Official Study Title: A Phase 3 Multicenter, Randomized, Double-Masked, Sham-Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura™ (Complement C5 Inhibitor) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

NCT#: NCT04435366

Document: Statistical Analysis Plan

Document Date: 07 April 2022

Signature Page for ISEE2008_SAP
Study ISEE2008 v4.0

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Study ISEE2008 v4.0

# STATISTICAL ANALYSIS PLAN

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|---|---|
| SPONSOR: | IVERIC BIO, INC. |
| PROTOCOL TITLE: | A PHASE 3 MULTICENTER, RANDOMIZED, DOUBLE-MASKED, SHAM CONTROLLED CLINICAL TRIAL TO ASSESS THE SAFETY AND EFFICACY OF INTRAVITREAL ADMINISTRATION OF ZIMURA™ (COMPLEMENT C5 INHIBITOR) IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION |
| STUDY CODE: | ISEE2008 (GATHER2) |
| VERSION: | 4.0 |
| DATE: | 07APR2022 |

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AMD | Age-Related Macular Degeneration |
| ATC | Anatomic Therapeutic Chemical |
| BCVA | Best Corrected Visual Acuity |
| BUN | Blood Urea Nitrogen |
| CI | Confidence Interval |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluorescein Angiography |
| FAF | Fundus Autofluorescence |
| FP | Fundus Photography |
| GA | Geographic Atrophy |
| GGT | Gamma-glutamyl Transferase |
| ICH | International Conference on Harmonization |
| DSMB | Data Safety Monitoring Board |
| IOP | Intraocular Pressure |
| ITT | Intention-to-Treat |
| LLN | Lower Limit Normal |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed Model for Repeated Measures |
| MNAR | Missing Not At Random |
| NA | Not Available / Not Applicable |
| OU | Oculus Uterque (Both Eyes) |
| PSC | Posterior Subcapsular Cataract |
| REML | Restricted Maximum Likelihood |
| [redacted] | [redacted] |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Study Eye |
| SGOT/AST | Aspartate Aminotransferase |
| SGPT/ALT | Alanine Aminotransferase |
| ULN | Upper Limit Normal |

| | |
|---|---|
| VA | Visual Acuity |
| WBC | White Blood Cells |
| WHO | World Health Organization |

## INTRODUCTION

This Statistical Analysis Plan describes the statistical methodology and data handling for the clinical trial with Protocol Number: ISEE2008 (GATHER2), Version Date: 18 December 2020.

The trial consists of a total treatment period of 24 months. This SAP covers all analyses to be performed on 1 year data. By pre-specification, this study will obtain evidence regarding the effect of Zimura on the mean rate of growth (slope) estimated based on geographic atrophy (GA) area measured by fundus autofluorescence (FAF) in at least 3 time points over 12 months, when compared with Sham (square root treansformation). Details of an analysis at 18 and 24 months, if applicable, will be specified in a separate SAP.

The ICH guideline E3 "Structure and Content of Clinical Study Reports" is used as a guide to the writing of the plan.

## STUDY DESIGN AND OBJECTIVES

### STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy of Zimura intravitreal administration in patients with geographic atrophy secondary to age-related macular degeneration (AMD).

#### Primary Efficacy Outcome

The primary efficacy outcome is the mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation).

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### Safety Outcomes

The following safety outcomes will be evaluated:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Vital signs (pulse, systolic and diastolic blood pressure)
- Ophthalmic variables (ophthalmic examination, best corrected visual acuity (BCVA), low luminance BCVA (LLBCVA), intraocular pressure (IOP))
- Electrocardiography (ECG) (12-lead)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)

## STUDY DESIGN AND SAMPLE SIZE

Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups:

- Zimura 2 mg
- Sham

Patients receiving monthly Zimura 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups:

- Zimura 2 mg administered monthly from Month 12 – Month 23
- Sham administered at Months 12, 14, 16, 18, 20, and 22, and Zimura 2mg administered every other month at Months 13, 15, 17, 19, 21, and 23

All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23.

All patients will have a final follow-up visit at Month 24.

The trial consists of a total treatment period of 24 months. This SAP covers all analyses to be performed on 1 year (12 months) data.

The sample size for this study is based on the 12-month results of the OPH2003 (GATHER1) pivotal international, multicenter, randomized, double masked, sham-controlled clinical trial that was performed to evaluate the safety and efficacy of Zimura in patients with geographic atrophy secondary to AMD. The prespecified primary endpoint, mean change in GA growth over 12 months, equivalent to the mean rate of GA growth used in this study, was measured by fundus autofluorescence (FAF) based on readings at three time points (Baseline, Month 6, and Month 12) and was calculated using the square root transformation of the GA area. The FAF images were assessed by an independent masked reading center. The reduction in the mean rate of GA growth over 12 months was 0.11 mm ($p = 0.0072$) for the Zimura 2 mg group compared to the Sham control group.

A total of approximately 400 patients will be randomized in the GATHER2 trial. The effect of treatment will be assessed on the square root transformation of the mean rate of GA growth (slope) estimated based on GA area measured in at least 3 time points over 12 months, where the analysis of variance will include the stratification factors. Suppose the standard deviation for the primary endpoint in GATHER2 is as assumed in the design of the GATHER1 trial, (which is 7% higher than was actually observed in that trial.) If the 2 mg dose of Zimura truly provides a 0.11 mm reduction in the mean rate of GA growth over 12 months, then the trial will have 97% power to detect that effect when using a test statistic having (one-sided) 2.5% false positive error rate. Furthermore, the trial will have nearly 90% power to achieving an even more robust significance level at two-sided $p<0.01$. Statistical significance at the traditional level of two-sided $p=0.05$ would be achieved with an estimated 0.057 reduction in the mean rate of GA growth over 12 months. Note that the power of the trial will be slightly lower when using an alpha-level that would be adjusted by (two-sided) 0.001 for each DSMB meeting at which any data are reviewed.

## RANDOMIZATION

Patients will be centrally allocated to one of the two treatment groups by a dynamic minimization procedure using clinical site in a 1:1 ratio stratified by factors known to be of prognostic importance in AMD:

- Baseline visual acuity < 50 ETDRS letters (20/100 Snellen equivalent) vs. ≥ 50 ETDRS letters
- Size of Baseline GA (< 4 disc areas vs. ≥ 4 disc areas)
- Pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse)

Patients initially randomized to Zimura 2 mg at Day 1 will be re-randomized at Month 12 in 1:1 ratio to Zimura 2 mg monthly vs every other month using the same minimization procedure as for the initial randomization (i.e., using the same factors at Baseline).

Randomization will be performed using an IRT system based on the stratification information above to randomize each subject and assign a treatment arm.

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## DEFINITION OF POPULATIONS

The analysis and reporting of the data from this study will be performed using the following analysis populations:

### Intention-To-Treat (ITT) Population

The intention-to-treat population (ITT) will consist of all randomized subjects who received at least one dose of study drug. Subjects will be analyzed in the treatment group assigned at randomization.

### Per-protocol (PP) Population

The per-protocol population (PP) will consist of all ITT subjects without any significant violation of the protocol. The significant and major protocol violations will be defined prior to database lock in a masked fashion.

### Safety Population

The safety population will include all subjects who received at least one dose of study drug. Subjects who have ever received an injection of Zimura during this trial will be analyzed in the Zimura group.

## DEFINITION OF SUBGROUPS

The mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation) will be displayed within the following subgroups:

- Size of Baseline geographic atrophy (< 4 disc area vs. ≥ 4 disc area)
- Baseline visual acuity < 50 ETDRS letters (20/100 Snellen equivalent) vs. ≥ 50 ETDRS letters
- Pattern of Fundus Auto Fluorescence (FAF) at the junctional zone of GA (None/focal vs. banded/diffuse)
- Age (<65 vs. 65 ~ 74 vs. 75 ~ 84 vs. ≥85)
- Gender (Male vs. Female)
- Race (American Indian/Alaska Native vs. Black or African American vs. Asian vs. Native Hawaiian/Pacific Islander vs. White vs. Other)
- Ethnicity (Hispanic or Latino vs. Not Hispanic or Latino)

## DATA HANDLING CONVENTIONS

### General Conventions

Data will be analyzed using SAS Studio (version 3.6) or R. Descriptive analyses will be performed on Baseline, safety and efficacy data. All tables will be created by treatment arm (Zimura and Sham) and overall.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, 1st quartile (Q1), 3rd quartile (Q3), and maximum values.

Listings with individual subjects' data will be provided for all CRF (including derived data) and central laboratory data or other external data. Data collected in the CRF that are *not* present in a table will also be listed (e.g., time and method of tonometry, comments fields, data on Fatal Outcomes page, etc.).

**Visit Windows**

The scheduled visits will be used in the analyses over time.

Missing scheduled follow-up visits will be substituted by an unscheduled or early withdrawal visit occurring within each follow-up visit window, if there is only one unscheduled or early withdrawal visit occurring within the window. If there are multiple unscheduled or early withdrawal visits occurring within the window, the closest one within the visit window will be used. If no unscheduled or early withdrawal visit occurred within the window, the visit will be considered as missing. The *details* are tabulated in **Appendix 1**.

**Procedures for Minimizing the Occurrence of Missing Data**

Of note, the proper approach to address missingness is the prevention of missing data. The sponsor will implement aggressive proactive approaches to minimize the number of patients who are not assessed at 12 months. Among these approaches are the following:

- The study protocol properly distinguishes between reasons for nonadherence (that is, for not receiving randomized therapy and hence for being "off study treatment") versus nonretention (that is, for not obtaining outcome information and hence for being "off study"). There are only 2 valid reasons a patient can be off study: withdrawal of consent or the achievement of all required efficacy and safety end point information
- The term 'withdrawal of consent' is used only when the patient no longer wishes to participate in the trial and no longer authorizes the investigators to make efforts to continue to obtain their outcome data
- Patients are educated during the informed consent process about the continued scientific relevance of their data even if they discontinue treatment, as well as the deleterious effect that missing data has on trial integrity and credibility
- To enable proper ITT analyses, all patients will be followed until death or trial completion, even if off they discontinue study treatment or initiate other treatment

- Creative and effective procedures are being implemented during enrollment and follow-up to enhance achieving targeted levels of retention.
- An oversight process by the sponsor is in place during trial conduct to ensure the achievement of performance standards, including targeted levels of data capture.

**Handling Missing Data in Efficacy analyses**

Methods that take into account the presence of missing data and that yield valid estimates under the assumption of data missing at random (MAR) will be used. In particular, a Mixed Model for Repeated Measures fitted by Restricted Maximum Likelihood method will be used in the primary analysis, where as-observed data will be used with no imputation. Multiple-imputation will be used in sensitivity analyses, whenever necessary, to impute the missing data, as described in Section 7.4.

