CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA217225
Product Name:	Avacincaptad pegol
Indication(s):	Treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
Applicant:	IVERIC bio, Inc
Dates:	Date Submitted: 12/19/2023 PDUFA Goal Date: 08/19/2023
Review Priority:	Priority
Biometrics Division:	DBIV
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Key words: Age related macular degeneration. Geographic Atrophy. Fundus Autofluorescence.

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1 EXECUTIVE SUMMARY

This is a statistical review of the New Drug Application (NDA) submitted by IVERIC bio, Inc. (Applicant) for the intravitreal (IVT) administration of avacincaptad pegol (Zimura). The proposed indication is for the treatment of adult subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The primary objective of this review is to evaluate whether the safety and efficacy results in the two pivotal Phase 3 studies, OPH2003 and ISEE2008, submitted in this NDA, support the proposed indication.

Study OPH2003 was an 18-month study, and consisted of two parts, Part I and Part 2. In Part 1, 77 subjects were randomized in an approximately 1:1:1 ratio to receive monthly injections with Zimura 1mg, Zimura 2mg or sham. In Part 2, 209 subjects were randomized in a 1:2:2 ratio to receive monthly injections with Zimura 2mg, Zimura 4mg (administered as 2 IVT injections of Zimura 2mg) or sham. Note, for the comparison of Zimura 2mg versus sham, subjects randomized to these two arms in Part 1 and 2 were combined. On the other hand, the comparison of Zimura 4mg versus sham was done using sham subjects randomized to the sham arm in Part 2 only. Per the Applicant, although the Zimura 1mg arm was included in the study, there was no plan to evaluate the efficacy of this dose.

Study ISEE2008 was a 24-month study. This study first randomized 448 subjects in an approximately 1:1 ratio to receive monthly Zimura 2mg or sham monthly injections for 12 months. At Month 12, subjects who were initially randomized to the monthly Zimura 2mg arm were re-randomized in a 1:1 ratio to receive Zimura 2mg administered monthly from Month 12 to Month 23 **or** Zimura 2mg administered every other month at Months 13, 15, 17, 19, 21, and 23. For the later, sham was administered at Months 12, 14, 16, 18, 20, and 22 to ensure masking. Note, subjects who were initially randomized to sham continued to receive monthly sham injections through Month 23. All patients had a final follow-up visit at Month 24.

In both studies, the main efficacy outcome of interest was the total area of GA lesions in the study eye measured by fundus autofluorescence (FAF) images. The protocol defined primary efficacy endpoint in Study OPH2003 was the mean change from baseline in GA area at Month 12 and is estimated as the least squares mean change from baseline based on a mixed effects model for repeated measures (MMRM). For Study ISEE2008, the protocol defined primary efficacy endpoint was the mean rate of GA growth and was estimated as a slope of a linear mixed effects model fitted using GA data collected at Baseline, Month 6 and Month12 (see Section 3.3.2 for details). Note, for this indication, the DOP requests the mean rate of growth (Slope) as a primary efficacy endpoint.

The Applicant's findings for the protocol defined primary efficacy endpoints are presented in Table 1 and Table 2. Both studies met the primary objective of demonstrating the efficacy of Zimura compared to sham. However, the percentage of patients with missing primary outcome data was relatively very high in both studies. Sensitivity analyses to assess the impact of missing data yield consistent findings with the primary analysis. Analyses across various patient subgroups are also presented. Results from these analyses are generally consistent with the primary analysis findings.

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Key secondary endpoints analyzed in this review are best corrected visual acuity (BCVA) and low luminous visual acuity (LL-BCVA). The analysis results for these endpoints provided treatment differences between Zimura and sham that were not statistically significant.

Table 1: Summary of Mean Change from Baseline in Total GA Area at Month 12 (Study OPH2003)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)[c]	
	Zimura 2mg [a] N=67	Sham [a] N=110	Zimura 4mg N=82	Sham [b] N=84	Zimura 2mg vs Sham	Zimura 4mg vs Sham
Mean Change[1]	0.292 (0.077)	0.402 (0.075)	0.321 (0.074)	0.444 (0.072)	0.110 (0.030, 0.190)	0.124 (0.038, 0.209)
Slope[2]	0.283 (0.070)	0.392 (0.068)	0.307 (0.069)	0.416 (0.066)	0.109 (0.031, 0.186)	0.109 (0.027, 0.192)

Source: [1]Table 18 of the Applicant's study report. [2]Table 14.2.1.5 and Table 14.2.1.1 of the Applicant's integrated summary of efficacy (ISE).
[a] Combination of Part 1 and Part 2 patients. [b] Sham from part 2 only. [c] Differecnes are taken as sham-Zimura.

Table 2: Summary of Efficacy at Month 12 (Study ISE2008)

Study	LS mean (SE)		Difference (95% Confidence Interval)[c]
	Zimura 2mg N=225	Sham N=222	
Slope[1]	0.336 (0.032)	0.392 (0.033)	0.056 (0.016, 0.096)
Mean Change[2]	0.333 (0.034)	0.392 (0.035)	0.059 (0.017, 0.100)

Source: [1]Table 14 of the Applicant's study reports. [2]Table 14.2.3.6 of the Applicant's study report. [c] Differecnes are taken as sham-Zimura.

