Official Study Title: A Phase 2/3 Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura™ (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration

NCT#: NCT02686658

Document: Statistical Analysis Plan

Document Date: 19 July 2019

STATISTICAL ANALYSIS PLAN

SPONSOR:	OPHTHOTECH
PROTOCOL TITLE:	[redacted] RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ASSESS THE SAFETY AND EFFICACY OF INTRAVITREOUS ADMINISTRATION OF ZIMURA™ (ANTI-C5 APTAMER) IN SUBJECTS WITH GEOGRAPHIC ATROPHY SECONDARY TO DRY AGE-RELATED MACULAR DEGENERATION
STUDY CODE:	OPH2003
VERSION:	Version 1.0
DATE:	19 July 2019

The undersigned certify that they have read, reviewed and approved this document.

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CNV	Choroidal Neovascularization
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
GEE	Generalized Estimating Equations
GGT	Gamma-glutamyl Transferase
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ITT	Intention-to-Treat
LLN	Lower Limit Normal
LOCF	Last Observation Carried Forward
MAR	Missing at Random
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MRM	Model for Repeated Measures
NA	Not Available / Not Applicable
OU	Oculus Uterque (Both Eyes)
PK	Pharmacokinetic
PP	Per-Protocol
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
[redacted]	[redacted]
WBC	White Blood Cells
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

1 INTRODUCTION

This Statistical Analysis Plan describes the statistical methodology and data handling for the clinical trial with Protocol Number: OPH2003 and Version Date: 28 March 2018.

The trial consists of a total treatment period of 18 months. This SAP covers all analyses to be performed on the 1 year data. By pre-specification, a [redacted] screening analysis will be performed to assess whether the effect of Zimura on the rate of Geographic Atrophy (GA) growth is plausibly more efficacious (or reliably more efficacious) than that of the sham control on the rate of GA growth over 12 months. Details of an analysis at 18 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.

2 STUDY DESIGN AND OBJECTIVES

2.1 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy of Zimura™ monotherapy intravitreous administration when administered in subjects with geographic atrophy secondary to dry age-related macular degeneration (AMD).

2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12

2.1.2 Secondary Efficacy Endpoints

Two secondary endpoints are pre-specified:

- The mean change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from Baseline to Month 12
- The mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 12

2.1.3 [redacted]

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2.1.5 Safety Endpoints

The following safety endpoints will be evaluated:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Vital signs (pulse, systolic and diastolic blood pressure)
- Ophthalmic findings (Intraocular Pressure [IOP], ophthalmic examination, fluorescein angiograms, and FAF)
- Electrocardiogram (ECG) (12-lead)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)

2.2 STUDY DESIGN AND SAMPLE SIZE

[redacted] Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreous Administration of Zimura (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration.

In Part 1, subjects will be randomized in a 1:1:1 ratio to the following dose groups:

- Zimura 1 mg/eye
- Zimura 2 mg/eye
- Sham

In Part 2, subjects will be randomized in a 1:2:2 ratio to the following dose groups:

- Zimura 2 mg/eye + Sham
- Zimura 4 mg/eye (administered as two injections of Zimura 2 mg/eye)
- Sham + Sham

Subjects will receive monthly intravitreal injections of Zimura and/or Sham for 18 months.

The sample size determination for this study is based on [redacted] screening methodology presented in Fleming and Richardson (2004). The power calculations are based on the recently released results from a clinical trial of a complement inhibitor, including the estimated precision of the estimated effects on rate of GA growth over 12 months, and including the plausible effect size for Zimura.

In Part 1, approximately 77 subjects are randomized to Zimura 1 mg vs. Zimura 2 mg vs. Sham control, in a 1:1:1 allocation. In Part 2, approximately 200 subjects are randomized to Zimura 2 mg vs Zimura 4 mg vs Sham control, in a 1:2:2 allocation. A total of approximately 277 subjects are to be randomized.