**Handling Missing Data in Descriptive Analyses**

When summarizing categorical variables, subjects with missing data are generally not included unless otherwise specified. When needed, the category of "Missing" is created and the number of subjects with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

**Handling Missing or Partially Missing Dates**

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservatively to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after treatment, the AE will be classified as after the start of treatment.

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## STUDY SUBJECTS

### DISPOSITION OF SUBJECTS

Efforts will be made to clearly record reasons for study and/or treatment discontinuations.

The number of subjects randomized and treated, by treatment arm will be presented. The reason for exclusion from one or more analysis sets will be summarized.

The frequency of premature discontinuations from the study treatment prior to Month 12 will be given by treatment arm and overall. The details of the 'Adverse Event', 'Protocol violation', 'Investigator decision', 'Sponsor Decision', 'Subject request', 'Lost to Follow-Up', 'Subject Non-Compliance', 'Death', or 'Other' will be included in a listing.

The frequency of premature discontinuations from the study prior to Month 12 will be given for the ITT and PP population by treatment arm and overall. The primary reason for non-completion of the study will be summarized.

### TREATMENT MISALLOCATIONS

For subjects with errors in treatment allocation, the following is described under which treatment groups they will be reported for efficacy and safety analyses:

For example, if subjects were:

- Randomized (regardless of error) but not treated, then they will be excluded for all efficacy and safety analyses. These subjects will be included in the summary of subject populations.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomization is missing, but will be reported under the treatment they actually received for all safety analyses.

[1] The ETDRS lines in order, from largest to smallest, are 20/800, 20/640, 20/500, 20/400, 20/320, 20/250, 20/200, 20/160, 20/125, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, 20/20, 20/16, 20/13, 20/10.

- Randomized but were administered the incorrect treatment at any time during the study, then they will be reported under their randomized treatment group for efficacy analyses on ITT population, but will be reported under the treatment they actually received for all safety analyses on Safety population (see Section 3.2.3); specifically, this implies that for safety analyses, a patient who ever received Zimura will be included in the Zimura group.

### PROTOCOL VIOLATIONS

All protocol violations will be assessed and identified prior to database lock in a masked fashion to determine whether they are significant, major, or neither by the sponsor. The final list of major and significant protocol violations will be provided prior to the database lock.

Subjects with significant protocol violations will be excluded from the Per-Protocol population.

The major protocol violations and significant protocol violations will be summarized for the ITT population. The details will be listed by subject and by treatment arm.

### INCLUSION AND EXCLUSION CRITERIA

A frequency table of all inclusion and exclusion criteria not met will be provided for the ITT population by treatment arm and overall. A detailed listing will be provided by subject.

### DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided to document Baseline and on-trial comparability, including demographic information and treatment administration. No tests of significance will be carried out to compare treatment groups on Baseline data because any observed differences between them must be attributed to chance.

Descriptive statistics with respect to subject characteristics at Baseline will be displayed for the ITT population; if the PP and safety populations are different than the ITT population, demographic data will also be provided for these populations. When several measurements are available before the first administration of study drug, the Baseline value is the last available value prior to first dose, except for the Baseline visual acuity score which is the mean of the Screening and Day 1 values, if both are available.

The variables to be summarized are:

- Gender, ethnicity, race, iris color, age, current smoking status
- Prior ocular history, both eyes (by MedDRA preferred term, including number and percentage of all subjects with at least one prior ocular history)
- Medical history (excluding ocular history) (by body system and preferred term, with number and percentage for both; including number and percentage of all subjects with at least one prior medical history)

- Prior surgeries/procedures (by body system and preferred term, with number and percentage for both; including number and percentage of all subjects with at least one prior surgery/procedure)
- Vital signs (height, weight, pulse, blood pressure)
- ECOG performance status
- Pregnancy test
- Visual acuity (ETDRS and Snellen equivalent), both eyes
- Low luminance visual acuity (ETDRS and Snellen equivalent), both eyes
- Tonometry, both eyes
- ECG
- Ophthalmic exam, both eyes (motility, lids/lacrimal/lashes, conjunctiva/sclera, cornea, anterior chamber activity: cells, iris, pupils, lens status, vitreous haze, vitreous hemorrhage, posterior vitreous detachment, optic nerve, macula, retinal vessels, peripheral retina)
- Fundus autofluorescence (FAF) imaging assessments, both eyes
    - Localization of hypo FAF (Foveal, Extrafoveal, Ungradeable or no hypo FAF present)
    - Localization of peripapillary atrophy (Temporal only, Nasal and temporal, ungradeable or not applicable)
    - Hyper FAF pattern (Fine granular-punctate spots, Branching, Fine granular-dusty, Trickling, Reticular, Patchy, Banded, Focal, Not determinable/NA)
    - Temporal peripapillary atrophy (N/Y/ungradable or NA)
    - Is peripapillary atrophy confluent with macular GA (N/Y/ungradable or NA)
    - Macular atrophy gradable (N/Y) and reason if not gradable
    - Area of macular atrophy ($mm^2$)
- Fluorescein angiography (FA) imaging assessment, both eyes
    - Evidence of CNV

## PRIOR AND CONCOMITANT MEDICATION

All prior and concomitant medications will be summarized separately by WHO Drug code (version 2020 v1) on the ITT population. Medication usage will be summarized according to the 2$^{nd}$ level (main therapeutic level) and the 4$^{th}$ level (preferred term level) Anatomic Therapeutic Chemical (ATC) classification. Subjects will only be included once in the summaries within each ATC 2$^{nd}$ level or ATC 4$^{th}$ level category. The summaries will include the number and percentage of all Subjects with at least one prior or concomitant medication, respectively.

### EFFICACY EVALUATION

All efficacy analyses will be conducted for the ITT population. The primary endpoint will also be conducted for the PP population in a supportive manner.

The primary analysis will use the ITT population and will be based on a Mixed Model for Repeated Measures (MMRM) to compare the treatment groups. This analysis provides valid estimates as long as the missing data mechanism fulfills the Missing at Random (MAR) assumption. However, sensitivity analyses (see Section 7.4.1) will be performed to assess the potential magnitude and direction of the impact of missing data.

### CONTROL OF ALPHA

The overall (one-sided) false positive error rate in this trial is 0.025.

An alpha-level adjustment will be made in the assessment of statistical significance at the time of the final analysis, equal to (two-sided) 0.001 for each DSMB meeting for any look at the data. There will not be formal interim analyses for early termination for benefit and, in turn, the DSMB will not make recommendations for early termination even if emerging data would provide strongly favorable evidence for benefit. Rather, the principal justification for the DSMB to have access to emerging data on efficacy as well as safety data during DSMB meetings is to enable the DSMB to more effectively safeguard interests of study participants through a properly informed assessment of benefit-to-risk.

[redacted]

### ANALYSIS OF PRIMARY EFFICACY OUTCOME

The primary efficacy endpoint is the mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation). To eliminate the dependency of GA growth rates on the Baseline lesion size (Feuer et al., 2013), instead of using the observed GA area measurement, the square root of the GA area will be used in the analysis.

Primary Estimand

In alignment with the primary objective of the study, the main estimand to be used for the evaluation of the primary outcome is described as:

The difference in the mean rate of growth (slope) estimated based on GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12 (square root transformation) between treatment conditions (Zimura versus Sham) in the target patient population, regardless of any non-adherence to or interruption of study treatment, and regardless of initiation of alternative treatment.

The following 5 attributes define the main estimand for primary endpoint evaluation:

A. Population:

Population defined through inclusion/exclusion criteria to reflect the targeted patient population. Analysis will be performed on all randomized patients who received at least one dose of study drug.

B. Treatment:

Zimura 2 mg versus Sham.

C. Primary variable:

Mean rate of growth (slope) of the square root of GA area over 12 months.

D. Intercurrent events (ICE's) and strategies:

1. Treatment changes (i.e., interruptions, non-adherence, dose changes, discontinuation): "treatment policy" – i.e., treatment changes will be ignored and all data collected will contribute to the analysis regardless of whether or not these follow such ICE's.
2. COVID-19: "treatment policy" – i.e., impact of COVID-19 pandemic will be ignored and all data collected will contribute to the analysis regardless of whether or not these follow such ICE's.

E. Population-level summary:

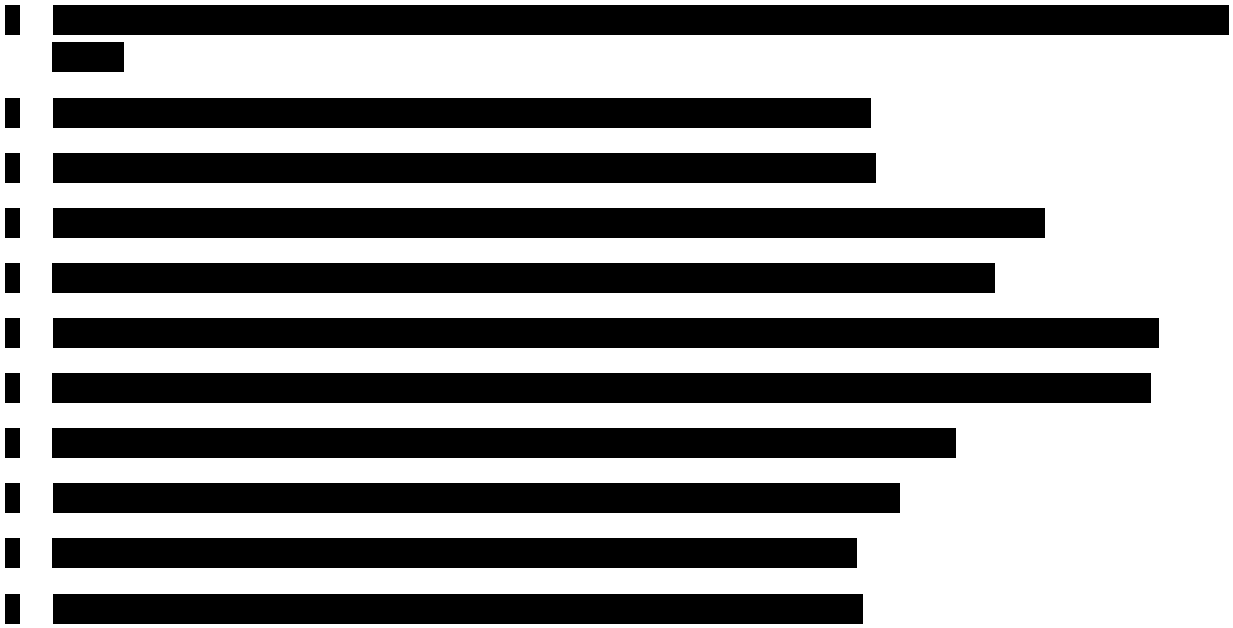
Difference between groups in mean rate of growth (slope) of the square root of GA area over 12 months.

