; the data will be forwarded to the central reading center.

[m] Performed for both eyes; results will be forwarded to the central reading center. See the center reading center manual. If a patient misses a study visit when ocular images are scheduled to be obtained, the images should be obtained at the next scheduled visit.

Appendix 1
Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arm: Day 1, Week 4 through Week 52, and Early Termination (cont.)

[n] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the physician within 15 minutes after study drug treatment. At study drug treatment visits, post-treatment IOP measurement in the study eye only between 30 and 50 minutes post-treatment with study drug will be performed by the qualified site staff (except for the VA examiner). If the IOP is increased by ≥10 mmHg from pre-treatment, the IOP will be measured again 60–80 minutes post-treatment. If there are no safety concerns, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. Both the last post-treatment IOP measured prior to any intervention for increased IOP (if applicable) and the last post-intervention IOP (if applicable) will be recorded on the Post-Treatment IOP eCRF. If the study eye is treated with a Lucentis® injection during the same visit as study drug treatment, the treatment with Lucentis must be performed first. Measure and record the post-Lucentis treatment IOP value on the eCRF.

[o] Record *on the concomitant medications log* any concomitant medications (i.e., any prescription medications or over-the-counter preparations **other than** protocol-specified procedural medications, such as proparacaine) that patients *continue* taking (no stop date) *after the Week 96* visit *of the parent study is completed or concomitant medications that patients started during the extension study. Record concomitant medications* through the patient's early termination visit.

[p] *Any* adverse events ongoing *after the Week 96 visit* from the parent study *is complete* should be transcribed to OLE Adverse Events eCRF log. *After the Week 96 visit completion for the parent study,* new adverse events will be recorded *in* the *extension* study through *a minimum of* 30 days after the last dose of study *drug or the last study visit, whichever is later*. Adverse events assessed by the investigator as related to the study drug should be followed until the event resolves or until the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has ended.

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

[r] Patients will be contacted by study site personnel 4 (±2) days after each study drug treatment to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. At sites where the investigator's decision is for the patients to take pre- and post-treatment antimicrobials, patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials. Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for a safety assessment visit.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Study Flowchart for Q4W Arm: Week 56 through Week 96 and Early Termination

	Week											ET [a]
	56	60	64	68	72	76	80	84	88	92	96 [b]	
Assessment Window (Days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	≥30
NEI VFQ-25 [c] (as applicable)											x	x
FRI Index [c] (as applicable)											x	x
Vital signs												x
Central laboratory samples (hematology, coagulation, chemistry panel, and urinalysis) [d]												x
Urine pregnancy test [d, e]	x	x	x	x	x	x	x	x	x	x	x	
Serum ATA sample [d]											x	x
Serum PK sample for lampalizumab concentration [d]											x	x
Optional aqueous sample [d, f]											x	
BCVA testing (starting at 4 m) [g]	x	x	x	x	x	x	x	x	x	x	x	x
LL BCVA (starting at 4 m) [g]											x	x
MNRead or Radner Reading Charts [g, h] (as applicable)											x	x
Pretreatment IOP measurement [g]	x	x	x	x	x	x	x	x	x	x	x	x
Mesopic microperimetry at selected sites (study eye only) [i]											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
FAF [j]					x						x	x
SD-OCT [j]					x						x	x

Appendix 1
Schedule of Assessments (cont.)

Table 2 Study Flowchart for Q4W Arm: Week 56 through Week 96 and Early Termination (cont.)

	Week											ET [a]
	56	60	64	68	72	76	80	84	88	92	96 [b]	≥30
Assessment Window (Days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	
Near-infrared imaging[j]					x						x	x
Color fundus photography[j]											x	x
Fluorescein angiography[j]												x
Administration of lampalizumab injection to study eye	x	x	x	x	x	x	x	x	x	x	x	
Post-treatment finger counting and IOP measurement[k]	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications[l]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events[m]	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures[n]	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call[o]	x	x	x	x	x	x	x	x	x	x	x	

ATA = anti-therapeutic antibody; BCVA = best corrected visual acuity; eCRF = electronic Case Report Form; ET = early termination; FAF = fundus autofluorescence; FRI = Functional Reading Independence; IOP = intraocular pressure; LL BCVA = low-luminance BCVA; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; OLE = open-label extension; PK = pharmacokinetic; Q4W = every 4 weeks; SD-OCT = spectral domain–optical coherence tomography; VA = visual acuity.

