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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STATISTICAL ANALYSIS PLAN

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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1. BACKGROUND

The purpose of this document is to provide details of the planned analyses for Study GX29176 (Chroma). Analyses for both the primary study analysis and the final study analysis are described.

The primary study analysis will be based on complete data from the first 48-weeks of the study, and performed after all patients have completed 48-weeks in the study or discontinued early, and all corresponding data have been entered into the database, reviewed, and verified. Analysis will include hypothesis testing of the primary efficacy endpoint (anatomic outcome) at Week 48. Secondary and exploratory endpoints (visual function outcomes) will be evaluated based on 48-week data in an exploratory manner, although formal statistical testing for these endpoints will be at Week 96. An analysis of the 48-week safety data will be performed.

At the time of the primary 48-week analysis, the second year of the study will be ongoing. An analysis of the available second year safety data (after Week 48 and up to a specified clinical cutoff date) will also be performed. Such results will be reported with, but separate from, the 48-week study results to provide additional safety information for lampalizumab.

The final study analysis will be based on data from the complete study, and performed after all patients have either completed 96-weeks in the study or discontinued early, and all data from the study are in the database and the database is locked. Secondary and exploratory endpoints (visual function outcomes) will be analyzed based on Week 96 data. At the time of the final analysis, safety summaries will be produced based on cumulative Week 96 data.

See Section 2.4 for further details on analysis timing.

The analyses specified in this document supersede the analysis plan described in the study protocol (Version 6). Of particular note, the hypotheses of interest and order of hypothesis tests for the primary efficacy endpoint (see Section 4.5.1) have been modified since the protocol was written based on information obtained from an interim analysis of Study GX29633, a prospective epidemiological study of the progression of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Study GX29633 is being conducted to gain a better understanding of the rate of GA lesion progression, the prognostic effect of the complement factor I (CFI)-profile biomarker, and the correlation of GA lesion area with visual function outcomes.

A separate analysis plan will be prepared for purposes of a health technology assessment. In addition, a separate analysis plan will be prepared for additional exploratory genetic analyses (see Section 4.5.4).

2. STUDY DESIGN

Study GX29176 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 every 4-weeks (Q4W) or every 6-weeks (Q6W) by intravitreal injection during a 96-week (approximately 2 year) treatment period in patients with GA secondary to AMD. The study consists of a screening period (of up to 28 days duration), followed by a 96-week treatment period.

Approximately 936 patients will be randomized into the study at approximately 140 investigational sites located globally. The study will enroll both CFI-profile biomarker-positive and CFI-profile biomarker-negative patients (see Section 2.2); enrollment will be in a ratio of 1.5:1 for biomarker-positive patients relative to biomarker-negative patients. Eligible patients are randomized in a 2:1:2:1 ratio to receive 10 mg lampalizumab Q4W, sham Q4W, 10 mg lampalizumab Q6W, or sham Q6W during the 96-week treatment period. Study treatment is given Day 1 to Week 92 for the Q4W treatment arms and Day 1 to Week 90 for the Q6W treatment arms, with a final study visit at Week 96 for all patients.

Efficacy, safety, and pharmacokinetic (PK) measures are assessed throughout the treatment period, as detailed in the Schedule of Assessments (see study protocol).

Further study design details are provided in the study protocol.

2.1 ENDPOINTS/OUTCOME MEASURES

Unless otherwise specified, ocular efficacy outcome measures refer to the study eye.

2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in GA area at 1 year (48-weeks) as assessed by fundus autofluorescence (FAF).

2.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed over time up to Week 96, with formal statistical testing at Week 96. Hypothesis testing for three key secondary endpoints will be performed in the order specified in Section 4.5.2.1 based on the Week 96 timepoint.

- Change from baseline in number of absolute scotomatous points as assessed by mesopic microperimetry
  - Assessed for subset of patients at selected study sites only. Endpoint will be evaluated based on pooled data from GX29176 and GX29185.

- Change from baseline in mean macular sensitivity as assessed by mesopic microperimetry
  - Assessed for subset of patients at selected study sites only. Endpoint will be evaluated based on pooled data from GX29176 and GX29185.
- Change from baseline in best corrected visual acuity (BCVA) as assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 m
- Patients with < 15 letters loss from baseline in BCVA score as assessed by the ETDRS chart at a starting distance of 4 m
- Change from baseline in low luminance visual acuity (LLVA) as assessed by the ETDRS chart at a starting distance of 4 m
  - Note: In the protocol, LLVA was referred to as BCVA score as assessed by ETDRS chart under low luminance conditions.
- Patients with < 15 letters loss from baseline in LLVA score as assessed by the ETDRS chart at a starting distance of 4 m
- Change from baseline in binocular maximum reading speed as assessed by Minnesota low-vision reading test (MNRead) or Radner Charts
- Change from baseline in monocular maximum reading speed as assessed by MNRead or Radner Charts
- Change from baseline in National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI VFQ-25) composite score
- Change from baseline in NEI VFQ-25 near activity subscale score
- Change from baseline in NEI VFQ-25 distance activity subscale score
- Change from baseline in Mean Functional Reading Independence (FRI) Index score

2.1.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be assessed over time up to Week 96, with formal statistical testing at Week 96.

- Patients with < 20% increase from baseline in GA area as assessed by FAF
- Change from baseline in GA area over time (all additional timepoints [Weeks 24, 36, 72, and 96]) as assessed by FAF
- Change from baseline in number of absolute or relative scotomatous points as assessed by mesopic microperimetry
  - Assessed for subset of patients at selected study sites only. Endpoint will be evaluated based on pooled data from GX29176 and GX29185.
- Percent change from baseline in binocular maximum reading speed as assessed by MNRead or Radner Charts

- Patients with at least a 2-level decline from baseline in binocular maximum reading speed (based on the following levels: $<40, \geq 40$ to $<60, \geq 60$ to <80, ≥ 80 to <120, ≥ 120 to <160, ≥ 160 wpm) as assessed by MNRead or Radner Charts
- Percent change from baseline in monocular maximum reading speed as assessed by MNRead or Radner Charts
- Patients with at least a 2-level decline from baseline in monocular maximum reading speed (based on the following levels: $<40, \geq 40$ to $<60, \geq 60$ to <80, ≥ 80 to <120, ≥ 120 to <160, ≥ 160 wpm) as assessed by MNRead or Radner Charts
- Change from baseline in binocular critical print size as assessed by MNRead or Radner Charts
- Change from baseline in monocular critical print size as assessed by MNRead or Radner Charts
- Change from baseline in binocular reading acuity as assessed by MNRead or Radner Reading Charts
- Change from baseline in monocular reading acuity as assessed by MNRead or Radner Reading Charts
- Patients with no decline from baseline in FRI Level score
- Patients with visual function worsening, as defined by (i) a ≥ 5 letter decrease in BCVA (as assessed by the ETDRS chart), AND (ii) a $\geq 20\%$ decrease in monocular maximum reading speed (as assessed by MNRead or Radner Reading Charts)
- Patients with overall disease worsening, as defined by (i) a ≥ 5 letter decrease in BCVA (as assessed by the ETDRS chart), AND (ii) a $\geq 20\%$ decrease in monocular maximum reading speed (as assessed by MNRead or Radner Reading Charts), AND (iii) a $\geq 20\%$ increase in GA area (as assessed by FAF)

2.1.4 Supplemental Efficacy Endpoints Related to Primary Endpoint

The following efficacy endpoints, closely related to the primary efficacy endpoint, will be assessed over time up to Week 48 to provide supplemental information to the primary endpoint analysis. The endpoints will also be assessed over time up to Week 96 at the time of the final study analysis.