The primary estimator is described as follows.

A mixed model for repeated measures (MMRM) will be applied to all available data, using as response variable the square root of GA area measured by FAF in at least 3 time points: Baseline, Month 6, and Month 12. The MMRM will be used to assess the difference between the treatment groups in terms of the rate of growth of the square root of GA area (slope) over 12 months. Previous trial OPH2003 (GATHER1) showed the change in the square root of geographic atrophy to be remarkably linear over time. As a result, a linear model is not only convenient and easily interpretable, but it is also appropriate given the natural history of the disease. A model will be fitted by using restricted maximum likelihood (REML) and include Baseline VA (< 50 letters vs. ≥ 50 letters), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. For the model, fixed effects will include time, treatment, Baseline VA (< 50 letters vs. ≥ 50 letters), pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse), treatment by time interaction, Baseline VA (< 50 letters vs. ≥ 50 letters) by time interaction, and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) by time interaction. The model will include an unstructured modelling of within-subject correlations. If this analysis fails to converge, alternative structures (e.g., heterogeneous autoregressive, heterogeneous compound symmetry, autoregressive, or compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The test of difference between the two arms in the mean rate of growth

(slope) of the square root of GA area over 12 months will be assessed by testing the appropriate contrast of the model parameter estimates. [redacted]

[redacted]



## SENSITIVITY ANALYSES

### Sensitivity Analyses for Missing Data

For the analyses of the primary outcome, the MMRM analysis does not require data imputation and uses only the observed data. Moreover, assuming that the missing data are MAR, the model yields valid results that are comparable to those obtained by applying MI under the MAR assumption.

Four analyses described by Miller et al. (2001) will be performed for further insight into the potential impact of missing data on the results:

1. the observed means from the active arm and the sham arm will be imputed to patients with missing data in the arm they were allocated to;
2. the average of observed means from the active arm and the sham arm will be imputed to all patients with missing data;
3. the observed mean from the sham arm will be imputed to all patients with missing data.
4. the observed means from the active arm and the sham arm will be imputed to patients with missing data in the opposite arm they were allocated to (a “cross-over” scheme);

These four sensitivity analyses make different assumptions about missing data, and are likely to be increasingly biased against a true treatment effect. A robust treatment effect would be expected to remain statistically significant in analyses 1 to 3, since these are likely to be much less biased than analysis 4 under the assumption of a true treatment effect.

To check the sensitivity of the results of the primary efficacy analysis (using the primary estimator as described in section 7.2) to the MAR assumption, MI based on models compatible with Missing Not At

Random (MNAR) missingness mechanisms will be used. Two approaches, using SAS' PROC MI, will be considered:

1. The "shift imputation" approach: for missing values at a particular visit, it will be assumed that their expected value is smaller (shifted) by a specified amount (i.e., a specified shift in the size of GA), than for the observed responses (implying that the missing values are more likely corresponding to smaller changes vs. Baseline than the observed ones). Increasing values of the shiftwill be explored to investigate the sensitivity of the results. This approach can be applied to data with arbitrary missing data patterns. The "tipping point" is the value of the shift that causes statistical significance to be lost. For a robust treatment effect, the tipping point would be considered an implausible value of the shift used in the missing data imputation.

2. The "pattern-mixture-model imputation" approach: missing values at Month 12 visit will be imputed by using the pattern-mixture-model restrictions. Pattern-mixture models provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. In particular, Complete-Case Missing Value (CCMV) and Neighbouring-Case Missing Value (NCMV) restrictions will be applied.

Of note, these imputation techniques are known to induce potential bias, hence they will be used only for sensitivity purposes.

**Sensitivity Analysis for Stratification Error**

On Monday November 16, 2020 the Duke Reading Center notified that an error occurred at the reading center in the reporting of fundus autofluorescence (FAF) results used as stratification factors for randomization of eligible patients into GATHER2 (ISEE2008) clinical trial.

As a result, 38 patients randomized with Baseline geographic atrophy size between 4 to 10 $mm^2$ were placed in a stratum that included participants with size $\geq$ 10 $mm^2$ rather than being placed in stratum that included participants with size < 10 $mm^2$.

To assess the impact of this stratification error, two sensitivity analyses will be done by performing analyses that stratify by 3-level covariates for the Baseline geographic atrophy size. The first analysis will stratify by: < 4 $mm^2$ vs. $\geq$ 4 to < 10 $mm^2$ vs. $\geq$ 10 $mm^2$, and the second analysis will stratify by: patients randomized prior to November 16, 2020 vs. < 4 $mm^2$ vs. $\geq$ 4 $mm^2$.

Since November 16$^{th}$, patients have been stratified correctly as indicated in the protocol based on their baseline geographic atrophy size: < 4 disc areas (10 $mm^2$) vs $\geq$ 4 disc areas (10 $mm^2$). The minimization procedure was not modified after November 16, 2020, because implementing any changes to this procedure would have meant putting the trial on hold while the changes were being implemented and validated. Furthermore, an inspection by the randomization center of the balance with respect to baseline geographic atrophy size achieved on November 16, 2021 provided reassurance that the minimization algorithm could continue unchanged.

### Sensitivity Analysis for Observed GA Measurement

The sensitivity of the results from the analyses of observed (non-square root transformed) area of GA over 12 months will be conducted using the same analysis model as specified in section 7.2.

[redacted]

### Descriptive Summaries by Visit

The change in score from Baseline will be analyzed as continuous variables. The composite score and the scores of each sub-scales at Baseline and the changes from Baseline will be summarized descriptively by visit and by treatment group using the observed cases (missing values will not be imputed).

[redacted]

### SUBSET ANALYSES

The trial is not designed to have adequate power to formally test for the presence of treatment by covariate interactions. Thus, true treatment by covariate interactions will likely be missed, unless they are quite substantial. Conversely, should particular subsets of subjects seem to benefit more or less from therapy than the total population, this will not be taken as reliable evidence of a true treatment by covariate interaction, given the likelihood that such an observation could be due to chance alone. With these caveats in mind, exploratory subset analyses will be performed to identify any major effect that might be worth testing in future trials. In a descriptive manner, treatment effect will be presented for subsets created by multiple covariates. Among these covariates will be the stratification factors: Baseline VA (< 50 vs. ≥ 50 ETDRS letters), Baseline GA (< 4 vs. ≥ 4 disc area), Pattern of FAF at the junctional zone of geographic atrophy (none/focal vs. banded/diffuse) as well as age (<65 vs. 65~74 vs. 75~84 vs. ≥85), gender (male vs. female) race (American Indian/Alaska Native vs. Black or African American vs. Asian vs. Native Hawaiian/Pacific Islander vs. White vs. Other), and ethnicity (Hispanic or Latino vs. Not Hispanic or Latino).

Since these analyses will be considered as exploratory, they will be conducted without any alpha-level adjustment.

### SAFETY EVALUATION

All safety analyses will be performed on the safety population. The analyses will be conducted according to the treatment that they actually received. However, subjects who have ever received an injection of Zimura will be analyzed in the Zimura group. Missing values of safety data will not be imputed and safety summaries will be based on the observed cases.

### EXTENT OF EXPOSURE

Exposure to study medication will be evaluated for each treatment group with respect to treatment duration (= Last injection date - First injection date + 30, in days), number of subjects treated at each planned visit, total injections received, using descriptive statistics (N, mean, standard deviation, median, minimum, Q1, Q3, maximum).

### ADVERSE EVENTS

Adverse events (AEs) will be recorded starting after the first dose of study drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. AE data will be evaluated for each treatment group.

Only first year AE data will be included in the following analyses. Treatment Emergent Adverse Events (TEAEs) from the first year will be defined as starting after the first dose of study drug until prior to Month 12 injection. If a Month 12 injection does not exist, the end of the first year is defined as the Month 12 visit (or target of 365.25 days after the first dose if no Month 12 visit) or 30 days after the last injection, whichever is later.

All AEs will be coded using MedDRA™ (version 23.0 update) terms.

- An overview of TEAEs will be provided. A second overview of TEAEs will be provided which displays the overall summary of TEAEs by the categories ‘Study Eye’, ‘Non-Study Eye’, and ‘Non-Ocular’. In addition, the number and percentage of patients with TEAEs will be tabulated for each treatment group and in total by system organ class (SOC) and preferred term (PT). The number and percentage of the subjects who experienced at least one TEAE will be included. Subjects will only be counted once for each preferred term. In case that a subject experienced the same event more than once, the worst severity will be presented.
- Tabular summaries of the following AEs will be provided by SOC and PT:
  - Summary of TEAEs
  - All TEAEs regardless of the relationship to study treatment
  - All TEAEs regardless of the relationship to study treatment with frequency of ≥ 5% in any treatment arm.

  - TEAEs related to study treatment
  - TEAEs related to injection procedure
  - TEAEs by the maximum severity grade
  - TEAEs related to study treatment by the maximum severity grade
  - TEAEs related to injection procedure by the maximum severity grade
  - All Ocular TEAEs by study eye and fellow eye
  - Treatment related Ocular TEAEs by study eye and fellow eye
  - Injection procedure related Ocular TEAEs by study eye and fellow eye
  - Ocular TEAEs (study eye) by the maximum severity grade
  - Treatment related Ocular TEAEs (study eye) by the maximum severity grade
  - Injection procedure related Ocular TEAEs (study eye) by the maximum severity grade
  - TEAEs with high level term of cataract conditions by study eye and fellow eye
  - TEAEs leading to discontinuation of study drug
  - Treatment related TEAEs leading to discontinuation of study drug
  - Injection procedure related TEAEs leading to discontinuation of study drug
  - Ocular TEAEs (study eye) leading to discontinuation of study drug
  - TEAEs leading to death
  - Treatment related TEAEs leading to death
  - Injection procedure related TEAEs leading to death
- Ocular TEAEs have been defined as TEAEs linked to the “Eye Disorders” system organ class and the ‘Intraocular pressure increased’ preferred term.
- All AEs, including non-TEAEs, will be included in individual subject listings.
- The listings will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, onset before injection, after first injection or after second injection, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study medication/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/not resolved/fatal).
- The same listings will be provided separately for severe AEs, AEs leading to permanent discontinuation of the study treatment, and for AEs leading to death.