Per the study results, the treatment difference between sham and the Zimura 2mg arm is roughly 50% lower in Study ISEE2008 compared to Study OPH2003. This appears mainly because of the difference in the growth rate in subjects treated with Zimura 2mg arms across the two studies. Subjects treated with Zimura 2mg in Study OPH2003 appear to have slower GA growth rate compared to similar subjects in Study ISEE2008. There does not appear to be notable difference in the demographic characteristics of age, sex and ethnicity among subjects randomized to the Zimura 2mg arms across the two studies. However, differences in some baseline and disease characteristics, missing data and treatment compliance rates were observed. Therefore, the difference in GA progression across the Zimura 2mg arms of the two studies could be partly attributed to the differences discussed above.

Regarding safety, a higher percentage of subjects in the Zimura arms of both studies reported at least one ocular adverse event compared to the corresponding subjects in the sham arms. The most frequently reported ocular adverse events in subjects randomized to the Zimura arms were conjunctival hemorrhage, conjunctival hyperemia, punctate keratitis, choroidal neovascularization (CNV) and visual acuity reduced. In addition, in both studies, a higher percentage of subjects discontinued the Zimura arms compared to the sham arm. In the two studies combined, 8 deaths, 6 of which were in the Zimura arms, are reported. Note, based on the drug exposure summary (See Section 3.3.1), approximately between 60-71% of the subjects randomized to the Zimura arms received the total allowed 12 injections during the 12-month period. Therefore, it is possible that the actual annual incidence of adverse events with a full treatment regimen might be higher.

In conclusion, the results of the primary efficacy analyses in the two pivotal studies demonstrated the efficacy of Zimura for the treatment of GA secondary to AMD. Because the incidence of adverse events was higher in the Zimura arms compared to sham, the final determination for the approval of this drug should be made based on the totality of evidence taking the potential safety issues into account.

2 INTRODUCTION

This is a statistical review of the NDA submitted by IVERIC bio, Inc., referred to as the Applicant on November 3, 2022, for intravitreal (IVT) avacincaptad pegol (Zimura). The proposed indication is for the treatment of GA secondary to AMD. The primary evidence of efficacy and safety for this NDA comes from two pivotal Phase 3 studies (OPH2003 and ISEE2008). The two studies were conducted across multiple sites located in the US, France, Germany, Italy, Spain, Croatia, Czech Republic, Estonia, Hungary, Israel, and Latvia. Study OPH2003 enrolled 286 subjects in 63 study sites while Study ISEE2008 enrolled 448 subjects in 205 sites.

The Applicant proposes to include findings from Study OPH2003 and Study ISEE2008 into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of intravitreal (IVT) avacincaptad pegol in the treatment of adult patients with GA secondary to AMD. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology Products (DOP) if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant's summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

Per the Applicant, Avacincaptad pegol is an inhibitor of complement activation that acts by binding to human complement component 5 (C5) with high affinity and specificity. Per the Applicant, given the natural history and long-term course of GA associated with AMD, there is a substantial medical need for new therapies that target the underlying cause and progression of the disease. To this end, the Applicant is developing Zimura for the treatment of GA secondary to AMD.

2.1.2 History of Drug Development

The protocols (original and amendments) and the statistical analysis plans (SAPs) for Studies OPH2003 and ISEE2008 were reviewed under IND77902. The Applicant had a series of discussions with the DOP to reach agreement on the development program for IVT Zimura. The summary of the relevant interactions between the Applicant and the DOP are provided below:

- On 09/29/2015, the Applicant had an end-of-phase 2 (EOP 2) meeting with the Division. As part of the meeting package, the statistical analysis plan (SAP) for Study OPH2003 was submitted. After the review of the submission, DOP requested clarification on the primary efficacy analysis, and provided several comments on the proposed 12-month interim analysis including, alpha level, handling of missing data, and sensitivity analyses. For example, the Division recommended the primary endpoint to be the mean

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rate of change over a 12 month or more period as opposed to the Applicant's proposed (b) (4). The Applicant accepted the Divisions recommendation.

- On 04/07/2021, the Applicant submitted a special-protocol assessment (SPA) for their confirmatory study, Study ISEE2008. The submission included the protocol and SAP of this study. The Division determined that the proposed study design and analysis, as was presented in the SAP, did not adequately address the objectives necessary to support a regulatory submission and issued a no-agreement letter to the Applicant. Specifically, the Division disagreed with the Applicant's proposed primary efficacy endpoint, (b) (4) The Division recommended the Applicant to use the mean rate of growth (slope) estimated based on GA area measured in at least 3 time points as the primary efficacy endpoint. In addition, the Division recommended that appropriate statistical adjustments should be taken for any looks at the data, not just for looks at efficacy and safety.

- On 05/24/2021, the Applicant submitted a second SPA for Study ISEE2008. The Applicant has incorporated the recommendations provided to them following the prior review of the SAP for this study. Specifically, they defined the primary endpoint as the mean rate of GA growth (Slope) at Month 12. After the review of the revised protocol and SAP, the Division agreed that the design and planned analysis of the study adequately address the objectives necessary to support a regulatory submission and issued SPA agreement letter. The Division advised the Applicant that if they made any changes to this protocol, this agreement may be invalidated.

- On 06/16/2022, the Applicant had a Type B Pre-NDA meeting with the DOP to discuss the format and content of their planned NDA. The Division agreed to the proposed format and content of the NDA.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary for the protocol defined primary efficacy endpoints, the mean change from baseline in total GA area at Month 12 for Study OPH2003 and the mean rate of GA growth (Slope) for Study ISEE2008, is presented in Table 3.