- Rate of change in GA area (growth slope) as assessed by FAF
- Change from baseline in square root of GA area as assessed by FAF
- Percent change from baseline in GA area as assessed by FAF

2.1.5 Pharmacokinetic and Pharmacodynamic Outcome Measures

As specified in the protocol, the PK outcome measure for this study is serum lampalizumab concentrations over time. Total lampalizumab and complement factor D (CFD) levels in aqueous humor are specified as an exploratory outcome measure. (Note, aqueous humor samples are only available for the subset of patients who consented to optional aqueous humor sampling.)

2.1.6 Safety Endpoints

The safety outcome measures are as follows:

- The incidence and severity of ocular adverse events
- The incidence and severity of non-ocular adverse events
- Changes and abnormalities in electrocardiogram (ECG) parameters
  - Assessed through Week 24 for patients at selected sites who have undergone ECG evaluation (approximately 100 patients in total)
- The incidence of anti-drug antibodies

2.1.7 Diagnostic Outcome Measures

The evaluation of the predictive value of the CFI-profile biomarker will be assessed through the evaluation of the primary efficacy endpoint. The evaluation of the prognostic value of the CFI-profile biomarker will be based on the primary clinical outcome of change from baseline in the GA area as measured by FAF in the sham arm.

In addition, the following exploratory diagnostic outcome measures are specified:

- The association of genetic variants in CFI and complement-pathway genes with disease characteristics and response to 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

2.2 BIOMARKER CONSIDERATIONS

Exploratory genetic analyses of data from the Phase II Study CFD4870g suggested that a biomarker-defined population (CFI-profile biomarker-positive) may have more rapid disease progression and potentially derive greater efficacy benefit from lampalizumab than the population that is negative for the biomarker (CFI-profile biomarker-negative). In order to further evaluate this hypothesis, this Phase III study (GX29176) will enroll both CFI-profile biomarker-positive and biomarker-negative patients; enrollment will be in a ratio of 1.5:1 for CFI-profile biomarker-positive patients relative to CFI-profile biomarker-negative patients.

Complement factor I profile is based on the common genetic variants of CFI, complement factor H (CFH), and complement component 2/complement factor B (C2/CFB). The following two patient groups are defined (see Table 1):

- **CFI profile biomarker-positive patients:** Patients who are carriers of CFI risk allele, who are also risk allele carriers at CFH and/or C2/CFB.
- **CFI profile biomarker-negative patients:** Patients who are (i) non-carriers of the CFI risk allele or (ii) carriers of the CFI risk allele, who are non-carriers of the risk alleles at both CFH and 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	+	–	–
	–	+	+
	–	+	–
	–	–	+
	–	–	–

C2 = complement component 2; CFB = complement factor B; CFH = complement factor H; CFI = complement factor I.

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.

For this study, CFI-profile biomarker status is determined using the investigational cobas® CFI Profile Clinical Trial Assay (CTA). The cobas® CFI Profile CTA biomarker status results are used for patient enrollment (to achieve a 1.5:1 ratio for biomarker-positive relative to biomarker-negative patients) and for stratification of patients at randomization. In addition, all biomarker-related analyses specified in this SAP will be performed on the basis of CFI profile results from the cobas® CFI Profile CTA.

Enrollment of both biomarker-positive and biomarker-negative patients allows for evaluation of the treatment benefit in both patient groups, as well as the overall enrolled population. The hypotheses of interest and order of hypothesis tests for the primary efficacy endpoint are specified in Section 4.5.1, and take precedence over that specified in the study protocol. In addition to data from exploratory analyses of Study CFD4870g, interim data from the epidemiological Study GX29633 were considered for the order of hypothesis testing.

2.3 SAMPLE SIZE

2.3.1 Determination of Sample Size

Approximately 936 patients will be enrolled in the study. Patients are 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 treatment arms will be pooled in the analysis.

The study was originally 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 each of the biomarker-positive and biomarker-negative groups and to meet health authority requirements for the size of the safety database. At the time of the study design, sample size and power calculations used assumptions based on results from the Phase II Study CFD4870g. For details of the determination of sample size, see study protocol Section 6.1.

As outlined in Section 6.1, the protocol also specified that the Sponsor may conduct a masked evaluation of the variance of the primary efficacy endpoint and study dropout rate before the end of enrollment, with the intent to potentially increase the study sample size if deemed necessary in order to maintain the desired study power. However, such an evaluation was not conducted and the sample size of the study remained unchanged from that originally planned.

2.3.2 Estimated Power Based on Information from Study GX29633

The primary efficacy endpoint is the change from baseline in GA area at 1 year (48 weeks) as assessed by FAF. As specified in Section 4.5.1, the primary efficacy objectives will be assessed by analysis of the primary efficacy endpoint in the overall patient population and in the biomarker-positive group for each dosing frequency separately.

Table 2 summarizes the power and minimum detectable difference for the primary endpoint analysis when evaluated for the overall patient population and the biomarker-positive group using progression rates and variability assumptions based on data from Study GX29633, a prospective epidemiological study of the progression of GA secondary to AMD (May 2017 interim analysis). Namely, calculations assumed a progression rate (mean change from baseline in GA area at 48-weeks) of 2.08 mm^2 for both the biomarker-positive and biomarker-negative patient groups and a SD of 1.53 mm^2 for the change from baseline in GA area at 48-weeks. With these assumptions, 312 patients per lampalizumab treatment arm and 156 patients per sham arm will provide 88% power to declare a difference between each lampalizumab treatment arm and the pooled sham arm in the overall patient population for a targeted difference of 0.42 mm^2 (approximately 20% reduction relative to sham control) in the change from baseline in GA area at 48 weeks (Table 2). Estimated power to detect specified differences in the primary efficacy endpoint within the biomarker-positive

patient population is as shown in Table 2. Calculations were based on two-sided t-tests at the $\alpha = 0.0496$ level (after adjustment for the four data reviews conducted by the iDMC prior to analysis of the primary efficacy endpoint), with the assumption of a 15% dropout rate by 48 weeks.

Table 2 Power and Minimum Detectable Difference for Analysis of Primary Endpoint Using Assumptions Based on the Epidemiological Study GX29633

Endpoint Summary and Population	Target Treatment Effect	Two-Sided $\alpha = 0.0496$	
		Power	MDD
Mean change from baseline in GA area at 1 year (48 weeks) in all patients (n = 312 per arm)	$\Delta = 0.42$ mm^2 (approximately 20%[a] reduction) SD = 1.53	88%	0.26 mm^2 (approximately 13%[a] reduction)
Mean change from baseline in GA area at 1 year (48 weeks) in biomarker-positive patients (n = 188 per arm)	$\Delta = 0.83$ mm^2 (approximately 40%[a] reduction) SD = 1.53	> 95%	0.34 mm^2 (approximately 16%[a] reduction)

GA = geographic atrophy; MDD = minimum detectable difference.

The sample size takes into account the dropout rate of 15% by 48 weeks. The power and MDD are for each comparison between one lampalizumab treatment arm and the pooled sham arm.

[a] Relative to the sham arm and assuming the mean change from baseline in GA area at 48 weeks is 2.08 mm^2 for both the biomarker-positive and biomarker-negative patient groups.