The study drug injection may be delayed for reasons specified in Section 3.1.1. All study visits will be scheduled relative to the Day 1 visit date.

[a] For patients who discontinue from the study, early termination assessments will be performed after a minimum of 30 days has elapsed following the last study drug treatment.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Study Flowchart for Q4W Arm: Week 56 through Week 96 and Early Termination (cont.)

[b] This study may potentially extend beyond Week 96. *The sites will be informed in timely manner.*

[c] To be administered by the site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

[d] If laboratory sample is being obtained on study visit day, it must be obtain prior to fluorescein angiography (if applicable) and prior to study drug treatment.

[e] Starting on Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study drug treatment visit. If positive, collect the serum pregnancy sample and forward to central laboratory for testing, do not administer study drug, and if positive withdraw the patient from the study.

[f] Optional aqueous sample will be collected from the patients who consented to it.

[g] Perform prior to dilating the eyes.

[h] Either MNRead charts or Radner Reading Charts will be performed during the study visit prior to dilating the eyes (see the tables in Appendix 14 and Appendix 15, respectively, for which chart to use according to country of the site). The test will be administered first monocularly (right/left eye) and then binocularly (both eyes).

[i] To be performed post-dilation on the study eye only; the data will be forwarded to the central reading center.

[j] Performed for both eyes; and results will be forwarded to the central reading center. See the center reading center manual. If a patient misses a study visit when ocular images are scheduled to be obtained, the images should be obtained at the next scheduled visit.

[k] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the physician within 15 minutes after study drug treatment. At study drug treatment visits, post-treatment IOP measurement in the study eye only between 30 and 50 minutes post-treatment with study drug will be performed by the qualified site staff (except for the VA examiner). If the IOP is increased by ≥10 mmHg from pretreatment, the IOP will be measured again 60–80 minutes post-treatment. If there are no safety concerns, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. Both the last post-treatment IOP measured prior to any intervention for increased IOP (if applicable) and the last post-intervention IOP (if applicable) will be recorded on the Post-Treatment IOP eCRF. If the study eye is treated with a Lucentis® injection during the same visit as study drug treatment, the treatment with Lucentis must be performed first. Measure and record the post-Lucentis treatment IOP value on the eCRF.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Study Flowchart for Q4W Arm: Week 56 through Week 96 and Early Termination (cont.)

[l] Record *on the concomitant medications log* any concomitant medications (i.e., any prescription medications or over-the-counter preparations **other than** protocol-specified procedural medications, such as proparacaine) that patients *continue* taking (no stop date) *after the Week 96* visit *of the parent study is completed or concomitant medications that patients started during the extension study. Record concomitant medications* through the patient's early termination visit.

[m] *Any* adverse events ongoing from the parent study *after Week 96 completion* should be transcribed to OLE Adverse Events eCRF log. *After the Week 96 visit completion for the parent study,* new adverse events will be recorded *in* the *extension* study through *minimum of* 30 days after the last dose of study *drug or the last study visit, whichever is later.*

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

[o] Patients will be contacted by study site personnel 4 (±2) days after each study drug treatment to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. At sites where the investigator's decision is for the patients to take pre- and post-treatment antimicrobials, patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials. Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for a safety assessment visit.

Appendix 1
Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arm: Day 1, Week 6 through Week 96, and Early Termination

	Day 1 [a]		Week															ET [b]
	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96 [c]	
Assessment Windows (Days)			±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	≥30
Written informed consent		x [d]																	
Review of inclusion and exclusion criteria		x																	
Demographic information (age, sex, self-reported race/ethnicity) [e]	x																		
NEI VFQ-25 [f] (as applicable)	x					x				x								x	x
FRI Index [f] (as applicable)	x					x				x								x	x
Vital signs [g]																			x
Central laboratory samples (hematology, coagulation, chemistry, panel, and urinalysis) [h]																			x
Biomarker plasma sample [h]		x																	
Urine pregnancy test [h, i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1
Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arm: Day 1, Week 6 through Week 96, and Early Termination (cont.)