Table 3: Efficacy Summaries of OPH2003 and APL2-304

Design	Treatment (Sample size)	Endpoint/Analysis	Applicant's findings
OPH2003 [1] RD, DM, SC	**Part 1:** • Zimura 1mg (N=26) • Zimura 2mg (N=25) • Sham: (N=26) **Part 2:** • Zimura 2mg: (N=42)	**Primary Endpoint**: Mean rate of change from baseline in total area of GA lesion(s) in the study eye at Month 12. The primary efficacy analysis provided the least squares (LS) mean difference in mean change from baseline at Month 12	The study **met** its primary objective of demonstrating the statistical superiority of the two dose levels of Zimura against sham. The reduction in the mean rate of GA growth over 12 months was 27.38% (p=0.0072) for the combined Zimura 2mg group compared with its corresponding combined Sham group and 27.81%

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	• Zimura 4mg: (N=83) • Sham: (N=84)	in GA area between treatment arms and a 2-sided 95% CI using a MMRM based on the intent to treat population (ITT). Multiplicity was controlled for the primary endpoint using the Hochberg procedure.	(p=0.0051) for the Zimura 4mg group compared with its corresponding Sham group, both meeting the pre-specified significance level incorporating an adjustment for multiplicity arising from comparing each dose with their corresponding Sham groups.
ISEE2008 [1] RD, DM, SC	• Zimura 2mg: (N=225) • Sham: (N=222)	**Primary Endpoint**: Mean rate of growth (slope) estimated based on GA area measured by FAF at 3 time points: Baseline, Month 6, and Month 12 (square root transformation). The primary efficacy analysis provided the least squares (LS) mean difference between Zimura 2mg and the sham group and its two-sided CI using a MMRM based on the intent to treat population (ITT).	The study **met** its primary objective of demonstrating the statistical superiority of Zimura 2mg against sham. The reduction in the mean rate of GA growth over 12 months was 14.25% (p=0.0064) for the Zimura group compared with the Sham group.

Source: Applicant's study reports. [1]RD: Randomized, DB: Double-Masked, SC: Sham-controlled.

2.2 Data Sources

This NDA application was submitted electronically and included full study reports as well as standardized datasets using SDTM and ADaM formats that are relevant for the analyses of studies OPH2003 and ISEE2008 presented in this review. Datasets and corresponding definition files can be found at the following location:

\\CDSESUB1\evsprod\NDA217225\0001\m5\datasets

For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt: contains the demographic and disposition data.
- adim.xpt: contains the GA area efficacy data.
- adae.xpt: contains the adverse event data.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the NDA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

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3.2 Evaluation of Efficacy

This section summarizes the design of studies OPH2003 and ISEE2008 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Studies OPH2003 and ISEE2008 were multicenter, double-masked, randomized, parallel-group, sham-controlled, studies. These studies were designed to evaluate the safety and efficacy of Avacincaptad pegol compared with sham injection in subjects with GA secondary to AMD. To be eligible for these studies, patients had to meet the following ocular inclusion criteria for the study eye:

- Non-foveal GA secondary to dry AMD
- The GA lesion must meet the following criteria as determined by the central reading center's assessment of FAF imaging at screening:
    - Total GA area must be ≥2.5 and ≤17.5 mm^2 (1 and 7 disk areas respectively)
    - If GA is multifocal, at least 1 focal lesion must be ≥1.25 mm^2 (0.5 disk areas)
    - GA in part within 1500 microns from the foveal center
    - The atrophic lesion must be able to be photographed in its entirety
- Best corrected visual acuity (BCVA) between 20/25 to 20/320, inclusive
- Intraocular pressure (IOP) of 21 mmHg

3.2.1.2 Randomization and Treatment

OPH2003

This study was conducted in two parts. The following randomization schemes were used in Part 1 and Part 2:

Part 1: Patients were randomized in a 1:1:1 ratio to the following dose groups:

- Zimura 1mg/eye administered via intravitreal (IVT) injection
- Zimura 2mg/eye administered via IVT injection
- Sham

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Part 2: Patients were randomized in a 1:2:2 ratio to the following dose groups:

- Zimura 2mg/eye administered via IVT injection + Sham
- Zimura 4mg/eye (administered as 2 IVT injections of Zimura 2mg/eye)
- Sham + Sham

Note, the Zimura 2mg and sham arms received sham injections to ensure masking.

ISEE2008

This study first randomized subjects in a 1:1 ratio to the following dose groups:

- Zimura 2mg/eye administered via IVT injection
- Sham

At Month 12, subjects who were initially randomized to the monthly Zimura 2mg arm were re-randomized in a 1:1 ratio to receive Zimura 2mg administered monthly from Month 12 to Month 23 **or** Zimura 2mg administered every other month at Months 13, 15, 17, 19, 21, and 23. For the 'every other month' arm, sham was administered at Months 12, 14, 16, 18, 20, and 22 to ensure masking. Note, subjects who were initially randomized to sham (Day 1) continued to receive monthly sham injections through Month 23. All patients had a final follow-up visit at Month 24.