### SERIOUS ADVERSE EVENTS AND DEATHS

- Treatment-Emergent Serious adverse events (SAEs) will be summarized by system organ class and preferred term. The number and percentage of the subjects who experienced at least one SAE will be included.
- SAE data will be evaluated for each treatment group.
- Tabular summaries of the following SAEs will be provided:
  - All SAEs regardless of the relationship to study treatment
  - SAEs related to study treatment
  - SAEs related to injection procedure
  - Ocular SAEs (study eye) regardless of the relationship to study treatment
  - Ocular SAEs (study eye) related to study treatment
  - Ocular SAEs (study eye) related to injection procedure
- In addition, separate listings will be created for deaths and all SAEs. List for SAEs will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, onset before injection, after first injection or after second injection, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study medication/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/not resolved/fatal).

### VITAL SIGNS

Descriptive statistics at each time point up through and including the Month 12 visit will be used to display the changes from Baseline for pulse and blood pressure (systolic and diastolic). Mean change of pulse and blood pressure (systolic and diastolic) from Baseline to the last measurement will be provided.

### OPHTHALMIC VARIABLES

**Ophthalmic Examination.** The following ophthalmic examination variables will be analysed by shift table from Baseline to the pre-injection examination on Month 12 or last visit available whichever comes later (normal/abnormal, unless otherwise specified below).:

- Examination of the motility
- Inspection of the lids/lacrimal/lashes
- Examination of the conjunctiva/sclera
- Inspection of the cornea

- Examination of the iris
- Examination of the pupils
- Inspection of the lens status (aphakic, pseudo-phakic, phakic; if phakic, nuclear/PSC/cortical 0, 1, 2, 3, 4), including a listing of subjects with a change in lens status for study eye and (separately) for fellow eye
- Examination for posterior vitreous detachment
- Inspection of the optic nerve
- Inspection of the macula
- Examination of the retinal vessels

The following ophthalmic examination variables will be analysed by shift table from Baseline through Month 12 or last visit available whichever comes later, on a monthly basis (normal/abnormal, unless otherwise specified below), and from pre-injection to post-injection at each monthly injection

- Examination of anterior chamber activity: Cells (0, trace, 1+, 2+, 3+, 4+)
- Inspection for vitreous haze (0, 1+, 2+, 3+, 4+)
- Examination for vitreous haemorrhage
- Examination of the peripheral retina

**Intraocular Pressure.** IOP will be summarized by visit, including all pre-injection, "IOP after first injection", and "IOP after second injection" measurements for applicable visits. An additional tabular summary of the percentage of subjects in categories of IOP will be presented by treatment group, visit, and injection time (pre-injection, IOP after first injection, IOP after second injection).

"IOP after injection" is defined as the IOP measurement that is closest in time to the protocol-specified post-injection timepoint (but at least 30 minutes post-injection). If there are two closest measurements equidistant to this timepoint, then the measurement after the protocol-specified timepoint will be used.

Mean IOP over time of all scheduled measurements (pre-injection, IOP after first injection, and IOP after second injection) will be plotted.

**CLINICAL LABORATORY DETERMINATION**

- All laboratory data will be listed and values falling outside normal ranges will be identified, whether they will be deemed clinically relevant or not.
- Laboratory data will also be summarized in tables presenting values at each scheduled visit up through the Month 12 visit
- Value changes from Baseline to each scheduled visit up through the Month 12 visit

- A summary table of all analytes with the Baseline mean and the mean change from Baseline to the last value observed
- A summary table of all analytes with the Baseline median and the median change from Baseline to the last value observed

For the following parameters:

- Hematological parameters (hemoglobin, white blood cells, platelets, neutrophils (absolute numbers), lymphocytes (absolute numbers), monocytes (absolute numbers), eosinophils (absolute numbers), basophils (absolute numbers)),
- Renal function parameters (serum creatinine and BUN),
- Hepatic function parameters (serum bilirubin, alkaline phosphatase, GGT, SGOT/AST, and SGPT/ALT),
- Electrolytes (sodium, potassium, chloride, carbon dioxide, calcium, and phosphate),
- Complete urinalysis parameters (complete urinalysis including specific gravity, protein, blood, etc.),
- Serum pregnancy test (if of child-bearing potential).

Additional urine or serum pregnancy testing may be performed during the course of the study at the discretion of the investigator, or in accordance with local requirements or regulations.

The incidence of subjects with "Notable Laboratory Values" after the first dose of study drug will be evaluated using the criteria for Notable Laboratory Values given below. Only data collected after the first dose of study drug, up to the laboratory data taken at the Month visit (before Month 12 treatment is administered) will be included; if there is no Month 12 visit, data will be included up to a target of 365.25 days after date of first dose, or 30 days after the last dose of study drug, whichever is later.

By-subject listings of all notable laboratory values will also be provided; for each subject who has an analyte with a notable value, all values of that particular analyte taken during the study will be presented in the listing, and the notable value, and any values outside of normal limits, will be identified.

For this "Notable Laboratory Values" analysis, *all* laboratory values after randomization will be taken in account, i.e., any values obtained after Day 1, at unscheduled visits, as well as values from the regularly scheduled laboratory visit at Month 12. Three Notable Laboratory Values tables and accompanying by-subject listings will be presented: (1) notable abnormalities for subjects with normal Baseline results, (2) notable abnormalities for subjects with abnormal Baseline results and (3) notable abnormalities without regard to Baseline abnormalities (i.e., normal or abnormal Baseline results). The table without regard to Baseline abnormalities will be a composite of the previous two tables (normal Baseline, abnormal Baseline).

Lab analytes and primary criteria used for Notable Laboratory Values:

a. HEMATOLOGY
   i. Hemoglobin < 0.75x Baseline
   ii. Platelets < 75 or > 750 (10^9/L)
   iii. WBC count < 2.5 or > 17.5 (10^9/L)
   iv. Neutrophils (absolute) < 0.5xLLN or > 1.5xULN
   v. Eosinophile (absolute) >1.5xULN
   vi. Lymphocytes (absolute) < 0.5xLLN or >1.5xULN
b. LIVER FUNCTION
   i. Total bilirubin > 1.5xULN
   ii. Alkaline phosphatase > 1.5xULN
   iii. ASAT (SGOT) > 3xULN
   iv. ALAT (SGPT) > 3xULN
   v. GGT > 3xULN
c. RENAL FUNCTION
   i. BUN > 1.3xULN
   ii. Creatinine > 1.3xULN
d. ELECTROLYTES
   i. Potassium < 0.9xLLN or > 1.1xULN
   ii. Sodium < 0.9xLLN or > 1.1xULN
   iii. Chloride < 0.9xLLN or > 1.1xULN
   iv. Carbon Dioxide < 0.9xLLN or > 1.1xULN
   v. Calcium < 0.9xLLN or > 1.1xULN
   vi. Phosphorus < 0.9xLLN or > 1.1xULN

Notable abnormalities for subjects with abnormal Baseline results are subject to the primary criteria above and the following secondary criteria:

a. HEMATOLOGY
   i. Hemoglobin < 0.75x Baseline (same as primary criterion)
   ii. Platelets < 0.75x Baseline or > 1.25x Baseline

iii. WBC count < 0.75x Baseline or > 1.25x Baseline

iv. Neutrophils (absolute) < 0.5x Baseline or > 1.5x Baseline

v. Eosinophils (absolute) > 1.5x Baseline

vi. Lymphocytes (absolute) < 0.5x Baseline or >1.5x Baseline

b. LIVER FUNCTION

i. Total bilirubin > 1.5x Baseline

ii. Alkaline phosphatase > 1.5x Baseline

iii. ASAT (SGOT) > 1.5x Baseline

iv. ALAT (SGPT) > 1.5x Baseline

v. GGT > 1.5x Baseline

c. RENAL FUNCTION

i. BUN > 1.3x Baseline

ii. Creatinine > 1.3x Baseline

d. ELECTROLYTES

i. Potassium < 0.9x Baseline or > 1.1x Baseline

ii. Sodium < 0.9x Baseline or > 1.1x Baseline

iii. Chloride < 0.9x Baseline or > 1.1x Baseline

iv. Carbon dioxide < 0.9x Baseline or >1.1x Baseline

v. Calcium < 0.9x Baseline or >1.1x Baseline

vi. Phosphorus < 0.9x Baseline or > 1.1x Baseline

**ECG**

ECG results will be tabulated as “normal” or “abnormal” at each visit, and will be presented in a normal/abnormal shift table between Baseline and each scheduled ECG visit, as well as between Baseline and the last ECG taken. Descriptive statistics will be presented for continuous variables (eg, heart rate and RR, PR, QRS, QT, QTcB and QTcF intervals) at each visit. A by-patient listing will be provided for ECGs which are deemed abnormal.

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## APPENDICES

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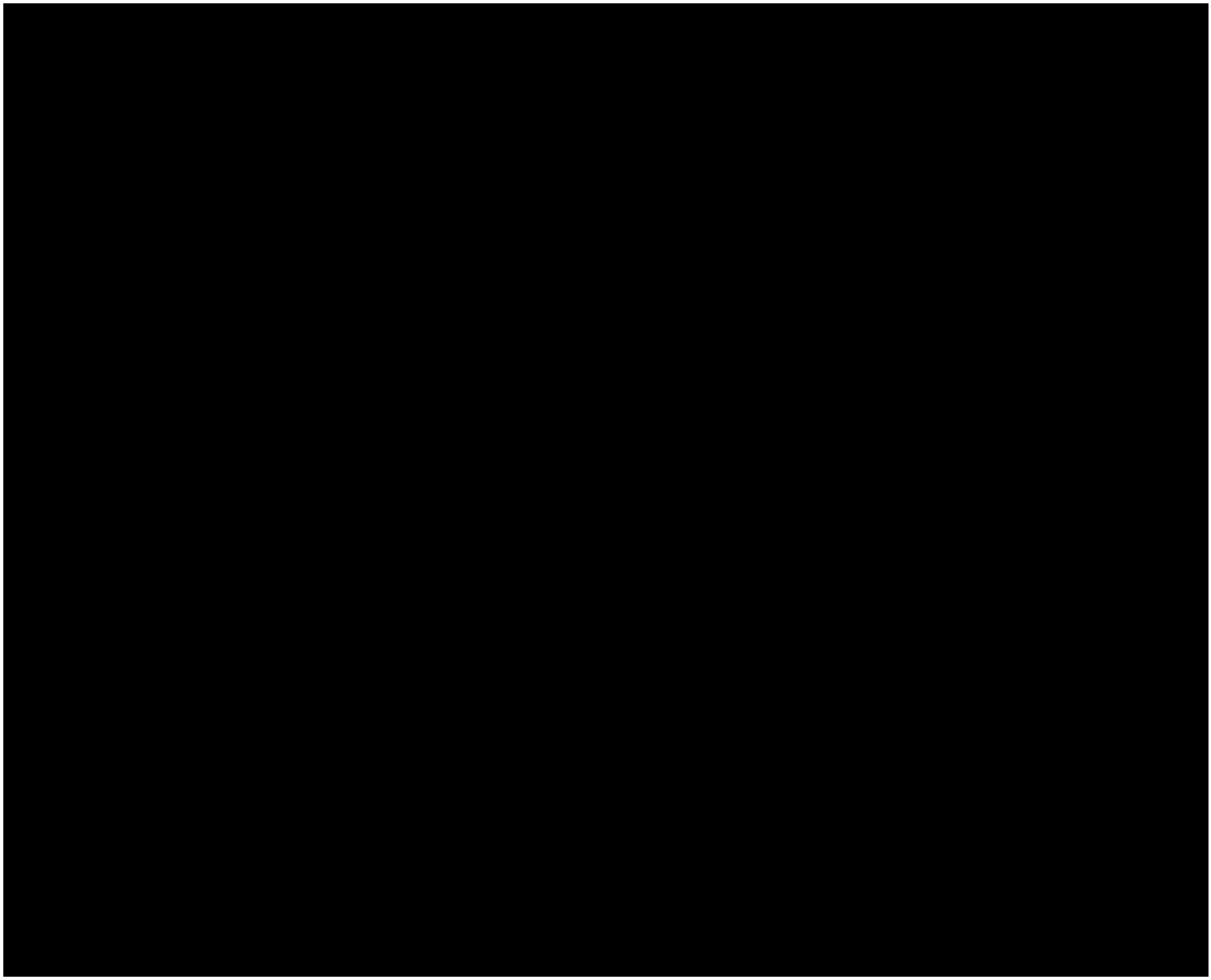