	Day 1 [a]		Week															ET [b]
Assessment Windows (Days)	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	6 ±5	12 ±5	18 ±5	24 ±5	30 ±5	36 ±5	42 ±5	48 ±5	54 ±5	60 ±5	66 ±5	72 ±5	78 ±5	84 ±5	90 ±5	96 [c] ±5	≥30
Serum ATA sample [h]	x									x								x	x
Serum PK sample for lampalizumab concentration [h]	x									x								x	x
Optional aqueous sample [h, j]										x								x	
BCVA testing (starting at 4 m) [k]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
LL BCVA testing (starting at 4 m) [k]	x		x	x						x								x	x
MNRead or Radner Reading Charts [k, l] (as applicable)	x									x								x	x
Pretreatment IOP measurement [k]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mesopic microperimetry at selected sites (study eye only) [m]	x									x								x	x
Slit lamp examination	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FAF [n]	x					x		x		x				x				x	x

Appendix 1
Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arm: Day 1, Week 6 through Week 96, and Early Termination (cont.)

	Day 1 [a]		Week															ET [b]
Assessment Windows (Days)	Data Extracted from Parent Study	Data Obtained at Day 1 Visit	6 ±5	12 ±5	18 ±5	24 ±5	30 ±5	36 ±5	42 ±5	48 ±5	54 ±5	60 ±5	66 ±5	72 ±5	78 ±5	84 ±5	90 ±5	96 [c] ±5	≥30
SD-OCT [n]	x					x				x				x				x	x
Near-infrared imaging [n]	x					x		x		x				x				x	x
Color fundus photography [n]	x									x								x	x
Fluorescein angiography [n]	x																		x
Administration of lampalizumab injection to study eye		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Post-treatment finger counting and IOP measurement [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call [s]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

ATA = anti-therapeutic antibody; BCVA = best corrected visual acuity; eCRF = electronic Case Report Form; ET = early termination; FAF = fundus autofluorescence; FRI Index = Functional Reading Independence Index; ICF = informed consent form; IOP = intraocular pressure; LL BCVA = low-luminance BCVA; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25-Item Version; OLE = open-label extension; PK = pharmacokinetic; Q6W = every 6 weeks; SD-OCT = spectral domain–optical coherence tomography; $VA = visual\ acuity$.

Appendix 1
Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arm: Day 1, Week 6 through Week 96, and Early Termination (cont.)

Note: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day except for study laboratory sample collection, which can be collected up to 7 days before or after scheduled visit. *The study drug injection may be delayed for reasons specified in Section 3.1.1.* All study visits will be scheduled relative to the Day 1 visit date.

[a] Day 1 visit will be performed on the same day as Week 96 visit in parent study. *If a site is not able to collect images at parent study Week 96 visit then Day 1 visit study treatment will be interrupted and the images will be collected as soon as possible and prior to study treatment administration at the next study treatment visit (e.g. Week 4 or Week 6). The reason for study treatment interruption at Day 1 visit will be recorded on the study treatment interruption eCRF.*

[b] For patients who discontinue early from the study, early termination assessments will be performed after a minimum of 30 days has elapsed following the last study drug treatment.

[c] This study may potentially extend beyond *the* Week 96 *visit. The sites will be informed in timely manner.*

[d] At the sites where investigator intends to ask his patients to self-administer antimicrobials pre and post injection, the ICF needs to be signed at an earlier date (e.g., Week 90 or 92 visit in parent study) in order to allow the ICF to be in place prior to the patient receiving pre-injection antimicrobials. In addition, during the Week 96 visit, if the ICF is signed prior to completion of the Week 96 assessments of the parent study, then the Week 96 parent study blood draws and the Day 1 OLE blood draw can be performed at the same time.

[e] The sites will transcribe demographics data from the parent study to OLE RAVE eCRF.

[f] To be administered by the site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.

[g] Vital signs include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for 5 minutes.

[h] If laboratory sample is being obtained on study visit day, it must be obtain prior to fluorescein angiography (if applicable) and prior to study drug treatment.

[i] Starting on Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study drug treatment visit. If positive, collect the serum pregnancy sample and forward to central laboratory for testing, do not administer study drug, and if positive, withdraw the patient from the study.

[j] Optional aqueous sample will be collected from the patients who consented to it

[k] Perform prior to dilating the eyes.

[l] Either MNRead charts or Radner Reading Charts will be performed during the study visit prior to dilating the eyes (see the tables in Appendix 14 and Appendix 15, respectively, for which chart to use according to country of the site). The test will be administered first monocularly (right/left eye) and then binocularly (both eyes).

