

Official Title: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LAMPALIZUMAB ADMINISTERED INTRAVITREALLY TO PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

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PROTOCOL

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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
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PROTOCOL AMENDMENT, VERSION 6: RATIONALE

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

- Section 1.3 was updated to reflect the number of patients who have received at least one 10-mg dose of lampalizumab as part of two completed clinical studies (Phase 1a Study CFD4711g and Phase 1b/II Study CFD4870g) and an ongoing study (Study GX28198), which is an extension of Study CFD4870g.
- Section 3.1 was updated to guide sites in handling specific patient screening and scheduling issues. Section 3.1.1 has been updated to provide a more accurate number of global sites that will be participating in Study GX29176.
- Section 3.1.2 was revised to remove repetitive information regarding Data Monitoring Committee review of efficacy data for Study GX29176.
- Section 3.5 had been added to indicate that exploratory substudies might be added to Study GX29176.
- Section 4.1 includes guidance regarding the procedure for handling patients who need an extended screening period to prevent unnecessary re-screening as a result of missing the screening visit window due to unforeseen circumstances.
- In Section 4.1.1, the inclusion criteria regarding contraceptive methods for women of childbearing potential and men have been harmonized with current international recommendations. The definition of women of childbearing potential has been harmonized with current international recommendations.
- In Section 4.1.2, the exclusion criteria for concurrent systemic conditions have been updated to include treatment for localized in addition to systemic infection and that ongoing prophylactic use of antimicrobial therapy should be discussed with Medical Monitor.
- Section 4.2.2 contains additional details regarding the masked and unmasked roles, how they are documented, and under what conditions they may be switched to maintain the study masking and proper conduct of study procedures.
- In Section 4.4.1 updated instructions are given in the event that Lucentis treatment is given at the same visit as a study eye treatment with lampalizumab/sham to help ensure patient safety.
- Section 4.5.1 was updated to include re-screening tests as events requiring written informed consent to remind the site personnel of this requirement.
- Section 5.1 was updated to include transient vision loss as a potential ocular safety issue currently thought to be associated with the route of administration to help ensure patient safety. Table 6 has been revised to provide more detailed guidance for the assessment of causality.
- Section 5.3.5.10 was updated to clarify criteria when hospitalization does not require immediate reporting as a serious adverse event (SAE).
- Sections 5.4–5.5 were revised to update the procedures for submitting various types of safety reports

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- Appendix 4 has been revised to further clarify the pre-treatment procedures for patients undergoing treatment or sham injections to help ensure patient safety.
- Appendix 5 has been revised to include equivalent study treatment supplies (needles) available outside of the United States and to further clarify the steps required to prepare and administer a lampalizumab injection to help ensure patient safety.
- Appendix 20 has been updated to emphasize that the treating physician collects the optional aqueous humor samples.

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

PROTOCOL AMENDMENT, VERSION 6: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

...A total of ~~433~~147 patients have received at least one 10-mg dose of larpalizumab as part of two completed clinical studies (Studies CFD4711g and CFD4870g) and an ongoing study (Study GX28198), which is an extension of Study CFD4870g.

SECTION 3.1: DESCRIPTION OF STUDY

...Screen-failed patients may be eligible for re-screening up to two additional times during the *enrollment period of the study*. *At re-screening, all screening visit assessments will be performed except for CFI biomarker sample and FA imaging collection, provided that a valid CFI result is available and reading center-eligible FA images were taken within 8 weeks before the new Day 1 visit (randomization)*.

...The first study treatment will be administered on the same day as randomization (Day 1 visit). *If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), with the Medical Monitor's permission, the patient's first study treatment may be administered within 3 working days of the Day 1 visit. The following assessments will be repeated on the day of the study treatment: slit lamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurement (recorded on Day 1 eCRF and dated accordingly)*.

...*After the Day 1 visit, if a patient misses a study visit when ocular images are scheduled to be taken (see Appendix 1), the images must be obtained at the next scheduled visit.*

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

SECTION 3.1.1: Planned Total Sample Size

Approximately 936 patients (188 biomarker-positive patients per treatment group [larpalizumab Q4W, larpalizumab Q6W, and pooled sham] and 124 biomarker-negative patients per treatment group [larpalizumab Q4W, larpalizumab Q6W, and pooled sham]) will be enrolled in the study at approximately ~~425~~140 sites located globally.

SECTION 3.1.2: Data Monitoring Committee

...The iDMC will meet approximately every 6 months (frequency adjustable as required) to evaluate the benefit-risk profile of larpalizumab treatment through reviewing both *safety and efficacy* data. No formal efficacy/futility analysis is planned to be done by

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iDMC. ~~If the iDMC deems a benefit risk assessment necessary, the iDMC may also review unmasked efficacy data.~~

SECTION 3.5: EXPLORATORY SUBSTUDIES

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GX29176 protocol. Each substudy will be documented in a separate substudy protocol and associated ICF(s).

SECTION 4.1: PATIENTS

Patient Selection and Sex Distribution

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

Note: Some patients may require an extended screening period as a result of repeated evaluation of images or other issues. Upon agreement with the Medical Monitor, the screening period may be extended for up to 5 days for such cases.

SECTION 4.1.1: Inclusion Criteria

General Inclusion Criteria

- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): of childbearing potential: agreement to remain abstinent ~~or (refrain from heterosexual intercourse) or use single or combined~~ contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of study ~~treatment drug~~

~~Abstinence~~ *A woman is ~~only acceptable~~ considered to be of childbearing potential if ~~she is in line~~ postmenarcheal, has not reached a postmenopausal state (≥ 12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).*

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

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

~~Examples of contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate~~

~~of <1% per year. Barrier methods must always be supplemented with the use of a spermicide.~~

~~Sexually active men will be required to use a barrier contraceptive method (condom), even if they have been surgically sterilized, for the duration of the~~ For men:

~~Agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:~~

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

SECTION 4.1.2: Exclusion Criteria

Ocular Exclusion Criteria: Concurrent Ocular Conditions

- History of recurrent infectious or inflammatory ocular disease *in either eye*

Concurrent Systemic Conditions Exclusion Criteria

- Treatment for active systemic *or localized* infection

The ongoing prophylactic use of antimicrobial therapy should be discussed with the Medical Monitor.

- Women who are pregnant or lactating or intending to become pregnant during the study

~~Women who are not postmenopausal (≥ 12 months of non therapy induced amenorrhea) or surgically sterile~~ *Women of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study treatment.*

SECTION 4.2.2: Masking

...At least one other investigator (and designated, unmasked assistant, as needed) will be designated as the treating (injecting) physician who will be unmasked to patients' treatment assignment and will administer injections (lampalizumab or sham). *The Principal Investigator must be masked to patients' treatment assignment. All roles for each study staff member should be clearly documented on the Site Delegation Log. The Delegation Log should be signed by the Principal Investigator.*

Once the designated *masked vs. unmasked* roles are ~~determined~~, delineated and the site study staff have started to perform them, the roles ~~will not~~ cannot be switched or reversed at any time during the conduct of the study. ~~In the event an alternate investigator needs to be substituted for an investigator, that alternate physician may assume only one role (i.e., treating physician or evaluating physician) for the duration of the study.~~ In case a site is ~~dealing with an~~ experiencing unexpected extreme situation, ~~sponsor~~ situations, the Medical Monitor's permission might be granted to switch an ~~investigator~~ the study staff member from the masked role (~~evaluating physician~~) to the unmasked role (~~treating physician~~), but not the other way around. *In the event an*

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alternate study staff member needs to be added or substituted, that alternate study staff member may assume only one role for the duration of the study.

Starting at ~~a~~ *the patient's Day 1 visit, the treating physician(s) (performing the lampalizumab or sham injections), post-treatment finger counting, and optional aqueous humor sample collection) must not continue their role as treating physician only, cannot be involved in any other aspect of the study, in any way and must not divulge treatment assignment to anyone.*

SECTION 4.4.1: Permitted Therapy

...NOTE: If (as per masked investigator judgment) treatment with Lucentis is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab/sham, the treatment with Lucentis must be administered first. Following this, a safety *assessment* (including an IOP check) ~~to proceed to~~ *must be completed by the physician in the masked role prior to the study eye treatment with lampalizumab/sham must be assessed prior to.* *If there are no concerns, the site may proceed with calling IxRS for the study treatment kit assignment.*

SECTION 4.5.1: Informed Consent Forms and Screening Log

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

SECTION 5.1: SAFETY PLAN

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 AEs (serious and non-serious) and pregnancies will be recorded ~~on eCRFs~~ for the duration of this study.

TABLE 6: Causal Attribution Guidance

Table 6 has been revised to update the guidance for causal attribution.

SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization or Surgery

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

- *Hospitalization for a preexisting condition, provided that the following criteria are met:*
 - *The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.*
 - *The patient has not experienced an adverse event.*

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, only SAEs caused by a protocol-mandated intervention should be reported. ~~A paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet provided to investigators should be completed and faxed to Roche Safety Risk Management submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or scanning and emailing the form using the fax numbers number or email address provided to investigators (“Protocol Administrative and Contact Information and List of Investigators”).~~

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

...In the event that the EDC system is unavailable, ~~a paper the Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet provided to investigators should be completed and faxed submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax numbers number or email address provided to investigators (“Protocol Administrative and Contact Information and List of Investigators”).~~ Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.4.3.1: 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 the last study visit. ~~A Clinical Trial Pregnancy Report eCRF Reporting Form should be completed by the investigator and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via), either by faxing or by scanning and emailing the EDC system. A pregnancy report will automatically be generated and sent to the Sponsor. 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 SAEs 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.*

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~~In the event that the EDC system is unavailable, a paper Clinical Study Pregnancy Reporting Form and fax cover sheet should be completed and faxed to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (“Protocol Administrative and Contact Information and List of Investigators”). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.~~

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or until the last study visit. ~~A Clinical Trial Pregnancy Report eCRF 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 the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system, 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. ~~Once~~ After the authorization has been signed, the investigator will ~~update the~~ submit a Clinical Trial Pregnancy Report eCRF with additional Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

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

SECTION 5.5.1: Investigator Follow-Up

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

APPENDIX 4: Pre-Injection Procedures for All Patients

Appendix 4 has been revised to further clarify the pre-treatment procedures for patients undergoing treatment or sham injections.

APPENDIX 5: Preparation and Administration of Lampalizumab Injection

Appendix 5 has been revised to include equivalent study treatment supplies (needles) available outside of the United States and to further clarify the steps required to properly prepare and administer a lampalizumab injection.

APPENDIX 20: Biological Sample Collection and Shipping Instructions

Appendix 20 has been revised to stress that the treating physician collects the optional aqueous humor samples.

MASTER INFORMED CONSENT FORM

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LAMPALIZUMAB ADMINISTERED INTRAVITREALLY TO PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

PROTOCOL NUMBER: GX29176

VERSION NUMBER: 6

EUDRACT NUMBER: 2014-000107-27

IND NUMBER: 104996

TEST PRODUCT: Lampalizumab (RO5490249)

MEDICAL MONITOR: [REDACTED], M.D., Ph.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 return the signed *copy* of this form to the local study monitor. Please retain *the original* for your study files.

PROTOCOL SYNOPSIS

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LAMPALIZUMAB ADMINISTERED INTRAVITREALLY TO PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

PROTOCOL NUMBER: GX29176

VERSION NUMBER: 6

EUDRACT Number: 2014-000107-27

IND NUMBER: 104996

TEST PRODUCT: Lampalizumab (RO5490249)

PHASE: III

INDICATION: Geographic Atrophy

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective of this study is to evaluate the efficacy of intravitreal injections of 10-mg lampalizumab administered every 4 weeks (Q4W) or every 6 weeks (Q6W) in complement factor I (CFI) profile biomarker-positive and CFI profile biomarker-negative patients compared with sham control assessed by change in the geographic atrophy (GA) area from baseline as measured by fundus autofluorescence (FAF).

The secondary efficacy objective of this study is to evaluate the effect of lampalizumab compared with sham control, with respect to:

- Macular functional response as assessed by mesopic microperimetry
- Best corrected visual acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (at a starting distance of 4 m)
- BCVA as measured by ETDRS chart (at a starting distance of 4 m) under low luminance conditions
- Binocular reading speed as assessed by the Minnesota Low-Vision Reading (MNRead) Test or by Radner Reading Charts
- Binocular critical print size as assessed by the MNRead or by Radner Reading Charts
- Patient-reported visual function as assessed by the National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25)
- Patient-reported independent reading as assessed by the Functional Reading Independence Index (FRI Index)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the local and systemic safety and tolerability of intravitreal injections of 10-mg lampalizumab administered Q4W or Q6W relative to sham control
- To evaluate the clinical significance of anti-therapeutic antibodies directed against lampalizumab

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Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the systemic PK of lampalizumab administered by 10-mg intravitreal injections Q4W or Q6W.

Diagnostic Objective

A diagnostic objective for this study is to evaluate the prognostic value of the CFI profile biomarker on the mean change in the GA area from baseline as measured by FAF.

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the effect of lampalizumab compared with sham control, with respect to:
 - Monocular reading speed as assessed by MNRead charts or by Radner Reading Charts
 - Monocular critical print size as assessed by MNRead charts or by Radner Reading Charts
 - Monocular reading acuity as assessed by MNRead charts or by Radner Reading Charts
 - Binocular reading acuity as assessed by MNRead charts or by Radner Reading Charts
- To evaluate the aqueous levels of total lampalizumab and factor D following study treatment
- To evaluate the potential association of genetic variants in CFI and complement-pathway genes with disease characteristics and response to administration of lampalizumab
- To evaluate the relationship of genetic variants in CFI and complement-pathway genes to levels in the blood of messenger RNA (mRNA) and proteins of CFI and complement-pathway genes

Study Design

Description of Study

This study is a Phase III, double-masked, multicenter, randomized, sham injection-controlled study evaluating the efficacy and safety of a 10-mg dose of lampalizumab administered Q4W or Q6W by intravitreal injections for approximately 2 years (96 weeks) treatment period in patients with GA secondary to age-related macular degeneration (AMD).

Number of Patients

The study will randomize approximately 936 patients at approximately 140 investigational sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

- Willingness and the 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.
- Age ≥ 50 years
- For women of childbearing potential: agreement to remain abstinent (*refrain from heterosexual intercourse*) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 30 days after the last dose of study drug

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

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

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

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

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

- Ability and willingness to undertake all scheduled visits and assessments
- Valid CFI profile biomarker result (i.e., CFI profile biomarker-positive or CFI profile biomarker-negative)

Ocular Inclusion Criteria: Study Eye

- BCVA letter score of ≥ 49 letters (Snellen equivalent of 20/100 or better) using ETDRS charts at starting distance of 4 m
 - If BCVA letter score is ≥ 79 letters (Snellen equivalent of 20/25 or better), at least one GA lesion must be within 250 μm of the foveal center
- Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV
The total GA lesion size $\geq 2.54 \text{ mm}^2$ (approximately ≥ 1 disc area [DA]) and $\leq 17.78 \text{ mm}^2$ (approximately ≤ 7 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea)
 - If GA is multifocal, at least 1 focal lesion must be $\geq 1.27 \text{ mm}^2$ (approximately ≥ 0.5 DA)
- Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to the area of GA
- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging

Ocular Inclusion Criteria: Non-study Eye

- GA secondary to AMD with no evidence of prior or active CNV

Exclusion Criteria

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

GA Characteristics Exclusion Criteria

- GA in either eye due to causes other than AMD (monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy])

Ocular Exclusion Criteria: Study Eye

- History of vitrectomy surgery, submacular surgery, or any surgical intervention for AMD
- Previous laser photocoagulation for CNV, diabetic macular edema, retinal vein occlusion, and proliferative diabetic retinopathy

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- Prior treatment with Visudyne[®], external-beam radiation therapy, or transpupillary thermotherapy
- History of prophylactic subthreshold laser treatment for AMD
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, or device implantation). A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.

Ocular Exclusion Criteria: Non-study eye

- Non-functioning non-study eye defined as either:
 - BCVA of hand motion or worse
 - OR
 - No physical presence of non-study eye (i.e., monocular)

Ocular Exclusion Criteria: Both Eyes

- Previous participation in interventional clinical trials for geographic atrophy or dry AMD (except of vitamins and minerals) irrespective of the route of administration (ocular or systemic)
- Previous treatment with eculizumab, lampalizumab, fenretidine or any other drugs for geographic atrophy or dry AMD treatment

Ocular Exclusion Criteria: Concurrent Ocular Conditions

- Retinal pigment epithelium (RPE) tear that involves the macula in either eye
- Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could do either of the following:
 - Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
 - If allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of BCVA during the study period
- Active uveitis and/or vitritis (grade trace or above) in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Current vitreous hemorrhage in the study eye
- History of retinal detachment or macular hole (Stage 3 or 4) in the study eye
- Aphakia or absence of the posterior capsule in the study eye
- Previous violation of the posterior capsule in the study eye unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia.
- Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding Day 1
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure [IOP] \geq 30 mm Hg despite treatment with anti-glaucoma medication)
- History of glaucoma-filtering surgery in the study eye
- History of corneal transplant in the study eye
- Proliferative diabetic retinopathy in either eye

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- Prior or active CNV in either eye
- Central serous retinopathy in either eye
- History of recurrent infectious or inflammatory ocular disease *in either eye*

Concurrent Systemic Conditions Exclusion Criteria

- Uncontrolled blood pressure (defined as systolic >180 mm Hg and/or diastolic >110 mm Hg while patient is sitting)
 - If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by anti-hypertensive medication, the patient can become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- 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
- Treatment for active systemic *or localized* infection
 - The ongoing prophylactic use of antimicrobial therapy should be discussed with the Medical Monitor.*
- Predisposition or history of increased risk of infection (i.e., history of splenectomy or chronic immunosuppression)
- Active malignancy within past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma and prostate cancer with a Gleason score of ≤ 6 and a stable prostate-specific antigen (PSA) for ≥ 12 months.
- History of allergy to fluorescein that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lampalizumab injection
- Inability to comply with study or follow-up procedures
- Inability to obtain color fundus photograph (CFP), FAF, and fluorescein angiogram (FA) of sufficient quality to be analyzed and graded by the central reading center
- Previous participation in any studies of investigational drugs within 3 months (except as listed in the section 4.1.2d) preceding Day 1 (excluding vitamins and minerals)
- Requirement for continuous use of any medications/treatments indicated in the "Prohibited Therapy" section of the protocol
- Women who are pregnant or lactating or intending to become pregnant during the study
- *Women of childbearing potential* must have a negative serum pregnancy test result within 28 days prior to initiation of study treatment.