2.4 ANALYSIS TIMING AND UNMASKING

The analysis of data from the first 48-weeks of the study will be performed when (i) all patients have completed study visits through Week 48 or have discontinued from the study prior to Week 48 and (ii) all data from the first 48-weeks of the study are in the database and have been reviewed per the Data Quality Review Plan and verified per the Trial Monitoring Plan.

At that time, Sponsor personnel who are analyzing data from the first 48-weeks of the study will be unmasked to treatment assignment. To maintain data integrity for the remainder of the study, internal guidelines are to be followed to avoid unnecessary unmasking of investigator site staff or patients.

Analyses will include formal hypothesis testing of the primary efficacy endpoint (anatomic outcome) at Week 48. Secondary and exploratory endpoints (visual function outcomes) will be evaluated based on 48-week data in an exploratory manner, although formal statistical testing for these endpoints will be at Week 96. An analysis of the 48-week safety data will also be performed.

The second year of the study will be ongoing at the time of the 48-week primary analysis. An analysis of the second year safety data that is available at the time of the 48-week primary analysis will be performed; it will include all safety data after Week 48 and up to a single specified calendar cutoff date. Such results will be reported with, but separate from, the 48-week study results to provide additional safety information for lampalizumab.

The final study analysis based on data from the complete study will be performed when all patients have either completed the 2-year study period (i.e., study visits through Week 96) or have discontinued early from the study, all data from the study are in the database, and the database is locked. Secondary and exploratory endpoints (visual function outcomes) will be analyzed based on Week 96 data. At the time of the final analysis, safety summaries will be produced based on cumulative Week 96 data.

Aggregate results of the 48-week analysis may be reported to the public before completion of the study. However, patients, masked study site personnel, and central reading center personnel will remain masked to individual treatment assignment until after the study is completed (after all patients have either completed Week 96 or discontinued early from the study), the database is locked, and the study analyses are final. Sponsor study team members who are aware of individual patient-level treatment assignments and have direct contact with the study site will sign a non-disclosure form and will not reveal treatment assignment information to site staff.

Table 3 provides an overview of the timing for the planned analyses.

Table 3 Timing of Planned Analyses

Analysis	Timing of Analysis	Adjusted Two-Sided Alpha Level
Primary	All patients complete 1 year (48 week) assessment or discontinue study early	0.0496 for primary endpoint tested at Week 48
Final	All patients complete 2 year (96 week) assessment or discontinue study early	0.0496 for secondary and exploratory endpoints tested at Week 96

Note: Secondary and exploratory efficacy endpoints (visual function outcomes) will be evaluated based on Week 48 data in an exploratory manner, although formal statistical testing for these endpoints will be at Week 96.

2.5 DEFINITION OF 48-WEEK DATA

All screening and post-baseline data with a clinical date (i.e., administration/assessment/onset/start date) on or before the defined Week 48 data cutoff date will be included in the primary 48-week analysis. The 48-week data cutoff will include all data regardless of the type of study visit at which it was collected. This may

include data collected at unscheduled visits or early termination visits, if the visit date was on or before the 48-week data cutoff date. The data cutoffs for Week 48 data are defined as follows:

- **For all assessments except imaging and microperimetry:** The Week 48 data cutoff will be Study Day 350 (i.e., Study Day 337 [Week 48 day]+13 day window) for the Q4W treatment arms and Study Day 357 (i.e., Study Day 337 [Week 48 day]+20 day window) for the Q6W treatment arms.
- **For all imaging (including FAF) and microperimetry assessments:** The Week 48 data cutoff will be Study Day 384 (i.e., Study Day 337 [Week 48 day]+47 day window) for all treatment arms. The wider analysis window for imaging and microperimetry assessments is to allow for capture of missed images that were taken at the next scheduled visit, as permitted by the protocol.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients are randomized to the treatment arms through an IxRS. After all patient eligibility requirements are confirmed at both the screening and Day 1 visit, patients are randomized in a 2:1:2:1 ratio to one of four arms (10 mg lampalizumab Q4W, sham Q4W, 10 mg lampalizumab Q6W, or sham Q6W). Study treatment is to be initiated on the same day that the patient is randomized (Day 1 visit).

Randomization is stratified by biomarker status (positive vs. negative, as determined by the cobas® CFI Profile CTA), baseline BCVA ETDRS chart Snellen equivalent (20/50 or better vs. worse than 20/50), sex (male vs. female), and microperimetry eligibility (yes vs. no). A permuted-block randomization method is 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-positive or CFI profile biomarker-negative patients necessary to achieve the targeted 1.5:1 ratio for biomarker groups (see Section 2.2), the additional screened patients who would have been randomized in the already filled biomarker group will be screen-failed.

Following randomization and during the treatment period, the IxRS makes study treatment kit assignments.

Patient randomization and study treatment kit assignments are verified on an ongoing basis by an external and independent data coordinating center (iDCC). The iDCC independently reviews the logs to ensure that randomization and kit assignments are conducted correctly by the IxRS.

3.2 INDEPENDENT DATA REVIEW

3.2.1 Central Reading Center

All ocular images and microperimetry results are obtained by trained site personnel at the study sites and forwarded to an external central reading center for independent analysis and storage. As part of the screening process, the central reading center evaluates ocular images and microperimetry results to provide an objective assessment of patient eligibility. Throughout the study, the central reading center evaluates ocular images and microperimetry data in an objective and masked manner (masked to patient treatment assignment), with resulting data forwarded to the Sponsor electronically.

3.2.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) monitors safety and study conduct on an ongoing basis. Members of the iDMC are external to the Sponsor and follow a charter that outlines the iDMC roles and responsibilities. The iDMC meets approximately every 6 months (frequency adjustable as required) to review unmasked safety and study conduct data prepared by an external iDCC. Further, the iDMC may review efficacy data if deemed necessary to assess the benefit-risk profile of lampalizumab.

The iDMC may recommend stopping the study early for safety reasons. No formal efficacy or futility analysis is planned for the study. While there are no formal efficacy or futility analyses, per FDA request, a nominal Type I error penalty of 0.0001 will be taken for each time the iDMC reviews unmasked data reports prior to the formal analysis of the primary efficacy endpoint. At the time of the primary efficacy endpoint analysis, four scheduled data reviews will have been conducted by the iDMC (July 2015, February 2016, August 2016, and March 2017); therefore, analyses of the primary efficacy endpoint will be performed at $\alpha = 0.0496$.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Two main analysis populations are defined for this study: the intent-to-treat (ITT) population and the safety-evaluable population. In addition, as microperimetry assessments and serial ECG evaluations were each performed on a subset of patients at selected study sites, a microperimetry-analysis population and an ECG-analysis population are defined.

4.1.1 Intent-to-Treat Population

The ITT population will be comprised of all patients who were randomized in the study. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization.

4.1.2 Safety-Evaluable Population

The safety-evaluable population will be comprised of all patients who received at least one injection of study treatment (lampalizumab or sham injection). For analyses based on this patient population, patients will be grouped according to the actual treatment received as follows. Patients who receive only sham injections will be classified in the sham treatment arm with the frequency (Q4W or Q6W) as assigned at randomization. Any patient who receives one or more injection of lampalizumab will be classified in the lampalizumab treatment arm with the frequency (Q4W or Q6W) as assigned at randomization. This includes patients randomized to sham who accidentally received one or more injections of lampalizumab.