In both studies, randomization was stratified according to visual acuity (VA) at baseline (<50 letters vs. ≥50 letters), baseline GA (< 4-disc areas [DA] vs. ≥4 DA) and pattern of FAF at the junctional zone of GA (none/focal vs. banded/diffuse). Per the Applicant, in both studies, the sham procedure included the blunt opening of an empty, needleless syringe barrel placed on the conjunctiva in the inferotemporal quadrant of the eyeball to simulate the pressure of an injection.

3.2.1.3 Efficacy Endpoints

The protocol defined primary efficacy endpoint in Study OPH2003 was the mean change from baseline in total GA area at Month 12. In Study ISE2008, the mean rate of growth (Slope) is the primary efficacy endpoint. Note, for this indication, the DOP's preferred primary efficacy endpoint is the mean rate of growth (Slope) estimated based on at least three GA measurements taken over time.

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, the primary estimand (Study ISEE2008) and methods to deal with missing data and intercurrent events and statistical analyses presented in this review that are performed by the Applicant, as described in the SAPs for studies OPH2003 and ISEE2008, as well as independent analyses performed by the statistical reviewer.

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3.2.2.1 Statistical Hypotheses and Sample size

- Hypothesis Testing

The primary null and alternative hypotheses related to the protocol defined primary efficacy endpoints for the comparison of Zimura against sham can be mathematically stated as follows:

$$H_{o1}: \mu zm = \mu sham$$
$$H_{a1}: \mu zm \neq \mu sham$$

where *μzm*, and *μsham* respectively represent the Zimura and sham arms mean change from baseline in total GA area at Month 12 (Study OPH2003) or the mean rate of growth (slopes) in total GA area at Month 12 (Study ISEE2008).

- Sample Size

Study OPH2003

A total of approximately 277 subjects were planned to be enrolled. Of these, approximately 77 patients were planned to be randomized in Part 1 to Zimura 1mg vs Zimura 2mg vs sham control, in a 1:1:1 allocation. In Part 2, approximately 200 patients were planned to be randomized to Zimura 2mg vs Zimura 4mg vs sham control, in a 1:2:2 allocation.

Study ISEE2008

The sample size for this study was determined based on the results of OPH2003. A total of approximately 400 patients were planned to be randomized. The sample size calculation assumed a standard deviation of 7% higher than was observed in Study OPH2003; a mean rate of growth (Slope) of 0.11 in the Zimura arm over 12 months; a one-sided 2.5% false positive error rate and a 97% power.

3.2.2.2 Analysis Populations

The two studies defined the analysis populations as follows:

Study OPH2003

- The intent-to-treat (ITT): The ITT set includes all randomized subjects who received at least one dose of study drug. Subjects were to be analyzed in the treatment arm assigned at randomization.

- Per-protocol (PP) population: The PP population consisted of all ITT patients that did not meet criteria excluding them from the PP analyses. Such criteria were defined prior to database lock in a masked fashion.

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- Safety population: The safety population included all patients who received at least one dose of study drug. Subjects who have ever received an injection of Zimura during this trial were analyzed in the Zimura group.

Study ISEE2008

- Intent-to-treat (ITT) population: The ITT population consisted of all randomized patients who received at least one dose of study drug, irrespective of the dose received. Patients were analyzed in the treatment group assigned at randomization.

- Per-protocol (PP) population: The PP population consisted of all ITT patients without any significant violation of the protocol. The significant and major protocol violations were defined prior to database lock in a masked fashion.

- Safety population: The safety population included all patients who received at least one dose of study drug. If patients received a dose that differed from the one assigned according to the randomization schedule; safety analyses were conducted according to the dose received rather than according to the dose assigned by randomization. Patients who received an injection of Zimura during this study were analyzed in the appropriate Zimura group according to the actual injections received.

3.2.2.3 Analysis Methods

A. Primary Analyses

- Analysis of the Protocol Defined Primary Efficacy Endpoint: Study OPH2003

The primary efficacy analysis for Study OPH2003 was conducted using two separate mixed-effects repeated measures (MRM) models; one for comparing Zimura 2mg vs sham and one for comparing Zimura 4mg vs sham. For the comparison of Zimura 2mg vs sham, the model included treatment, visit, Part (Part 1 vs Part 2), treatment by visit interaction, the stratification factors, and the stratification factors by visit interactions. For Zimura 4mg vs sham model, the same fixed effects except Part (Part 1 vs Part 2) were used. For both models, visit was included as factor, and an unstructured (co)variance matrix was used to model the within-patient errors. From each model, the least square mean changes from baseline at Month 12 for each treatment arm, the difference in mean change from baseline at Month 12 between each Zimura arm and sham, together with the associated two-sided confidence intervals were estimated. Multiplicity arising from comparing each Zimura arm with the sham was adjusted using the Hochberg procedure.

- Analysis the Primary Efficacy Endpoint (Slope): Study ISEE2008

The Applicant pre-defined the primary estimand of the study 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

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(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 Applicant provided the following as attributes of the primary estimand:

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

- Treatment: Zimura 2mg versus Sham.

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

- Intercurrent events (ICE's) and strategies:

  - Treatment changes (i.e., interruptions, non-adherence, dose changes, discontinuation): "treatment policy" – i.e., treatment changes were ignored, and all data collected contributed to the analysis regardless of whether or not these followed such ICE's.

  - Coronavirus Disease 2019 (COVID-19): "treatment policy"- i.e., impact of COVID-19 pandemic was ignored, and all data collected contributed to the analysis regardless of whether or not these followed such ICE's.