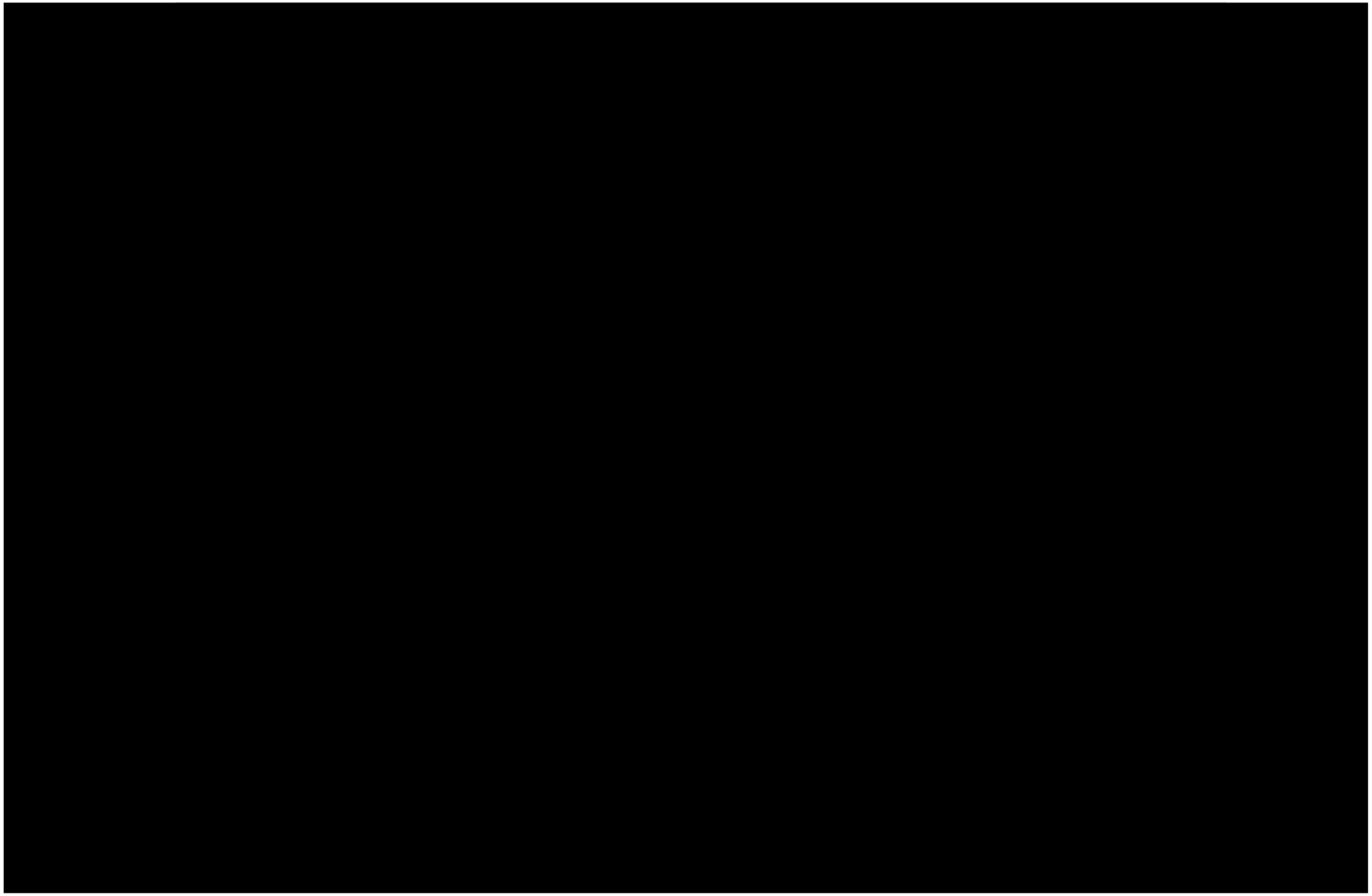
2.3 RANDOMIZATION

Subjects will be centrally allocated to one of the three treatment groups stratified by factors known to be of prognostic importance in dry AMD:

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

3 GENERAL ANALYSIS DEFINITIONS

[redacted]



3.2 DEFINITION OF POPULATIONS

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

3.2.1 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, irrespective of the dose actually received. Subjects will be analyzed in the treatment group assigned at randomization. Subjects will be included in a particular analysis, for a particular population, if relevant data is available for analysis (e.g., the primary analysis will require both Baseline and at least one post-Baseline GA measurement, to calculate a change score).