# STATISTICAL ANALYSIS PLAN

## Year 2 Cumulative Data

**Protocol Title: a phase 3 multicenter, randomized, double-masked, sham controlled clinical trial to assess the safety and efficacy of intravitreal administration of Avacincaptad Pegol (complement c5 inhibitor) in patients with geographic atrophy secondary to age-related macular degeneration**

**Protocol Number: ISEE2008**

**Compound Number: ARC1905**

**Short Title: Gather 2 (Year 2)**

**Sponsor Name: Iveric Bio, Inc.**

Approvers:

## Table of Contents

## Version History

| SAP version | Date | Change | Rationale |
|---|---|---|---|
| 2.0 | 22 June 2023 | • Analysis populations and Expand analysis visit windows up to year 2 | Population at the re-randomization is defined. Analysis visit windows are defined to cover visits up to year 2 in the analysis data sets |
| | | • Untransformed response outcome (growth rate of GA) without square root transformation will be used | Untransformed data is direct and easy to interpret the growth of GA area |
| | | • Remove the per-protocol analysis | Intent-to-treat population is the primary analysis set. Per-protocol analysis set doesn't provide additional meaningful information in this superiority study |
| | | • Revise the MMRM model to fit the design for year 2 analysis | With re-randomization at the end of year 1, the stratification factors from the initial randomization are no-longer applicable to the cumulative data at year 2. In addition, the untransformed GA area will be used in the model. Several sensitivity analyses are added. |
| | | • Revise analysis on fellow eye (FE) | The study is on the study eye (SE) for efficacy and safety evaluation. FE will not provide additional information |
| | | • Vision loss analysis | Time-to-event analysis is added with the vision loss event defined as BCVA ≥ 15 letters loss from baseline in 2 or more consecutive visits |
| 1.0 | 3 August 2022 | | Original version: a brief SAP addendum for year 2 analysis |

**List of Abbreviations**

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| AMD | Age-Related Macular Degeneration |
| ACP | Avacincaptad Pegol |
| ATC | Anatomic Therapeutic Chemical |
| BCVA | Best Corrected Visual Acuity |
| BUN | Blood Urea Nitrogen |
| CI | Confidence Interval |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluorescein Angiography |
| FAF | Fundus Autofluorescence |
| FP | Fundus Photography |
| GA | Geographic Atrophy |
| GGT | Gamma-glutamyl Transferase |
| ICH | International Conference on Harmonization |
| DSMB | Data Safety Monitoring Board |
| IOP | Intraocular Pressure |
| ITT | Intention-to-Treat |
| LLN | Lower Limit Normal |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed Model for Repeated Measures |
| MNAR | Missing Not At Random |
| NA | Not Available / Not Applicable |
| OU | Oculus Uterque (Both Eyes) |
| PSC | Posterior Subcapsular Cataract |
| REML | Restricted Maximum Likelihood |
| CCI | [redacted] |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Study Eye |
| SGOT/AST | Aspartate Aminotransferase |
| SGPT/ALT | Alanine Aminotransferase |
| ULN | Upper Limit Normal |

| | |
|---|---|
| VA | Visual Acuity |
| WBC | White Blood Cells |
| WHO | World Health Organization |

# 1. Introduction

This Statistical Analysis Plan (Year 2) describes the statistical methodology and data handling of Year 2 for the clinical trial with Protocol Number: ISEE2008 (GATHER2), Version Date: 18 December 2020.

The trial consists of a total treatment period of 24 months. This SAP covers the final analyses to be performed on Year 2 cumulative data including visits at 18 and 24 months. The primary analysis on year 1 was conducted and documented separately in the SAP for the primary analysis.

At the end of year 1, patients receiving monthly ACP 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups (denoted as EM or EOM):

- EM: ACP 2 mg administered monthly from Month 12 - Month 23
- EOM: Sham administered at Months 12, 14, 16,18, 20, and 22, and ACP 2 mg administered every other month at Months 13, 15, 17, 19, 21, and 23

The name Zimura was used previously in the protocol and other document. Moving forward, a scientific name ACP will be used instead.

A final analysis of the double-masked phase of the study, including all double-masked data will be performed when all participants have completed the Month 24 visit or discontinued earlier.

A brief SAP addendum (version 1.0) for cumulative Year 2 data of ISEE2008 study was approved on 3 August 2022 before the unmasking of Year 1 data for primary analysis. The addendum prespecified mainly sequential statistical testing procedure on Year 2 (Supporting Document).

The purpose of this SAP (Year 2) is to expand the addendum to provide technical details for the Year 2 and the final analysis of the study.

## 1.1. Objectives and Endpoints

**Efficacy objectives and corresponding Endpoints are tabulated below**

| Efficacy objectives | Endpoints |
|---|---|
| • Demonstrate ACP 2mg in EM or EOM intravitreal injection after re-randomization reduces GA growth (slope) compared to Sham in patients with geographic atrophy secondary to age-related macular degeneration (AMD) up to Year 2. | • GA area measured by FAF in 5 time points: Baseline, Month 6, Month 12, Month 18, and Month 24. |
| • Demonstrate ACP 2mg intravitreal injection reduces rate of persistent vision loss (BCVA) compared to Sham up to Month 24 | • Time to vision loss (defined as BCVA loss $\geq$ 15 letters from baseline at two or more consecutive visits up to Month 24). |

| | |
|---|---|
| • CCI [redacted] | [redacted] |
| Safety | |
| • Safety of ACP 2mg in EM or EOM intravitreal injection compared to Sham in patients with geographic atrophy secondary to age-related macular degeneration (AMD) up to Year 2.<br>• Safety of ACP 2mg intravitreal injection compared to Sham in patients with geographic atrophy secondary to age-related macular degeneration (AMD) up to Year 2. | • Adverse events (AEs)<br>• Serious adverse events (SAEs)<br>• Vital signs (pulse, systolic and diastolic blood pressure)<br>• Ophthalmic variables (ophthalmic examination, best corrected visual acuity (BCVA), low luminance BCVA (LLBCVA), intraocular pressure (IOP)<br>• Electrocardiography (ECG)<br>• Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis) |

## 1.2. Study Design

Approximately 400 patients will be randomized at Day 1 in a 1:1 ratio to the following monthly treatment groups:

- ACP 2 mg
- Sham

Patients receiving monthly ACP 2 mg will be re-randomized at Month 12 in a 1:1 ratio to the following treatment groups: EM or EOM as described above. ACP 2mg denotes the treatment group from the initial randomization.

All patients who were initially randomized to Sham (at Day 1) will continue with monthly Sham injections through Month 23. All patients will have a final follow-up visit at Month 24. The trial consists of a total treatment period of 24 months. This SAP covers all analyses to be performed on Year 2 cumulative data.

## 1.3. Study Period and Visit Window Definition

Study assessments in Year 2 are summarized below.

Year 2

# 2. Statistical Hypotheses

The following hypothesis testing will be conducted sequentially.

1. Hypothesis testing in EM vs. Sham for mean GA growth rate are:

$$H_0: \Delta = 0$$

$$\text{versus } H_1: \Delta \neq 0,$$

where $\Delta = \mu_1 - \mu_2$, $\mu_i$ is the mean growth rate (slope) of GA over 24 months for treatment EM, or Sham, respectively.

2. Hypothesis testing in ACP 2mg vs Sham for time to vision loss will be conducted using Kaplan-Meier method with a log-rank test
3. Hypothesis testing in EOM vs. Sham for mean GA growth: similarly, as in (1)
4. Hypothesis testing in ACP 2mg vs Sham for mean change in best corrected visual acuity (BCVA in ETDRS letters) from Baseline to Month 24
5. Hypothesis testing in ACP 2mg vs Sham for mean change in low luminance best corrected visual acuity (LL BCVA in ETDRS letters) from Baseline to Month 24
6. [redacted] CCI

The hypothesis testing will be evaluated according to a pre-specified hierarchical testing procedure to control overall type-1 error at a 5% two-sided significance level. If the primary analysis testing GA growth rate (ACP 2mg vs Sham) based on Year 1 data is statistically significant, the hypotheses tests will be performed in a sequential way as described above to control familywise type I error rate with 2-sided significance level of 0.05. A test will be performed only if all the preceding tests are statistically significant.

## 2.1. Multiplicity Adjustment

There will be no adjustment for the multiplicity as the hypotheses will be tested in a hieratical procedure on the primary endpoint and the secondary endpoints described above.

# 3. Analysis Sets

For the purposes of analyses, the following analysis sets (populations) will be used and are defined below.

| **Participant Analysis Set** (population) | **Description** |
|---|---|
| Intent-to-treat analysis set (ITT) | All randomized participants who received at least one dose of study drug. Participants will be analyzed in the treatment group assigned at randomization |
| Safety analysis set (Safety) | All participants who received at least one dose of study drug. Subjects who have ever received an injection of ACP during this trial will be analyzed in the ACP group. |
| Re-randomized analysis set (Re-Rand) | The subset of ITT population who are re-randomized at Month 12 |

In the ITT/Safety population, ACP (ARC1905 2mg) and Sham will be used as treatment groups. Subjects who were discontinued from the study in Year 1 will be included. In the Re-randomized population, ARC1905 2mg EM, ARC1905 2mg EOM, and Sham will be used as treatment groups. Subjects who were discontinued from the study in Year 1 will be excluded.