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

The primary analysis in Study ISEE2008 was also conducted using an MRM model. The model included visit, treatment, treatment by visit interaction, the stratification factors, and the interaction of the stratification factors by visit. Visit was included in the model as a linear continuous variable. An unstructured covariance matrix was used to model the within-subject correlations. From the model, the mean rate of growth (slope) for each treatment arm, the difference in slope and the associated two-sided 95% confidence interval was estimated. Because there was only one primary comparison between Zimura 2mg and sham, no multiplicity adjustment was implemented in Study ISEE2008.

B. Sensitivity and Supplemental Analyses

❑ Sensitivity Analysis for Missing Data

To check the sensitivity of the results of the primary efficacy analysis to deviation from the missing at random (MAR) assumption based on which the analysis using the MMRM is valid, the Applicant conducted the following sensitivity analyses:

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a) The pattern-mixture-model imputation approach: In this approach, missing values at Month 12 visit were imputed by using the pattern-mixture-model restrictions. Specifically, the Neighboring-Case Missing Value restrictions were applied.

b) Control-based imputation and trimmed mean: Following an information request by this reviewer, the Applicant also provided results of sensitivity analyses based on a placebo-controlled imputation and two different trimmed mean analyses approaches.

c) Miller 2001: Four analyses described by Miller 2001 were also performed

   i. The observed means from the active arm and the Sham arm were to be imputed for patients with missing data in the arm they were allocated to.

   ii. The observed means from the active arm and the Sham arm were imputed for patients with missing data in the opposite arm they were allocated to (a "cross-over" scheme).

   iii. The average of observed means from the active arm and the Sham arm was imputed for all patients with missing data.

   iv. The observed mean from the Sham arm was imputed for all patients with missing data.

d) Tipping point analysis: For missing values at a particular visit, it was assumed that their expected value was higher (shifted) by a specified amount than for the observed responses (implying that the missing values were more likely corresponding to bigger changes vs Baseline than the observed ones). Different values of the shift were explored to investigate the sensitivity of the results.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Recall, Study OPH2003 was an 18-month study while Study ISEE2008 was a 24-month study. Both studies had two database locks. The first database lock occurred after all subjects completed Month 12 or exited the study early. The second database lock occurs after the completion of the respective studies: Month 18 for OPH2003 and Month 24 for ISEE2008. Because Study ISEE2008 was still ongoing at the time of this NDA submission, the patient disposition for this study will only be for Month 12. For Study OPH2003, the disposition summaries for Month 12 and Month 18 are provided.

As can be seen from Table 4--Table 6, in both studies, the proportion of subjects who discontinued the study is slightly higher in the Zimura arms compared to the sham arm. The main reported reasons for study discontinuation were *withdrawal by the patient* (in both studies) and *Sponsor's decision* (in OPH2003 only).

Note, the Applicant's response to an information request regarding subjects whose reason is listed as "withdrawal by subject" shows that most of these subjects had reported adverse events (AE) prior to discontinuation. For example, of the 13 such subjects randomized to the Zimura

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4mg arm of Study OPH2003, 10 had AE (8 subjects reported ocular AE in the study eye and 2 reported non-ocular AE). Similarly, of the 17 such subjects in Study ISEE2008, 8 had ocular AE in the study eye, 9 had non-ocular AE and 3 had serious non-ocular AE (See Table 28 and Table 29). Therefore, it is possible that these subjects might have withdrawn from the study due to the reported AEs. Similarly, per the Applicant's summary provided following an information request, most of the subjects whose reason for discontinuation was reported as "Sponsor decision" are in fact subjects who developed choroidal neovascularization (CNV). Note, in Study OPH2003, subjects who developed CNV were withdrawn from the study by the investigators while similar subjects in Study ISEE2008 remained in the study and were treated with an anti-VEGF therapy. In the two studies combined, a total of 8 subjects died. Of these, only 2 were in sham arm.

Also note, in both studies, in addition to subject's who dropped out altogether, additional subjects who remained in the study also had missing GA data. This has resulted in a notable missing GA data (Table 7).

- In Study OPH2003, 26.9% of subjects randomized to the Zimura 2mg had missing GA data at Month 12. This figure increased to 38.8% at Month 18. A slightly lower missing data was observed in the sham arm. At Month 12, 18.1% of subjects in sham arm had missing GA data; and this has increased to 29.1% by Month 18.

- In Study ISEE2008, 19.6% of subjects randomized to the Zimura 2mg compared to 16.2% of subjects in the sham arm had missing GA data at Month 12.

Table 4: Patient Disposition (OPH2003 Month 12: ITT)