Appendix 1
Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arm: Day 1, Week 6 through Week 96, and Early Termination (cont.)

[m] To be performed post-dilation on the study eye only; the data will be forwarded to the central reading center.

[n] Performed for both eyes; results will be forwarded to the central reading center. See the center reading center manual. If a patient misses a study visit when ocular images are scheduled to be obtained, the images should be obtained at the next scheduled visit.

[o] Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the physician within 15 minutes after study drug treatment. At study drug treatment visits, post-treatment IOP measurement in the study eye only between 30 and 50 minutes post-treatment with study drug will be performed by the qualified site staff (except for the VA examiner). If the IOP is increased by ≥10 mmHg from pretreatment, the IOP will be measured again 60–80 minutes post-treatment. If there are no safety concerns, the patient will be permitted to leave the clinic. If the IOP value is of concern to the investigator, the patient will remain in the clinic and will be managed in accordance with the investigator's clinical judgment. Both the last post-treatment IOP measured prior to any intervention for increased IOP (if applicable) and the last post-intervention IOP (if applicable) will be recorded on the Post-Treatment IOP eCRF. If the study eye is treated with a Lucentis® injection during the same visit as study drug treatment, the treatment with Lucentis must be performed first. Measure and record the post-Lucentis treatment IOP value on the eCRF.

[p] Record *on the concomitant medications log* any concomitant medications (i.e., any prescription medications or over-the-counter preparations **other than** protocol-specified procedural medications, such as proparacaine) that patients *continue* taking (no stop date) *after the Week 96* visit *of the parent study is completed or concomitant medications that patients started during the extension study Record concomitant medications* through the patient's early termination visit.

[q] *Any* adverse events ongoing from the parent study *after Week 96 completion* should be transcribed to OLE Adverse Events eCRF log. *After the Week 96 visit completion for the parent study,* new adverse events will be recorded *in* the *extension* study through *minimum of* 30 days after the last dose of study drug or the *last* study *visit, whichever is later.* Adverse events assessed by the investigator as related to the study drug should be followed until the event resolves or until the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has ended.

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

[s] Patients will be contacted by study site personnel 4 (±2) days after each study drug treatment to elicit reports of any decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. At sites where the investigator's decision is for the patients to take pre- and post-treatment antimicrobials, patients will also be asked whether they have taken the prescribed, self-administered, post-treatment antimicrobials. Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for a safety assessment visit.

Appendix 2
Study Flowchart: Unscheduled Safety Assessment Visit

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

IOP = intraocular pressure.

[a] If determined to be necessary by the investigator, perform the 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 event causality to be evaluated by the qualified ophthalmologist.

Appendix 3
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells

Table 1 Grading Scale for Anterior Chamber Flare or Cells

Grade	Description
	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 to 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 per 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. With regard to 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 et al. (1959).

Appendix 3
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells (cont.)

Table 2 Grading Scale for Vitreous Cells

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

Modified from: Nussenblatt et al. (1996).

REFERENCES

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

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

Appendix 4
Best Corrected Visual Acuity Testing

SCOPE

Best corrected visual acuity will be measured by trained and certified personnel at the study sites. The visual acuity (VA) examiner will be masked to patients' study eye assignment. VA will be measured at the intervals specified in the protocol (see Section 4.5.4 and Appendix 1).

EQUIPMENT

The following are needed to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts (modified Early Treatment Diabetic Retinopathy Study Charts R, 1, and 2 in the United States and Charts 1, 2, and 3 in the European Union)
- Retro-illuminated box
- Study frame
- Study lens set

TRAINING AND CERTIFICATION

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

Appendix 5
Low-Luminance Best Corrected Visual Acuity Testing

There are the same requirements as the best corrected visual acuity described in Appendix 4; however, low-luminance visual acuity will be measured by placing a 2.0-log–unit neutral density filter (Kodak Wratten 2.0 Neutral Density Filter) over the best correction for that eye and having the participant read the normally illuminated Early Treatment Diabetic Retinopathy Study Chart.

Appendix 6
Color Fundus Photography

SCOPE

Stereo color fundus photographs will be obtained by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the protocol (see Appendix 1). Analysis (if applicable) of fundus photographs will be performed by the Central Reading Center.

EQUIPMENT

See the Central Reading Center manual.