It is expected that most patients will receive their assigned treatment at all dosing timepoints and that only a small number of dosing errors will occur. Nonetheless, dosing errors will be reviewed in conjunction with the corresponding patient safety data to assess for any impact on the defined safety populations or the overall safety conclusions.

4.1.3 Microperimetry-Analysis Population

Microperimetry assessments were performed on a subset of patients at selected study sites only. The microperimetry analysis population will be comprised of all ITT patients with microperimetry assessments who met the microperimetry eligibility criteria as evaluated by the central reading center, and validation checks will be applied to identify microperimetry assessments of sufficient quality for inclusion in the analysis. For analyses based on this patient population, patients will be grouped according to the treatment assigned at randomization. Due to the smaller sample size enrolled than anticipated, statistical inferences for efficacy endpoints based on microperimetry assessments will be based on pooled data from Studies GX29176 and GX29185.

4.1.4 ECG-Analysis Population

Electrocardiogram assessments were performed on a subset of patients at selected U.S. study sites only. The ECG-analysis population will be comprised of all safety-evaluable patients who did not have atrial fibrillation at baseline per ECG assessment, and who had numerical results reported from at least one ECG assessment. For analyses based on this patient population, patients will be grouped according to the actual treatment received, consistent with patient groupings for the safety-evaluable population.

4.2 DEFINITION OF BASELINE

Baseline will be defined as the last available pre-treatment value taken on or before the day of randomization, and will be used for summary of demographic characteristics, as well as for all change-from-baseline analyses of efficacy and safety endpoints.

4.3 ANALYSIS OF STUDY CONDUCT

The number of patients randomized will be tabulated by region, country, study site, and treatment arm. Patient disposition (the number of patients randomized, receiving at

least one dose of study treatment [lampalizumab or sham], completing study treatment [through Week 48 or Week 96, as appropriate], and completing study visit assessments [through Week 48 or Week 96, as appropriate]) and time on study will be tabulated by treatment arm in the overall and biomarker patient groups. Reasons for premature discontinuation from study treatment and reasons for premature discontinuation from study assessment visits will be summarized. Eligibility criteria deviations, dosing errors, and other major protocol deviations will be summarized. All summaries for analysis of study conduct will be produced based on the primary 48-week analysis data, and also based on the final study data as appropriate.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, ethnicity, and baseline ocular characteristics (such as baseline GA area, location of GA lesion, GA lesion multifocality, baseline BCVA, baseline LLVA, and history of glaucoma, glaucoma suspect, and ocular hypertension) will be summarized for the ITT population by treatment arm in the overall and biomarker patient groups using descriptive statistics.

4.5 EFFICACY ANALYSIS

Efficacy analyses will be based on the ITT patient population or microperimetry-analysis population, as appropriate (Section 4.1.1), with patients grouped according to the treatment assigned at randomization. Available data from all randomized and treated patients regardless of adherence to the protocol will be included in the efficacy analyses; this includes data from patients who discontinued study drug early but continued with study assessments.

Unless otherwise noted, hypothesis testing and estimation of treatment effects will be performed with a regression model that includes data from all three treatment arms (sham pooled, lampalizumab Q4W, and lampalizumab Q6W). When analyzing data by biomarker group, separate regression models will be fit for the biomarker-positive and biomarker-negative patient groups (as defined in Section 2.2). All hypothesis tests for efficacy endpoints will be two-sided.

Unless otherwise noted, analyses of efficacy endpoints (primary, secondary, and exploratory) in the overall patient population will be adjusted for the following randomization stratification factors and baseline covariates:

- Biomarker status (positive vs. negative, as determined by the cobas® CFI Profile CTA)
- Baseline BCVA ETDRS chart Snellen equivalent (20/50 or better vs. worse than 20/50)
- Sex (male vs. female)
- Baseline GA lesion contiguity (multifocal vs. non-multifocal)

  - For efficacy endpoints based on GA area and microperimetry assessments (e.g. number of absolute scotomatous points) only.
- Baseline GA lesion location (subfoveal vs. non-subfoveal)
  - For efficacy endpoints based on GA area, microperimetry assessments (e.g. number of absolute scotomatous points), and visual acuity (BCVA or LLVA) only.

Analyses of efficacy endpoints performed by biomarker group will include the above listed randomization stratification factors and baseline covariates with the exception of biomarker status.

All patients are expected to have the randomization stratification factors and baseline covariates that are specified above. One exception is that a small number of patients do not have a valid baseline BCVA score recorded per the corresponding electronic case report form. In order to include these patients in the efficacy analyses based on regression modeling with covariate adjustment, the BCVA category (20/50 or better vs. worse than 20/50) captured in the IxRS will be used.

For endpoints that are defined in terms of change from baseline, patients who do not have a baseline value reported for a particular assessment will be excluded from the change-from-baseline analyses for that assessment. Similarly, in general, patients who do not have at least one post-baseline value reported for a particular assessment will be excluded from the change from baseline analyses for that assessment. For selected endpoints, sensitivity analyses that include patients without observed post-baseline values will be performed.

For continuous outcomes, a data-as-observed approach with a mixed-effect model repeated measures (MMRM) will be used to handle missing data, which assumes that the missing data are missing at random (MAR). For binary outcomes, analysis of the outcome at a specific time point will be based on observed data, unless otherwise noted. Study discontinuations and the reasons for study discontinuations will be summarized by treatment arm (see Section 4.3) to evaluate the potential impact of missing data on the results. In addition, a number of sensitivity analyses to assess the robustness of the primary analysis results to missing data assumptions will be performed.

For patient-reported outcome measures (e.g., NEI VFQ-25), there are two types of missing data: missing at the form level and missing at the item level. Missing form level data will be handled as described above. Missing item values will follow the rules for scoring and handling of missing item-level data as described in the user's manual.

4.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in GA area at 1 year (48-weeks) as assessed by FAF. The primary efficacy endpoint will be analyzed for the overall patient population (Section 4.5.1.1), in addition to being analyzed for the

biomarker-positive and biomarker-negative groups separately (Section 4.5.1.2). The hypotheses of interest and Type I error management for analyses of the primary endpoint are specified below, and take precedence over that specified in the study protocol.

The null hypotheses for the primary efficacy endpoint are the following:

- H_{01}: There is no difference between lampalizumab Q4W and sham with regard to mean change from baseline in GA area at Week 48 measured by FAF for the overall patient population.
- H_{02}: There is no difference between lampalizumab Q4W and sham with regard to mean change from baseline in GA area at Week 48 measured by FAF for the CFI-profile biomarker-positive patient population.
- H_{03}: There is no difference between lampalizumab Q6W and sham with regard to mean change from baseline in GA area at Week 48 measured by FAF for the overall patient population.
- H_{04}: There is no difference between lampalizumab Q6W and sham with regard to mean change from baseline in GA area at Week 48 measured by FAF for the CFI profile biomarker-positive patient population.

For hypothesis testing of the primary efficacy endpoint, Type I error will be controlled using a fixed sequencing approach by testing the four hypotheses (H_{01}, H_{02}, H_{03}, and H_{04}) sequentially, beginning with H_{01}. All hypothesis tests for the primary endpoint will be based on a two-sided alpha level of 0.0496. Testing for statistical significance proceeds to a subsequent hypothesis only if the tests for all prior hypotheses are significant at the 0.0496 level. Note, the study will be considered positive if the first hypothesis (H_{01}) is rejected (i.e., if a statistically significant difference is observed when comparing the lampalizumab Q4W arm with the sham pooled arm for the primary efficacy endpoint in the overall patient population).