	Part 1			Part 2			Combined	
	Zimura 1mg N=26	**Zimura 1mg N=25**	**Sham N=26**	**Zimura 2mg N=42**	**Zimura 4mg N=83**	**Sham N=84**	**Zimura 2mg N=67**	**Sham N=110**
Completed through Month 12	24 (92.3%)	20 (80.0%)	21 (80.8%)	35 (83.3%)	58 (69.9%)	75 (89.3%)	55 (82.1%)	96 (87.3%)
Discontinued prior to Month 12	2 (7.7%)	5 (20.0%)	5 (19.1%)	7 (16.7%)	25 (30.1%)	9 (10.7%)	12 (17.9%)	14 (12.7%)
Adverse event	0	0	1 (3.8%)	0	1 (1.2%)	0	0	1 (0.9%)
Protocol violation	0	0	0	0	0	0	0	0
Investigator's decision	0	0	0	1 (2.4%)	2 (2.4%)	1 (1.2%)	1 (1.5%)	1 (0.9%)
Sponsor decision	1 (3.8%)	2 (8.0%)	0	3 (7.1%)	8 (9.6%)	2 (2.4%)	5 (7.5%)	2 (1.8%)
Withdrawal by patient	1 (3.8%)	3 (12.0%)	3 (11.5%)	3 (7.1%)	13 (15.7%)	5 (6.0%)	6 (9.0%)	8 (7.3%)
Loss to follow up	0	0	1 (3.8%)	0	0	0	0	1 (0.9%)
Patient non-compliance	0	0	0	0	0	0	0	0
Death	0	0	0	0	1 (1.2%)	1 (1.2%)	0	1 (0.9%)
Other	0	0	0	0	0	0	0	0
Number of subjects who completed through								
Month 3 visit	25 (96.2%)	23 (92.0%)	23 (88.5%)	40 (95.2%)	76 (91.6%)	81 (96.4%)	63 (94.0%)	104 (94.5%)
Month 6 visit	25 (96.2%)	21 (84.0%)	21 (80.8%)	36 (85.7%)	68 (81.9%)	78 (92.9%)	57 (85.1%)	99 (90.0%)
Month 9 visit	24 (92.3%)	20 (80.0%)	21 (80.8%)	35 (83.3%)	62 (74.7%)	742 (88.1%)	55 (81.1%)	95 (86.4%)
Month 12 visit	23 (88.5%)	18 (72.0%)	17 (65.4%)	34 (81.0%)	56 (67.5%)	72 (85.7%)	52 (77.6%)	89 (80.9%)

Source: Table 4 of the Applicant's study reports. Discrepancy between 'Number of patients completing through Month 12' and 'Number of patients who completed through Month 12 visit' are due to ongoing patients who missed Month 12 visit.

Table 5: Patient Disposition (OPH2003 Month 18: ITT)

	Part 1			Part 2			Combined	
	Zimura 1mg N=26	**Zimura 1mg N=25**	**Sham N=26**	**Zimura 2mg N=42**	**Zimura 4mg N=83**	**Sham N=84**	**Zimura 2mg N=67**	**Sham N=110**
Completed through Month 18	22 (84.6%)	18 (72.0%)	17 (65.4%)	30 (71.4%)	46 (55.4%)	68 (81.0%)	48 (71.6%)	85 (77.3%)
Discontinued prior to Month 18	4 (15.4%)	7 (28.0%)	9 (34.6%)	12 (28.6%)	37 (44.6%)	16 (19.0%)	19 (28.4%)	25 (22.7%)
Adverse event	0	0	1 (3.8%)	1 (2.4%)	2 (2.4%)	1 (1.2%)	1 (1.5%)	2 (1.8%)
Protocol violation	0	0	0	0	0	0	0	0

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Investigator's decision	0	0	0	1 (2.4%)	2 (2.4%)	1 (1.2%)	1 (1.5%)	1 (0.9%)
Sponsor decision	1 (3.8%)	2 (8.0%)	1 (3.8%)	5 (11.9%)	13 (15.7%)	2 (2.4%)	7 (10.4%)	3 (2.7%)
Withdrawal by patient	2 (7.7%)	5 (20.0%)	4 (15.4%)	4 (9.5%)	17 (20.5%)	8 (9.5%)	9 (13.4%)	12 (10.9%)
Loss to follow up	0	0	2 (7.7%)	0	0	1 (1.2%)	0	3 (2.7%)
Patient non-compliance	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)
Death	1 (3.8%)	0	0	1 (2.4%)	1 (1.2%)	1 (1.2%)	1 (1.5%)	1 (0.9%)
Other	0	0	1 (3.8%)	0	2 (2.4%)	1 (1.2%)	0	2 (1.8%)
Number of subjects who completed through								
Month 3 visit	25 (96.2%)	23 (92.0%)	23 (88.5%)	40 (95.2%)	76 (91.6%)	81 (96.4%)	63 (94.0%)	104 (94.5%)
Month 6 visit	25 (96.2%)	21 (84.0%)	21 (80.8%)	36 (85.7%)	68 (81.9%)	78 (92.9%)	57 (85.1%)	99 (90.0%)
Month 9 visit	24 (92.3%)	20 (80.0%)	21 (80.8%)	35 (83.3%)	62 (74.7%)	74 (88.1%)	55 (82.1%)	95 (86.4%)
Month 12 visit	23 (88.5%)	19 (76.0%)	19 (73.1%)	34 (81.0%)	56 (67.5%)	72 (85.7%)	53 (79.1%)	91 (82.7%)
Month 15 visit	22 (84.6%)	18 (72.0%)	18 (69.2%)	32 (76.2%)	50 (60.2%)	70 (83.3%)	50 (74.6%)	88 (80.0%)

Source: Table 5 of the Applicant's study reports.