Microperimetry criteria at selected sites only

Inclusion Criteria

- Patients must meet all other eligibility criteria for study entry.
- Microperimetry screening test criteria for eligibility:

Must be able to detect fixation target.

Total elapsed time to complete the 10-2 68 point exam is ≤ 30 minutes in duration.

Reliability Test ratio $\leq 20\%$ (false positive rate).

Ability and willingness to undertake MP assessment as determined by investigator.

Exclusion Criteria

- Any exclusion criteria listed for the study entry
- Investigator determines that patient is unable to perform the test reliably (e.g. Difficulty sitting still against the supporting chinrest for >10 minutes; Unable to physically operate the clicker or joystick; Unable to follow the instructions for the test [i.e. cognitive impairment])

Note: disqualification from the microperimetry assessment doesn't exclude a patient from the trial participation if she/he qualifies as per the rest of the study entry criteria.

Length of Study

The duration of the study is approximately 2 years (96 weeks) after the last patient is randomized to the study.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 96 weeks after the last patient is randomized to the study.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is GA area at 1 year as assessed by FAF.

The secondary efficacy outcome measures for this study over time are as follows:

- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response
- Change in macular sensitivity as assessed by mesopic microperimetry for the evaluation of the macular functional response
- GA area as assessed by FAF
- BCVA score as assessed by ETDRS chart at a starting distance of 4 m
- BCVA score as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m
- Binocular reading speed as assessed by MNRead charts or Radner Reading Charts
- Binocular critical print size as assessed by MNRead charts or Radner Reading Charts
- NEI VFQ-25 composite score
- NEI VFQ-25 near activity subscale score
- NEI VFQ-25 distance activity subscale score
- FRI Index score

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- The incidence and severity of ocular adverse events
- The incidence and severity of systemic (non-ocular) adverse events
- Changes and abnormalities in ECG parameters
- The incidence of anti-lampalizumab antibodies

Pharmacokinetic Outcome Measure

The PK outcome measure for this study is serum lampalizumab concentration over time.

Diagnostic Outcome Measure

The evaluation of the prognostic value of the CFI profile biomarker will be based on the biomarker status at baseline and the primary clinical outcome of change in the GA area from baseline as measured by FAF.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Monocular reading speed as assessed by MNRead charts or Radner Reading Charts over time
- Monocular critical print size as assessed by MNRead charts or Radner Reading Charts over time
- Monocular reading acuity as assessed by MNRead charts or Radner Reading Charts over time
- Binocular reading acuity as assessed by MNRead charts or Radner Reading Charts over time
- Total lampalizumab and factor D levels in aqueous humor as assessed by ELISA
- To evaluate the potential association of genetic variants in CFI and complement-pathway genes with disease characteristics and response to administration of lampalizumab
- To evaluate the relationship of genetic variants in CFI and complement-pathway genes to levels in the blood of mRNA and proteins of CFI and complement-pathway genes

Exploratory Substudies

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GX29176 protocol. Each substudy will be documented in a separate substudy protocol and associated ICF(s).

Investigational Medicinal Products

Lampalizumab

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

Lampalizumab intravitreal injections

A 10-mg dose of lampalizumab will be used in this study and will be administered to patients randomized to lampalizumab treatment arms intravitreally Q4W or Q6W during the 2-year treatment period.

Comparator

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

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

Patients randomized to the control arms will receive sham injections Q4W or Q6W during the 2-year treatment period and will undergo the same assessments as the lampalizumab treatment arm.

Non-Investigational Medicinal Products

None

Statistical Methods

Primary Analysis

The primary and secondary efficacy analyses will be based on the intent-to-treat (ITT) approach. All randomized patients (i.e., ITT population) will be included in the analysis, with patients grouped according to the treatment assigned at randomization.

Detailed specifications of the statistical methods will be described in the statistical analysis plan (SAP).

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Determination of Sample Size

Patients will be randomized in a 2:1:2:1 ratio to receive treatment with lampalizumab Q4W, sham Q4W, lampalizumab Q6W, or sham Q6W. Data from the two sham groups will be pooled in the analysis.

The study is sized to achieve adequate power for detecting a meaningful reduction rate in the GA area growth for a given lampalizumab dosing frequency compared with pooled sham within CFI profile biomarker-positive and CFI profile biomarker-negative groups and to meet health authority requirements for the safety database.

The primary endpoint is the mean change in GA area from baseline to 1 year as assessed by FAF. Assuming a standard deviation of 2.51 mm² for the change from baseline in GA area at 1 year in biomarker-positive patients, 188 CFI profile biomarker-positive patients per lampalizumab treatment group and 94 CFI profile biomarker-positive patients per sham group will provide >95% power to declare a difference between each lampalizumab treatment group and the pooled sham for a targeted difference of 1.45 mm² (approximately 40% reduction relative to sham control) in the change from baseline in GA area at 1 year. Assuming a standard deviation of 1.68 mm² for the change from baseline in GA area at 1 year in CFI profile biomarker-negative patients, 124 CFI profile biomarker-negative patients per lampalizumab treatment group and 62 CFI profile biomarker-negative patients per sham group will provide 80% power to detect a targeted difference of 0.66 mm² (approximately 40% reduction) between each lampalizumab treatment group and the pooled sham group in the change from baseline in GA area at 1 year. Calculations were based on two-sided t-test at the $\alpha=0.0495$ level (after adjustment for planned interim data reviews conducted by the iDMC prior to analysis of the primary efficacy endpoint; see Section 3.1.4), with the assumption of a 15% dropout rate by 1 year. Due to lack of reliable information to estimate the impact of partially missing data on the power, the power calculation is based on the analysis of data from the patients who complete the first year of the study. However, the primary analysis of the study will include all available data from patients in all treatment arms, which will have more power than an analysis of just those patients completing the first year of the study period.

The Sponsor may conduct a masked evaluation of the variance of the primary efficacy endpoint and study dropout rate before the end of enrollment and compare the information to the assumptions used in planning the study. If this comparison suggests the initial assumptions for the dropout rate and/or the variance of the primary efficacy endpoint were substantially lower and the study is consequently underpowered, the study sample size will be increased to maintain the desired study power and safety database. Details will be provided in the SAP.

For patients who are eligible to undergo a microperimetry assessment, at least 46 CFI profile biomarker-positive patients per lampalizumab treatment group and 23 CFI profile biomarker-positive patients per sham group will provide 80% power to detect a targeted difference of 6.91 points with a standard deviation of 9.88 points between each lampalizumab treatment group and the pooled sham group in the change from baseline in the number of scotomatous points at 2 years. Calculation was based on a two-sided t-test at $\alpha=0.05$ level with the assumption of a 25% dropout rate by 2 years.

Optional Interim Analyses

In order to adapt to information that may emerge during the course of this study (e.g., additional information of the biomarker characteristics, additional results of natural history studies), the Sponsor may choose to conduct one interim efficacy analysis. Section 6.7 contains the specifications in place to ensure the study continues to meet the highest standards of integrity when such an optional interim analysis is executed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACP	alternative complement pathway
AE	adverse event
AESI	adverse event of special interest
AH50	Alternative Complement Pathway activity assay
AMD	age-related macular degeneration
anti-VEGF	anti-vascular endothelial growth factor
ATA	anti-therapeutic antibody
BCVA	best corrected visual acuity
C	complement component
CFB	complement factor B
CFD	complement factor D
CFH	complement factor H
CFI	complement factor I
CFP	color fundus photograph
CNV	choroidal neovascularization
CTA	clinical trial assay
DA	disc area
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiogram
FAF	fundus autofluorescence
FDA	U.S. Food and Drug Administration
FRI Index	Functional Reading Independence Index
GA	geographic atrophy
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
iDCC	independent data coordinating center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
IOP	intraocular pressure

IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	Interactive Voice and Web Response Systems
LPLV	last patient, last visit
MNRead	Minnesota Low-Vision Reading Test
mRNA	messenger RNA
MTD	maximum tolerated dose
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25-item Version
NI	near infrared
OCT	optical coherence tomography
OCT-A	optical coherence tomography angiography
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic(s)
PRO	patient-reported outcome
Q4W	every 4 weeks
Q6W	every 6 weeks
qAF	quantitative fundus autofluorescence
RCR	Roche Clinical Repository
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	spectral domain optical coherence tomography
SNP	single nucleotide polymorphism
ULN	upper limit of normal
VA	visual acuity
YAG	yttrium aluminum garnet

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) (Lindblad et al. 2009; Sunness et al. 1999b). 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 at 70 years of age is 0.70%, rising to 2.91% at 80 years of age and 11.29% at 90 years of age (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 with a decline in activities of daily living (Lindblad and Clemons 2005). Moreover, GA is bilateral in most patients with advanced AMD (Lindblad et al. 2009; Sunness et al. 1999b). 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. The Phase III clinical development plan for lampalizumab is designed to test the efficacy and safety of lampalizumab in patients with GA secondary to AMD.

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 with 17,000 AMD cases and >60,000 control that identified multiple genetic risk loci, including four genes (complement factor H [CFH],

complement factor B [CFB], complement factor I [CFI], and complement component [C3]) in the ACP as confirmed genetic risk factors ([Fritsche et al. 2013](#)).

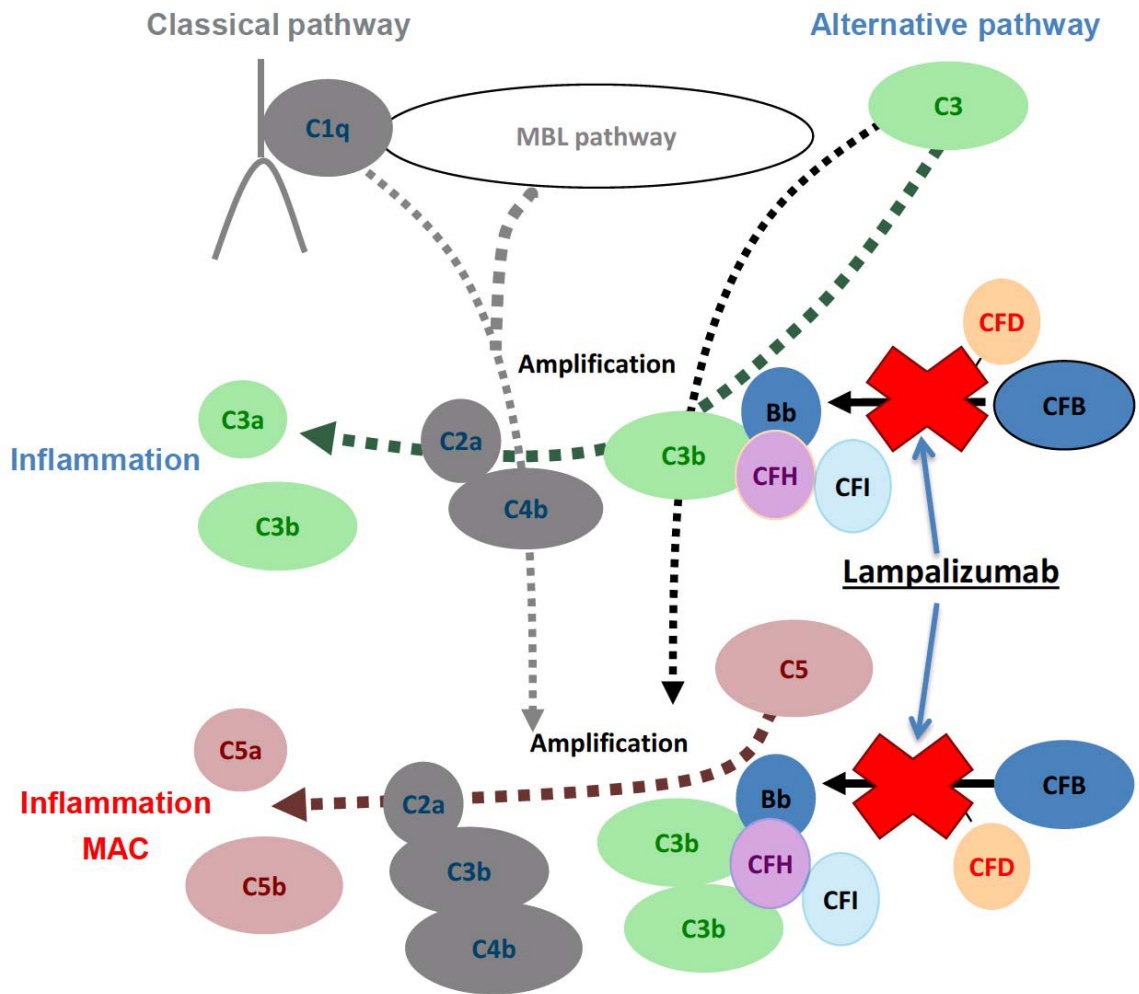
Complement factor D (CFD) is a highly specific chymotrypsin-like serine protease that plays a pivotal and rate-limiting role in the activation and amplification of the ACP (see [Figure 1](#)). The substrate for CFD is another alternative pathway, serine protease, factor B. Following cleavage by CFD,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

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 included protection against oxidative stress-mediated photoreceptor degeneration in a murine model with genetic deficiency of factor D ([Rohrer et al. 2007](#)) and detection of increased systemic activation of complement components, including CFD, in the serum of patients with AMD versus controls, 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.

Figure 1 Pathways of Complement Activation and Site of Inhibition by Lampalizumab



MAC=membrane attack complex; MBL=Mannose binding lectin.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

A total of 147 patients have received at least one 10-mg dose of lampalizumab as part of two completed clinical studies (Studies CFD4711g and CFD4870g) and an ongoing study (Study GX28198), which is an extension of Study CFD4870g.

1.3.1 Study CFD4711g: Phase Ia

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

1.3.2 Study CFD4870g: Phase Ib/II Phase Ib

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

Phase II

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

Preliminary clinical evidence of lampalizumab's efficacy was demonstrated in the Phase Ib/II Study CFD4870g. The Phase II component of Study CFD4870g met its primary endpoint of mean change from baseline in GA area at 18 months as measured by fundus autofluorescence (FAF) and met its secondary endpoint of mean change from baseline in GA area at 18 months as assessed by color fundus photographs (CFPs) in the lampalizumab monthly group. A positive treatment effect in slowing the progression of GA area growth was observed in the monthly group beginning at 6 months and extending through 18 months. The mean difference in GA growth between the monthly group compared to the sham group at Month 18 was 0.595 mm² (80% CI: 0.109, 1.081; p=0.1170, less than the pre-specified type I error rate of 0.2), corresponding to a reduction rate in GA of 20.4% (80% CI: 4%, 37%); the reduction rate is calculated as

$100\% \times [(\text{mean change in sham pooled} - \text{mean change in lampalizumab group}) / \text{mean change in sham pooled}]$.

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

The reported safety data from Study CFD4870g demonstrated an acceptable safety and tolerability profile with no clinically important safety concerns observed with lampalizumab administered as 10-mg intravitreal injections monthly or every other month over 18 months.

Exploratory Genetic Analysis Using Four Single Nucleotide Polymorphisms (SNPs) in the ACP

Although AMD risk involves many factors, it is well accepted that there is a strong genetic contribution. The largest study evaluating AMD genetics to date, a meta-analysis with > 17,000 AMD cases and > 60,000 controls, identified AMD-associated single nucleotide polymorphisms (SNPs) at multiple genetic loci, including five genes (CFH, CFB, CFI, C2, and C3) in the complement pathway (Fritsche et al. 2013). Except for C2, all of these proteins are implicated in the ACP. The strong correlation of these genetic variants in the ACP with the risk of AMD led to the hypothesis that patients with GA and with risk-associated variants at the ACP loci may have higher basal complement activation through the ACP and may derive greater potential benefit from inhibition of the ACP by lampalizumab.

Four SNPs representing CFH, C2/CFB, C3, and CFI were selected and individually tested for an association with the observed efficacy of lampalizumab and for an association with the rate of GA progression in patients in the sham treatment group. The SNPs were chosen based on the most statistically significant AMD risk SNPs in these ACP genes that had previously been reported in a genome-wide meta-analysis (Fritsche et al. 2013). C2 and CFB are tightly linked genetically and, thus, are represented by a single risk SNP. Patients who were heterozygous or homozygous for the risk alleles were grouped together for this analysis and were referred to as risk allele carriers. In patients who had genetic testing performed in the Phase II component of Study CFD4870g, approximately 96%, 98%, 47%, and 57% were carriers of CFH, C2/CFB, C3, and CFI risk alleles, respectively.

Results of Exploratory Analyses of the Phase II Component of CFH, C2/CFB, C3, and CFI SNPs

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

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

Exploratory analysis of the CFI SNPs indicated that there was greater efficacy in the subgroup of patients who were carriers of the CFI risk allele compared to patients who were non-carriers of the CFI risk allele. In CFI risk allele carriers, the mean difference in GA growth between the monthly group and the sham group at Month 18 was 1.839 mm², corresponding to a reduction rate of 44% (approximately 80% CI: 25%, 63%; p=0.0037). In CFI risk allele carriers, the mean difference in GA growth between the every-other-month group and the sham group at Month 18 was 0.734 mm², corresponding to a reduction rate of 18% (approximately 80% CI: -1%, 36%; p=0.2266). In non-carriers of the CFI risk allele, there was no apparent lampalizumab treatment response in either the monthly or every-other-month group.

The prognostic effects of the CFI risk allele were also examined. In patients in the sham group, the change in GA area at Month 18 was 4.169 mm² (80% CI: 3.582, 4.756) in CFI risk allele carriers and 2.792 mm² (80% CI: 2.293, 3.292) in non-carriers of the CFI risk allele; the difference in the GA progression between CFI risk allele carriers and non-carriers was approximately 49%.

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

Definition of CFI Profile Biomarker

The CFI profile biomarker-positive is defined as risk allele carriers of CFI that are also risk allele carriers at CFH and/or C2/CFB, and the CFI profile biomarker-negative is defined as non-carriers of the CFI risk allele or carriers of the CFI risk allele that are non-carriers of the risk alleles at both CFH and C2/CFB (see [Table 1](#)). The CFI profile biomarker was defined using these three risk alleles on the basis of the association of the CFI risk allele with lampalizumab response and on the basis of the high frequency of risk alleles at CFH and C2/CFB in Study CFD4870g and the fact that the CFH and C2/CFB SNPs are highly significant in genome-wide studies of AMD genetic risk (p=1 × 10⁻⁴³⁴ and p=4 × 10⁻⁸⁹, respectively; [Fritsche et al. 2013](#)). The inclusion of CFH and C2/CFB genotypes in the definition of the CFI profile biomarker-positive is intended to increase the likelihood of identifying patients with complement-driven GA disease. Of note, all CFI risk allele carriers in Study CFD4870g were also risk allele carriers at CFH and/or C2/CFB.