PROCEDURE

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

Appendix 7
Fluorescein Angiography

SCOPE

Fluorescein angiography (FA) will be performed at study sites by trained personnel who are certified by the Central Reading Center. The FA assessments will be extracted from the Week 96 visit of the parent study and will be obtained at the early termination visit (see Appendix 1). Analysis (if applicable) of FAs will be performed by the Central Reading Center.

EQUIPMENT

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

Film-based angiography is not acceptable.

DIGITAL IMAGING SYSTEMS AND CERTIFICATION

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

PROCEDURES

The Central Reading Center will provide a study manual and training materials. Photographers, systems, and software will be certified prior to obtaining angiograms of patients.

Appendix 8
Fundus Autofluorescence

SCOPE

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

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

The Central Reading Center will provide the study manual and training materials. FAF operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 9
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 Appendix 1).

The SD-OCT images of both eyes will be obtained at protocol-specified visits and will be forwarded to the Central Reading Center.

EQUIPMENT

Equipment utilized during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed 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 10
Near-Infrared Imaging

Near-infrared (NI) images will be obtained to complement the Central Reading Center's evaluation of fundus autofluorescence images.

SCOPE

NI imaging will be performed at the study sites by trained personnel who are certified by the Central Reading Center. NI imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1).

The NI images of both eyes will be obtained at protocol-specified visits and will be forwarded to the Central Reading Center.

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

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

Appendix 11
Optional Mesopic Microperimetry (Selected Sites Only)

SCOPE

Mesopic microperimetry of the study eye only will be performed at selected study sites for the patients who signed the optional microperimetry consent section of the Informed Consent Form by trained personnel who are certified by the central reading center. The microperimetry will be performed on patients who meet eligibility criteria as defined in the Central Reading Center Manual and in this protocol.

The microperimetry results of the study eye will be obtained at protocol-specified visits (see Appendix 1) and will be forwarded to the central reading center.

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version

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

The following form, based upon NEI VFQ-25, was developed at RAND under the sponsorship of the NEI and was adapted by the Sponsor for use in this study. Six questions from the appendix of optional additional questions for the NEI VFQ pertaining to the near activities and distance activities were added to the form. Minor changes (not affecting the items of the questionnaire) were made to the form, and a header was added with the study number, Sponsor's name, visit, and patient identifiers.

INSTRUCTIONS TO THE PATIENT

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

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

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

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

(Circle One)

READ CATEGORIES:

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

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

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

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

PART 2 - DIFFICULTY WITH ACTIVITIES

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

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

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

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

(Circle One)

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

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

No..... 2

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

(Circle One)

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

Gave up 2

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

(Circle One)

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

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

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

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

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

PART 3: RESPONSES TO VISION PROBLEMS

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

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One On Each Line)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

SUBSCALE: NEAR VISION

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

(Circle One)

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

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

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

(Circle One)

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

SUBSCALE: DISTANCE VISION

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

(Circle One)

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

Appendix 12
National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

A5. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

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

A6. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(READ CATEGORIES AS NEEDED)

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

That's the end of the interview. Thank you very much for your time and your help.

Appendix 13
Functional Reading Independence Index

Please read the following instructions to the patient.

INSTRUCTIONS TO PATIENT

"We are interested in learning more about how your vision affects your everyday reading. I'm going to ask you about seven activities that involve reading. If you wear eyeglasses or contact lenses, please answer all the questions as if you were wearing them during the activity.

Please take as much time as you need to answer each question. Remember, there are no right or wrong answers. All of your answers are confidential. Do you have any questions before we begin?

Please think about your vision over the past 7 DAYS when answering each question."

Appendix 13
Functional Reading Independence Index (cont.)

1. In the past 7 DAYS, did you read written print such as books, magazines or newspapers? ☐ Yes ☐ No	
If "Yes"	**I'd like to know more about that. I will read you a list of statements – Please answer "Yes" or "No" to each:** a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the text closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? (example, if needed: using a large print book) ☐ Yes ☐ No e. Did another person help you read written print such as books, magazines or newspapers? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 2. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? Please choose one answer. (Go to Question 2)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? Please choose one answer. (example, if needed: no time or opportunity to read written print)

Appendix 13
Functional Reading Independence Index (cont.)