For the primary efficacy endpoint, a number of additional subgroup analyses (Section 4.5.1.3), sensitivity analyses (Section 4.5.1.4), and supplemental analyses (Section 4.5.1.5) will be performed. Included in the sensitivity analyses are analyses to assess the robustness of the primary analysis results to missing data assumptions.

4.5.1.1 Overall Patient Population Analysis

For the overall patient population, the mean change in GA area from baseline at Week 48 will be compared between each lampalizumab treatment arm (Q4W or Q6W) and the pooled sham arm by use of a MMRM analysis. The primary analysis will be based on all available data up to Week 48, with no imputation for missing data. The model will use absolute change from baseline in GA area at post-baseline visits, up to and including 48-weeks, as the response variable, and will include independent variables for treatment arm, study visit, treatment arm by study visit interaction, baseline GA area, and the randomization stratification factors and baseline covariates as

described in Section 4.5. Study visit will be included as a categorical variable. An unstructured covariance matrix will be used to model the within-subject errors. If there are convergence problems with the model, then a heterogeneous compound symmetry covariance structure will be used.

Point estimates, 95% CIs, and p-values for the treatment effect (difference in mean change in GA area from baseline for lampalizumab vs. sham pooled) will be calculated for each lampalizumab treatment arm on the basis of the model for each assessed timepoint, including Week 48.

4.5.1.2 Biomarker Subgroup Analyses

For each biomarker group (CFI-profile biomarker-positive and CFI-profile biomarker-negative, defined per Section 2.2), the mean change in GA area from baseline at Week 48 will be compared between each lampalizumab treatment arm (Q4W or Q6W) and the pooled sham arm by use of a MMRM analysis. The regression model will be the same as that specified for the primary analysis in the overall patient population (Section 4.5.1.1), with the exception that the model will be fit separately for each biomarker group. In addition, given a separate model fit for each biomarker group, biomarker status will not be included as an independent variable in the model. Point estimates for the treatment effect (lampalizumab vs. sham) within each biomarker group will be presented for each lampalizumab treatment arm, along with corresponding 95% CIs and p-values.

Patient profile of GA lesion size change over time will be plotted by treatment arm and biomarker group.

To compare the treatment effect in the biomarker-positive patients vs. the biomarker-negative patients, the difference in the treatment effect between biomarker-positive and biomarker-negative patient groups (as estimated from the individual models above) will be calculated. A corresponding 95% CI for the difference in the treatment effect and the associated p-value will be provided based on the property that the treatment effect estimates from the individual models are independent and asymptotically normally distributed.

4.5.1.3 Other Subgroup Analyses

Exploratory subgroup analyses will be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. Analyses will be performed for the primary efficacy endpoint (change from baseline in GA area at Week 48) for each of the following subgroups (as appropriate per actual subgroup sample size):

- Age ($<$75 years, 75 to $<$85 years, $\geq$85 years)
- Sex (male, female)

- Race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, unknown)
  - Note: If the vast majority of patients (e.g. > 95%) are of a single race, this analysis will not be conducted.
- Geographic region
  - US and Canada
  - Western Europe (Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK)
  - Rest of World (Argentina, Australia, Hungary, Mexico, Peru, Poland, Russia, Slovakia, Turkey)
- Baseline BCVA (< 64 letters [worse than 20/50], ≥ 64 letters [20/50 or better])
- Baseline low luminance deficit (LLD) (< 30 letters, ≥ 30 letters), where LLD = BCVA - LLVA
  - Note: The median LLD at baseline is expected to be approximately 30 letters based on data from Study GX29633.
- Baseline GA area (≤ 4DA, > 4DA), where 1 disc area (DA) = 2.54 mm^2
- Baseline GA contiguity (multifocal, non-multifocal)
- Baseline GA lesion location (subfoveal, non-subfoveal)
- Tobacco use history (ever, never)

Subgroup analyses based on CFI-profile biomarker status are specified in Section 4.5.1.2.

For the primary efficacy endpoint, a MMRM similar to that specified for the primary analysis (Section 4.5.1.1) will be used for each subgroup analysis based on the data subset for the patient subgroup of interest. Baseline covariates included in the primary analysis but no longer relevant given the subgroup of interest will be excluded from the model. The estimated treatment effects (lampalizumab vs. sham) and corresponding 95% CIs from the models will be displayed graphically for each lampalizumab treatment arm and each level of the subgroups specified (e.g. via forest plots).

4.5.1.4 Sensitivity Analyses

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis results. Analyses will be performed for the overall patient population and/or the biomarker subgroup populations, as deemed appropriate based on the outcome of the primary analyses including all patients in the ITT population.

Multiple Imputation

The following sensitivity analysis based on multiple imputation will be performed, as appropriate, using the same statistical approach as the one used in the primary analysis:

- Change from baseline in GA area as measured using FAF, with missing data imputed by multiple imputation using the Markov Chain Monte Carlo (MCMC) method assuming MAR
- Change from baseline in GA area as measured using FAF, with missing data imputed by multiple imputation using regression method assuming MAR
- Change from baseline in GA area as measured using FAF, with missing data imputed by multiple imputation using pattern mixture model method assuming missing not at random (MNAR)
- Change from baseline in GA area as measured using FAF, with missing data imputed by multiple imputation using tipping point analysis method assuming MNAR

Considering the details of the four multiple imputation methods (MCMC, regression method, pattern mixture model, and tipping point analysis) further, MCMC and regression methods assume MAR, where the imputed data will follow the same distribution as the observed data within the same treatment group. Pattern mixture model and tipping point analysis methods assume MNAR, where the imputed data for the active treatment group will follow either the distribution of the control group or adjusted by a shift parameter.

Geographic atrophy is progressive and irreversible, so changes in GA area over time should be ≥ 0 mm^2. In order to incorporate this data pattern, imputation for missing data will be performed on the difference in GA area at a visit from the previous visit. Imputation for the non-monotone missing pattern (i.e., arbitrary missing pattern) will be performed prior to the multiple imputation for the monotone missing pattern (i.e., where a missing GA area measurement at a visit for a patient implies that GA area measurements at all subsequent visits for that patient are missing). For the non-monotone missing pattern, missing value(s) between two visits with measured GA area will be imputed according to a linear growth line passing through the two measured sizes. Multiple imputation will only be carried out for monotone missing pattern.

All four imputation methods will be implemented in SAS using the three standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step.

1. The missing data are filled in 100 times to generate 100 complete data sets.
2. The 100 complete data sets are analyzed by using the same approach as for the analysis for the primary objective.
3. The results from the 100 complete data sets are combined for the inference.

Methods used in the imputation step are described below. The actual parameters used in all imputations will be documented in the programming specifications. Analysis and

pooling steps will be carried out following the imputation step will also be documented in the programming specifications.