Table 1 Definition of Biomarker Status Using the CFI Profile Test

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

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

See Section 3.3.2.2 for details on the assay used to determine valid CFI biomarker status and Appendix 22 for the full specifications of the cobas® CFI Profile Test.

1.3.3 **Study GX28198 Open-Label Extension**

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

1.3.4 **Summary**

In summary, the Phase II results from Study CFD4870g provided evidence that inhibition of the ACP with lampalizumab may slow the progression of GA and that lampalizumab administered as 10-mg intravitreal injections monthly over 18 months demonstrated an acceptable safety and tolerability profile in patients with GA secondary to AMD. In addition, the exploratory genetic analyses suggest that there may be a biomarker-defined population (CFI profile biomarker-positive) that may have more rapid progression of disease and potentially derive greater efficacy benefit from lampalizumab than a group that is negative for the biomarker (CFI profile biomarker-negative).

On the basis of the findings from the Phase I and II studies, the Phase III study aims to further evaluate the efficacy and safety of lampalizumab as well as the potential for the CFI profile biomarker to identify patients who may have more rapid progression of disease and may derive greater benefit from lampalizumab treatment.

For additional details regarding nonclinical and clinical studies, see the Lampalizumab Investigator’s Brochure.

2. OBJECTIVES

The study will assess the efficacy and safety of 10-mg lampalizumab administered by intravitreal injections every 4 weeks (Q4W) or every 6 weeks (Q6W) relative to sham control for the treatment of GA secondary to AMD. Efficacy, safety, and PK will be evaluated in CFI profile biomarker-positive and CFI profile biomarker-negative patients.

2.1 EFFICACY OBJECTIVES

The primary efficacy objective of this study is to evaluate the efficacy of intravitreal injections of 10-mg lampalizumab administered Q4W or Q6W in CFI profile biomarker-positive and CFI profile biomarker-negative patients compared with sham control assessed by change in the GA area from baseline as measured by FAF.

The secondary efficacy objective of this study is to evaluate the effect of lampalizumab compared with sham control, with respect to:

- Macular functional response as assessed by mesopic microperimetry
- Best corrected visual acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (at a starting distance of 4 m)
- BCVA as measured by ETDRS chart (at a starting distance of 4 m) under low luminance conditions
- Binocular reading speed as assessed by the Minnesota Low-Vision Reading Test (MNRead) or by Radner Reading Charts
- Binocular critical print size as assessed by the MNRead or by Radner Reading Charts
- Patient-reported visual function as assessed by the National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25)
- Patient-reported independent reading as assessed by the Functional Reading Independence Index (FRI Index)

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the local and systemic safety and tolerability of intravitreal injections of 10-mg lampalizumab administered Q4W or Q6W relative to sham control
- To evaluate the clinical significance of anti-therapeutic antibodies directed against lampalizumab

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the systemic PK of lampalizumab administered by 10-mg intravitreal injections Q4W or Q6W.

2.4 DIAGNOSTIC OBJECTIVE

A diagnostic objective for this study is to evaluate the prognostic value of the CFI profile biomarker on the mean change in the GA area from baseline as measured by FAF.

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the effect of lampalizumab compared with sham control, with respect to:
 - Monocular reading speed as assessed by MNRead charts or by Radner Reading Charts
 - Monocular critical print size as assessed by MNRead charts or by Radner Reading Charts
 - Monocular reading acuity as assessed by MNRead charts or by Radner Reading Charts
 - Binocular reading acuity as assessed by MNRead charts or by Radner Reading Charts
- To evaluate the aqueous levels of total lampalizumab and factor D following study treatment
- To evaluate the potential association of genetic variants in CFI and complement-pathway genes with disease characteristics and response to administration of lampalizumab
- To evaluate the relationship of genetic variants in CFI and complement-pathway genes to levels in the blood of messenger RNA (mRNA) and proteins of CFI and complement-pathway genes

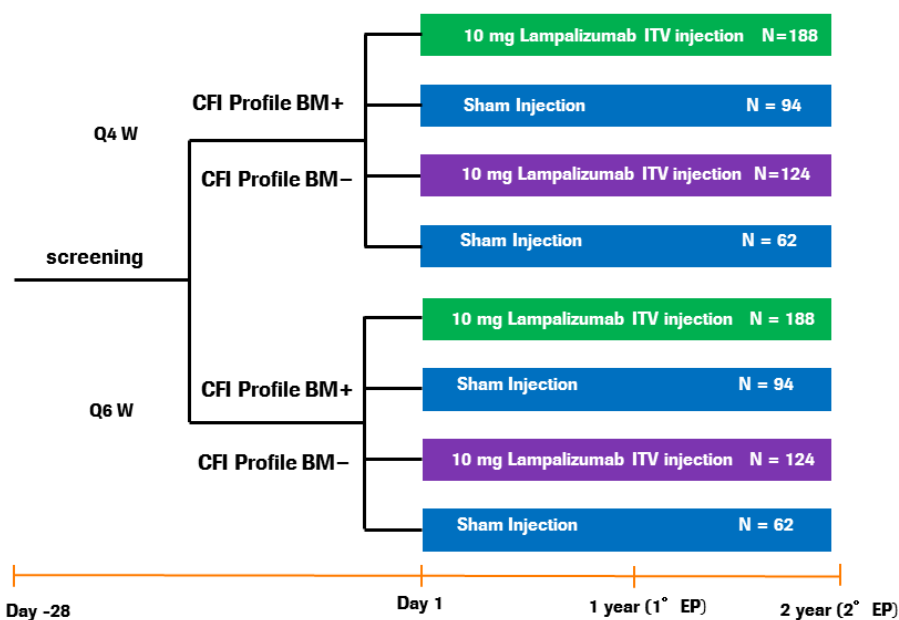
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a Phase III, double-masked, multicenter, randomized, sham injection-controlled study evaluating the efficacy and safety of a 10-mg dose of lampalizumab administered Q4W or Q6W by intravitreal injections for approximately 96 weeks, excluding screening period, in patients with GA secondary to AMD. The study will randomize approximately 936 patients at approximately 140 investigational sites globally. The site investigators will be qualified ophthalmologists.

The study will consist of a screening period of up to 28 days (–28 to –1) and an approximately 2-year treatment period (Day 1 to Week 92 for the Q4W treatment arms and Day 1 to Week 90 for the Q6W treatment arms; see [Table 2](#) and [Table 3](#), respectively), followed by the final study visit at Week 96. The duration of the study is approximately 2 years (96 weeks) after the last patient is randomized to the study (see [Figure 2](#)).

Figure 2 Study Schema



1 year=Week 48; 1° EP=primary endpoint; 2 year=Week 96; 2° EP=secondary endpoint; CFI Profile BM+=CFI profile biomarker-positive; CFI Profile BM-=CFI profile biomarker-negative; Day -28=end of screening period; Day 1=randomization and first study treatment visit; ITV=intravitreal; Q4W=every 4 weeks; Q6W=every 6 weeks.

Each consented patient must satisfy all eligibility criteria at both the screening period and the Day 1 visit. As part of the screening process, the central reading center will evaluate FAF images, CFPs, and fluorescein angiograms (FA) to provide an objective, masked assessment of patient eligibility. The investigational cobas® CFI profile assay results of blood sample analysis will be used to determine a patient's biomarker-positive or -negative status and must be obtained during the screening period prior to Day 1 visit. Patients must also meet BCVA and other eligibility criteria (see Section 4.1 for details). Screen-failed patients may be eligible for re-screening up to two additional times during the enrollment period of the study. *At re-screening, all screening visit assessments will be performed except for CFI biomarker sample and FA imaging collection, provided that a valid CFI result is available and reading center-eligible FA images were taken within 8 weeks before the new Day 1 visit (randomization).*

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

After screening has been completed, eligible patients will be randomized in a 2:1:2:1 ratio so that approximately 312 patients will receive study drug treatment Q4W and 156 patients will receive sham treatment Q4W for a total of 24 treatments; 312 patients will receive study drug treatment Q6W and 156 patients will receive sham treatment Q6W for a total of 16 treatments. The study population will be enriched (ratio of 1.5:1) for the biomarker-positive population relative to the biomarker-negative population (see Section [3.3.2.2](#)).

Randomization will be stratified by biomarker status (positive vs. negative) (as determined by the investigational cobas[®] CFI Profile assay), baseline BCVA ETDRS chart Snellen equivalent (20/50 or better vs. worse than 20/50), sex (women vs. men), and microperimetry eligibility (yes vs. no).

Patients will be treated according to the dosing schedule for the assigned treatment arms as outlined in [Table 2](#) and [Table 3](#).

Table 2 Every 4 Weeks Dosing Treatment Arms

Treatment Arm	Day Visit		Week Visit																									
	1	8 ^a	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96 ^a		
BM+ Lampalizumab (N = 188)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
BM+ Sham (N = 94)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
BM- Lampalizumab (N = 124)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
BM- Sham (N = 62)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

^a Study treatment is not administered at the Day 8 visit and Week 96 (final visit).

BM+ = CFI profile biomarker-positive; BM – = CFI profile biomarker-negative.

Table 3 Every 6 Weeks Dosing Treatment Arms

Treatment Arm	Day Visit		Week Visit															
	1	8 ^a	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96 ^a
BM+ Lampalizumab (N = 188)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
BM+ Sham (N = 94)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
BM- Lampalizumab (N = 124)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
BM- Sham (N = 62)	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

^a Study treatment is not administered at the Day 8 visit and Week 96 (final visit).

BM+ =CFI profile biomarker-positive; BM- =CFI profile biomarker-negative

The first study treatment will be administered on the same day as randomization (Day 1 visit). *If a site has an unexpected issue (e.g., the IxRS is not able to assign the study kit), with the Medical Monitor's permission, the patient's first study treatment may be administered within 3 working days of the Day 1 visit. The following assessments will be repeated on the day of the study treatment: slit lamp examination, indirect ophthalmoscopy, and pre- and post-treatment IOP measurement (recorded on Day 1 eCRF and dated accordingly).*

Study treatment visits will be scheduled Q4W (± 5 days) or Q6W (± 5 days) relative to the Day 1 visit date. Randomized patients will have the first intravitreal injection of lampalizumab or sham injection administered by the investigator on Day 1 and will have safety and ocular assessments performed on Day 8 (± 2 days) visit. At the subsequent scheduled visits (Q4W or Q6W), patients will have safety evaluations performed by the investigator prior to receiving study drug or sham injection. They 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](#)). Patient self-administered antimicrobials pre- and post-injection may be used at the investigator's discretion. Patients will be instructed to contact the investigator at any time if they have any health-related concerns.

All assessments for a scheduled visit are to be performed on the same day, except those performed during the screening period.

Study treatment should not occur earlier than 22 days after the previous treatment. Missed study treatments will not be made up.

After the Day 1 visit, if a patient misses a study visit when ocular images are scheduled to be taken (see [Appendix 1](#)), the images must be obtained at the next scheduled visit.

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

For masking requirements, see [Section 4.2.2](#).

Patients who are prematurely discontinued from study treatment will be encouraged to undergo as many scheduled visits as possible with emphasis on completing Week 48 and Week 96 visits.

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

3.1.1 Planned Total Sample Size

Approximately 936 patients (188 biomarker-positive patients per treatment group [lampalizumab Q4W, lampalizumab Q6W, and pooled sham] and 124 biomarker-negative patients per treatment group [lampalizumab Q4W, lampalizumab Q6W, and pooled sham]) will be enrolled in the study at approximately 140 sites located globally.

At selected sites, microperimetry assessment will be performed on a subgroup of approximately 138 CFI profile biomarker-positive patients and approximately 90 CFI profile biomarker-negative patients.

At selected sites, serial ECG evaluations will be performed on approximately 100 study patients, independent of CFI profile biomarker status (see Section 4.5.7).

3.1.2 Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis. 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 efficacy/futility analysis is planned to be done by iDMC. The iDMC may recommend stopping the study early for safety reasons.

A nominal type I error penalty of 0.0001 will be taken for each time the iDMC reviews unmasked data prior to the formal analysis of the primary efficacy endpoint. At the time of the primary efficacy endpoint analysis, it is estimated that five interim data reviews will have been conducted by the iDMC; therefore, efficacy analyses will be performed with a family-wise significance level of 0.0495.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 96 weeks after the last patient is randomized to the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Lampalizumab Dose and Schedule

To provide assessment of the dose response to lampalizumab and to allow for additional masking for the study, two lampalizumab treatment arms are included in this Phase III study. The 10-mg dose of lampalizumab will be administered intravitreally at Q4W or Q6W intervals.

The 10-mg 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.

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In Study CFD4870g, the 10-mg every-other-month dosing regimen did not result in efficacy for the overall study population but did result in efficacy in the biomarker-positive group. On the basis of PK/pharmacodynamic (PD) and efficacy modeling of the biomarker-positive group, 10 mg administered Q6W is expected to achieve lower but efficacious drug exposures relative to 10-mg Q4W. Additionally, the Q6W dosing regimen represents less of a treatment burden to patients, caregivers, and physicians relative to a Q4W dosing regimen.

Taken together, the two dosing regimens included in this Phase III study are expected to demonstrate a dose response, with 10-mg Q4W expected to provide maximally feasible efficacious dosage, whereas the 10-mg Q6W is expected to be an effective dose while reducing treatment burden to patients, caregivers, and physicians.

3.3.2 Rationale for Patient Population and Analysis Groups

3.3.2.1 Rationale for Evaluating Lampalizumab Treatment Effect in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

Currently, there are no approved treatments to prevent the progression of GA secondary to AMD and the associated decrease in visual function. Consequently, a significant unmet need exists for treatment of this serious condition. This study will enroll a target population of patients with the diagnosis of GA secondary to AMD. Key eligibility criteria were chosen to enrich the study population for GA patients who may have more rapid growth of GA lesions to maximize the chances of detecting progression of disease and treatment effects over the planned study duration as well as to identify the patients most likely to potentially benefit from the treatment. The key eligibility criteria and rationale for the criteria are presented below:

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

Bilateral GA represents the majority of the population (approximately 60%–67%) diagnosed with GA as reported in two natural history studies ([Holz et al. 2007](#); [Sunness et al. 2007](#)) and has been associated with an increased rate of GA lesion growth compared to unilateral GA ([Sunness et al. 2007](#)).

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

Holz et al. ([2007](#)) described four major perilesional FAF patterns (none, focal, banded, and diffuse) that were correlated with the rate of GA lesion growth in the longitudinal natural history arm of patients with GA secondary to AMD in the multi-center FAM-study. Holz reported that GA lesions with banded or diffuse junctional patterns expanded at a significantly higher rate than lesions with focal or no hyperautofluorescence. Of note, approximately 70% of the patients in the FAM study exhibited the banded or diffuse junctional perilesional FAF patterns.

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Best Corrected Visual Acuity 20/100 or Better (Snellen Equivalent) in the Study Eye Using Early Treatment Diabetic Retinopathy Study Chart

Sunness et al. (1999b) have reported on populations of patients with GA who may have worsening of VA loss in a manner and timeframe that would be suitable for study in a clinical study. In a study of the natural history of GA, approximately 41% of patients with GA with baseline VA of 20/50 or better lost at least three lines of vision at 2 years and 70% by 4 years. Among these, patients with VA 20/100 or better but worse than 20/50, 15% lost at least three lines of vision at 2 years.

Association between Female Sex and Rate of GA Progression

Caire et al. reported on a prospective study of 73 patients with GA in which they evaluated whether certain genetic and demographic risk factors were associated with the progression of established GA secondary to AMD. In the logistic regression analysis, Caire et al. reported a statistically significant risk association between female sex and the rate of progression of GA ($p=0.02$ with an adjusted odds ratio of 7.31 [95% CI of 1.30-41.80]; Caire et al. 2014).

A similar trend of females having a faster rate of GA progression relative to males was also observed in the Phase II Study CFD4870g. At month 18, the subgroups of female vs. male patients had a mean change from baseline in GA area of 3.831 mm² with 80% CI of (3.340, 4.321) and 2.310 mm² with 80% CI of (1.813, 2.808). Similar trends were also noted when evaluating the subgroups of sex by CFI profile biomarker status. Note that the subgroups analyses in the Phase II study contained small numbers and should be interpreted with caution.

3.3.2.2 Enrichment of Complement Factor I Profile Biomarker-Positive Patients

Exploratory analyses of the Phase II component of Study CFD4870g suggest that the CFI profile biomarker-positive population may have a greater benefit from lampalizumab treatment than the CFI profile biomarker-negative population. As the data from this Phase II study were exploratory and hypothesis-generating (based on a small sample size), the Phase III study population will be enriched (ratio of 1.5:1) for the CFI profile biomarker-positive population relative to the CFI profile biomarker-negative population. Enriching for CFI profile biomarker-positive patients ensures a comprehensive evaluation of the CFI profile biomarker-positive population while, importantly, also studying a sufficient number of the CFI profile biomarker-negative patients to allow adequate benefit-risk assessment in this group. Biomarker status will be determined using the investigational cobas[®] CFI profile assay that will be run at a designated study laboratory testing site.

The cobas[®] CFI Profile Clinical Trial Assay

A valid CFI biomarker result will be determined at a designated study laboratory testing site using the cobas[®] CFI Profile Clinical Trial Assay (CTA), which is a real-time polymerase chain reaction (PCR) test developed by Roche Molecular Systems to

identify genotypes of three SNPs associated with CFH, CFI, and C2/CFB in DNA extracted from whole blood samples from patients with GA secondary to AMD. The cobas[®] CFI Profile CTA is intended to be used as an Investigational Use Only assay to characterize the complement factor profile of study participants. The cobas[®] CFI Profile CTA biomarker status results will then be used to stratify patients at randomization.

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

3.3.3 Rationale for Control Group

A sham control group will be used in this study to assess the differences in GA progression, change in clinical function measures, and safety in patients who receive lampalizumab compared with patients who receive sham. Patients randomized to the sham control group will undergo the same assessments as patients randomized to the study drug intravitreal injection group.

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

3.3.4 Rationale for Biomarker Assessments

The response to lampalizumab treatment will be evaluated in pre-specified subgroups defined by the genetic biomarker test (cobas[®] CFI Profile Trial Assay) based on the common genetic variants of CFI, CFH, and C2/CFB. The whole blood sample CFI profile results will be determined by utilizing an investigational cobas[®] CFI Profile CTA (see [Appendix 22](#)) at the designated central laboratory. Although the CFI profile test is based on the common genetic variants of CFI, CFH, and C2/CFB test, recent studies have identified rare variants in CFI that have been associated with increased AMD risk ([van de Ven et al. 2013](#)). Given the potential for rare variants in CFI and other complement pathway genes to affect disease characteristics including progression and the response to lampalizumab treatment, additional exploratory genetic analysis will be conducted using the biomarker clinical genotyping sample including sequencing of CFI and other complement-pathway genes.