# 4. Statistical Analyses

## 4.1. General Considerations

Data will be analyzed using SAS 9.4 or R. In the ITT/Safety population, ACP (ARC1905 2mg), Sham will be used as treatment groups. Subjects who were discontinued from the study in Year 1 will be included. In the Re-randomized population, ARC1905 2mg EM, ARC1905 2mg EOM, and Sham will be used as treatment groups.

Descriptive statistics will be tabulated as follows:

Categorical data will be summarized in contingency tables presenting frequencies and percentages.

Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, 1st quartile (Q1), 3rd quartile (Q3), and maximum values.

Graphic display and visualization will be utilized to summarize descriptive statistics.

### 4.1.1. Visit Windows

The scheduled visits will be used in the analyses over time.

Missing scheduled follow-up visit will be substituted by an unscheduled or early withdrawal visit occurring within each follow-up visit window if there is only one unscheduled or early withdrawal visit occurring within the window. If there are multiple unscheduled or early withdrawal visits occurring within the window, the closest one within the visit window will be used. If no unscheduled or early withdrawal visit occurred within the window, the visit will be considered as missing. The details are tabulated in the Supporting Document section.

### 4.1.2. Handling Missing Data in Efficacy Analyses

Methods that take into account the presence of missing data and that yield valid estimates under the assumption of data missing at random (MAR) will be used. The Mixed Model on Repeated Measures fitted by Restricted Maximum Likelihood method will be used in the mean growth GA analysis, where the observed data will be used with no imputation. Several imputation methods will be used in sensitivity analyses, whenever necessary, to impute the missing data, as described in Section 4.2.4 sensitivity analyses.

### 4.1.3. Handling Missing Data in Descriptive Analyses

When summarizing categorical variables, subjects with missing data are generally not included unless otherwise specified. When needed, the category of “Missing” is created and the number of subjects with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

### 4.1.4. Handling Missing or Partially Missing Dates

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after treatment, the AE will be classified as after the start of treatment.

CCI [redacted]

### 4.1.6. Disposition of Subjects

The number of subjects randomized and treated, by treatment arm will be presented. The reason for exclusion from one or more analysis sets will be summarized.

The number of subjects re-randomized and treated post-randomization, by treatment arm will also be presented.

The frequency of premature discontinuations from the study treatment prior to study completion (Month 24) will be given by treatment arm and overall. The details of the 'Adverse Event',

'Protocol violation', 'Investigator decision', 'Sponsor Decision', 'Subject request', 'Lost to Follow-Up', 'Subject Non-Compliance', or 'Other' will be included in a listing.

The frequency of premature discontinuations from the study prior to Month 24 will be given for the ITT population and re-randomized population, by treatment arm and overall. The primary reason for non-completion of the study will be summarized.

### 4.1.7. Treatment Misallocation

For subjects with errors in treatment allocation, the following is described under which treatment groups they will be reported for efficacy and safety analyses:

For example, if subjects were:

- Randomized (regardless of error) but not treated, then they will be excluded for all efficacy and safety analyses. These subjects will be included in the summary of subject dispositions.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomization is missing but will be reported under the treatment they actually received for all safety analyses.
- Randomized but were administered the incorrect treatment at any time during the study, then they will be reported under their randomized treatment group for efficacy analyses on ITT population but will be reported under the treatment they actually received for all safety analyses on SAFETY population (see Section 3.2.3); specifically, this implies that for safety analyses, a patient who ever received ACP will be included in the ACP group based on actual injections received.
- Re-randomized population will be used for both efficacy and safety analysis in Year 2 with the treatment as re-randomized.

### 4.1.8. Protocol Deviations

All protocol deviations will be assessed and identified prior to database lock in a masked fashion to determine whether they are major by the sponsor. The final list of major protocol deviations will be provided prior to the database lock.

The major protocol deviations will be summarized for the ITT population and re-randomized population. The details will be listed by subject and by treatment arm.

### 4.1.9. Demographic and Baseline Characteristics

Descriptive statistics will be provided on Baseline information including demographics and disease characteristics. No tests of significance will be conducted.

Descriptive statistics with respect to subject characteristics at Baseline will be displayed for the ITT population and re-randomized population. When several measurements are available before the first administration of study drug, the Baseline value is the last available value prior to first

dose, except for the Baseline visual acuity score which is the mean of the Screening and Day 1(D0) values if both are available.

The variables to be summarized are:

- Gender, ethnicity, race, iris color, age, current smoking status.
- Prior ocular history, both eyes (by MedDRA preferred term, including number and percentage of all subjects with at least one prior ocular history)
- Medical history (excluding ocular history) (by body system and preferred term, with number and percentage for both; including number and percentage of all subjects with at least one prior medical history)
- Prior surgeries/procedures (by body system and preferred term, with number and percentage for both; including number and percentage of all subjects with at least one prior surgery/procedure)
- Vital signs (height, weight, pulse, blood pressure)
- ECOG performance status
- Pregnancy test
- Visual acuity (ETDRS), study eye
- Tonometry, study eye
- ECG
- Ophthalmic exam, both eyes (motility, lids/lacrimal/lashes, conjunctiva/sclera, cornea, anterior chamber activity: cells, iris, pupils, lens status, vitreous haze, vitreous hemorrhage, posterior vitreous detachment, optic nerve, macula, retinal vessels, peripheral retina)
- Fundus autofluorescence (FAF) imaging assessments, study eye
- Fluorescein angiography (FA) imaging assessment

### 4.1.10. Prior and Concomitant Medications

All prior and concomitant medications will be summarized separately by WHO Drug code (WHO Drug Dictionary, released on 1 September 2020) on the ITT population and re-randomized population. Medication usage will be summarized according to the 2$^{nd}$ level (main therapeutic level) and the 4$^{th}$ level (preferred term level) Anatomic Therapeutic Chemical (ATC) classification. Subjects will only be included once in the summaries within each ATC 2$^{nd}$ level or ATC 4$^{th}$ level category. The summaries will include the number and percentage of all Subjects with at least one prior or concomitant medication, respectively.

## 4.2. Efficacy Analysis

### 4.2.1. Mean GA growth (slope): EM, EOM vs. Sham

#### 4.2.1.1. Definition of Estimand

The objective is to demonstrate efficacy of ACP EM or EOM versus Sham in mean GA growth rate (slope) after re-randomization regardless of any non-adherence to or interruption of study treatment, and regardless of initiation of alternative treatment.

The following 5 attributes define the Estimand for the objective evaluation:

A. Population: re-randomized population

B. Interventions:

ACP EM or EOM versus Sham.

C. Endpoint:

GA area over 24 months from Baseline, Month 6, Month 12, Month 18, and Month 24.

D. Intercurrent events (ICE's) and strategies:

1. Treatment changes (i.e., interruptions, non-adherence, dose changes, discontinuation): "treatment policy" – i.e., treatment changes will be ignored, and all data collected will contribute to the analysis regardless of whether these follow such ICE's.
2. COVID-19: "treatment policy" – i.e., impact of COVID-19 pandemic will be ignored, and all data collected will contribute to the analysis regardless of whether these follow such ICE's.

E. Population-level summary:

Difference between groups (EM vs. Sham, EOM vs. Sham) in mean growth rate (slope) of the GA area over 24 months.

#### 4.2.1.2. Statistical Method

With a re-randomization at the end of Year 1, the initial stratification factors from the randomization are no longer applicable in the analysis of Year 2. Therefore, the stratifications factors will be removed from the MMRM model as in the primary analysis.

The revised model is described below.

A mixed model for repeated measures (MMRM) will be applied to all available data, using response variable of the GA growth area over time up to Month 24 in 5 time points: Baseline, Month 6, Month 12, Month 18, and Month 24. The MMRM will be used to assess the difference between the treatment groups in terms of the rate of growth (slope) of the GA over time of 24 months. Time is defined as a continuous variable in number of study days since the baseline assessment. Treatment groups include ACP EM, ACP EOM, and Sham. A model will be fitted

by using restricted maximum likelihood (REML) and include time, treatment, and treatment by time interaction as fixed effects, subject as random effect.

Notice that in the primary analysis at Year 1 (Month 12), the square root transformation of GA growth area was used. However, the mean GA growth (slope) has shown similar results with or without square root transformation. In addition, it is difficult to interpret the transformed data in context. Therefore, in the Year 2 analysis, the untransformed GA growth using observed GA area of measurement will be used as the primary endpoint.

#### 4.2.1.3. Sensitivity or Supportive Analyses

The following sensitivity or supportive analyses will be performed.

##### *4.2.1.3.1. Miller imputation of missing data*

For the analyses of the endpoint, the Mixed-Effects Repeated Measures (MMRM) analysis does not require data imputation and uses only the observed data.

Four analyses described by Miller et al. (2001) will be performed for further insight into the potential impact of missing data on the results:

1. the observed means from the active arm and the sham arm will be imputed to patients with missing data in the arm they were allocated to;
2. the average of observed means from the active arm and the sham arm will be imputed to all patients with missing data;
3. the observed mean from the sham arm will be imputed to all patients with missing data.
4. the observed means from the active arm and the sham arm will be imputed to patients with missing data in the opposite arm they were allocated to (a “cross-over” scheme);

These four sensitivity analyses make different assumptions about missing data and are likely to be increasingly biased against a true treatment effect. Therefore, they will be used only for sensitivity purposes.

##### *4.2.1.3.2. Multiple imputation with tipping point analysis*

In addition to filling a single value for the missing value at a visit as described in Miller method, multiple imputation with tipping point analysis will be conducted. Please refer to primary analysis CSR Appendix for technical details.

##### *4.2.1.3.3. Time (visit) as a categorical variable in the MMRM model*

Time will be replaced as a categorical variable in the MMRM model above with the visits (Baseline, Month 6, Month 12, Month 18, and Month 24) to assess the change from baseline over time.

##### *4.2.1.3.4. Piece-wise analysis by every 6-month interval*

The MMRM model assumes a liner growth rate of GA over time. A linear spline approximation by every 6-month interval is to provide more detail on the GA growth curve by time interval over 2 years. The MMRM model in Section 4.2.1.2 will be used to fit every 6-month interval data.

### 4.2.2. Time to Vision Loss Analysis

In the evaluation of vision, BCVA is an important measurement tool to assess the changes over time. However, substantial differences in mean change of visual acuity between treatment and sham are difficult to demonstrate within the timeframe of a clinical trial in patients with GA. Nonetheless, at various time points in the study, patients can experience a significant and permanent drop in visual acuity. Hence, it is more appropriate to analyze vision data by using the time-to-event analysis to better characterize patient's vision loss by accounting for instances of clinically significant vision loss in terms of change in BCVA Scores (ETDRS Letters) from Baseline to Month 24. In this time-to-event analysis, a vision loss event was defined as a loss of ≥ 15 letters (equivalent to a loss of 3 lines on the ETDRS chart) in BCVA from Baseline measured at any two or more consecutive visits up to Month 24. These parameters were chosen as a 3-line BCVA loss (equivalent to doubling of visual angle) is widely recognized as a significant deterioration in vision and a minimum of two consecutive visits is representative of persistent disease progression. The framework of this analysis is formulated as the secondary Estimand below.