3.2.2 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.

3.2.3 Safety Population

The safety population will include all subjects who received at least one study drug. In the event that subjects receive a dose that differs from the one assigned according to the randomization schedule, safety analyses will be conducted according to the dose actually received rather than according to the dose assigned by randomization. However, subjects who have ever received an injection of Zimura during this trial will be analyzed in the appropriate Zimura group according to the actual injections received.

3.3 DEFINITION OF SUBGROUPS

Forest plots will be used to display the primary efficacy results 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)
- Subjects from Part 1 vs. Part 2.

3.4 DATA HANDLING CONVENTIONS

3.4.1 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 (2 mg), Zimura (4 mg), 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, Unscheduled Visit pages, etc.).

3.4.2 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 **Appendix 1**.

3.4.3 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 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 7.6.1.

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.

3.4.4 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.

3.4.5 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.

[redacted]

[redacted]

4 STUDY SUBJECTS

4.1 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 frequency of premature discontinuations from the study treatment prior to Month 12 will be given by treatment arm and overall. The details of the 'Non-fatal 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 populations by treatment arm and overall. The primary reason for non-completion of the study will be summarized.

4.2 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 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 Zimura will be included in the applicable Zimura group based on actual injections received.

4.3 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 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.

4.4 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.

5 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 ETDRS, 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 (mm2)
- Fluorescein angiogram (FA) imaging assessment, both eyes
    - Evidence of CNV

6 PRIOR AND CONCOMITANT MEDICATION

- All prior and concomitant medications will be summarized separately by WHO Drug code (WHO Drug Dictionary version B2 enhanced March, 2016) on the ITT population. Medication usage will be summarized according to the 2nd level (main therapeutic level) and the 4th level (preferred term level) Anatomic Therapeutic Chemical (ATC) classification. Subjects will only be included once in the summaries within each ATC 2nd level or ATC 4th level category. The summaries will include the number and percentage of all Subjects with at least one prior or concomitant medication, respectively.

7 EFFICACY EVALUATION

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

The analyses will be based on comparisons of Zimura 2 mg vs. the Sham control, and Zimura 4 mg vs. Sham control. For the comparison of Zimura 2 mg vs. Sham control, the subjects randomized from Part 1 will be combined with the subjects randomized to from Part 2, where the analysis will be stratified by Part 1 vs. Part 2. The comparison of Zimura 4 mg vs. Sham control will only based on subjects randomized in Part 2.

The primary analysis will use the ITT population and will be based on a Model for Repeated Measures (MRM) 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 7.6) will be performed to assess the potential magnitude and direction of the impact of missing data. Although Zimura 1 mg dose is not of an interest, a

descriptive analysis for a treatment effect of Zimura 1 mg dose vs. Sham control will be conducted in a supportive manner.

The primary analysis [redacted] for each of the two pairwise comparisons of an active dose of Zimura vs the Sham control is formally based on a three-category decision guideline. The decision guideline for this trial is based on whether the estimated mean reduction in rate of square root of GA area growth over 12 months for a dose of Zimura versus Sham control is less than 14%, is from 14% up to 24.5%, or is at least 24.5%. These numbers may be adjusted based on the final sample size and standard deviation.

1. If the estimated reduction in the rate of GA growth over 12 months for a dose of Zimura vs. Sham control is less than 14%, then this dose of Zimura is not plausibly more efficacious than the Sham control; its utility in this indication should be reconsidered.
2. If the estimated reduction in the rate of GA growth over 12 months for a dose of Zimura vs. Sham control is from 14% to up to 24.5%, then this dose of Zimura is plausibly more efficacious than the Sham control and should be evaluated in a subsequent Phase 3 clinical trial.
3. If the estimated reduction in the rate of GA growth over 12 months for a dose of Zimura vs. Sham control is at least 24.5%, then this dose of Zimura would be statistically significantly more effective than the Sham control, with strength of evidence meeting the standard requirement of a 0.0125 one-sided false positive error rate (incorporating an adjustment for multiplicity arising from comparing each dose with the Sham control).