- **MCMC Method.** The MCMC method will be implemented for each treatment arm (the two sham arms will be pooled) and by biomarker status.
- **Regression Method.** The regression method will be implemented for each treatment arm and by biomarker status. This method assumes MAR, and serves as the reference for the pattern mixture model and tipping point analysis methods which assume MNAR.
- **Pattern Mixture Model Method.** The pattern mixture model method will be implemented for each active treatment arm and by biomarker status. For the active treatment arms, the missing data will be imputed based on the observed values in the pooled sham arm.
- **Tipping Point Analysis Method.** The tipping point analysis method will be implemented for each active treatment arm and by biomarker status under the MNAR assumption by searching for a tipping point that reverses the conclusion regarding positive treatment effect. For the active treatment arms, monotone missing data will be imputed based on the available values (observed values plus values imputed for non-monotone missing data) in the same treatment arm with a shift parameter added to the imputed values. Multiple imputation will be implemented on the differences between two consecutive visits, with the shift parameter allocated to the missing data point(s) proportionally across the 48 weeks. (e.g. For a shift parameter of 1 mm^2, incremental shifts of 0.5 mm^2, 0.25 mm^2, and 0.25 mm^2 would apply to Week 24, Week 36, and Week 48, respectively.) The range of the shift parameters will depend on the observed treatment effect, i.e., the difference in the change of GA area from baseline at Week 48 between lampalizumab and the pooled sham arms. The precision of the tipping point will be at one decimal point. A tipping point may not exist within reasonable clinical assumptions.

Additional Sensitivity Analyses:

Moreover, the following sensitivity analysis will be conducted based on observed data for the primary endpoint:

- **ANCOVA:** Comparison of the mean change in GA area from baseline at Week 48 between each lampalizumab arm (Q4W or Q6W) and the pooled sham arm using an analysis of covariance (ANCOVA) regression model with change from baseline at Week 48 as the response variable and independent variables for treatment arm, baseline GA area, and the randomization stratification factors and baseline covariates as described in Section 4.5.
- **Van Elteren Test:** Comparison of the distribution of change in GA area from baseline at Week 48 between each lampalizumab arm (Q4W or Q6W) and the pooled sham arm respectively, using the non-parametric Van Elteren test stratified by baseline GA area (≤ 4DA, >4DA, where 1 disc area [DA] = 2.54 mm^2) and the randomization stratification factors and baseline covariates as described in Section 4.5.

4.5.1.5 Supplemental Analyses

Analyses of the following endpoints, closely related to the primary efficacy endpoint, will be performed to provide supplemental information. Analyses will be performed for the overall patient population and/or the biomarker subgroup populations, as deemed appropriate based on the outcome of the primary analyses.

Rate of Change in GA Area (Growth Slope) over 48 Weeks

The mean rate of change in GA area (mm^2/year [365.25 days]) will be compared between each lampalizumab treatment arm (Q4W or Q6W) and the pooled sham arm by use of a random intercept and random slope regression model. GA area (at baseline and post-baseline visits up to Week 48) will be used as the response variable, and the model will include terms for treatment arm, time (continuous variable assuming linearity), treatment arm by time interaction, and the randomization stratification factors and baseline covariates as described in Section 4.5. Random effects will include the intercept and slope (time) with an unstructured covariance matrix, with all other variables as fixed effects. The within patient error will be assumed to be independent and normally distributed with variance component as the covariance structure.

Change in Square Root of GA Area at Week 48

For each patient and timepoint, the square root of GA area will be calculated. The change from baseline in square root of GA area will be analyzed using the same methodology as described for the primary endpoint analysis, except that change from baseline in the square root of GA area will be the response variable.

Percent Change in GA Area at Week 48

For each patient and timepoint, the percent change in GA area will be defined as the change from baseline in GA area (mm^2) divided by the GA area (mm^2) at baseline. The percent change in GA area from baseline will be analyzed using the same methodology as described for the primary endpoint analysis, except that percent change from baseline will be the response variable. In addition, baseline GA area will not be included as a covariate in the model.

4.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in Section 2.1.2. At the time of primary analysis, all secondary endpoints will be evaluated based on data from baseline to Week 48 (see Section 2.4). At the time of the final study analysis, all secondary endpoints will be evaluated based on data from baseline to Week 96.

Analysis of secondary efficacy endpoints assessed by mesopic microperimetry will be based on the microperimetry-analysis population. Statistical inferences for efficacy endpoints based on microperimetry assessments will be based on pooled data from Studies GX29176 and GX29185. Analysis of all other secondary efficacy endpoints will be based on the ITT patient population.

Hypothesis testing for three key secondary endpoints will be performed in the order specified in Section 4.5.2.1 based on the Week 96 timepoint. Subgroup analyses (Section 4.5.2.2) for the key secondary efficacy endpoints will be performed.

Treatment-effect related analyses to compare each lampalizumab treatment arm (Q4W or Q6W) and the pooled sham arm for secondary efficacy endpoints will be undertaken as follows. In general, continuous secondary endpoints will be analyzed using a MMRM analysis, with change from baseline as the response variable. For the Week 48 analyses, post-baseline visits, up to and including Week 48, will be included. For the Week 96 analyses, post-baseline visits, up to and including Week 96, will be included. Independent variables for treatment arm, study visit (categorical variable), treatment arm by study visit interaction, baseline value of the endpoint, and the randomization stratification factors and baseline covariates as described in Section 4.5 will be included in the model. An unstructured covariance matrix will be used to model the within-subject errors. If there are convergence problems with the model, then a heterogeneous compound symmetry covariance structure will be used.

In general, binary secondary endpoints will be analyzed using a logistic regression model. The model will include independent variables for treatment arm, baseline value of the endpoint (continuous scale), and the randomization stratification factors and baseline covariates as described in Section 4.5, as appropriate. If the response rate is low, an unadjusted analysis may be performed. Analyses will be based on the observed data for the timepoint, with no imputation for missing data.

For analyses of BCVA, the model will include the major assessment timepoints of Weeks 12, 24, 36, 48, 60, 72, 84, and 96 that are in common between the Q4W and Q6W dosing arms. In addition, the stratification factor of baseline BCVA category will not be included in the model, given baseline BCVA is included as a continuous covariate.

Reading speed will be calculated per the MNRead or Radner user's manuals, with no adjustment for reading inaccuracy. An addition step to cap resulting reading speed values at a maximum of 300 words per minute will be implemented. Values above 300 words per minute exceed values reported in the literature for adults with no vision impairment for MNRead (Calabrese et al. 2016) or Radner (Radner et al. 2002; Radner and Diendorfer 2014) assessments. Maximum reading speed will be calculated as the mean of the three highest reading speeds obtained per the user's manuals. Data collected via the two reading charts will be pooled for analysis and the model will include an additional covariate for reading chart type (MNRead or Radner). Additional subgroup analyses will be performed to assess the consistency of finding across the two reading charts (see Section 4.5.2.2).

NEI VFQ-25 scores (composite, near activity subscale, and distance activity subscale) and mean FRI Index scores will be calculated per the scoring algorithms in the corresponding user's manuals.

For analyses of binocular maximum reading speed, NEI VFQ-25 composite score, NEI VFQ-25 near activity subscale score, NEI VFQ-25 distance activity subscale score, and mean FRI Index score, an additional adjustment for baseline BCVA of the better seeing eye will be included (instead of study eye baseline BCVA [20/50 or better vs. worse than 20/50]). In the event that baseline BCVA is missing for the study or fellow eye (but not both), then the non-missing baseline BCVA will be used for this covariate.

4.5.2.1 Type I Error Management

Significance testing for secondary efficacy endpoints will be gated on the success of the primary efficacy endpoint evaluated at Week 48. Secondary efficacy endpoints will be tested at Week 96 for the lampalizumab dose frequency or frequencies (Q4W or Q6W) and patient populations (overall or biomarker-positive) found to demonstrate statistically significant treatment effect for the primary efficacy endpoint.