In addition to the genetic analysis, pre-injection plasma levels and whole blood mRNA levels of CFI and complement-pathway genes will be measured. Exploratory analyses will evaluate the relationship of blood levels of CFI and complement-pathway mRNA and proteins to genetic variants in the complement pathway and to disease characteristics, including progression and the response to lampalizumab treatment.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is GA area at 1 year as assessed by FAF.

The secondary efficacy outcome measures for this study over time are as follows:

- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response
- Change in macular sensitivity as assessed by mesopic microperimetry for the evaluation of the macular functional response
- GA area as assessed by FAF
- BCVA score as assessed by ETDRS chart at a starting distance of 4 m
- BCVA score as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m
- Binocular reading speed as assessed by MNRead charts or Radner Reading Charts
- Binocular critical print size as assessed by MNRead charts or Radner Reading Charts
- NEI VFQ-25 composite score
- NEI VFQ-25 near activity subscale score
- NEI VFQ-25 distance activity subscale score
- FRI Index score

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- The incidence and severity of ocular adverse events
- The incidence and severity of systemic (non-ocular) adverse events
- Changes and abnormalities in ECG parameters
- The incidence of anti-lampalizumab antibodies

3.4.3 Pharmacokinetic Outcome Measure

The PK outcome measure for this study is serum lampalizumab concentration over time.

3.4.4 Diagnostic Outcome Measure

The evaluation of the prognostic value of the CFI profile biomarker will be based on the biomarker status at baseline and the primary clinical outcome of change in the GA area from baseline as measured by FAF.

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Monocular reading speed as assessed by MNRead charts or Radner Reading Charts over time
- Monocular critical print size as assessed by MNRead charts or Radner Reading Charts over time
- Monocular reading acuity as assessed by MNRead charts or Radner Reading Charts over time
- Binocular reading acuity as assessed by MNRead charts or Radner Reading Charts over time
- Total lampalizumab and factor D levels in aqueous humor as assessed by ELISA
- The association of genetic variants in CFI and complement-pathway genes with disease characteristics and response to administration of lampalizumab
- The relationship of genetic variants in CFI and complement-pathway genes to levels in the blood of mRNA and proteins of CFI and complement-pathway genes

3.5 EXPLORATORY SUBSTUDIES

At selected sites, the Sponsor may propose exploratory substudies associated with the Study GX29176 protocol. Each substudy will be documented in a separate substudy protocol and associated ICF(s).

4. MATERIALS AND METHODS

4.1 PATIENTS

Patient Selection and Sex Distribution

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

Note: Some patients may require an extended screening period as a result of repeated evaluation of images or other issues. Upon agreement with the Medical Monitor, the screening period may be extended for up to 5 days for such cases.

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

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

4.1.1 **Inclusion Criteria**

Patients must meet the following criteria for study entry:

General Inclusion Criteria

- Willingness and the 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.
- Age ≥ 50 years
- For women of *childbearing potential*: agreement to remain abstinent (*refrain from heterosexual intercourse*) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of study drug

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

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

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

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

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

- Ability and willingness to undertake all scheduled visits and assessments
- Valid CFI profile biomarker result (i.e., CFI profile biomarker-positive or CFI profile biomarker-negative)

Ocular Inclusion Criteria: Study Eye

- BCVA letter score of ≥ 49 letters (Snellen equivalent of 20/100 or better) using ETDRS charts at starting distance of 4 m

If BCVA letter score is ≥ 79 letters (Snellen equivalent of 20/25 or better), at least one GA lesion must be within 250 μm of the foveal center

- Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV

The total GA lesion size $\geq 2.54 \text{ mm}^2$ (approximately ≥ 1 disc area [DA]) and $\leq 17.78 \text{ mm}^2$ (approximately ≤ 7 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea)

If GA is multifocal, at least 1 focal lesion must be $\geq 1.27 \text{ mm}^2$ (approximately ≥ 0.5 DA)

- Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to the area of GA
- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging

Ocular Inclusion Criteria: Non-study Eye

GA secondary to AMD with no evidence of prior or active CNV

4.1.2 Exclusion Criteria

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

GA Characteristics Exclusion Criteria

- GA in either eye due to causes other than AMD (monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy])

Ocular Exclusion Criteria: Study Eye

- History of vitrectomy surgery, submacular surgery, or any surgical intervention for AMD
- Previous laser photocoagulation for CNV, diabetic macular edema, retinal vein occlusion, and proliferative diabetic retinopathy
- Prior treatment with Visudyne[®], external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy
- History of prophylactic subthreshold laser treatment for AMD
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, or device implantation). A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.

Ocular Exclusion Criteria: Non-Study Eye

- Non-functioning non-study eye defined as either:
 - BCVA of hand motion or worse
 - OR
 - No physical presence of non-study eye (i.e., monocular)

Ocular Exclusion Criteria: Both Eyes

- Previous participation in interventional clinical trials for geographic atrophy or dry AMD (except of vitamins and minerals) irrespective of the route of administration (ocular or systemic)
- Previous treatment with eculizumab, lampalizumab, fenretidine or any other drugs for geographic atrophy or dry AMD treatment

Ocular Exclusion Criteria: Concurrent Ocular Conditions

- RPE tear that involves the macula in either eye
- Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could do either of the following:
 - Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
 - If allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of BCVA during the study period
- Active uveitis and/or vitritis (grade trace or above) in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye
- Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Current vitreous hemorrhage in the study eye
- History of retinal detachment or macular hole (Stage 3 or 4) in the study eye
- Aphakia or absence of the posterior capsule in the study eye
- Previous violation of the posterior capsule in the study eye unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error in the study eye demonstrating >8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia.
- Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding Day 1
- Uncontrolled glaucoma in the study eye (defined as intraocular pressure [IOP] ≥ 30 mm Hg despite treatment with anti-glaucoma medication)
- History of glaucoma-filtering surgery in the study eye
- History of corneal transplant in the study eye
- Proliferative diabetic retinopathy in either eye
- Prior or active CNV in either eye
- Central serous retinopathy in either eye

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- History of recurrent infectious or inflammatory ocular disease *in either eye*

Concurrent Systemic Conditions Exclusion Criteria

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

If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by anti-hypertensive medication, the patient can become eligible if medication is taken continuously for at least 30 days prior to Day 1.

- 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
- Treatment for active systemic *or localized* infection

The ongoing prophylactic use of antimicrobial therapy should be discussed with the Medical Monitor.

- Predisposition or history of increased risk of infection (i.e., history of splenectomy or chronic immunosuppression)
- Active cancer within past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma and prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen (PSA) for > 12 months.
- History of allergy to fluorescein that is not amenable to treatment
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lampalizumab injection
- Inability to comply with study or follow-up procedures
- Inability to obtain CFP, FAF, and FA of sufficient quality to be analyzed and graded by the central reading center
- Previous participation in any studies of investigational drugs within 3 months (except as listed in the above Section 'Ocular Exclusion Criteria: Both Eyes') preceding Day 1 (excluding vitamins and minerals)
- Requirement for continuous use of any medications/treatments indicated in the "Prohibited Therapy" section of the protocol (see Section 4.4.2)
- Women who are pregnant or lactating or intending to become pregnant during the study

Women of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study treatment.

4.1.3 Microperimetry Criteria at Selected Sites Only

Inclusion Criteria

- Patients must meet all other eligibility criteria for study entry.

- Microperimetry screening test criteria for eligibility:
 - Must be able to detect fixation target.
 - Total elapsed time to complete the 10-2 68 point exam is ≤ 30 minutes in duration.
 - Reliability Test ratio $\leq 20\%$ (false positive rate).
 - Ability and willingness to undertake MP assessment as determined by investigator.

Exclusion Criteria

- Any exclusion criteria listed for the study entry
- Investigator determines that patient is unable to perform the test reliably (e.g. Difficulty sitting still against the supporting chinrest for > 10 minutes; Unable to physically operate the clicker or joystick; Unable to follow the instructions for the test [i.e. cognitive impairment])

Note: disqualification from the microperimetry assessment doesn't exclude a patient from the trial participation if she/he qualifies as per the rest of the study entry criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

After written informed consent has been obtained, all patients will receive a screening number assigned through the Interactive Voice and Web Response Systems (IxRS). A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) at both the screening and the Day 1 visit (first study treatment) prior to randomization. As part of the screening process, the central reading center (masked to patient treatment assignment) will evaluate FAF images, CFP, and FA to provide an objective, masked assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IxRS on Day 1 visit for assignment of a patient identification number (a separate number from the screening number). Patients will be randomized in a 2:1:2:1 ratio to one of the study treatment arms (lampalizumab Q4W, sham Q4W, lampalizumab Q6W, or sham Q6W). The study treatment kit number will be also assigned by IxRS at that time. Patients will be randomized on the same day the study treatment is to be initiated (Day 1 visit).

Randomization will be stratified by biomarker status (positive vs. negative, as determined by the investigational cobas[®] CFI Profile assay), baseline BCVA ETDRS chart Snellen equivalent (20/50 or better vs. worse than 20/50), sex (woman vs. man), and microperimetry eligibility (yes vs. no). A permuted-block randomization method will be used to obtain an approximately 2:1 ratio between lampalizumab and sham arms for each dosing frequency within each stratum.

Once the study randomizes the allotted number of CFI profile biomarker-negative or CFI profile biomarker-positive patients (see [Figure 2](#)), the additional screened patients who would have been randomized in the already-filled biomarker arms will be screen-failed.

Patients and all study site personnel will be masked for CFI profile biomarker status until study completion. Sponsor study team members who have direct contact with study sites will be masked to CFI profile biomarker status, but team members who do not interact with study sites may review individual patient CFI profile biomarker status.

Details of the randomization procedure will be described in the Statistical Analysis Plan (SAP).

4.2.2 Masking

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study. Study visits must be scheduled when both investigators are present. At least one investigator will be designated as the evaluating physician who will be masked to patients' treatment assignment and will evaluate all ocular assessments. At least one other investigator (and designated, unmasked assistant, as needed) will be designated as the treating (injecting) physician who will be unmasked to patients' treatment assignment and will administer injections (lampalizumab or sham). *The Principal Investigator must be masked to patients' treatment assignment. All roles for each study staff member should be clearly documented on the Site Delegation Log. The Delegation Log should be signed by the Principal Investigator.*

Once the designated *masked vs. unmasked* roles are delineated and the site study staff have started to perform them, the roles *cannot* be switched or reversed at any time during the conduct of the study. In case a site is *experiencing* unexpected extreme situations, the Medical Monitor's permission might be granted to switch the study staff member from the masked role to the unmasked role, but not the other way around. In the event an alternate study staff member needs to be added or substituted, that alternate study staff member may assume only one role for the duration of the study.

Starting at the patient's Day 1 visit, the treating physician(s) (performing the lampalizumab or sham injections), *post-treatment finger counting, and optional aqueous humor sample collection*) *must continue their role as treating physician only, cannot* be involved in any other aspect of the study, and must not divulge treatment assignment to anyone.

Patients, study site personnel (with the exception of the treating physician[s], assistant[s], and pharmacist if any), the designated evaluating physician(s), central reading center personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) will be masked to treatment assignment.

The VA examiner (performing the refraction, BCVA examinations, and reading speed assessment) will be masked to patient treatment assignment and the treated study eye and will only perform refraction, BCVA, BCVA under low luminance conditions, and reading speed assessments. The BCVA examiner will have no access to the VA scores of a patient's previous visits and may have access only to patient's refraction data from previous visits. The VA examiner is not allowed to perform any other tasks involving direct patient care.

Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study. There must be no more than five unmasked personnel at an investigative site at one time. In special circumstances more than five unmasked personnel may be permitted after consultation with the medical monitor.

Documented procedures will be put in place to avoid inadvertently unmasking study team members. Only the IxRS provider and the external iDCC responsible for verifying a patient's randomization and study treatment kit assignment, who are not otherwise involved in the study, will have access to the unmasking code.

For the duration of the study, the patient treatment assignment will not be unmasked unless required for patient safety.

All study visit assessments, except those at screening, should be performed by masked site personnel only. Starting at a patient Day 1 visit, the unmasked treating physician will only perform the study treatment and the 15 minutes post-treatment vision testing (finger counting and, if applicable, hand movement and/or light perception). The injecting physician will also perform a Lucentis injection if it was prescribed for either eye.

Study assessments include PK sample collection in all patients (Section 4.5.9.3). While PK samples must be collected from patients assigned to the sham arm to maintain the masking of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK assays will be unmasked to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the sham arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

4.2.3 Unmasking

If unmasking is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study treatment for any other reason, he or she should contact the Medical Monitor directly. The investigator

should document and provide an explanation for any premature unmasking (e.g., accidental unmasking or unmasking due to serious adverse events).

For regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, 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 Type 1 glass vial and is intended for intravitreal administration. For the Phase III clinical studies, each glass vial contains a nominal 40 mg of lampalizumab. After reconstitution with Sterile Water for Injection, the drug product is formulated as 100 mg/mL lampalizumab in 40 mM L-histidine hydrochloride, 28 mM sodium chloride, 160 mM sucrose, 0.04% (w/v) polysorbate 20, pH 5.3.

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

4.3.1.2 Sham

Sham vial is empty and will remain empty throughout the sham treatment. It does not contain any lyophilized powder. There is no reconstitution process for the sham vial.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Lampalizumab and Sham

Dosage

Study treatment should not occur earlier than 22 days after the previous treatment.

Guidelines for treatment interruption or discontinuation are provided in Section [4.6.2](#) and Section [4.4.3](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events

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associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Lampalizumab Intravitreal Injections

A 10-mg dose of lampalizumab will be used in this study and will be administered intravitreally to patients randomized to the lampalizumab Q4W or Q6W treatment arms during the 2-year treatment period (see [Appendix 1](#) for the study flowcharts).

Sham Injections

Patients randomized to the control arms will receive sham injections Q4W or Q6W during the 2-year treatment period and will undergo the same assessments as the lampalizumab treatment arm (see [Appendix 1](#) for the study flowcharts).

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

Administration

See [Appendix 4](#) for the pre-injection procedures of both treatments (lampalizumab and sham) for all patients, [Appendix 5](#) for the injection procedures of the study drug, [Appendix 6](#) for the injection procedures of the sham treatment procedure, and [Appendix 7](#) for the post-injection procedures for all treated patients.

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

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

The Sponsor will offer post-study access to the study drug lampalizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to IMPs as outlined below.

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

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

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

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for GA
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for GA
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to IMPs is available at http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant medications are any prescription drugs or over-the-counter preparations other than protocol-specified procedural medications (e.g., dilating drops or fluorescein dyes) and pre- and post-injection medications (e.g., proparacaine or antimicrobials [if applicable]) used by a patient within 7 days preceding Day 1 visit and 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 of Lucentis[®] for either eye treatment (if applicable), which will have a separate eCRF.

Patients required to use medications that are prohibited (see Section 4.4.2) will not be eligible for the study. Patients who use other maintenance therapies should continue their use. Of note, the following are some common therapies that are permitted:

- Onset of ocular hypertension or glaucoma in the study eye during a patient's study participation should be treated as clinically indicated
- Onset of cataract or posterior capsular opacification in either eye during the patient's study participation may be treated as clinically indicated. Dose-interruption criteria (see Section 4.4.3, Table 4) may apply with cataract surgery.
- Short-term use of topical corticosteroids after cataract surgery, YAG capsulotomy, or peripheral iridotomy
- At the discretion of the evaluating physician, randomized patients who are receiving study treatment may be treated with Lucentis[®] if they are diagnosed in either eye with an ocular condition for which Lucentis is approved in the country. Consult with the region specific Lucentis Prescribing Information for the recommended dose and frequency of treatment.

NOTE: If (as per masked investigator judgment) treatment with Lucentis is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab/sham, the treatment with Lucentis must be administered first. Following this, a safety *assessment* (including an IOP check) *must be completed by the physician in the masked role prior to the study eye treatment with lampalizumab/sham. If there are no concerns, the site may proceed with calling* IxRS for the study treatment kit assignment. Individual trays and sterile prep must be separately prepared for each treatment. The injecting physician will perform the treatment with Lucentis to preserve the masking.

- Oral corticosteroids at doses ≤ 10 mg/day prednisone or equivalent

4.4.2 Prohibited Therapy

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions. However, the following medications/treatments are prohibited from use during the patient's participation in the study treatment, and patients will be discontinued from study treatment and/or study to receive these therapies:

- 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, anti-tumor necrosis factors, eculizumab)
- Treatment with Visudyne in study eye
- Other experimental therapies (except those with vitamins and minerals)

4.4.3 Dose-Interruption and/or Treatment Discontinuation Criteria

Study treatment interruption and patient discontinuation from the study treatment for adverse events will be determined using the criteria listed in [Table 4](#). 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/discontinuation should be recorded on the *appropriate* eCRF and, if applicable, on the Adverse Event eCRF.

Table 4 Dose-Interruption and Treatment Discontinuation Criteria

Event	Dose-Interruption Criteria
Intraocular inflammation	Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis or vitritis) is $\geq 1+$ in the study eye (see the grading scales of intraocular inflammation in Section 5.3.5 and Appendix 3). Patients with $\geq 3+$ intraocular inflammation will be discontinued from the study treatment.
VA loss	Interrupt study treatment if there is a treatment-related decrease in BCVA of ≥ 30 letters in the study eye compared with the last assessment of BCVA prior to the most recent treatment. Study treatment may be permitted subsequently as determined by the Sponsor and investigator.
Elevated IOP	Interrupt study treatment if IOP in the study eye is ≥ 30 mm Hg. Treatment may be permitted when IOP has been lowered to < 30 mm Hg, either spontaneously or by treatment, 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 Sponsor and 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 patients from study treatment for the duration of the study if rhegmatogenous retinal detachment or Stage 3 or 4 macular holes is observed.
<i>Active local</i> or systemic infection	Interrupt study treatment if any of the following are present: infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye or if the patient is currently receiving treatment for an active <i>local or</i> systemic infection. Patients with endophthalmitis in the study eye will be discontinued from the study treatment.

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

Table 4 Dose-Interruption and Treatment Discontinuation Criteria (cont.)

Event	Dose-Interruption Criteria
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 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; YAG=yttrium aluminum garnet.

If a patient misses more than 2 doses of study treatment within any 24-week treatment period, the investigator and the Sponsor may consider discontinuing the patient from the study treatment.