Note that these categories should not be interpreted as providing strict decision rules but rather as guidelines that will be factored into a broader scientific assessment of the benefit to risk profile of the Zimura dose regimen.

7.1 CONTROL OF ALPHA

The overall (one-sided) false positive error rate in this trial, accounting for the conduct of two pairwise comparisons (2 mg and 4 mg) with Sham control, is 0.025 for the analysis of the primary endpoint. The actual test of each dose *vs.* sham will use a Hochberg procedure for significance testing.

An analysis of secondary endpoints will be carried with a descriptive intent only, without alpha-adjustment.

7.2 ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at three time points: Baseline, Month 6, and Month 12. 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.

For analyses of the primary endpoint, a Mixed-Effects Repeated Measures (MMRM) model will be used to assess the differences between the treatment groups in rate of change of GA area over 12 months. Two separate models will be fitted for comparing Zimura 4 mg vs. Sham control, and Zimura 2 mg vs. Sham control. Both models will be fitted by using restricted maximum likelihood (REML) and include Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. For Zimura 2 mg vs. Sham control model, fixed effects will include treatment, visit, part (Part 1 vs. Part 2), the Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), pattern of FAF at the junction zone of GA (none/focal vs. banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions. For Zimura 4 mg vs. Sham control model, the same fixed effects will be used excluding part (Part 1 vs. Part 2). An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The test of the mean rate of change over 12 months will be assessed by testing the appropriate contrast of the model parameter estimates.[redacted]

[redacted]

In addition to the analyses described above, a similar analysis will be conducted using the observed GA area measurement.

The analyses described above will also be repeated in a supportive manner for the PP population.

7.3 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

Two secondary efficacy endpoints are pre-specified:

- Mean change in best corrected visual acuity (ETDRS letters) from Baseline to Month 12
- Mean change in low luminance best corrected visual acuity (ETDRS letters) from Baseline to Month 12

Secondary efficacy analysis will be conducted for ITT population for these pre-specified secondary endpoints. The analyses described above will also be repeated in a supportive manner for the PP population.

Descriptive tables will be provided for secondary endpoints based on the observed data, but due caution will be exercised in interpreting descriptive tables because of the potential impact of missing data. Sensitivity analyses of the secondary endpoints will also be performed (see Section 7.6).

Any hypothesis testing performed as part of analyzing secondary efficacy endpoints will be considered exploratory.

For analyses of the secondary endpoints, a Model for Repeated Measures (MRM) will be used to assess the differences between the treatment groups at month 12 visit. The model will be fitted by using restricted maximum likelihood (REML). The model will include Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse) as used in the randomization as covariates. Fixed effects will include treatment, visit, part (Part 1 vs. Part 2), the Baseline VA (< 50 letters vs. ≥ 50 letters), size of the Baseline GA (< 4 disc area vs. ≥ 4 disc area), pattern of FAF at the junction zone of GA (none/focal vs. banded/diffuse), treatment by visit interaction, and the stratification factors by visit interactions for Zimura 2 mg vs. Sham control model. For Zimura 4 mg vs. Sham control model, the same fixed effects will be used excluding part (Part 1 vs. Part 2). An unstructured (co)variance structure will be used to model the within-subject errors. If this analysis fails to converge, alternative structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on appropriate treatment contrasts at month 12.

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7.4 [redacted]

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7.5 [redacted]

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[redacted]

7.5.1 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).

The proportions (%) of subjects gaining/losing $\geq$ 10 points in score for the 4 pre-specified sub-scales, as well as the composite score, will be tabulated by visit and by treatment group using the observed cases (missing values will not be imputed).

Change in mean score from Baseline over time will be plotted by visit and by treatment group.

[redacted]

7.6 SENSITIVITY ANALYSES

7.6.1 Sensitivity analyses for the primary analysis

For the analyses of the primary endpoint, the Model for Repeated Measures (MRM) 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.