The following secondary efficacy endpoints will be tested in the order listed below:

- Change from baseline in number of absolute scotomatous points at Week 96 as assessed by mesopic microperimetry
  - Note: Due to small sample size, statistical inferences for this endpoint to be based on pooled data from Studies GX29176 and GX29185.
- Change from baseline in LLVA at Week 96 as assessed by ETDRS chart at a starting distance of 4 m
- Change from baseline in binocular maximum reading speed at Week 96 as assessed by MNRead or Radner Charts

A list of the hypothesis testing of the key secondary clinical endpoints is given below:

- H_{05}: There is no difference between lampalizumab and sham with regard to mean change from baseline in the number of absolute scotomatous points at Week 96.
- H_{06}: There is no difference between lampalizumab and sham with regard to mean change from baseline in LLVA at Week 96.
- H_{07}: There is no difference between lampalizumab and sham with regard to mean change from baseline in binocular maximum reading speed at Week 96.

For each lampalizumab dosing frequency and patient population found to be statistically different from sham for the test of the primary endpoint, testing of the three key secondary endpoints will be performed (e.g. if H_{01} is positive per the Type I error control plan, then the key secondary endpoints would be tested for the Q4W dose frequency in the overall patient population). The aim is to manage the Type I error rate with respect to conclusions about secondary endpoints within a given dose frequency and patient population. Thus, within each dose frequency and patient population, Type I error for key secondary endpoints will be controlled using a fixed sequencing approach by testing the secondary endpoint hypotheses sequentially in the order specified above, beginning with H_{05}.

All hypotheses for the key secondary endpoints will be tested for significance at the study level, except for H_{05}. The secondary endpoint of number of absolute scotomatous points will be based on the microperimetry-analysis population, which is estimated to be 10-15% of the total ITT population. Microperimetry was assessed in a subset of patients at selected study sites only. For this secondary endpoint, data from both Studies GX29176 and GX29185 will be combined to achieve a sample size sufficient to evaluate and test for treatment differences with a reliable level of precision.

As a consequence of this, for analyses of secondary efficacy endpoints at the individual study level:

- For H_{05}, the study-level p-value will be presented. However, interpretation of significance in a confirmatory manner will be based on the analysis of pooled data from Studies GX29176 and GX29185.
- H_{06} will be tested in a confirmatory manner at the study-level if and only if, based on an analysis of pooled data from Studies GX29176 and GX29185, H_{05} is rejected (i.e., pooled analysis $p \leq 0.0496$).
- H_{07} will be tested in a confirmatory manner at the study-level if and only if H_{06} is rejected at the study-level

As noted above, significance testing for H_{05} will not be done at the study level, but rather interpretation of significance in a confirmatory manner will be based on the analysis of pooled data from Studies GX29176 and GX29185 for the microperimetry-based endpoint.

All hypothesis tests for the secondary endpoints will be on the basis of a two-sided alpha level of 0.0496.

4.5.2.2 Subgroup Analyses

Exploratory subgroup analyses will be performed to evaluate the consistency of the analysis results for two of the key secondary efficacy endpoints (change from baseline in LLVA at Week 96 and change from baseline in binocular maximum reading speed at Week 96). Subgroup analyses will not be performed at the study level for the key secondary endpoint of change from baseline in number of absolute scotomatous points at Week 96 due to the smaller sample size in the microperimetry-analysis population.

The subgroups evaluated for secondary endpoints will be based on demographic and baseline characteristics, as done for the primary efficacy endpoint (see Section 4.5.1.3). For binocular maximum reading speed, an additional subgroup analysis based on eye with greater BCVA at baseline (study vs. fellow) will be performed. Patients with equivalent baseline BCVA in the study and fellow eye (if any) will be grouped with patients with greater BCVA in the study eye for this subgroup analysis.

For analysis maximum reading speed assessed by MNRead or Radner charts, additional subgroup analyses by reading chart type (MNRead or Radner) will also be performed to assess the consistency of findings across the two reading charts.

For each endpoint, a MMRM similar to that specified for the main analysis (Section 4.5.2) will be used for each subgroup analysis based on the data subset for the patient subgroup of interest. Baseline covariates included in the main analysis but no longer relevant given the subgroup of interest will be excluded from the model. The estimated treatment effects (lampalizumab vs. sham) and corresponding 95% CIs from the models will be displayed graphically for each lampalizumab treatment arm and each level of the subgroups specified (e.g. via forest plots).

4.5.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are listed in Section 2.1.3. Similar to the secondary endpoints, exploratory endpoints will be summarized based on data from baseline to Week 48 at the time of the primary analysis. At the time of the final study analysis, exploratory endpoints will be evaluated based on data from baseline to Week 96.

Exploratory efficacy endpoints based on mesopic microperimetry assessments will be based on the microperimetry-analysis population; statistical inferences for efficacy endpoints based on microperimetry assessments will be based on pooled data from Studies GX29176 and GX29185. All other secondary efficacy endpoints will be based on the ITT patient population.

Analysis of exploratory endpoints is planned for the overall patient population and for each biomarker subgroup. However, similar to the secondary efficacy endpoints, analysis of the exploratory efficacy endpoints may focus on the evaluation for either the overall patient group or the biomarker subgroups depending on the primary endpoint results.

Treatment-effect related analyses to compare each lampalizumab treatment arm (Q4W or Q6W) and the pooled sham arm for exploratory efficacy endpoints will be similar to that for secondary endpoints. In general, continuous secondary endpoints will be analyzed using a MMRM analysis, with change from baseline as the response variable. Independent variables for treatment arm, study visit (categorical variable), treatment arm by study visit interaction, baseline value of the endpoint, and the randomization stratification factors and baseline covariates as described in Section 4.5 will be included in the model. An unstructured covariance matrix will be used to model the within-subject errors, and a heterogeneous compound symmetry covariance structure used if there are convergence problems.

In general, binary secondary endpoints will be analyzed using a logistic regression model. The model will include independent variables for treatment arm, baseline value of the endpoint (continuous scale), and the randomization stratification factors and baseline covariates as described in Section 4.5, as appropriate. If the response rate is low, an unadjusted analysis may be performed. Unless noted otherwise, analyses will be based on the observed data for the timepoint, with no imputation for missing data.

For the analysis of the proportion of patients with $<20\%$ increase in GA area, patients with missing GA assessment at the analysis timepoint (e.g. Week 48) will be included in the analysis and counted as having a $\geq 20\%$ increase if such an outcome was observed at any earlier timepoint.

Reading function scores will be calculated per MNRead or Radner user's manuals, with no adjustment for reading inaccuracy. For reading function endpoints (maximum reading speed, critical print size, and reading acuity), data collected via the two reading charts will be pooled for analysis and the model will include an additional covariate for reading chart type (MNRead or Radner). Additional subgroup analyses by reading chart type (MNRead or Radner) will be performed to assess the consistency of findings across the two reading charts. In addition, for analyses based on percent change in reading speed, the baseline reading speed will not be included in the model.

FRI Level will be calculated per the scoring algorithm in the FRI Index user's manual.

For analyses of binocular maximum reading speed, binocular critical print size, and binocular reading acuity, an additional adjustment for better seeing eye BCVA at baseline will be included (instead of study eye baseline BCVA [20/50 or better vs. worse than 20/50]).

In addition, the relationship between GA area and visual function outcomes (e.g. LLVA etc.) will be explored. Observed data will be used. Spearman correlation coefficient will be estimated and a 95% CI for the correlation coefficient provided.