4.5 STUDY ASSESSMENTS

See [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations and evaluations at Day 1 must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, including chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, and ophthalmic history); tobacco use; surgeries; cancer history; reproductive status; previous ECGs (if available within the previous 12 months from patients who are not part of selected sites serial ECG collection); and all medications (e.g., prescription drugs, over-the-counter drugs, herbal

or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Day 1 visit.

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

4.5.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. A patient's height and weight will be collected as well. If any abnormalities are noted during the study, the patient may be referred to another doctor.

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, heart rate, and systolic and diastolic blood pressures; taken with the patient in a seated position after resting for 5 minutes.

4.5.5 Other Disease-Specific Assessments

Patient-Reported Outcomes

The PRO measures (NEI VFQ-25 and FRI Index; see [Appendix 16](#) and [Appendix 17](#), respectively) will be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed.

Ocular Assessments

- BCVA assessed on ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes; see [Appendix 8](#))
- BCVA assessed by ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes; see [Appendix 9](#)) under low luminance conditions
- MNRead charts (see [Appendix 18](#) for details on specific countries where test will be administered) or Radner Reading Charts (see [Appendix 19](#) 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).
- IOP measurement of both eyes (perform prior to dilating eyes; the method of IOP measurement used for a patient must remain consistent throughout the study)
- Slit-lamp examination (for grading scales for anterior and vitreous cells, see [Appendix 3](#))
- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within 15 minutes post-injection for the study eye only by the treating physician who has unmasked role

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- At study treatment visits, post-injection IOP measurement in the study eye only between 30 and 50 minutes after study treatment (drug or sham) by qualified masked site staff (except for the VA examiner). If the IOP is increased by ≥ 10 mm from pre-injection, the 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 (if applicable) will be recorded on the post-treatment IOP eCRF.

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

The method of IOP measurement used for a patient must remain consistent throughout the study.

Ocular Imaging and Microperimetry

The central reading center will provide sites with the Central Reading Center 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, and systems and software (where applicable) will be certified/validated by the reading center as specified in the Central Reading Center manual. 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 10](#), [Appendix 11](#), [Appendix 12](#), [Appendix 13](#), [Appendix 14](#), and [Appendix 15](#)).

Note: after randomization, if a patient misses a study visit during which ocular images were scheduled to be taken (see [Appendix 1](#)), the images should be obtained at the next scheduled visit.

Ocular images, keratometry, and microperimetry obtained include the following:

- Stereoscopic, CFP of both eyes
- FAs of both eyes (performed after laboratory samples are obtained)
- FAF (with keratometry measurements), near infrared (NI), and spectral domain optical coherence tomography (SD-OCT) images of both eyes
- Mesopic Microperimetry (at selected sites) of selected study eye only; to account for testing learning curve, patient is allowed up to 3 attempts to meet screening criteria

Note: if the Investigator determines that both eyes of a patient meet the eligibility criteria for study eye, mesopic microperimetry will be performed on both eyes at screening.

Additional details on obtaining these images, keratometry, and microperimetry are included in the Central Reading Center Manual.

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4.5.6 Laboratory Biological Samples Collection

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. The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to Sponsor or its designee for analysis and/or storage. The CFI profile biomarker whole blood samples (will be tested on the investigational cobas[®] CFI Profile Assay) and buccal swab will be forwarded from the sites directly to the Sponsor designated central laboratory testing site for testing and/or storage. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the Laboratory Manual. Laboratory supply kits will be provided to the sites by the central laboratory. See [Appendix 1](#) for sample collection timepoints and [Appendix 20](#) for biological sample collection and shipping instructions. Except as noted (see [Appendix 1](#)), all samples collected during screening from patients who are not randomized will be discarded.

The following assessments will be performed:

- 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)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total and direct bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and uric acid
- 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)
- Coagulation: activated partial thromboplastin time and prothrombin time
- Initial serum pregnancy test (β -human chorionic gonadotropin) for women of childbearing potential, including those who have had tubal ligation. If positive, study treatment will not be administered.
- Urine pregnancy test prior to each study treatment for women of childbearing potential, including those who have had tubal ligation. If positive, perform the serum pregnancy test. If the serum pregnancy test is positive, do not administer the study treatment.
- Alternative Complement pathway assessment assay (AH50)
- Serum samples for measurement of anti-lampalizumab antibodies
- Serum samples to measure lampalizumab concentration
- Optional anterior chamber (aqueous humor) paracentesis samples to measure lampalizumab and CFD levels for assessment of PK and PD relationships

CFI profile biomarker whole blood sample for determination of CFI profile to stratify patients at randomization and to support further development of the investigational

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cobas® CFI Profile assay (see Section 3.3.2.2). The sample will be retained for screen-failed patients as well.

- CFI biomarker buccal swab to support further development of the CFI profile assay. The sample will be retained for the screen-failed patients as well.
- Biomarker plasma sample for determination of levels of CFI and complement-pathway proteins
- Biomarker paxgene tube sample for determination of complement pathway mRNA expression levels
- Biomarker whole blood sample for clinical genotyping of CFI and other complement pathway genes

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

In addition, remainders of serum PK, serum anti-therapeutic antibodies (ATAs), biomarker plasma, biomarker paxgene sample, biomarker whole blood clinical genotyping sample, 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 the remainders of the samples to be stored for the optional research.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

Drug concentration will be determined in serum using an ELISA method. ATAs will be detected in serum using a bridging ELISA.

4.5.7 Serial Electrocardiogram Evaluation (Selected Sites)

Serial electrocardiogram evaluations will be conducted at selected U.S. sites participating in this study. The evaluations will be performed to characterize and compare common clinical ECG parameters in patients treated with lampalizumab and those receiving sham interventions for GA secondary to AMD. These evaluations will utilize study-supplied ECG devices to collect digital patient ECGs at Day 1 (prior to first study treatment), Day 8, Week 4 (for Q4W arms) or Week 6 (for QW6 arms), Week 24, and Early Termination visits (collect only if early termination occurs prior to Week 24 visit) in approximately 100 patients. All ECGs will undergo central interpretation by qualified cardiologists. The details of the evaluations are in the ECG manual and also detailed in [Appendix 21](#).

Optional Historical ECG

Study patients who are not part of the serial ECG evaluation will provide (if available) historical results from a clinical 12-lead ECG performed within the 12 months preceding Day 1 study treatment. The results should be stored in a patient source document. *If no baseline ECG is available, sites are not required to obtain a Screening/Day 1 ECG.*

4.5.8 Patient-Reported Outcomes

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

The questionnaires will be translated as required to different languages. The questionnaires will be administered by the masked 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 16](#)). The appendix items for the near and distance domains will also be included (three additional 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 a 7-item, interviewer-administered assessment of functional reading independence (see [Appendix 17](#)). It has one total index score. The index score is an ordinal scale with higher levels representing higher functional reading independence. The FRI Index has a specified recall period of 7 days.

4.5.9 Samples for Roche Clinical Repository

4.5.9.1 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

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- To discover genetic changes and study variants within the genome that underlie disease through use of whole genome sequencing
- 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

4.5.9.2 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 Informed Consent Form by each site's IRB or 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 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related AMD and related diseases, lamplelizumab, 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
- Residual biomarker paxgene sample
- Residual biomarker whole blood clinical genotyping sample

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

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

The non-genetic RCR biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens (residual whole blood clinical genotyping sample) will undergo additional processes to ensure confidentiality as described below.

4.5.9.4 Confidentiality for RCR Genetic Specimens

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

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

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

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

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

4.5.9.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section or separate Informed Consent Form 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 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.

4.5.9.6 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 using the RCR Patient Withdrawal Form and, if the study 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 study is closed. A patient's withdrawal from Study GX29176 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 GX29176.

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

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

Patients withdrawn from the study prior to completion will be asked to return for an early termination evaluation after a minimum of 30 days lapsed 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 study discontinuation should be recorded on the appropriate eCRF. Discontinued patients will not be replaced or allowed to re-enter the study.

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time

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

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

If a patient discontinued the study but has not withdrawn the informed consent, the site should make every effort to continue to follow up on serious adverse events, deaths, and adverse events of special interest (AESIs) 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 can 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

The investigator has the right to discontinue a patient from the study treatment for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study treatment, for reasons of non-compliance (e.g., missed doses, visits), if the patient becomes pregnant, or if the investigator determines it is in the best interest of the patient. The reason for the treatment discontinuation should be recorded on the appropriate eCRF.

Treatment discontinued patients will not be replaced or allowed to re-start the study treatment. However, they should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible with emphasis on the Weeks 48 and 96 visits.

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:

- 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

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- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for GCP
- No study activity (i.e., all patients have completed 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 this study is designed to help minimize patient risk and will include specific eligibility criteria and monitoring assessments as detailed below.

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 AEs (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, masked aggregate AE 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 pneumoniae*, and *Haemophilus influenzae*).

The incidence and characteristics of AEs, SAEs, and laboratory abnormalities will be assessed as described within this protocol. An iDMC will be established to monitor patient safety and study conduct on an ongoing basis (see Section 3.1.2). The iDMC will conduct periodic reviews (approximately every 6 months but the frequency is adjustable as required) of unmasked ocular and systemic (non-ocular) safety events with an emphasis on the evaluation of the rates of ocular inflammation, increased IOP, endophthalmitis, and clinically significant decreases in BCVA, which will be prepared for them by an iDCC.

After the first study treatment on Day 1, all patients will return for a safety assessment visit on Day 8 (± 2 days). For subsequent injections, 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

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antimicrobials, the patients will also be asked whether they have taken the prescribed, self-administered, pre- and post-injection 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 an unscheduled safety assessment visit (see [Appendix 2](#)).

A finger-counting test will be conducted for each patient within 15 minutes following study treatment by the treating physician; 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 for the study eye only by masked (except for the VA examiner) site staff; if the IOP is increased by ≥ 10 mm Hg from pre-injection 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 page will also be completed.

Note: if the study eye treatment with Lucentis injection is performed at the same visit as the study treatment (lampalizumab/sham), 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 study treatment administration later.

Detailed ocular examinations, including indirect ophthalmoscopy and slit-lamp examination, will be performed throughout the study. Blood samples for serum study drug concentrations, AH50 assays, and antibodies to lampalizumab and other biomarker samples (see [Appendix 1](#)) will be obtained from all patients at selected timepoints. The optional aqueous humor samples will be obtained from the patients who consent to this procedure and sample collection.

Patients discontinued from the study prior to completion (Week 96) will be asked to return for early termination visit assessments if a minimum of 30 days have elapsed following the last study treatment visit (see [Appendix 1](#)). The visit will include assessment of all AEs (serious and non-serious; ocular and non-ocular). SAEs will be reported in compliance with GCP guidelines.

Treatment interruption and/or treatment discontinuation for AEs will be determined using the criteria in [Table 4](#).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (AESIs); 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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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 considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

This does not include any AE 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 AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 AE (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 AE recorded on the eCRF.

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

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

Non-serious or serious AESIs 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). AESIs for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.
- AEs 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 AE, the primary event term should reflect the AE that occurred as a result of the medication error and identify it in "other suspected causes of SAE/AE" data field as a medication error.
- Sight-threatening AEs
An AE is considered to be sight threatening and should be reported expeditiously if it meets one or more of the following criteria:
 - It causes a decrease of ≥ 30 letters in VA score (compared with the last assessment of VA prior to the most recent assessment) lasting more than 1 hour
 - It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight

- It is associated with severe intraocular inflammation (i.e., endophthalmitis, 4+ anterior chamber cell/flare or 4+ vitritis; see Section 5.3.5 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 AEs should be reported as serious events, listing the underlying cause (if known) of the event as primary event term.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (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 AE 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 AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient’s medical record and on the Adverse Event eCRF.

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

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

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE 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 AE severity grading scale in Table 5 will be used for assessing AE severity.

Table 5 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

The masked, evaluating 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 AE is considered to be related to the study drug, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration (see Table 6):

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

AE = adverse event; SAE = serious adverse event.

5.3.5 Procedures for Recording Adverse Events

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

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

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

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

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

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 AEs based on signs and symptoms should be nullified and replaced by one AE 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, AEs occurring 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. However, medically significant AEs occurring secondary to

an initiating event that are separated in time should be recorded as independent events 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 AEs 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 AE is one that extends continuously, without resolution, between patient evaluation timepoints. The initial severity (intensity) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 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 SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE 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 AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- 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
- 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 AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. 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, if applicable, should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 AE.

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, if applicable, should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) 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 AE the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or as a non-serious AESI (see Section 5.4.2).

5.3.5.7 Deaths

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

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

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 AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., worsening, exacerbation, or more frequent headaches).

5.3.5.9 Worsening of Geographic Atrophy in Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of the normal progression of GA of the study eye should be recorded as an AE only if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of study eye GA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated GA”). The expedited reporting requirements for sight threatening events (listed in the Section 5.2.3) apply to these unexpected changes in the study eye GA.

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

5.3.5.10 Hospitalization or Prolonged Hospitalization or Surgery

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

- *Hospitalization for a preexisting condition, provided that the following criteria are met:*
 - *The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.*
 - *The patient has not experienced an adverse event.*

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF as an AESI (see Section 5.2.3) and 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

AE 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 AE are identified during site review of the PRO data, the investigator will determine whether the criteria for an AE 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 study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- Non-serious AESIs
- Pregnancies

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for Western Hemisphere

Medical Monitor: [REDACTED], M.D., Ph.D. (primary)

Mobile Telephone No.: [REDACTED]

or

Medical Monitor: [REDACTED], M.D.

Mobile Telephone No.: [REDACTED]

Medical Monitor Contact Information for Eastern Hemisphere

Medical Monitor: [REDACTED], M.D.

Telephone No.: [REDACTED]

Mobile Telephone No.: [REDACTED]

or

Medical Monitor: [REDACTED], MBChB, MFPM, MRCOphth

Mobile Telephone No.: [REDACTED]

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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 Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see “Protocol Administrative and Contact Information and List of Investigators”).

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. A 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 scanning and emailing the form* using the *fax number or email address* provided to investigators (“Protocol Administrative and Contact Information and List of Investigators”).

5.4.2.2 Events That Occur after Study Drug Initiation

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

In the event that the EDC system is unavailable, *the 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 (“Protocol Administrative and Contact Information and List of Investigators”). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study AEs 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 the last study visit. 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 SAEs 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 Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or until the last study visit. *A Clinical Trial Pregnancy 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 an SAE (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 an SAE, 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 AE 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 SAEs considered

to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the last study visit), if the event is believed to be related to 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 and non-serious AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document{s}:

- 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

Analysis of data for the first year of the study period will be performed when all patients have either completed the first year of study period or have discontinued from the study prior to Year 1 (i.e., Week 48), and all data from this period are in the database and have been cleaned and verified. The analysis of complete data for the study will be performed when all patients have either completed the 2-year study period (i.e., Week 96) or discontinued early from the study, all data from the study are in the database, and the database is locked.

Results of the first year analysis, summarized by treatment group and biomarker group, may be reported to the public before completion of the study. However, patients, masked study site personnel, central reading center personnel, and Sponsor study team members who have direct contact with study sites will remain masked to individual treatment assignment until the study is completed, the database is locked, and the study analyses are final.

Detailed specifications of the statistical methods will be described in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

Patients will be randomized in a 2:1:2:1 ratio to receive treatment with lampalizumab Q4W, sham Q4W, lampalizumab Q6W, or sham Q6W. Data from the two sham groups will be pooled in the analysis.

The study is sized to achieve adequate power for detecting a meaningful reduction rate in the GA area growth for a given lampalizumab dosing frequency compared with pooled sham within CFI profile biomarker-positive and CFI profile biomarker-negative groups and to meet health authority requirements for the safety database.

The primary endpoint is the mean change in GA area from baseline to 1 year as assessed by FAF. [Table 7](#) summarizes the power calculation and minimum detectable difference for this primary endpoint. Assuming a standard deviation of 2.51 mm² for the change from baseline in GA area at 1 year in biomarker-positive patients, 188 CFI profile biomarker-positive patients per lampalizumab treatment group and 94 CFI profile biomarker-positive patients per sham group will provide >95% power to declare a difference between each lampalizumab treatment group and the pooled sham for a targeted difference of 1.45 mm² (approximately 40% reduction relative to sham control) in the change from baseline in GA area at 1 year. Assuming a standard deviation of 1.68 mm² for the change from baseline in GA area at 1 year in CFI profile biomarker-negative patients, 124 CFI profile biomarker-negative patients per lampalizumab treatment group and 62 CFI profile biomarker-negative patients per sham group will

provide 80% power to detect a targeted difference of 0.66 mm² (approximately 40% reduction) between each lampalizumab treatment group and the pooled sham group in the change from baseline in GA area at 1 year. Calculations were based on two-sided t-test at the $\alpha=0.0495$ level (after adjustment for planned interim data reviews conducted by the iDMC prior to analysis of the primary efficacy endpoint; see Section 3.1.2), with the assumption of a 15% dropout rate by 1 year. Due to lack of reliable information to estimate the impact of partially missing data on the power, the power calculation is based on the analysis of data from the patients who complete the first year of the study. However, the primary analysis of the study will include all available data from patients in all treatment arms, which will have more power than an analysis of just those patients completing the first year of the study period.

Table 7 Power and Minimum Detectable Difference for Primary Endpoint in This Study

Endpoint	Target Treatment Effect	Two-Sided $\alpha=0.0495$	
		Power	MDD
Mean change from baseline in GA area at 1 year in biomarker-positive patients (n=188 per arm)	$\Delta=1.45$ mm ² (approximately 40% ^a reduction) SD=2.51	>95%	0.56 mm ² (approximately 15% ^a reduction)
Mean change from baseline in GA area at 1 year in biomarker-negative patients (n=124 per arm)	$\Delta=0.66$ mm ² (approximately 40% ^a reduction) SD=1.68	80%	0.46 mm ² (approximately 28% ^a reduction)

GA=geographic atrophy; MDD=minimum detectable difference.

The sample size takes into account the dropout rate of 15% by 1 year. The power and MDD are for each comparison between one lampalizumab treatment group and the pooled sham group.

^a Relative to the sham group and assuming the mean change from baseline in GA area at 1 year (48 weeks) is 1.645 mm² for biomarker-negative group and 3.631 mm² for biomarker-positive group.

The Sponsor may conduct a masked evaluation of the variance of the primary efficacy endpoint and study dropout rate before the end of enrollment and compare the information to the assumptions used in planning the study. If this comparison suggests the initial assumptions for the dropout rate and/or the variance of the primary efficacy endpoint were substantially lower, and the study is consequently underpowered, the study sample size will be increased to maintain the desired study power and safety database. Details will be provided in the SAP.