2. In the past 7 DAYS, did you read to pay bills or write a check? ☐ Yes ☐ No	
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the bill or text closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? (example, if needed: using a check-writing template) ☐ Yes ☐ No e. Did another person help you read to pay bills or write a check? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 3. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to Question 3)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need or opportunity to pay bills)

Appendix 13
Functional Reading Independence Index (cont.)

3. In the past 7 DAYS, did you read in order to take your medicine such as reading a prescription, medicine label, or a syringe? ☐ Yes ☐ No	
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the medicine bottle or prescription closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read in order to take your medicine? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 4. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to Question 4)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need to take medicines)

Appendix 13
Functional Reading Independence Index (cont.)

4. In the past 7 DAYS, did you read labels such as price tags, food labels, or clothing labels?	☐ Yes ☐ No
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting? ☐ Yes ☐ No b. Did you move the price tag or label closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read labels? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 5. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to Question 5)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need or opportunity to read labels)

Appendix 13
Functional Reading Independence Index (cont.)

5.	**In the past 7 DAYS, did you make or receive a telephone call that required you to read the numbers on a telephone, answering machine or caller-ID device? This includes cell phones.**	☐ Yes ☐ No
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use extra lighting or less lighting? ☐ Yes ☐ No b. Did you move the telephone closer to you? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No (example, if needed: using a "talking caller-ID") e. Did another person help you read to make or receive a telephone call? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 6. f. In the past 7 days, how often did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to Question 6)	
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need or opportunity to make phone calls)	

Appendix 13
Functional Reading Independence Index (cont.)

6. In the past 7 DAYS, did you read words or numbers on your screen while watching television?	☐ Yes ☐ No
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use less lighting? ☐ Yes ☐ No b. Did you move closer to the television? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read words or numbers on the television screen? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 7. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to Question 7)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need or opportunity to watch television)

Appendix 13
Functional Reading Independence Index (cont.)

7. In the past 7 DAYS, did you read when using a computer? ☐ Yes ☐ No	
If "Yes"	If needed: I will read you a list of statements – Please answer "Yes" or "No" to each: a. Did you use less lighting or change the contrast on the screen? ☐ Yes ☐ No b. Did you move closer to the computer screen or increase the font size? ☐ Yes ☐ No c. Did you use a magnifying glass? ☐ Yes ☐ No d. Did you use any other vision aids, not already mentioned? ☐ Yes ☐ No e. Did another person help you read when using a computer? ☐ Yes ☐ No ↓ If "Yes" to Item e, ask Item f. If "No" to Item e, go to concluding statements. f. In the past 7 days, <u>how often</u> did someone help you? Was it… ☐ Some of the time, ☐ Most of the time, or ☐ All of the time? (Go to concluding statements)
If "No"	g. **Was this because of…** ☐ Your vision, or ☐ For other reasons? (example, if needed: no need or opportunity to use a computer)

"This concludes our interview. Thank you for your time."

Appendix 14
Minnesota Low-Vision Reading Test

READING SPEED ASSESSMENT

THE MNREAD READING SPEED ASSESSMENT

The Minnesota Low-Vision Reading Test (MNRead) acuity cards are continuous-text reading-acuity cards suitable for measuring the reading acuity and reading speed of normal and low-vision patients. These cards were developed at the Minnesota Laboratory for Low-Vision Research, University of Minnesota, Minneapolis, Minnesota, in research funded by the National Institutes of Health (please refer to Table 1 for MNRead selected countries list).

MEASURING READING SPEED

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

EQUIPMENT

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

TESTING

Card Illumination

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

Viewing Distance

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

Appendix 14
Minnesota Low-Vision Reading Test (cont.)

Testing Procedure

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

The card should be read from a distance of exactly 32 cm. To keep the testing distance constant, use a piece of transparent fishing line, premeasured at 32 cm from the card. Measure the 32 cm to the patient's eye by holding the fishing line parallel to the floor. A ruler or 32-cm measuring device may also be used to set and monitor the distance. Instruct the patient that the card may be moved up and down or side to side but not closer to or farther from the eyes. The card must remain upright and must not tilt away from or toward the patient. Either the patient or the examiner may hold the card, depending on the physical ability of the patient. Alternatively, the card may be placed on an easel or adjustable stand.