To check the sensitivity of the results of the primary efficacy analysis 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 than for the observed responses (implying that the missing values are more likely corresponding to smaller changes vs. Baseline than the observed ones). Different values of the shift will be explored to investigate the sensitivity of the results. Scenarios with treatment-dependent shift values will also be explored. This approach can be applied to data with arbitrary missing data patterns.

2. The "pattern-mixture-model imputation" approach: missing values at Month 12 visit will be imputed by using the pattern-mixture-model restrictions. In particular, Neighbouring-Case Missing Value (NCMV) restrictions will be applied.

In addition to these two analyses, 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 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);
3. the average of observed means from the active arm and the sham arm will be imputed to all patients with missing data;
4. the observed mean from the sham arm will be imputed to all patients with missing data.

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

7.6.2 Sensitivity analyses on the secondary endpoints

Sensitivity analyses on the secondary endpoints will also be performed using different methods of data imputation for missing values at a particular visit if applicable, namely 1) the "shift imputation" approach; and 2) the "pattern-mixture-model imputation" approach.

The latter approach can be applied to data with monotone missing data patterns. Hence, if necessary to apply the approach, the data will be transformed into the monotone patterns by considering the

longest uninterrupted sequences of the measurements for the subjects and/or excluding a few measurement visits from modelling, to increase the number of monotone patterns in the data. In case data are re-shaped, the primary analysis MRM model will be applied to the re-shaped data as well.

7.7 SUBSET ANALYSES

The trial is not sized to test for the presence of treatment by subset interactions. Thus, true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset 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. Clinically meaningful subsets will be looked at, including stratification factors: Baseline visual acuity (< 50 vs. ≥ 50 ETDRS letters), Baseline geographic atrophy (<4 vs. ≥ 4 disc area), Pattern of Fundus Auto Fluorescence at the junctional zone of geographic atrophy (none/focal vs. banded/diffuse).

These analyses will be considered as supportive efficacy analyses and conducted without any alpha-level adjustment.

8 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.

8.1 EXTENT OF EXPOSURE

Exposure to study medication will be evaluated for each treatment group (Zimura 4 mg, 2 mg, and 1 mg) 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).

8.2 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. AE data will be evaluated for each treatment group (Zimura 4 mg, 2 mg, and 1 mg).

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

is later. AEs from the first year will be defined as AEs from the start of the first dose until prior to the first injection at Month 12 or 30 days after the last dose, within the first year as defined above.

The safety analyses on AEs will be primarily based on the Treatment-Emergent Adverse Events (TEAEs), which is defined as an AE occurring after the first injection on Day 1 (day of the first planned dose of study drug) and up to and including 30 days after the last dose of study drug, within the first year as defined above.

All AEs will be coded using MedDRA (the most recent Version 18.1) 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 /unresolved / 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.

8.3 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 (Zimura 4 mg, 2 mg, and 1 mg).
- 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/unresolved/fatal).

8.4 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.

8.5 OPHTHALMIC VARIABLES

Ophthalmic Examination. The following ophthalmic examination variables will be analysed by shift table from Baseline to the pre-injection examination on Month 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 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 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 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. 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 25 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.

8.6 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, bicarbonate, calcium and phosphate), urinalysis parameters (complete urinalysis including specific gravity, protein, blood, etc.).

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 in the first year after the first dose of study drug, up to the laboratory data taken at the Month 12 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) < 0.5x LLN or > 1.5xULN
    v. Eosinophils (absolute) > 1.5xULN
    vi. Lymphocytes (absolute) < 0.5x LLN 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 < 0.75 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

8.7 ECG

ECG results will be tabulated at Baseline as “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”. At follow-up visits, ECG results will be tabulated as “no change from Baseline”, “NOT clinically significant change from Baseline” or “clinically significant change from Baseline”. A by-patient listing will be provided for ECGs which are deemed clinically significant.

Continuous data (heart rate; PR, QRS, QT and QTc intervals) will be summarized using mean, standard deviation, median, minimum and maximum values at each scheduled visit, and change from Baseline at each visit.

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APPENDICES

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