For patients who are eligible to undergo a microperimetry assessment, at least 46 CFI profile biomarker-positive patients per lampalizumab treatment group and 23 CFI profile biomarker-positive patients per sham group will provide 80% power to detect a targeted difference of 6.91 points with a standard deviation of 9.88 points between each

lampalizumab treatment group and the pooled sham group in the change from baseline in the number of scotomatous points at 2 years. Calculation was based on a two-sided t-test at $\alpha=0.05$ level with the assumption of a 25% dropout rate by 2 years.

6.2 SUMMARIES OF STUDY CONDUCT

The clinical database will be used to assess study conduct. The number of patients randomized will be tabulated by treatment arm and biomarker status. Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment arm and biomarker status. Reasons for premature study treatment discontinuation and study discontinuation, any eligibility criteria deviation, and other major protocol deviations will also be tabulated.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, region, and baseline safety (such as baseline vital signs and laboratory test results), baseline disease characteristics (such as baseline GA area, baseline BCVA, and baseline VA under low luminance conditions) will be summarized for all randomized patients by treatment group and biomarker status using descriptive statistics. Exposure to study treatment (number of study treatments and duration of treatment) will be summarized by treatment arm and biomarker status.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be based on the intent-to-treat (ITT) approach. All randomized patients (i.e., ITT population) will be included in the analysis, with patients grouped according to the treatment assigned at randomization.

Unless otherwise noted, analyses of efficacy outcome measures will be stratified by biomarker status (positive vs. negative), baseline BCVA (20/50 [inclusive] or better vs. worse than 20/50), sex (woman vs. man), and eligibility for microperimetry assessment (yes vs. no). A data-as-observed approach with the mixed-effect model will be used to handle missing data in the primary analysis, which assumes that the missing data are missing at random. Sensitivity/supportive analyses based on imputed data will be provided in the SAP.

In addition to the analyses described in Sections [6.4.1](#) and [6.4.2](#), the following analyses will be performed for the primary efficacy endpoint and key secondary efficacy endpoints. Details of these analyses, including additional missing data handling rules, will be described in the SAP.

- Sensitivity analyses to evaluate the robustness of the results to the primary analysis method (e.g., missing data handling, derivation of primary outcome measure based on the rate of change)

- Subgroup analyses to evaluate the consistency of the results across prespecified subgroup (e.g., based on age, sex, baseline BCVA)

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in GA area from baseline at 1 year (Week 48) as assessed by FAF.

For each biomarker group, the mean change in GA area from baseline will be compared between each active treatment arm and the pooled sham arm by use of a linear mixed-effect model. The primary analysis will be based on all available data up to 1 year, with no imputation for missing data.

The dependent variable in the mixed-effect model is the change from baseline in GA area at post-baseline visits, up to 1 year, and the independent variables are the randomized treatment group, time, treatment-by-time interaction, baseline GA area, and the randomization stratification factors of (biomarker status, baseline BCVA ETDRS chart Snellen equivalent category, sex, and microperimetry eligibility). The mixed-effect model will assume an unstructured covariance structure. If there are convergence problems with the model, then a compound symmetry covariance structure will be fitted. A similar model with two additional independent variables, the biomarker status and the interaction of treatment and biomarker status, will be used to evaluate the predictive value of the genetic-defined biomarker. Also, for patients treated with sham, a comparison of change from baseline in GA area between biomarker-positive patients and biomarker-negative patients will be performed to evaluate the prognostic value of the CFI profile biomarker.

To manage the type I error of 0.0495 (two-sided), testing of the primary endpoint will be conducted in the following sequential order:

- Step 1: lampalizumab Q4W CFI profile biomarker-positive group versus pooled sham CFI profile biomarker-positive group

If there is no statistically significant difference found in this treatment comparison at the significance level of 0.0495, then the test for the next stage will not be considered statistically significant regardless of the p-value.

- Step 2: lampalizumab Q4W CFI profile biomarker-negative group versus pooled sham CFI profile biomarker-negative group, and lampalizumab Q6W CFI profile biomarker-positive group versus pooled sham CFI profile biomarker-positive group

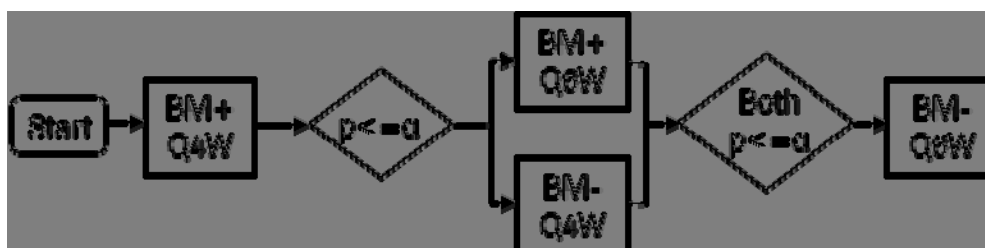
If statistically significant difference is not found in both treatment comparisons at the significance level of 0.0495, then the test for the next stage will not be considered statistically significant regardless of the p-value. If a statistically significant difference is found in only one treatment comparison at the significance level of 0.0495, then the statistical significance will be concluded only for that testing of the primary endpoint.

- Step 3: lampalizumab Q6W CFI profile biomarker-negative group versus pooled sham CFI profile biomarker-negative group

The statistical test will be conducted at a significance level of 0.0495.

Figure 3 illustrates the order in which hypothesis tests for the primary endpoint will be performed.

Figure 3 Order of Hypothesis Tests for the Primary Endpoint



BM+ = CFI profile biomarker-positive; BM- = CFI profile biomarker-negative; Q4W = every 4 weeks; Q6W = every 6 weeks.

Note: The arrows indicate the order of subsequent comparisons for the primary endpoint. Testing proceeds to a subsequent comparison only if all prior test(s) leading to that comparison are significant at $\alpha = 0.0495$. p refers to the p-value of a statistical testing.

6.4.2 Secondary Efficacy Endpoints

The secondary endpoints for this study are as follows:

- Mean change in number of scotomatous points from baseline to 2 years as assessed by mesopic microperimetry
- Mean change in macular sensitivity from baseline to 2 years as assessed by mesopic microperimetry
- Mean change from baseline in GA area at 2 years as assessed by FAF
- Mean change from baseline in GA area over time (all timepoints) as assessed by FAF
- Mean change from baseline in BCVA at 2 years as assessed by ETDRS chart at a starting distance of 4 m
- Mean change from baseline in BCVA over time as assessed by ETDRS chart at a starting distance of 4 m

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- Mean change from baseline in BCVA at 2 years as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m
- Mean change from baseline in BCVA over time as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m
- Proportion of patients with < 15 letters loss in BCVA score compared to baseline at 2 years as assessed by ETDRS chart at a starting distance of 4 m
- Proportion of patients with < 15 letters loss in BCVA score compared to baseline at 2 years as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m
- Mean change from baseline in mean binocular reading speed at 2 years as assessed by MNRead charts or Radner Reading Charts
- Mean change from baseline in binocular critical print size at 2 years as assessed by MNRead charts or Radner Reading Charts
- Mean change from baseline in NEI VFQ-25 composite score at 2 years
- Mean change from baseline in NEI VFQ-25 near activity subscale score at 2 years
- Mean change from baseline in NEI VFQ-25 distance activity subscale score at 2 years
- Mean change from baseline in FRI Index score at 2 years

The continuous secondary endpoints will be analyzed in the same fashion as the primary endpoint: using a linear mixed-effect model. Baseline is defined here as the last available value prior to randomization. The binary secondary endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by adequate randomization stratification factors, biomarker status (positive or negative), baseline BCVA (20/50 [inclusive] or better vs. worse than 20/50), sex (woman vs. man), and eligibility for microperimetry assessment (yes vs. no).

For three key secondary endpoints (mean change in the number of scotomatous points from baseline to 2 years as assessed by microperimetry, mean change from baseline in BCVA at 2 years as assessed ETDRS chart under low luminance conditions at a starting distance of 4 m, and mean change from baseline in mean binocular reading speed at 2 years), within each dosing frequency and CFI profile biomarker group, the hypothesis testing will be gated on the success of the primary endpoint test for that specific dosing frequency and CFI profile biomarker group and be performed sequentially at a significance level of 0.0495. For a specific dosing frequency, if both lampalizumab CFI profile biomarker groups are considered significantly different from the corresponding sham group in the primary endpoint, the hypothesis testing for the key secondary endpoints may be conducted on the basis of combined CFI profile biomarker groups for that specific dosing frequency.

Additional details regarding the analysis of secondary and exploratory endpoints will be provided in the SAP.

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6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who receive at least one lampalizumab injection or sham injection, with patients grouped according to the treatment actually received. Safety summaries will be presented for all treated patients.

Safety will be assessed through descriptive summaries of AEs, death, alternative complement assessment, serial ECG, anti-therapeutic antibodies to lampalizumab, and ocular assessments.

6.5.1 Adverse Events

Verbatim descriptions of treatment-emergent AEs will be coded and their incidence will be summarized, as appropriate. A treatment-emergent AE is defined as any new AE reported or any worsening of an existing condition on or after the first dose of study treatment. In addition, separate summaries will be generated for SAEs, deaths, AEs leading to discontinuation of study treatment, and AEs judged to be related to treatment (lampalizumab or sham). Separate summaries will be prepared for systemic (non-ocular) and ocular AEs, with events in the study eye and non-study eye (fellow eye) summarized separately.

6.5.2 Alternative Complement Pathway Activity Assessment

Descriptive summaries of alternative complement pathway activity assessments will be generated.

6.5.3 Anti-Therapeutic Antibodies

Data on ATAs directed against lampalizumab will be summarized by the number and percentage of patients with confirmed positive ATAs.

6.5.4 Death

Patient deaths and primary cause of death will be summarized.

6.5.5 Electrocardiogram Evaluation at Selected Sites

Descriptive summaries of common clinical ECG parameters at baseline and throughout the study will be generated. The number and percentage of patients with abnormal ECG findings will be summarized. See Section 4.5.7 for details of serial ECG subgroup assessment.

6.5.6 Ocular Assessments

Descriptive summaries will be generated for ocular assessments, such as VA and IOP.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include all randomized patients who have at least one serum sample, with patients grouped according to treatment actually received. Serum concentrations of lampalizumab will be summarized descriptively.

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.

6.7 OPTIONAL INTERIM ANALYSES

In order to adapt to information that may emerge during the course of this study (e.g., additional information of the biomarker characteristics, additional results of natural history studies), the Sponsor may choose to conduct one interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when such an optional interim analysis is executed.

The Sponsor will remain masked to individual treatment assignment. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter to ensure integrity.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be submitted to relevant Health Authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α -spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis ([DeMets et al. 1994](#)). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, as described in the standard Lan-DeMets theory.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance. If the predictive probability is below 20%, the iDMC should consider recommending that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 40% information has been accumulated.

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 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 EDC by sites.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to help text 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, PRO measures, 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 study.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for 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 Application (IND) will comply with 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 Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of in the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternative consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. 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 Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

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

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol violations. The investigator should promptly report any violations that might affect 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.

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The Sponsor will perform project management, study management, monitoring, vendor management, and statistical programming. An IxRS will be used for patient screening and 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 (e.g., serial ECG data). A central reading center will be used for ocular imaging analyses (FAF, NI, CFP, FA, and SD-OCT) and microperimetry data, which will be forwarded to Sponsor electronically.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies 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).

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10. REFERENCES

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Appendix 1 Schedule of Assessments

Table 1 Study Flowchart for Q4W Arms: Day 1, Day 8, Week 4 through Week 52, and Early Termination

	Screening	Day		Week Visit													Early Term ^a	
		1	8	4	8	12	16	20	24	28	32	36	40	44	48	52		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Written informed consent	x																	
Review of inclusion and exclusion criteria	x	x																
Medical and surgical history including tobacco history ^b	x																	
Demographic information	x																	
NEI VFQ-25 ^c		x													x			x
FRI Index ^c		x													x			x
Physical examination	x																	x
Height and weight	x																	
Historical ECG ^d	x																	
ECG at selected sites ^{e, f}		x	x	x					x									x
Vital signs ^{f, g}	x	x																x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) ^f	x																	x

Appendix 1 Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arms: Day 1, Day 8, Week 4 through Week 52, and Early Termination (cont.)

	Screening	Day		Week Visit													Early Term ^a	
		1	8	4	8	12	16	20	24	28	32	36	40	44	48	52		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
CFI whole blood sample (SF patients included) ^{f, h}	x																	
CFI buccal swab sample (SF patients included) ^{f, h}	x																	
Biomarker plasma sample ^f		x																
Biomarker paxgene sample ^f		x																
Biomarker whole blood clinical genotyping sample ^f		x																
Serum pregnancy sample ^{f, i, j}	x																	x
Urine pregnancy test ^{f, j}		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum ATA sample ^f		x							x							x		x
Serum PK sample for lampalizumab concentration ^f		x	x	x					x							x		x
Optional aqueous sample ^f		x							x					x				
AH50 sample ^f		x														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
MNRead or Radner Reading Charts ^{k, l}		x														x		x

Appendix 1 Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arms: Day 1, Day 8, Week 4 through Week 52, and Early Termination (cont.)

	Screening	Day		Week Visit													Early Term ^a	
		1	8	4	8	12	16	20	24	28	32	36	40	44	48	52		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Pre-treatment 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		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
Keratometry ⁿ	x																	
SD-OCT ⁿ	x								x							x		x
Near infrared imaging ⁿ	x								x			x				x		x
Fundus photography ⁿ	x															x		x
Fluorescein angiography ⁿ	x															x		x
Administration of lampalizumab injection/sham to study eye		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	
Concomitant medications ^p	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
Concurrent ocular procedures ^r		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	

Appendix 1 Schedule of Assessments (cont.)

Table 1 Study Flowchart for Q4W Arms: Day 1, Day 8, Week 4 through Week 52, and Early Termination (cont.)

AH50=Alternative Complement Pathway activity assay; ATA=anti-therapeutic antibody; BCVA=best corrected visual acuity; CFI=complement factor I; eCRF=electronic Case Report Form; FAF=fundus autofluorescence; FRI Index=Functional Reading Independence Index; IOP=intraocular pressure; LL BCVA=Low Luminance BCVA; MNRead=Minnesota Low-Vision Reading Test; NA=not applicable; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire 25-item Version; PK=pharmacokinetic; Q4W=every 4 weeks; SD-OCT=spectral domain optical coherence tomography; SF=screen fail.

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 those at screening. All study visits will be scheduled relative to date of Day 1 visit (first study treatment).

- ^a For patients who discontinue early from the study, early termination assessments will be performed after minimum of 30 days have lapsed following the last study treatment.
- ^b Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history), and tobacco use.
- ^c To be administered by the masked site staff (except for the VA examiner) prior to any other visit assessments being performed on that day.
- ^d If available, the study patients who are not part of the serial ECG evaluation (Section 4.5.7) will provide historical results of a clinical 12-lead ECG performed within the 12 months preceding Day 1 study treatment. The results will be stored in a patient source document. If there was no ECG performed within the 12 months preceding Day 1, it is not required to obtain at Screening/Day 1 ECG.
- ^e At selected sites, ECG will be performed at the timepoints listed. Perform ECG at early termination visit only if a patient is discontinuing study prior to the Week 24 visit. Patients should be in a resting position for 10 min. prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be minimized before and during ECG recording. The ECG result will be read by the central reader. See ECG manual for details.
- ^f Obtain prior to fluorescein angiograph (if applicable) and prior to study treatment.
- ^g Vital signs consist of blood pressure, respiratory rate, heart rate, and temperature; on Day 1 visit; this should be collected before study treatment.
- ^h CFI whole blood sample and CFI buccal swab sample will be collected at screening and will also be retained for the screen-failed patients.
- ⁱ At screening, collect serum pregnancy sample for women of childbearing potential, including those who have had tubal ligation. If positive, record the patient as a screen fail.
- ^j Starting at Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward to central lab for testing; if the serum pregnancy test is positive, do not administer the study treatment. At ET visit, collect the serum pregnancy sample and forward to the central lab for testing.
- ^k Perform the assessments prior to dilating the eyes.
- ^l MNRead charts or Radner Reading Charts can be done during study visit, prior to dilating the eyes (see the tables in [Appendix 18](#) and [Appendix 19](#) 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 1 Study Flowchart for Q4W Arms: Day 1, Day 8, Week 4 through Week 52, and Early Termination (cont.)

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- ^m Microperimetry assessments will be performed post-dilation on the study eye only, and the data will be forwarded to the central reading center. Note: If the Investigator determines that both eyes of a patient meet the eligibility criteria for the study eye, mesopic microperimetry will be performed on both eyes at screening.
- ⁿ SD-OCT and FAF images (including keratometry), near infrared images, fluorescein angiograms, and fundus photographs (as applicable) will be performed for both eyes and will be forwarded to the central reading center. See reading center manual. Note: after randomization, if a patient misses a study visit when ocular images were scheduled to be taken ([Appendix 1](#)), 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 unmasked physician within 15 minutes after study treatment. At study treatment visits, post-treatment IOP measurement in the study eye only between 30–50 minutes after study treatment (drug or sham) will be performed by the masked site staff (except for the VA examiner). If the IOP is increased by ≥ 10 mm Hg from pre-treatment, the IOP will be measured again at 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. Note: if the study eye is treated with a Lucentis injection during the same visit as the study treatment (lampalizumab/sham), the treatment with Lucentis must be performed first. Measure and record the post-Lucentis treatment IOP value on the eCRF.
- ^p Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit.
- ^q After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., procedures such as fluorescein angiography) should be reported. Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to lampalizumab should be followed until the event resolves or 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 on the study or non-study eye.
- ^s Starting at Week 4, study patients will be contacted by study site personnel 4 (± 2) days after each study 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 Arms: Week 56 through Week 96 and Early Termination

	Week Visit											Early Term ^a
	56	60	64	68	72	76	80	84	88	92	96	
Assessment Windows (Days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Written informed consent												
Review of inclusion and exclusion criteria												
Medical and surgical history including tobacco history ^b												
Demographic information												
NEI VFQ-25 ^c					x						x	x
FRI Index ^c					x						x	x
Physical examination												x
Height and weight												
Historical ECG ^d												
ECG at selected sites ^{e, f}												
Vital signs ^{f, g}												x
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) ^f												x
CFI whole blood sample (SF patients included) ^{f, h}												
CFI buccal swab sample (SF patients included) ^{f, h}												
Biomarker plasma sample ^f												
Biomarker paxgene sample ^f												
Biomarker whole blood clinical genotyping sample ^f												

Appendix 1 Schedule of Assessments (cont.)