Table 6: Patient Disposition (ISEE2008:Month 12: ITT)

Number of patients (%)	**Zimura 2mg N=225**	**Sham N=222**	**Total N=447**
Patients completing through Month 12	200 (88.9%)	205 (92.3%)	405 (90.6%)
Number of patients who discontinued early in Year 1	25 (11.1%)	17 (7.7%)	42 (9.4%)
Adverse event	3 (1.3%)	2 (0.9%)	5 (1.1%)
Protocol violation	0	0	0
Investigator decision	0	0	0
Sponsor decision	0	0	0
Withdrawal by patient	17 (7.6%)	13 (5.9%)	30 (6.7%)
Lost to follow-up	2 (0.9%)	1 (0.5%)	3 (0.7%)
Patient non-compliance	1 (0.4%)	0	1 (0.2%)
Death	3 (1.3%)[a]	1 (0.5%)	4 (0.9%)
Other	0	0	0
Number of patients who completed through			
Month 3 visit	216 (96.0%)	220 (99.1%)	436 (97.5%)
Month 6 visit	209 (92.9%)	215 (96.8%)	424 (94.9%)
Month 9 visit	204 (90.7%)	206 (92.8%)	410 (91.7%)
Month 12 visit	194 (86.2%)	199 (89.6%)	393 (87.9%)

Source: Adapted from Table 5 of the Applicant's study reports. ITT = intent-to-treat. Note: Discrepancy between 'Number of patients completing through Month 12' and 'Number of patients who completed through Month 12 visit' are due to ongoing patients who missed the Month 12 visit. [a] Patient (b) (6) (Zimura) died due to the AE of bilateral pneumonia 3 months after last study visit date (Month 9 visit) shortly after Month 12 visit would have occurred. The patient had not completed any additional study visits since Month 9 visit due to atrial fibrillation, bronchitis, and pneumonia. The Applicant has not included this patient in the disposition table citing that the death occurred after the Year 1 cutoff date.

Table 7: Summary of GA Outcome Observed and Missing (ITT)

Visit		**OPH2003**		**ISEE2008**	
		Zimura 2mg [a] N=67	**Sham [a] N=110**	**Zimura 2mg N=225**	**Sham N=222**
Baseline	Available	67 (100%)	110 (100%)	225 (100%)	222 (100%)
	Missing	0	0	0	0
Month 6	Available	58 (86.6%)	92 (83.8%)	204 (90.7%)	206 (92.8%)
	Missing	9 (13.4%)	18 (16.4%)	21 (9.3%)	18 (7.2%)
	Missed visit	6 (9.0%)	13 (11.8%)	19 (8.4%)	12 (5.4%)
	Attended Visit but no GA	3 (4.5%)	5 (4.5%)	2 (0.9%)	4 (1.8%)
	No observable GA	*0*	*0*	*0*	*0*
	Lesion exceeds image	*1 (1.5%)*	*1 (0.9%)*	*0*	*1 (0.5%)*
	Poor image quality	*2 (3.0%)*	*1 (0.9%)*	*0*	*1 (0.5%)*
	Ill-defined lesion borders	*0*	*3 (2.7%)*	*2 (0.9%)*	*2 (0.9%)*
	Ungradable	*0*	*0*	*0*	*0*
	Missing	*0*	*0*	*0*	*0*

Month 12	Available	49 (73.1%)	90 (81.8%)	181 (80.4%)	186 (83.8%)
	Missing	18 (26.9%)	20 (18.2%)	44 (19.6%)	36 (16.2%)
	Missed visit	13 (19.4%)	17 (15.5%)	34 (15.1%)	28 (12.6%)
	Attended Visit but no GA	5 (7.5%)	3 (2.7%)	10 (4.4%)	8 (3.6%)
	No observable GA	*0*	*0*	*0*	*0*
	Lesion exceeds image	*1 (1.5%)*	*3 (2.7%)*	*1 (0.4%)*	*2 (0.9%)*
	Poor image quality	*2 (3.0%)*	*3 (2.7%)*	*6 (2.7%)*	*5 (2.3%)*
	Ill-defined lesion borders	*1 (1.5%)*	*0*	*2 (0.9%)*	*1 (0.5%)*
	Ungradable	*0*	*0*	*0*	*0*
	Missing	*1 (1.5%)*	*(1.5%)*	*1 (0.4%)*	*0*
Month 18	Available	41(61.2%)	78 (70.9%)	*Not Applicable*	
	Missing	26 (38.8%)	32 (29.1%)		
	Missed visit	20 (29.9)	27(24.5)		
	Attended Visit but no GA	6 (9.0%)	5 (4.5%)		
	No observable GA	*0*	*0*		
	Lesion exceeds image	*1 (1.5%)*	*1 (0.9%)*		
	Poor image quality	*3 (4.5%)*	*3 (2.7%)*		
	Ill-defined lesion borders	*2 (3.0%)*	*0*		
	Ungradable	*0*	*0*		
	Missing	*0*	*1 (0.9%)*		

Source: Table 14.2.3.5 of the Applicant's study report. [a] Combination of Part 1 and Part 2 patients.

Reviewer's remark [for stats]: Based on my understanding of the study population and the nature of the disease, it appears to me that the missing data, and to some degree the treatment compliance issue might be related to the age of the population, the nature of the disease and the effect of the drug in the immediate visual function:

- *First, this is a relatively older population, with a median age of 77. It has been shown in several studies that this study population tend to have a high attrition rate and consequently a higher missing data rate is observed.*

- *Second, the nature of the disease is that some subjects may not have any notable symptoms until the GA is large enough or is located centrally at which time it would affect their vision. For others where the lesion has caused blind spots, unless the blind spot occurs at the same spot in both eyes, they might not have substantial vision issues as one eye will compensate for the other.*

- *Third, the drug does not prevent GA growth, it just slows down the growth to hopefully prevent eventual visual impairment due to continued GA growth. Thus, even those with vision impairment due to GA might not see vision improvement during the duration of the study (this is reflected in the visual acuity outcome results). Besides, the treatment might lead to CNV in some subjects.*

Therefore, because of the issues outlined above, for some subjects, there might be little motivation to continue in the study especially continually receiving intravitreal injection in the eye. This might partly explain the overall high missing data in both arms; the disproportionate missing data in the Zimura arms compared to the sham arm, and the lower rate of treatment compliance.