#### 4.2.2.1. Definition of the Estimand

This secondary efficacy objective is to demonstrate that ACP 2 mg can significantly reduce the rate of persistent vision loss compared to Sham up to Month 24.

The following 5 attributes define the secondary Estimand for the secondary endpoint evaluation:

A. Population:

Subjects with geographic atrophy secondary to dry age-related macular degeneration. Analysis will be performed on all randomized patients who received at least one dose of study drug (ITT population).

B. Interventions:

ACP 2mg versus Sham.

C. Endpoint:

Time to persistent vision loss (BCVA ≥ 15 letters loss from Baseline at 2 or more consecutive visits) during the study from Baseline to Month 24.

D. Intercurrent events (ICE's) and strategies:

1. Treatment changes (i.e., interruptions, non-adherence, dose changes, discontinuation): "treatment policy" – i.e., treatment changes will be ignored, and all data collected will contribute to the analysis regardless of whether these follow such ICE's.

2. COVID-19: "treatment policy" – i.e., impact of COVID-19 pandemic will be ignored, and all data collected will contribute to the analysis regardless of whether these follow such ICE's.

E. Population-level summary:

Cumulative rate of persistent vision loss

#### 4.2.2.2. Vision Analysis Method

Time-to-vision loss is defined as the time to the first occurrence of BCVA ≥ 15 letters loss from Baseline in 2 or more consecutive visits for the ITT population. Subjects without vision loss event are censored at the last assessment of BCVA prior to the end of the study, or at the randomization if no post baseline BCVA assessment is available.

Time-to-event analysis will be conducted using Kaplan-Meier method with a log-rank test and a Cox proportional hazards regression model with the hazard ratio and associated two-sided 95% confidence interval. Statistical significance of testing with the p-value from the log-rank test will be used in the hierarchical testing procedure.

#### 4.2.2.3. Sensitivity Vision Analyses

Recognizing that time-to-vision loss analysis depends on the thresholds of the loss of ETDRS letters, the following sensitivity analyses on different thresholds will be performed:

- Sensitivity vision loss thresholds: BCVA ≥ 10 or 20 letters loss from Baseline at 2 or more consecutive visits

Similar analyses using time-to-first event will be used.

#### 4.2.2.4. Supportive Vision Analyses

In addition, the following analyses will be conducted.

- Vision loss thresholds: BCVA ≥ 10, 15 or 20 letters loss from Baseline in at least one visit. Similar analyses using time-to-first event will be used.
- Vision loss as a categorical response (BCVA ≥15 letters of loss from Baseline) at Month 24. Statistical test (Chi-squared) will be conducted.

### 4.2.3. Other Secondary Endpoints

#### 4.2.3.1. Mean change in best corrected visual acuity (BCVA in ETDRS letters) from Baseline to Month 24.

ACP 2mg vs. Sham will be compared using MMRM model with change from Baseline as the response, with visit, treatment, and treatment by visit interaction as fixed effects, subject as random effect using the ITT population. Treatment groups include ACP 2mg and Sham in the ITT population.

#### 4.2.3.2. Mean change in low luminance best corrected visual acuity (LL BCVA in ETD RS letters) from Baseline to Month 24.

The endpoint will be analyzed similarly as in the BCVA described above with change from Baseline of LL BCVA as the response variable.

#### 4.2.3.3. [redacted]

CCI

[redacted]

#### 4.2.3.4. [redacted]

CCI

[redacted]

## 4.3. Safety Analyses

All safety analyses will be performed on the Safety population and Re-randomized population. The analyses will be conducted according to the treatment that they received. However, subjects who have ever received an injection of ACP will be analyzed in the ACP group. Missing values of safety data will not be imputed, and safety summaries will be based on the observed cases.

### 4.3.1. Extent of Exposure

Exposure to study medication will be evaluated for each treatment group with respect to treatment duration (= Last injection date - First injection date + 30, in days), number of subjects treated at each planned visit, total injections received, using descriptive statistics (N, mean, standard deviation, median, minimum, Q1, Q3, maximum).

### 4.3.2. Adverse Events

Adverse events (AEs) will be recorded starting after the first dose of study drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later. Treatment-emergent AEs (TEAE) will be used and be evaluated for each treatment group.

All AEs will be coded using MedDRA (version 25.1 or latest) terms.

- An overview of TEAEs will be provided. In addition, the number and percentage of patients with TEAEs will be tabulated for each treatment group and in total by system organ class (SOC) and preferred term (PT). The number and percentage of the subjects who experienced at least one TEAE will be included. Subjects will only be counted once for each preferred term. In case that a subject experienced the same event more than once, the worst severity will be presented.
- Tabular summaries of the following AEs will be provided by SOC and PT:
  - Summary of TEAEs
  - Summary of TEAE of special interest (AESI)
  - All TEAEs regardless of the relationship to study treatment
  - All TEAEs regardless of the relationship to study treatment with frequency of ≥ 5% in any treatment arm.
  - TEAEs related to study treatment
  - TEAEs related to injection procedure
  - TEAEs by the maximum severity grade
  - TEAEs related to study treatment by the maximum severity grade
  - TEAEs related to injection procedure by the maximum severity grade

  - Ocular TEAEs by study eye and fellow eye
  - Treatment related Ocular TEAEs by study eye and fellow eye
  - Injection procedure related Ocular TEAEs by study eye and fellow eye
  - Ocular TEAEs (study eye) by the maximum severity grade
  - Treatment related Ocular TEAEs (study eye) by the maximum severity grade
  - Injection procedure related Ocular TEAEs (study eye) by the maximum severity grade
  - TEAEs with high level term of cataract conditions by study eye and fellow eye
  - TEAEs leading to discontinuation of study drug
  - Treatment related TEAEs leading to discontinuation of study drug
  - Injection procedure related TEAEs leading to discontinuation of study drug
  - Ocular TEAEs (study eye) leading to discontinuation of study drug
  - TEAEs leading to death
  - Treatment related TEAEs leading to death
  - Injection procedure related TEAEs leading to death
- All AEs, including non-TEAEs, will be included in individual subject listings.
  - The listings will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, onset before injection, after first injection or after second injection, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study medication/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/not resolved/fatal).
  - The same listings will be provided separately for severe AEs, AEs leading to permanent discontinuation of the study treatment, and for AEs leading to death.

### 4.3.3. Serious Adverse Events

Treatment-Emergent Serious adverse events (SAEs) will be summarized by system organ class and preferred term. The number and percentage of the subjects who experienced at least one SAE will be included.

SAE data will be evaluated for each treatment group.

Tabular summaries of the following SAEs will be provided:

- All SAEs regardless of the relationship to study treatment
  - related to study treatment
  - related to injection procedure
- Ocular SAEs (study eye) regardless of the relationship to study treatment
  - related to study treatment (SE)
  - related to injection procedure (SE)

In addition, separate listings will be created for deaths and all SAEs. List for SAEs will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, onset before injection, after first injection, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study medication/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/not resolved/fatal).

**Vital Signs**

Descriptive statistics at each time point up through and including the Month 24 visit will be used to display the changes from Baseline for pulse and blood pressure (systolic and diastolic). Mean change of pulse and blood pressure (systolic and diastolic) from Baseline to the last measurement will be provided.

### 4.3.5. Ophthalmic Variables

**Ophthalmic Examination.** The following ophthalmic examination variables will be analysed by shift table from Baseline to the pre-injection examination on Month 24 or last visit available whichever comes later (normal/abnormal, unless otherwise specified below).:

- Examination of the motility
- Inspection of the lids/lacrimal/lashes
- Examination of the conjunctiva/sclera
- Inspection of the cornea
- Examination of the iris
- Examination of the pupils
- Inspection of the lens status (aphakic, pseudo-phakic, phakic; if phakic, nuclear/PSC/cortical 0, 1, 2, 3, 4), including a listing of subjects with a change in lens status for study eye and (separately) for fellow eye
- Examination of the posterior vitreous detachment
- Inspection of the optic nerve
- Inspection of the macula
- Examination of the retinal vessels

The following ophthalmic examination variables will be analysed by shift table from Baseline through Month 24 or last visit available whichever comes later, on a monthly basis (normal/abnormal, unless otherwise specified below), and from pre-injection to post-injection at each monthly injection

- Examination of the anterior chamber activity: Cells (0, trace, 1+, 2+, 3+, 4+)
- Inspection of the vitreous haze (0, 1+, 2+, 3+, 4+)
- Examination of the vitreous haemorrhage

- Examination of peripheral retina

**Intraocular Pressure.** IOP will be summarized by visit, including all pre-injection, "IOP after first injection", and "IOP after second injection" measurements for applicable visits. An additional tabular summary of the percentage of subjects in categories of IOP will be presented by treatment group, visit, and injection time (pre-injection, IOP after first injection, IOP after second injection).

"IOP after injection" is defined as the IOP measurement that is closest in time to the protocol-specified post-injection timepoint (but at least 30 minutes post-injection). If there are two closest measurements equidistant to this timepoint, then the measurement after the protocol-specified timepoint will be used.

Mean IOP over time of all scheduled measurements (pre-injection, IOP after first injection, and IOP after second injection) will be plotted.

### 4.3.6. Clinical Laboratory

All laboratory data will be listed and values falling outside normal ranges will be identified, whether they will be deemed clinically relevant or not.

Laboratory data will also be summarized in tables presenting values at each scheduled visit up through the Month 24 visit.

Value changes from Baseline to each scheduled visit up through the Month 24 visit.

A summary table of all analytes with the Baseline mean and the mean change from Baseline to the last value observed.

A summary table of all analytes with the Baseline median and the median change from Baseline to the last value observed.

The following parameters will be summarized:

- Hematological parameters (hemoglobin, white blood cells, platelets, neutrophils (absolute numbers), lymphocytes (absolute numbers), monocytes (absolute numbers), eosinophils (absolute numbers), basophils (absolute numbers)),
- Renal function parameters (serum creatinine and BUN),
- Hepatic function parameters (serum bilirubin, alkaline phosphatase, GGT, SGOT/AST, and SGPT/ALT),
- Electrolytes (sodium, potassium, chloride, carbon dioxide, calcium, and phosphate),
- Complete urinalysis parameters (complete urinalysis including specific gravity, protein, blood, etc.),
- Serum pregnancy test (if of child-bearing potential).