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

	Week Visit											Early Term ^a
	56	60	64	68	72	76	80	84	88	92	96	
Serum pregnancy sample ^{f,i}												
Urine pregnancy test ^{f,j}	x	x	x	x	x	x	x	x	x	x		
Serum ATA sample ^f					x						x	x
Serum PK sample for lampalizumab concentration ^f					x						x	x
Optional aqueous sample ^f					x					x		
AH50 sample ^f											x	x
BCVA testing (starting at 4 m) ^k	x	x	x	x	x	x	x	x	x	x	x	x
LL BCVA (starting at 4 m) ^k					x						x	x
MNRead or Radner Reading Charts ^{k,l}					x						x	x
Pre-treatment IOP measurement ^k	x	x	x	x	x	x	x	x	x	x	x	x
Mesopic microperimetry at selected sites(study eye only) ^m					x						x	x
Slit-lamp examination	x	x	x	x	x	x	x	x	x	x	x	x
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x
FAF ⁿ					x						x	x
Keratometry ⁿ												
SD-OCT ⁿ					x						x	x
Near infrared imaging ⁿ					x						x	x
Fundus photography ⁿ											x	x

Appendix 1 Schedule of Assessments (cont.)

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

	Week Visit											Early Term ^a	
	56	60	64	68	72	76	80	84	88	92	96		
Fluorescein angiography ⁿ												x	x
Administration of lampalizumab injection/sham to study eye	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		
Concomitant medications ^p	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
Concurrent ocular procedures ^r	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		

AH50=Alternative Complement Pathway activity assay; ATA=anti-therapeutic antibody; BCVA=best corrected visual acuity; CFI=complement factor I; eCRF=electronic Case Report Form; FAF=fundus autofluorescence; FRI Index=Functional Reading Independence Index; IOP=intraocular pressure; LL BCVA=Low Luminance BCVA; MNRead=Minnesota Low-Vision Reading Test; NA=not applicable; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire 25-item Version; PK=pharmacokinetic; Q4W=every 4 weeks; SD-OCT=spectral domain optical coherence tomography; SF=screen fail.

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 those at screening. All study visits will be scheduled relative to date of Day 1 visit (first study treatment).

^a For patients who discontinue early from the study, early termination assessments will be performed after minimum of 30 days have lapsed following the last study treatment.

^b Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history), and tobacco use.

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

^d If available, the study patients who are not part of the serial ECG evaluation (Section 4.5.7) will provide historical results of a clinical 12-lead ECG performed within the 12 months preceding Day 1 study treatment. The results will be stored in a patient source document. If there was no ECG performed within the 12 months preceding Day 1, it is not required to obtain a Screening/Day 1 ECG.

Appendix 1 Schedule of Assessments (cont.)

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

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- ^e At selected sites, ECG will be performed at the timepoints listed. Perform ECG at early termination visit only if a patient is discontinuing study prior to the Week 24 visit. Patients should be in a resting position for 10 min. prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be minimized before and during ECG recording. The ECG result will be read by the central reader. See ECG manual for details.
- ^f Obtain prior to fluorescein angiograph (if applicable) and prior to study treatment.
- ^g Vital signs consist of blood pressure, respiratory rate, heart rate, and temperature; on Day 1 visit; this should be collected before study treatment.
- ^h CFI whole blood sample and CFI buccal swab sample will be collected at screening and will also be retained for the screen-failed patients.
- ⁱ At screening, collect serum pregnancy sample for women of childbearing potential, including those who have had tubal ligation. If positive, record the patient as a screen fail.
- ^j Starting at Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward to central lab for testing; if the serum pregnancy test is positive, do not administer the study treatment. At ET visit, collect the serum pregnancy sample and forward to the central lab for testing.
- ^k Perform the assessments prior to dilating the eyes.
- ^l MNRead charts or Radner Reading Charts can be done during study visit, prior to dilating the eyes (see the tables in [Appendix 18](#) and [Appendix 19](#) 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).
- ^m Microperimetry assessments will be performed post-dilation on the study eye only, and the data will be forwarded to the central reading center. Note: If the Investigator determines that both eyes of a patient meet the eligibility criteria for the study eye, mesopic microperimetry will be performed on both eyes at screening.
- ⁿ SD-OCT and FAF images (including keratometry), near infrared images, fluorescein angiograms, and fundus photographs (as applicable) will be performed for both eyes and will be forwarded to the central reading center. See reading center manual. Note: after randomization, if a patient misses a study visit when ocular images were scheduled to be taken ([Appendix 1](#)), 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 unmasked physician within 15 minutes after study treatment. At study treatment visits, post-treatment IOP measurement in the study eye only between 30–50 minutes after study treatment (drug or sham) will be performed by the masked site staff (except for the VA examiner). If the IOP is increased by ≥ 10 mm Hg from pre-treatment, the IOP will be measured again at 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. Note: if the study eye is treated with a Lucentis injection during the same visit as the study treatment (lampalizumab/sham), 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 Arms: Week 56 through Week 96 and Early Termination (cont.)

- ^p Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit.
- ^q After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., procedures such as fluorescein angiography) should be reported. Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to lampalizumab should be followed until the event resolves or 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 on the study or non-study eye.
- ^s Starting at Week 4, study patients will be contacted by study site personnel 4 (\pm 2) days after each study 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 Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination

	Screening	Day		Week Visit																Early Term ^a
		1	8	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Written informed consent	x																			
Review of inclusion and exclusion criteria	x	x																		
Medical and surgical history including tobacco history ^b	x																			
Demographic information	x																			
NEI VFQ-25 ^c		x								x				x					x	x
FRI Index ^c		x								x				x					x	x
Physical examination	x																			x
Height and weight	x																			
Historical ECG ^d	x																			
ECG at selected sites ^{e, f}		x	x	x			x													x
Vital signs ^{f, g}	x	x																		x

Appendix 1 Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

	Screening	Day		Week Visit																	Early Term ^a
		1	8	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote ^a
Central laboratory samples (hematology, coagulation, serum chemistry, and urinalysis) ^f	x																				x
CFI whole blood sample (SF patients included) ^{f, h}	x																				
CFI buccal swab sample (SF patients included) ^{f, h}	x																				
Biomarker plasma sample ^f		x																			
Biomarker paxgene sample ^f		x																			
Biomarker whole blood clinical genotyping sample ^f		x																			
Serum pregnancy sample ^{f, i, j}	x																				x
Urine pregnancy test ^{f, j}		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Serum ATA sample ^f		x					x				x				x					x	x

Appendix 1 Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

	Screening	Day		Week Visit																Early Term ^a	
		1	8	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Serum PK sample for lampalizumab concentration ^f		x	x	x			x				x				x					x	x
Optional aqueous sample ^f		x					x			x					x				x		
AH50 sample ^f		x									x									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	x	x	x
LL BCVA testing (starting at 4 m) ^k		x					x				x				x					x	x
MNRead or Radner Reading Charts ^{k,l}		x									x				x					x	x
Pre-treatment IOP measurement ^k	x	x	x	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				x					x	x
Slit-lamp examination	x	x	x	x	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 Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

	Screening	Day		Week Visit																Early Term ^a	
		1	8	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Dilated binocular indirect ophthalmoscopy	x	x	x	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
Keratometry ⁿ	x																				
SD-OCT ⁿ	x						x				x				x					x	x
Near infrared imaging ⁿ	x						x		x		x				x					x	x
Fundus photography ⁿ	x										x									x	x
Fluorescein angiography ⁿ	x										x									x	x
Administration of lampalizumab injection/sham 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		

Appendix 1 Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

	Screening	Day		Week Visit																Early Term ^a	
		1	8	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96		
Assessment Windows (Days)	-28 to -1	NA	±2	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	See footnote a
Concomitant medications ^p	x	x	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	x	x
Concurrent ocular procedures ^r		x	x	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			

AH50=Alternative Complement Pathway activity assay; ATA=anti-therapeutic antibody; BCVA=best corrected visual acuity; CFI=complement factor I; eCRF=electronic Case Report Form; FAF=fundus autofluorescence; FRI Index=Functional Reading Independence Index; IOP=intraocular pressure; LL BCVA=Low Luminance BCVA; MNRead=Minnesota Low-Vision Reading Test; NA=not applicable; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire 25-item Version; PK=pharmacokinetic; Q4W=every 4 weeks; SD-OCT=spectral domain optical coherence tomography; SF=screen fail.

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 those at screening. All study visits will be scheduled relative to date of Day 1 visit (first study treatment).

^a For patients who discontinue early from the study, early termination assessments will be performed after minimum of 30 days have lapsed following the last study treatment.

^b Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, and ophthalmic history), and tobacco use.

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

^d If available, the study patients who are not part of the serial ECG evaluation (Section 4.5.7) will provide historical results of a clinical 12-lead ECG performed within the 12 months preceding Day 1 study treatment. The results will be stored in a patient source document. If there was no ECG performed within the 12 months preceding Day 1, it is not required to obtain a Screening/Day 1 ECG.

Appendix 1 Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

- ^e At selected sites, ECG will be performed at the timepoints listed. Perform ECG at early termination visit only if a patient is discontinuing study prior to the Week 24 visit. Patients should be in a resting position for 10 min. prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be minimized before and during ECG recording. The ECG result will be read by the central reader. See ECG manual for details.
- ^f Obtain prior to fluorescein angiograph (if applicable) and prior to study treatment.
- ^g Vital signs consist of blood pressure, respiratory rate, heart rate, and temperature; on Day 1 visit; this should be collected before study treatment.
- ^h CFI whole blood sample and CFI buccal swab sample will be collected at screening and will also be retained for the screen-failed patients.
- ⁱ At screening, collect serum pregnancy sample for women of childbearing potential, including those who have had tubal ligation. If positive, record the patient as a screen fail.
- ^j Starting at Day 1, collect and perform the urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect the serum pregnancy sample and forward to central lab for testing; if the serum pregnancy test is positive, do not administer the study treatment. At ET visit, collect the serum pregnancy sample and forward to the central lab for testing.
- ^k Perform the assessments prior to dilating the eyes.
- ^l MNRead charts or Radner Reading Charts can be done during study visit, prior to dilating the eyes (see the tables in [Appendix 18](#) and [Appendix 19](#) 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).
- ^m Microperimetry assessments will be performed post-dilation on the study eye only, and the data will be forwarded to the central reading center. Note: If the Investigator determines that both eyes of a patient meet the eligibility criteria for the study eye, mesopic microperimetry will be performed on both eyes at screening.
- ⁿ SD-OCT and FAF images (including keratometry), near infrared images, fluorescein angiograms, and fundus photographs (as applicable) will be performed for both eyes and will be forwarded to the central reading center. See reading center manual. Note: after randomization, if a patient misses a study visit when ocular images were scheduled to be taken ([Appendix 1](#)), the images should be obtained at the next scheduled visit.

Appendix 1 Schedule of Assessments (cont.)

Table 3 Study Flowchart for Q6W Arms: Day 1, Day 8, Week 6 through Week 96, and Early Termination (cont.)

- ^o Finger-counting test followed by hand-motion and light-perception tests (when necessary) will be performed by the unmasked physician within 15 minutes after study treatment. At study treatment visits, post-treatment IOP measurement in the study eye only between 30–50 minutes after study treatment (drug or sham) will be performed by the masked site staff (except for the VA examiner). If the IOP is increased by ≥ 10 mm Hg from pre-treatment, the IOP will be measured again at 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. Note: if the study eye is treated with a Lucentis injection during the same visit as the study treatment (lampalizumab/sham), the treatment with Lucentis must be performed first. Measure and record the post-Lucentis treatment IOP value on the eCRF.
- ^p Record any concomitant medications (i.e., any prescription medications or over-the-counter preparations other than protocol-specified procedural medications such as proparacaine, etc.) used by the patient within 7 days preceding Day 1 and through the conclusion of the patient's study participation or early termination visit.
- ^q After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., procedures such as fluorescein angiography) should be reported. Adverse events will be recorded starting on Day 1 after the study treatment through the last study visit. Adverse events assessed by the physician as related to lampalizumab should be followed until the event resolves or 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 on the study or non-study eye.
- ^s Starting at Week 6, study patients will be contacted by study site personnel 4 (± 2) days after each study 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
Intraocular pressure ^c
Adverse events ^d
Concurrent ocular procedures
Concomitant medications

IOP = intraocular pressure.

^a If determined to be necessary by the physician, 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 masked 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.
2–3+	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 designations 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.

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

Table 1 Grading Scale for Anterior Chamber Flare or Cells (cont.)

Grade	Description
3+	25–50 cells are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains circulating cells. Keratic precipitates or cellular deposits on the anterior lens capsule may be present.
4+	More than 50 cells are seen when the slit-lamp beam is swept across the anterior chamber. When the instrument is held stationary, every optical section contains cells, or hypopyon is noted. As for fibrin deposition, hypopyon may persist for some period of time after the active exudation of cells into the anterior chamber has diminished or ceased entirely, making it possible to have 1+ circulating cells in the anterior chamber with a resolving hypopyon.

Modified from: Hogan et al. (1959).

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. In: Nussenblatt RB, Whitcup SM, Palestine AG, eds. *Examination of the patient with uveitis*. 2nd ed. St Louis: Mosby, 1996; 64.

Appendix 4 Pre-Injection Procedures for All Patients

Note: If (as per masked investigator judgment) treatment with Lucentis is to be given (to study and/or non-study eye) at the same visit as a study eye treatment with lampalizumab/sham, the treatment with Lucentis must be administered first. Following this, *a safety assessment (including an IOP check) must be completed prior to proceeding* to the study eye treatment with lampalizumab/sham. *If there are no concerns, proceed with* calling IxRS for the study treatment kit assignment. Individual trays and sterile prep must be separately prepared for each treatment. The injecting physician will perform the treatment with Lucentis to preserve the masking.

PRE-INJECTION PROCEDURES

The pre-injection procedure, lampalizumab reconstitution and intravitreal injection *or* sham (fake) injection procedures and post-injection procedures are also described in details in the Pharmacy Binder.

While reconstituting lampalizumab, a sterile field must be used and any personnel must wear a surgical face mask. Lampalizumab should be administered within 2 hours following reconstitution; the prepared dose may be maintained at room temperature prior to administration. There is no reconstitution process for the sham injection.

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

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

PROCEDURE FOR LIDOCAINE-BASED ANESTHESIA

The injecting physician or technician (if applicable) assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4 × 4 sterile pads, a pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride (or equivalent), 5% povidone iodine ophthalmic solution, 1% or 2% lidocaine for injection, ophthalmic antimicrobial solution (if applicable) and injection supplies. The procedure is as follows:

- Instill two drops of 0.5% proparacaine hydrochloride (or equivalent) into the study eye, followed by two drops of antimicrobial solution (if applicable)

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Appendix 4 Pre-Injection Procedures for All Patients (cont.)

- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The physician will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned study treatment (lampalizumab/sham) site on the conjunctiva.
- Wait 90 seconds.
- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride (or equivalent) drops and hold the swab against the planned injection site for 10 seconds in preparation for the subconjunctival injection of 1% or 2% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Inject lidocaine (without epinephrine) subconjunctivally.
- Use a sterile 4 × 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.

Note: For patients that develop adverse reaction to povidone-iodine, the following approaches are permitted:

- irrigate the eye with sterile saline after the study treatment (lampalizumab/sham) aiming to rinse away any remaining povidone-iodine
- or
- use a limited amount of povidone-iodine by placing a swab directly on the treatment site after the lid speculum has been placed

Appendix 5 Preparation and Administration of Lampalizumab Injection

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

Reconstitute for the 10-mg lampalizumab dose as follows:

1. Remove the plastic flip-off seal from one vial of lampalizumab lyophilized powder (6-cc vial), and swab the top of the vial with an alcohol swab.
2. Remove the plastic flip-off seal from **one vial of Sterile Water for Injection (SWFI)** (10-cc vial), and swab the top of the vial with an alcohol swab.
3. Using a 1 cc tuberculin (or equivalent) syringe *with an 18 or 19-gauge needle*, withdraw *enough volume* of SWFI (10-cc vial), *to deliver 0.50 mL of SWFI*, expel any air bubbles, insert the *needle* into the lampalizumab vial, and add.
4. Swirl the lampalizumab vial gently until the lyophilized powder dissolves; **do not shake or vortex the vial vigorously**. Let stand for approximately 5 minutes until bubbles dissolve.

Filter the lampalizumab as follows:

1. Withdraw 0.2 mL of lampalizumab dose solution through *an 18 or 19-gauge, 5- μ m filter needle attached to a new 1-cc tuberculin (or equivalent) syringe*.
2. After withdrawing lampalizumab in through the filter; **remove filter needle; replace it with a 30-gauge, 0.5-inch needle** (*without safety needle device attached*); and expel excess lampalizumab *and air bubbles* so that the syringe contains 0.1 mL of lampalizumab solution for dosing.

Appendix 5 Preparation and Administration of Lampalizumab Injection (cont.)

Table 1 Lampalizumab Reconstitution

Step	Procedure	Materials	Methods
1	<p>Reconstitute the lyophilized lampalizumab</p> <p>Note: Vials of lampalizumab should remain refrigerated (2°C-8°C or 36°F-46°F) until just prior to reconstitution with SWFI.</p>	<ul style="list-style-type: none"> • One vial of lyophilized lampalizumab • 18 or 19-gauge needle • 1-cc tuberculin (or equivalent) syringes • 10-cc vial of SWFI • Alcohol swabs 	<p>Swab the top of lampalizumab vial with an alcohol swab after removing the flip-top seal.</p> <p>Swab the top of SWFI vial with an alcohol swab after removing the flip-top seal.</p> <p><i>Using a 1 cc tuberculin (or equivalent) syringe with an 18 or 19-gauge needle, withdraw enough volume of SWFI (10-cc vial) to deliver 0.50 mL of SWFI, expel any air bubbles, insert the needle into the lampalizumab vial, and add.</i></p> <p>Swirl the lampalizumab vial containing the SWFI gently until the lyophilized powder dissolves. Do not shake vigorously or vortex the vials. Let stand for approximately 5 minutes until bubbles dissolve.</p>
2	<p>Filter the lampalizumab</p>	<ul style="list-style-type: none"> • 5-µm filter needle (needle is 18 or 19-gauge) • <i>New</i> 1-cc tuberculin (or equivalent) syringe • 30 gauge, 0.5-inch needle (<i>without safety needle device attached</i>) 	<p>Withdraw 0.2 mL of lampalizumab dose solution through a <i>new</i> 5-µm filter needle attached to a <i>new</i> 1-cc tuberculin (or equivalent) syringe.</p> <ul style="list-style-type: none"> • After withdrawing lampalizumab in through the filter, remove filter needle, replace it with a 30-gauge, 0.5-inch, needle (without safety needle device attached), expel excess lampalizumab and air so that the syringe contains 0.1 mL of lampalizumab solution.