4.5.4 Additional Biomarker Analyses

Additional biomarker-related analyses will be performed as specified below:

- Analysis of biomarker prognostic effects:
  - For patients in the sham treatment group, 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 using a similar model as the primary analysis.
- Analysis of potential association of genetic variants in CFI and complement pathway genes with disease characteristics and response to administration of lampalizumab
  - Patients with rare coding variants in CFI will be identified by sequencing and a modified exploratory analysis will be conducted in which all rare coding variant carriers are combined with CFI-profile biomarker-positive to define an exploratory "CFI-profile plus rare variant" biomarker-positive subgroup. For this exploratory analysis, the primary efficacy analysis as described in Section 4.5.1 (including predictive and prognostic aspects) will be performed, but using this modified exploratory biomarker definition.

- A pre-specified set of SNPs associated with complement-related genes will be evaluated using multivariate statistical methods for an exploratory evaluation of genetics associated with disease characteristics and/or lampalizumab treatment response. Detailed methods will be described separately in an Exploratory Genetic Analysis Plan that will be finalized prior to Sponsor unmasking for the analysis of the primary efficacy endpoint. Given the exploratory nature of these analyses, the results may not be included in the CSR.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The PK analyses will include all randomized patients who have at least one serum and/or aqueous humor PK sample, with patients grouped according to treatment actually received. Lampalizumab concentrations in serum and aqueous humor, as well as complement factor D levels (PD) in aqueous humor will be summarized by timepoint using descriptive statistics. Noncompartmental analysis may be performed with serum PK as appropriate.

Additional PK and exposure-response analyses may be conducted as appropriate. Population PK and PK/PD modeling may be performed to characterize the lampalizumab pharmacokinetics, GA area dynamic over time with and without lampalizumab treatment, and their associated variability, with results reported separately from the CSR. A separate modeling and simulation analysis plan will be prepared prior to any analysis.

4.7 SAFETY ANALYSES

The safety profile of lampalizumab will be assessed through the summary of adverse events, deaths, laboratory results for alternative complement pathway activity, serial ECG results, incidence of anti-drug antibodies, and ocular assessments (e.g., intraocular pressure [IOP]).

At the time of the Week 48 primary efficacy analysis, safety summaries will be produced based on the complete Week 48 data. In addition, summaries for ongoing second year safety data (after Week 48 and up to a single specified clinical cutoff date) will also be produced. At the time of the final analysis, safety summaries will be produced based on cumulative Week 96 data.

Safety outcomes will be summarized based on the safety-evaluable population or ECG-analysis population as appropriate, with patients grouped according to the treatment actually received (see Sections 4.1.2 and 4.1.4).

4.7.1 Exposure of Study Medication

Exposure to study treatment (total number of injections [lampalizumab or sham] and duration of treatment [through Week 48 or Week 96, as appropriate]) will be summarized by treatment arm. Duration of treatment will be defined based on the difference (in days)

between the dates of the first and last injection (lampalizumab or sham) plus 1 day for the time period summarized.

4.7.2 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded using the latest version of MedDRA. A treatment-emergent adverse event is defined as any new adverse events reported or any worsening of an existing condition on or after the first dose of study treatment. Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the initial study treatment date.

Adverse events will be tabulated by body system and preferred term. Separate summaries will be prepared for all non-ocular and all ocular adverse events, with ocular events in the study eye and fellow eye summarized separately as appropriate. Summaries will be provided for each of the following categories:

- All adverse events
- All adverse events by severity
- Serious adverse events
- Adverse events suspected to be caused by study treatment as assessed by the investigator
- Adverse events leading to discontinuation of study treatment
- Adverse events leading to interruption of study treatment
- Adverse events of special interest as defined in the protocol, specifically:
  - Sight-threatening adverse events (causes a decrease of $\geq$30 letters in visual acuity score lasting more than 1 hour, requires surgical intervention to prevent permanent loss of sight, associated with severe intraocular inflammation, in the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight)
  - Suspected transmission of an infectious agent by the study drug
  - Adverse events resulting from medication error
  - Cases of potential drug-induced liver injury

Ocular adverse events will also be presented on a per-injection basis (i.e., number of events/total number of injections given). Selected adverse events will be reviewed separately (e.g. adverse events that occurred in patients who received treatment with both Lucentis® [ranibizumab injection] and lampalizumab in the study eye or adverse events that are IOP-related).

Patient deaths and primary cause of death will be summarized.

4.7.3 Laboratory Data

A descriptive summary of laboratory values for alternative complement pathway activity (AH50), including changes from baseline and values outside the normal limits, will be generated.

General chemistry, hematology, and urinalysis laboratory results were collected as part of screening eligibility and subsequently only for patients who discontinued study treatment early. Therefore, laboratory results are reviewed by the Sponsor on an individual patient basis. Aggregate summaries will not be provided. Clinically significant laboratory abnormalities will be reported as adverse events and evaluated as part of the adverse event assessments.

4.7.4 Immunogenicity

The number and percentage of patients with positive serum anti-drug antibodies at baseline and post-baseline during the study period will be tabulated. Adverse events occurring in patients with positive serum anti-drug antibodies will be reviewed.

4.7.5 Ocular Assessments

Results of the following ocular assessments will be summarized by timepoint and by eye (study vs. fellow) using descriptive summaries: IOP, slit-lamp examination, and indirect ophthalmoscopy. Changes from baseline in pre-dose IOP and changes between pre-dose and post-dose IOP will be summarized. In addition, the incidence of IOP above specified thresholds (e.g. ≥ 30 mmHg) will be summarized. The presence of intraocular inflammation and vitreous hemorrhage, as determined on slitlamp examination, will be tabulated by grade. Ophthalmoscopy results, including retinal breaks and retinal detachments, will be summarized.

4.7.6 ECG Results

For the ECG-analysis population, ECG results for patients with normal ECG findings at baseline and abnormal ECG findings at any post-baseline timepoint based on the overall interpretation will be listed and discussed.

ECG interval data will also be summarized. For corrected QT interval using Fridericia's method (QTcF), PR, and QRS intervals as well as heart rate (HR), the values at baseline, Day 8, Week 4 (Q4W arms), Week 6 (Q6W arms), and Week 24, as well as changes from baseline, will be summarized descriptively by treatment arm. The proportion of patients with a QTcF value ≤ 450, > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec at a given visit, or an increase from baseline in QTcF of > 30 and > 60 ms will be summarized. As ECG data was collected on a subset of patients, interpretation of these ECG results will also be conducted on pooled data from Studies GX29176 and GX29185.

4.8 INTERIM ANALYSES

No formal efficacy or futility interim analyses are currently planned or have been conducted.

Safety and study conduct is monitored on a regular basis by an iDMC (see Section 3.2.2).

5. REFERENCES

Calabrese A, Cheong AMY, Cheung S-H, et al. Baseline MNREAD measures for normally sighted subjects from childhood to old age. Invest Ophthalmol Vis Sci 2016;57(8):3836-3843.

Radner W and Diendorfer G. English sentence optotypes for measuring reading acuity and speed - The English version of the Radner Reading Charts. Graefes Arch Clin Exp Ophthalmol. 2014;252:1297-1303.

Radner W, Obermayer W, Richter-Meuksch S, et al. The validity and reliability of short German sentences for measuring reading speed. Graefes Arch Clin Exp Ophthalmol. 2002;240:461-367.