Additional urine or serum pregnancy testing may be performed during the study at the discretion of the investigator, or in accordance with local requirements or regulations.

The incidence of subjects with "Notable Laboratory Values" after the first dose of study drug will be evaluated using the criteria for Notable Laboratory Values given below. Only data

collected after the first dose of study drug, up to the laboratory data taken at the Month 18 visit or 30 days after last dose will be included.

Subject listings of all notable laboratory values will also be provided; for each subject who has an analyte with a notable value, all values of that analyte taken during the study will be presented in the listing, and the notable value, and any values outside of normal limits, will be identified.

For this "Notable Laboratory Values" analysis, *all* laboratory values after randomization will be taken in account, i.e., any values obtained after Day 1, at unscheduled visits, as well as values from the regularly scheduled laboratory visit at Month 18. Three Notable Laboratory Values tables and accompanying subject listings will be presented: (1) notable abnormalities for subjects with normal Baseline results, (2) notable abnormalities for subjects with abnormal Baseline results and (3) notable abnormalities without regard to Baseline abnormalities (i.e., normal, or abnormal Baseline results). The table without regard to Baseline abnormalities will be a composite of the previous two tables (normal Baseline, abnormal Baseline).

Lab analytes and primary criteria used for Notable Laboratory Values:

a. HEMATOLOGY
    i. Hemoglobin < 0.75x Baseline
    ii. Platelets < 75 or > 750 (10^9/L)
    iii. WBC count < 2.5 or > 17.5 (10^9/L)
    iv. Neutrophils (absolute) < 0.5xLLN or > 1.5xULN
    v. Eosinophils (absolute) >1.5xULN
    vi. Lymphocytes (absolute) < 0.5xLLN or >1.5xULN
b. LIVER FUNCTION
    i. Total bilirubin > 1.5xULN
    ii. Alkaline phosphatase > 1.5xULN
    iii. ASAT (SGOT) > 3xULN
    iv. ALAT (SGPT) > 3xULN
    v. GGT > 3xULN
c. RENAL FUNCTION
    i. UN > 1.3xULN
    ii. Creatinine > 1.3xULN
d. ELECTROLYTES
    i. Potassium < 0.9xLLN or > 1.1xULN
    ii. Sodium < 0.9xLLN or > 1.1xULN
    iii. Chloride < 0.9xLLN or > 1.1xULN
    iv. Bicarbonate < 0.9xLLN or > 1.1xULN

v. Calcium < 0.9xLLN or > 1.1xULN

vi. Phosphate < 0.9xLLN or > 1.1xULN

Notable abnormalities for subjects with abnormal Baseline results are subject to the primary criteria above and the following secondary criteria:

a. HEMATOLOGY

i. Hemoglobin < 0.75x Baseline (same as primary criterion)

ii. Platelets < 0.75x Baseline or > 1.25x Baseline

iii. WBC count < 0.75x Baseline or > 1.25x Baseline

iv. Neutrophils (absolute) < 0.5x Baseline or > 1.5x Baseline

v. Eosinophils (absolute) > 1.5x Baseline

vi. Lymphocytes (absolute) < 0.5x Baseline or >1.5x Baseline

b. LIVER FUNCTION

i. Total bilirubin > 1.5x Baseline

ii. Alkaline phosphatase > 1.5x Baseline

iii. ASAT (SGOT) > 1.5x Baseline

iv. ALAT (SGPT) > 1.5x Baseline

v. GGT > 1.5x Baseline

c. RENAL FUNCTION

i. UN > 1.3x Baseline

ii. Creatinine > 1.3x Baseline

d. ELECTROLYTES

i. Potassium < 0.9x Baseline or > 1.1x Baseline

ii. Sodium < 0.9x Baseline or > 1.1x Baseline

iii. Chloride < 0.9x Baseline or > 1.1x Baseline

iv. Bicarbonate < 0.9x Baseline or >1.1x Baseline

v. Calcium < 0.9x Baseline or >1.1x Baseline

vi. Phosphate < 0.9x Baseline or > 1.1x Baseline

### 4.3.7. ECG

ECG results will be tabulated as “normal” or “abnormal” at each visit and will be presented in a normal/abnormal shift table between Baseline and each scheduled ECG visit, as well as between Baseline and the last ECG taken. Descriptive statistics will be presented for continuous variables (e.g., heart rate and RR, PR, QRS, QT, QTcB, and QTcF intervals) at each visit. A by-patient listing will be provided for ECGs which are deemed abnormal.

## 4.4. Other Analyses

### 4.4.1. Subgroup

The following subgroups are defined. Analyses on subgroups are considered as exploratory.

Baseline VA (< 50 vs. ≥ 50 ETDRS letters), Baseline GA (< 4 vs. ≥ 4 disc area), Pattern of FAF at the junctional zone of geographic atrophy (none/focal vs. banded/diffuse) as well as age (<65 vs. 65~74 vs. 75~84 vs. ≥85), gender (male vs. female), race (American Indian/Alaska Native vs. Black or African American vs. Asian vs. Native Hawaiian/Pacific Islander vs. White vs. Other), and ethnicity (Hispanic or Latino vs. Not Hispanic or Latino).

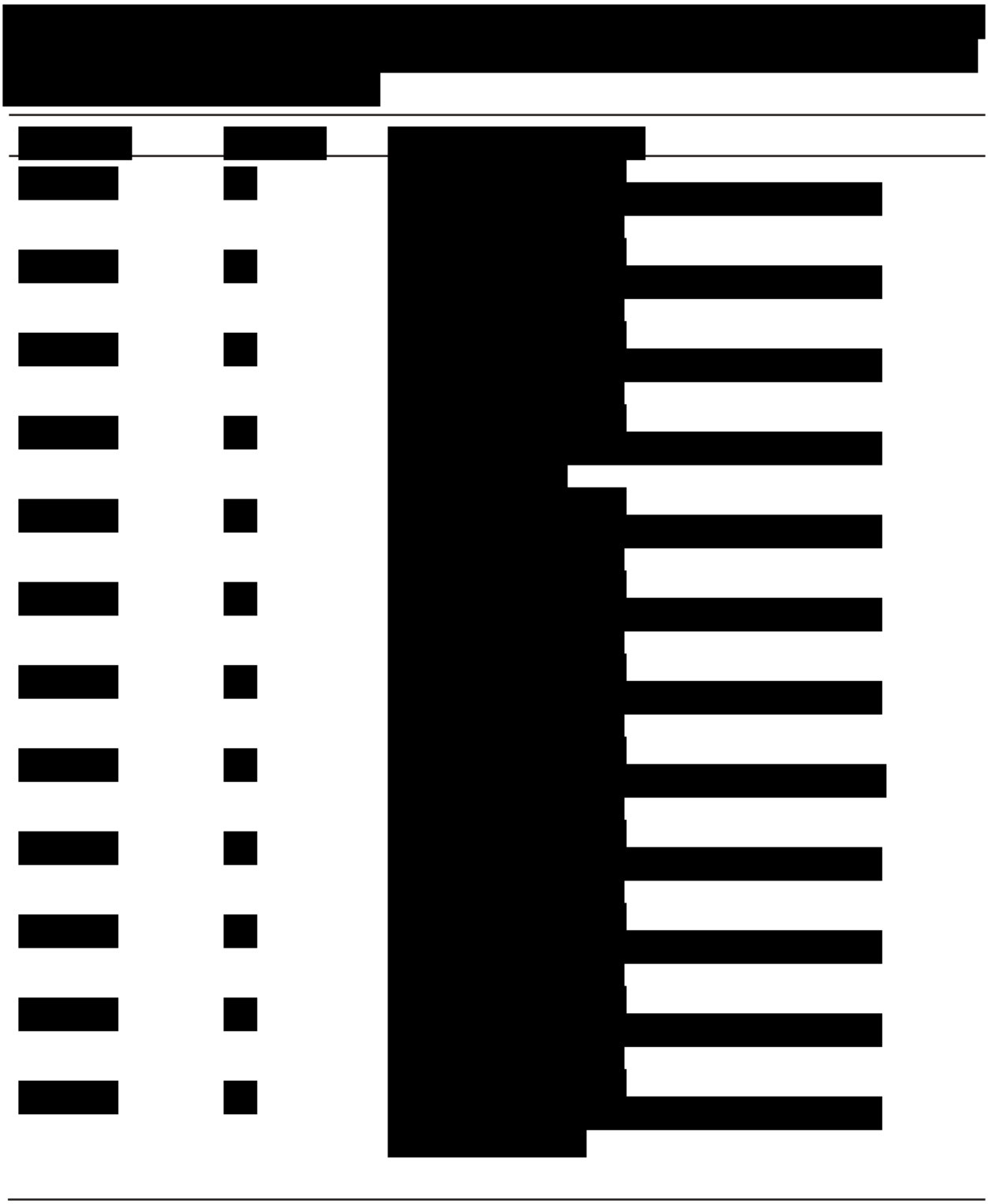
## 4.5. Changes to Protocol-planned Analyses

The following changes are made from protocol planned analyses:

- Time to vision loss analysis based on BCVA was added after primary analysis on Year 1
- GA growth rate without square root transformation
- Piece-wise analysis by every 6-month interval on GA growth rate

# 5. Supporting Documentation

## 5.1. [redacted] CCI



[redacted]

## 5.2. Statistical Analysis Plan Addendum for Cumulative Year 2 Data

Cumulative ISEE2008 year 2 data will be analyzed in a similar way as year 1 data with the following changes.

The data will be summarized in 4 groups: Sham, ACP every month (EM), ACP every other month (EOM), ACP overall. ACP overall group will include patients who discontinued from the study in year 1.

If the primary analysis testing GA growth rate (ACP vs Sham) based on year 1 data is statistically significant, the following ranked hypotheses tests will be performed in a sequential way to control familywise type I error rate with 2-sided significance level of 0.05 using similar MMRM specified in year 1 SAP without the stratifications factors. A test will be performed only if all the preceding tests are statistically significant.

1. Mean GA growth rate of ACP EM is lower than Sham based on GA area measured by FAF in 5 time points: baseline, month 6, month 12, month 18 and month 24.

2. Mean GA growth rate of ACP EOM is lower than Sham based on GA area measured by FAF in 5 time points: baseline, month 6, month 12, month 18 and month 24.

3. Mean change in best corrected visual acuity (BCVA in ETDRS letters) from Baseline to Month 24 in ACP is different from Sham based on monthly data from month 1 to month 24.

4. Mean change in low luminance best corrected visual acuity (LL BCV A in ETD RS letters) from Baseline to Month 24 in ACP is different from Sham based on change from baseline data from the following 4 time points: month 6, month 12, month 18 and month 24.

5. [redacted]

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