SWFI= Sterile Water for Injection.

Appendix 5 Preparation and Administration of Lampalizumab Injection (cont.)

ADMINISTRATION OF LAMPALIZUMAB

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

- Put on gloves, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye, ensuring that the drops cover the planned injection site on the conjunctiva.
- Wait *approximately* 90 seconds.
- Saturate a sterile, cotton-tipped applicator with 0.5% proparacaine hydrochloride drops (*or equivalent*) and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% or 2% lidocaine hydrochloride solution for injection (without epinephrine).
- Inject 1% or 2% lidocaine (without epinephrine) subconjunctivally.
 - For patients who become intolerant to lidocaine as evidenced by an associated adverse event, alternative anesthetic drug for sub-conjunctival anesthesia may be permitted after consultation with the Medical Monitor.
- Use a sterile 4 × 4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct the patient to direct gaze away from syringe prior to lampalizumab injection.
- Physician will wear surgical face mask and refrain from talking, coughing, or sneezing during the injection.

Administer lampalizumab as follows:

- Insert the needle through an area 3.5–4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe. Rotate the injection site at every treatment visit.
- *At the physician's discretion, maneuvers such as mild ocular digital massage may be applied to the globe prior to the injection to reduce the risk of complications secondary to increased IOP. Inject the dose solution slowly.*
- Remove the needle slowly to ensure that all drug solution is in the eye.
- Refer to [Appendix 7](#) for detailed post-injection procedures

Appendix 6 Preparation and Administration of Sham Injection

Refer to [Appendix 4](#) for detailed instructions for pre-injection procedures.

The designated unmasked technician (if applicable) or treating physician will prepare the sham (fake) injection as outlined below.

PREPARATION

Assembly of the tray for the sham (fake) injection will appear identical to that of the study drug injection (see [Appendix 5](#)).

Sham vial is empty and will remain empty throughout the sham treatment. It does not contain any lyophilized powder. There is no drug reconstitution step performed for the sham treatment.

ADMINISTRATION

Patients receiving sham (fake) injections do not receive an actual intravitreal injection. The treating physician will use a needle only for the lidocaine injection given subconjunctivally. The procedures for cleansing and anesthetizing the study eye will be performed as outlined in [Appendix 4](#). The patient should be instructed to direct his or her gaze away from the syringe prior to administration of the sham injection. The treating physician will withdraw the tuberculin (or equivalent) syringe plunger to the 0.1-mL mark on the syringe, and then place the hub of the syringe-**without the needle**—against the pre-anesthetized conjunctival surface. The treating physician will then press the syringe hub firmly against the globe and then slowly depress the plunger, mimicking the action of an injection.

It is essential that the sham injection, including preparation and the sham injection itself, mimic as much as possible those used for the administration of study drug. For subsequent sham injection the criteria governing the selection of the study eye when both eyes meet eligibility criteria, follow the same procedure of rotating the location of the injection site, as is done with the study drug injections (see [Appendix 5](#)).

The treating physician or unmasked technician (if applicable) will discard all injection materials (i.e., syringes and needles) in a sharps container immediately following each sham injection, and the empty vial will be placed in the kit box. Refer to [Appendix 7](#) for detailed post-injection procedures.

Appendix 7 Post-Injection Procedures for All Patients

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

The unmasked technician or treating physician will discard the supplies in order to preserve patient's masking. Discard all syringes and needles in the sharps container.

Unless country regulatory prohibits, the used study drug or sham kit, including the used vial should be stored until the Sponsor representative conducts the study drug or sham accountability and the site is instructed to discard or ship to the Sponsor.

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

As per individual site investigator decision, patients may self-administer antimicrobial drops pre- and post-injection (study drug or sham).

A measurement of intraocular pressure in the study eye only will be obtained between 30 and 50 minutes after study treatment (drug or sham) by the qualified masked (except for the VA examiner) site staff. If the IOP is increased by ≥ 10 mm from pre-injection, the 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 page will be completed.

Appendix 8 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 must be masked to each patient's study (treated) eye and treatment arm (study drug vs. sham) assignment. VA will be measured at the intervals specified in the protocol (see Section 4.5 of the protocol 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, 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 9 Low Luminance Best Corrected Visual Acuity Testing

There are the same requirements as the best corrected visual acuity described in [Appendix 8](#); however, the 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 10 Color Fundus Photography

SCOPE

Stereo color fundus photographs will be taken by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the protocol (see [Appendix 1](#)). 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 11 Fluorescein Angiography

SCOPE

Fluorescein angiography will be performed at the study sites by trained personnel who are certified by the central reading center. The fluorescein angiograms (FAs) will be obtained at the intervals specified in the protocol (see [Appendix 1](#)). 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 12 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 13 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 14 Near-Infrared Imaging

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

SCOPE

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

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

EQUIPMENT

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

PROCEDURES AND CERTIFICATION

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

Appendix 15

Mesopic Microperimetry at Selected Sites

SCOPE

Mesopic microperimetry of the study eye only will be performed at selected study sites 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.

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.

Note: If the Investigator determines that both eyes of a patient meet the eligibility criteria for study eye, mesopic microperimetry will be performed on both eyes at screening.

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 16 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 PARTICIPANTS

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 16 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 16 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 16 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 16 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 16 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 16 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 16 National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

16. How much difficulty do you have driving at night? Would you say you have:

(READ CATEGORIES AS NEEDED)

(Circle One)

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

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic?

Would you say you have:

(READ CATEGORIES AS NEEDED)

(Circle One)

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

Appendix 16 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.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. <u>Do you accomplish less than you would like because of your vision?</u>	1	2	3	4	5
18. <u>Are you limited in how long you can work or do other activities because of your vision?</u>	1	2	3	4	5
19. <u>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:</u>	1	2	3	4	5

Appendix 16 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 <u>stay home most of the time</u> because of my eyesight.....	1	2	3	4	5
21. I feel <u>frustrated</u> a lot of the time because of my eyesight	1	2	3	4	5
22. I have <u>much less control</u> over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to <u>rely too much on</u> <u>what other people tell me</u>	1	2	3	4	5
24. I <u>need a lot of help</u> from others because of my eyesight	1	2	3	4	5
25. I worry about <u>doing things</u> <u>that will embarrass myself or</u> <u>others</u> , because of my eyesight	1	2	3	4	5

Appendix 16 National Eye Institute Visual Functioning Questionnaire 25-Item Version (cont.)

SUBSCALE: NEAR VISION

A1. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms?

Would you say:

(READ CATEGORIES AS NEEDED)

(Circle One)

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

A2. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(READ CATEGORIES AS NEEDED)

(Circle One)

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

Appendix 16 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 16 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 17 Functional Reading Independence Index

THE FUNCTIONAL READING INDEPENDENCE INDEX (FRI 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 (7) 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?

Appendix 17 Functional Reading Independence Index (cont.)

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

1. In the past 7 DAYS, did you read written print such as books, magazines or newspapers?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If "Yes"	<p>I'd like to know more about that. I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use extra lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move the text closer to you? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? (example, if needed: using a large print book) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read written print such as books, magazines or newspapers? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 2.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time,</p> <p style="margin-left: 20px;"><input type="checkbox"/> Most of the time, or</p> <p style="margin-left: 20px;"><input type="checkbox"/> All of the time? Please choose one answer. (Go to Question 2)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or</p> <p style="margin-left: 20px;"><input type="checkbox"/> For other reasons? Please choose one answer. (example, if needed: no time or opportunity to read written print)</p>

Appendix 17 Functional Reading Independence Index (cont.)

2. In the past 7 DAYS, did you read to pay bills or write a check? <input type="checkbox"/> Yes <input type="checkbox"/> No	
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use extra lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move the bill or text closer to you? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? (example, if needed: using a check-writing template) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read to pay bills or write a check? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 3.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time,</p> <p style="margin-left: 20px;"><input type="checkbox"/> Most of the time, or</p> <p style="margin-left: 20px;"><input type="checkbox"/> All of the time? (Go to Question 3)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or</p> <p style="margin-left: 20px;"><input type="checkbox"/> For other reasons? (example, if needed: no need or opportunity to pay bills)</p>

Appendix 17 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?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use extra lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move the medicine bottle or prescription closer to you? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read in order to take your medicine? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 4.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time, <input type="checkbox"/> Most of the time, or <input type="checkbox"/> All of the time? (Go to Question 4)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or <input type="checkbox"/> For other reasons? (example, if needed: no need to take medicines)</p>

Appendix 17 Functional Reading Independence Index (cont.)

4. In the past 7 DAYS, did you read labels such as price tags, food labels, or clothing labels?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use extra lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move the price tag or label closer to you? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read labels? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: right;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 5.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time, <input type="checkbox"/> Most of the time, or <input type="checkbox"/> All of the time? (Go to Question 5)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or <input type="checkbox"/> For other reasons? (example, if needed: no need or opportunity to read labels)</p>

Appendix 17 Functional Reading Independence Index (cont.)

5.	<p>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.</p> <p style="text-align: right;"><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p style="margin-left: 20px;">a. Did you use extra lighting <u>or</u> less lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="margin-left: 20px;">b. Did you move the telephone closer to you? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="margin-left: 20px;">c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="margin-left: 20px;">d. Did you use any other vision aids, not already mentioned? (example, if needed: using a "talking caller-ID") <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="margin-left: 20px;">e. Did another person help you read to make or receive a telephone call? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center; margin-left: 400px;">↓</p> <p style="text-align: center; margin-left: 200px;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 6.</p> <p style="margin-left: 20px;">f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 40px;"><input type="checkbox"/> Some of the time,</p> <p style="margin-left: 40px;"><input type="checkbox"/> Most of the time, or</p> <p style="margin-left: 40px;"><input type="checkbox"/> All of the time? (Go to Question 6)</p>
If "No"	<p style="margin-left: 20px;">g. Was this because of...</p> <p style="margin-left: 40px;"><input type="checkbox"/> Your vision, or</p> <p style="margin-left: 40px;"><input type="checkbox"/> For other reasons? (example, if needed: no need or opportunity to make phone calls)</p>

Appendix 17 Functional Reading Independence Index (cont.)

6. In the past 7 DAYS, did you read words or numbers on your screen while watching television?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use less lighting? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move closer to the television? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read words or numbers on the television screen? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: right;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to Question 7.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time, <input type="checkbox"/> Most of the time, or <input type="checkbox"/> All of the time? (Go to Question 7)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or <input type="checkbox"/> For other reasons? (example, if needed: no need or opportunity to watch television)</p>

Appendix 17 Functional Reading Independence Index (cont.)

7. In the past 7 DAYS, did you read when using a computer? <input type="checkbox"/> Yes <input type="checkbox"/> No	
If "Yes"	<p>If needed: I will read you a list of statements – Please answer "Yes" or "No" to each:</p> <p>a. Did you use less lighting or change the contrast on the screen? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. Did you move closer to the computer screen or increase the font size? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. Did you use a magnifying glass? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d. Did you use any other vision aids, not already mentioned? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e. Did another person help you read when using a computer? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: center;">↓</p> <p style="text-align: right;">If "Yes" to Item e, ask Item f. If "No" to Item e, go to concluding statements.</p> <p>f. In the past 7 days, <u>how often</u> did someone help you? Was it...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Some of the time, <input type="checkbox"/> Most of the time, or <input type="checkbox"/> All of the time? (Go to concluding statements)</p>
If "No"	<p>g. Was this because of...</p> <p style="margin-left: 20px;"><input type="checkbox"/> Your vision, or <input type="checkbox"/> For other reasons? (example, if needed: no need or opportunity to use a computer)</p>

This concludes our interview. Thank you for your time.

Appendix 18 Minnesota Low-Vision Reading Test (MNRead)

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.

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 card is 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 between 80–120 cd/m².

Viewing Distance

The print sizes and markings on the cards are designed for a testing distance of 40 cm, but may be tested at a distance of 32 cm. We recommend using a headrest set to the appropriate viewing distance in front of the cards, to prevent the patient from creeping forward throughout the test. For patients with central field loss, we find it 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.

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

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Appendix 18 Minnesota Low-Vision Reading Test (MNRead) (cont.)

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, pre-measured 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 PARTICIPANT

"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.

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Clinical Study Report: Lampalizumab - F. Hoffmann-La Roche Ltd/Genentech, Inc.
Protocol GX29176 Report Number 1085641

Appendix 18 Minnesota Low-Vision Reading Test (MNRead) (cont.)

MEASURING READING FUNCTION

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

Detailed Table for Administration of MNRead

Selected Countries	Primary language	MNRead
Argentina	Spanish	x
Australia	English	x
Mexico	Spanish	x
Peru	Spanish	x
US	English/Spanish	x
UK	English	x

Appendix 19 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, and critical print size.

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, MD, in Vienna 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 Cards assessment is to be conducted 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.

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/m².

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, pre-measured 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

Appendix 19 Radner Reading Cards (cont.)

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 PARTICIPANT

“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 visual acuity will be calculated using the data transcribed from the scoring sheet to the electronic Case Report Form (eCRF) and will not be calculated by the interviewers.

Appendix 19 Radner Reading Cards (cont.)

Detailed Table for Administration of Radner Reading Card

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

Appendix 20 Biological Sample Collection and Shipping Instructions

BIOLOGICAL SAMPLES

Biological samples for the assessment of lampalizumab concentrations (pharmacokinetics), anti-lampalizumab antibodies, Alternative Complement Pathway activity assay, complement factor I (CFI) whole blood sample, biomarker plasma, biomarker paxgene and biomarker whole blood clinical genotyping samples, and laboratory assessment (hematology, serum chemistry, 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 the treating 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.

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

BUCCAL SWAB COLLECTION

Note: See Central Laboratory Manual for the details of buccal swab collection.

Buccal swabs kits are special collection devices to collect mucosal cells from the cheek. They are designed for the collection, storage, stabilization, and transportation of total samples for CFI profile testing from the clinical swab material. They include the swab and swab collection tube, which includes stabilizer/polymerase chain reaction lysis buffer.

Appendix 20 Biological Sample Collection and Shipping Instructions (cont.)

Buccal swab collection will take place at the screening visit. The buccal swabs will be the alternative sample source collection devices for the genetic testing of patients for the CFI profile biomarker status. The reason for collecting this additional sample is to investigate the equivalence of the recovery, quality, and genotype information from whole blood versus that from cheek swabs. Because this collection process is less invasive than the whole blood collection process, the CFI profile sample may be collected by this more preferable method in the future, if both systems are proven to give comparable genotyping results.

The clinical site personnel/coordinator will be trained in this process in order to ensure the appropriate collection and storage of buccal swabs from patients. The buccal swabs will be banked for future concordance analysis with the whole blood CFI profile test prior to regulatory filings and not for exploratory purposes.

Appendix 21 Electrocardiogram Data Collection at Selected Sites

PURPOSE

Cardiovascular effects of lampalizumab are not anticipated based on nonclinical data and clinical studies conducted to date. However, in order to fulfill a regulatory requirement, an evaluation of clinical cardiovascular parameters using ECGs will be conducted in approximately 100 patients at selected sites within the United States. The purpose is to summarize common clinical cardiovascular parameters across a sample of active-treatment and sham-treatment patients over time.

DESCRIPTION

Each patient enrolled at participating sites will automatically participate in the ECG data collection activities. Using study-provided equipment, each patient will undergo four digital 12-lead ECGs (see [Appendix 1](#) for the timepoints). To minimize variability, it is important that patients be in a resting position for approximately 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be minimized before and during ECG recording.

INTERPRETATION AND DATA ENTRY

All ECGs will be transferred electronically to the study-designated central vendor for data extraction, central cardiology interpretation, and final direct data exportation. Central ECG interpretation will be performed for each patient recording, and the results will be forwarded to the relevant site's Principal Investigator (or designee) for clinical correlation and inclusion in the appropriate site records. In the case of a new-onset or changed clinically meaningful abnormal finding(s), the central vendor will contact the site's Principal Investigator (or designee) directly with an expedited report (within 24 hours) of the abnormal findings for the purpose of adverse event reporting or any other necessary clinical intervention(s). Any clinically meaningful ECG changes (in the opinion of the investigator) relative to Day 1 assessment, which are associated with symptoms, lead to a change in study treatment or concomitant treatment, or lead to discontinuation from study treatment, must be reported as an adverse event on the Adverse Event electronic Case Report Form.

Appendix 22 The cobas[®] CFI Profile Clinical Trial Assay (CTA)

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

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

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

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

Appendix 22 The cobas[®] CFI Profile Clinical Trial Assay (CTA) (cont.)

MMx1	MMx2	MMx3	
<i>CFI</i>	<i>C2/CFB</i>	<i>CFH</i>	<i>Biomarker Status</i>
rs4698775 GG	rs429608 GG	rs1329428 CC	+
rs4698775 GG	rs429608 GG	rs1329428 CT	+
rs4698775 GG	rs429608 GG	rs1329428 TT	+
rs4698775 GG	rs429608 GA	rs1329428 CC	+
rs4698775 GG	rs429608 GA	rs1329428 CT	+
rs4698775 GG	rs429608 GA	rs1329428 TT	+
rs4698775 GG	rs429608 AA	rs1329428 CC	+
rs4698775 GG	rs429608 AA	rs1329428 CT	+
rs4698775 GG	rs429608 AA	rs1329428 TT	-
rs4698775 TG	rs429608 GG	rs1329428 CC	+
rs4698775 TG	rs429608 GG	rs1329428 CT	+
rs4698775 TG	rs429608 GG	rs1329428 TT	+
rs4698775 TG	rs429608 GA	rs1329428 CC	+
rs4698775 TG	rs429608 GA	rs1329428 CT	+
rs4698775 TG	rs429608 GA	rs1329428 TT	+
rs4698775 TG	rs429608 AA	rs1329428 CC	+
rs4698775 TG	rs429608 AA	rs1329428 CT	+
rs4698775 TG	rs429608 AA	rs1329428 TT	-
rs4698775 TT	rs429608 GG	rs1329428 CC	-
rs4698775 TT	rs429608 GG	rs1329428 CT	-
rs4698775 TT	rs429608 GG	rs1329428 TT	-
rs4698775 TT	rs429608 GA	rs1329428 CC	-
rs4698775 TT	rs429608 GA	rs1329428 CT	-
rs4698775 TT	rs429608 GA	rs1329428 TT	-
rs4698775 TT	rs429608 AA	rs1329428 CC	-
rs4698775 TT	rs429608 AA	rs1329428 CT	-
rs4698775 TT	rs429608 AA	rs1329428 TT	-

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