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

INSTRUCTIONS TO THE PATIENT

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

SCORING

Two pieces of information are required to be recorded on the score sheet for each test sentence: the time and the number of errors. Use a stopwatch to record the time taken to read each sentence (to the nearest 0.1 second). For each sentence on the score sheet, mark the total number of words missed, read incorrectly, or not able to be read, and the time taken to read the sentence (i.e., the time between when you say "start" and

when the patient finishes uttering the last word in the sentence). Sentences that could not be read or were not attempted due to vision should be recorded as 0 for time and 10 for errors.

MEASURING READING FUNCTION

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

Table 1 Detailed Table for Administration of MNRead

Selected Countries	Primary Language	MNRead
Argentina	Spanish	X
Australia	English	X
Mexico	Spanish	X
Peru	Spanish	X
U.S.	English or Spanish	X
UK	English	X

Appendix 15
Radner Reading Cards

The Radner reading cards consist of “sentence optotypes,” which are optimized reading test items, standardized by construction and statistical selection. The Radner reading cards are suitable for measuring reading speed, reading visual acuity (VA), and critical print size (please refer to Table 1 for Radner Reading Cards selected countries list).

MEASURING READING SPEED

The test consists of 24 short sentences that are highly comparable in terms of number of words, word length, position of words, lexical difficulty, and syntactical complexity. These cards were developed by ophthalmologist Wolfgang Radner, M.D., in Vienna, Austria in interdisciplinary cooperation with psychologists, linguists, physicists, and statisticians.

EQUIPMENT

The Radner reading cards are in the form of a letter-sized booklet with the reading cards and includes clear instructions and evaluation sheets. Eight sentences are printed per page. Each sentence of 14 words is printed on three lines, and print sizes vary from 6.3 M to 0.25 M (20/400 to 20/16 at 32 cm).

A stopwatch is required to record time to a tenth of a second. An easel or adjustable stand may be needed for some patients.

TESTING

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

CARD ILLUMINATION

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

VIEWING DISTANCE

The test should be conducted at a viewing distance of 32 cm. To keep the testing distance constant, use a piece of transparent fishing line, premeasured at 32 cm from the card. Measure the 32 cm to the patient’s eye by holding the fishing line parallel to the floor. A ruler or 32-cm measuring device may also be used to set and monitor the distance. Instruct the patient that the card may be moved up and down or side to side,

but not closer to or farther from the eyes. The card must remain upright and must not tilt away from or toward the patient. Either the patient or the examiner may hold the card, depending on the physical ability of the patient. Alternatively, the card may be placed on an easel or adjustable stand.

TESTING PROCEDURE

Check to ensure that the reading card number on the scoring sheet corresponds to the reading card number that you are using. Sentences should be covered with a piece of paper, and the patient should be asked to uncover sentence by sentence and to read only one sentence per measurement. Start the measurement with the stopwatch when the patient starts reading and measure the reading time until the end of the sentence. Write the reading time on the scoring sheet (to the nearest 0.1 second), and record any reading errors on the sheet. The reading test should be stopped when the reading time is longer than 20 seconds or when the patient is making severe errors.

INSTRUCTIONS TO THE PATIENT

“Please read the sentences aloud as quickly and accurately as possible. Read each sentence to the end, and do not correct reading errors.

Please uncover the first sentence and start reading.”

MEASURING READING FUNCTION

Patient’s average reading speed, critical print size, and VA will be calculated using the data transcribed from the scoring sheet to the electronic Case Report Form and will not be calculated by the interviewers.

Appendix 15
Radner Reading Cards (cont.)

Table 1 Detailed Table for Administration of Radner Reading Card

Selected Countries	Primary Language	Radner
Austria	German	x
Brazil	Portuguese	x
Canada	English or French	x
Denmark	Danish	x
France	French	x
Germany	German	x
Italy	Italian	x
Netherlands	Dutch	x
Spain	Spanish	x
Switzerland	German, Italian, or French	x
Belgium	French, German, or Dutch	x
Hungary	Hungarian	x
Turkey	Turkish	x
Portugal	Portuguese	x
Sweden	Swedish	x
Turkey	Turkish	x

Appendix 16
Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLES

Biological samples for the assessment of lampalizumab concentrations (pharmacokinetics), anti-lampalizumab antibodies, biomarker plasma, and laboratory assessment (hematology, chemistry panel, coagulation, and urinalysis) samples will be collected at the timepoints specified in Appendix 1.

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

OPTIONAL ANTERIOR CHAMBER (AQUEOUS HUMOR) SAMPLE COLLECTION

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

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

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