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3.2.3.2 Demographic and Baseline Characteristics

Within each study, there were no significant baseline imbalances between arms in the demographics of age, gender, or race (Table 8 and Table 9). In all arms, there were more female participants than male participants, and most of the study participants were White and over 65 years of age (over 20% of subjects in both studies were over the age of 85 years). Black and Asian subjects appear to be severely under-represented, comprising of ≤1.5% of the ITT subjects in the two studies combined.

Table 8: Baseline and Demographic Characteristics (OPH2003: ITT)

	Part 1			**Part 2**			**Combined[a]**	
Number of patients (%)	**Zimura 1mg N=26**	**Zimura 2mg N=25**	**Sham N=26**	**Zimura 2mg N=42**	**Zimura 4mg N=83**	**Sham N=84**	**Zimura 2mg N=67**	**Sham N=110**
Sex, n (%)								
Male	11 (42.3%)	7 (28.0%)	8 (30.8%)	15 (35.7%)	25 (30.1%)	23 (27.4%)	22 (32.8%)	31 (28.2%)
Female	15 (57.7%)	18 (72.0%)	18 (69.2%)	27 (64.3%)	58 (69.9%)	61 (72.6%)	45 (67.2%)	79 (71.8%)
Ethnicity, n (%)								
Not Hispanic or Latino	25 (96.2%)	24 (96.0%)	25 (96.2%)	42 (100%)	82 (98.8%)	83 (98.8%)	66 (98.5%)	108 (98.2%)
Hispanic or Latino	1 (3.8%)	1 (4.0%)	1 (3.8%)	0	1 (1.2%)	1 (1.2%)	1 (1.5%)	2 (1.8%)
Race, n (%)								
American Indian/Alaska Native	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	1 (1.2%)	0	1 (0.9%)
Asian	1 (3.8%)	0	0	0	0	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	0	0	0
White	25 (96.2%)	25 (100%)	25 (96.2%)	42 (100%)	82 (98.8%)	82 (97.6%)	67 (100%)	107 (97.3%)
Other	0	0	1 (3.8%)	0	1 (1.2%)	1 (1.2%)	0	2 (1.8%)
Age (years)								
Mean	73.8	77.7	78.1	79.4	79.2	78.2	78.8	78.2
Standard Deviation	7.97	9.57	8.43	10.65	8.31	8.98	10.22	8.82
Median	75.5	80.0	79.0	83.0	80.0	78.0	82.0	79.0
Q1;Q3	67.0; 79.0	73.0; 86.0	74.0; 85.0	71.0; 87.0	74.0; 86.0	71.0; 83.0	72.0; 87.0	73.0; 83.0
Range	56; 91	58; 94	57; 90	52; 94	57; 95	54; 97	52; 94	54; 97
Age Group (years), n (%)								
<65	3 (11.5%)	4 (16.0%)	2 (7.7%)	6 (14.3%)	5 (6.0%)	4 (4.8%)	10 (14.9%)	6 (5.5%)
65 to 74	8 (30.8%)	5 (20.0%)	5 (19.2%)	8 (19.0%)	19 (22.9%)	22 (26.2%)	13 (19.4%)	27 (24.5%)
75 to 84	14 (53.8%)	9 (36.0%)	12 (46.2%)	12 (28.6%)	38 (45.8%)	38 (45.2%)	21 (31.3%)	50 (45.5%)
≥85	1 (3.8%)	7 (28.0%)	7 (26.9%)	16 (38.1%)	21 (25.3%)	20 (23.8%)	23 (34.3%)	27 (24.5%)
Current Smoking Status, n (%)								
Non-active	20 (76.9%)	15 (60.0%)	19 (73.1%)	27 (64.3%)	57 (68.7%)	55 (65.5%)	42 (62.7%)	74 (67.3%)
Active	6 (23.1%)	10 (40.0%)	7 (26.9%)	15 (35.7%)	26 (31.3%)	29 (34.5%)	25 (37.3%)	36 (32.7%)
Lens status, n (%)								
Aphakic	0	0	0	0	0	0	0	0
Pseudophakic	17 (65.4%)	15 (60.0%)	16 (61.5%)	29 (69.0%)	56 (67.5%)	62 (73.8%)	44 (65.7%)	78 (70.9%)

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Phakic	9 (34.6%)	10 (40.0%)	10 (38.5%)	13 (31.0%)	27 (32.5%)	22 (26.2%)	23 (34.3%)	32 (29.1%)
Not Done	0	0	0	0	0	0	0	0
If Phakic, Grade:								
Nuclear								
0	4 (15.4%)	3 (12.0%)	4 (15.4%)	1 (2.4%)	3 (3.6%)	1 (1.2%)	4 (6.0%)	5 (4.5%)
1	2 (7.7%)	6 (24.0%)	5 (19.2%)	10 (23.8%)	14 (16.9%)	17 (20.2%)	16 (23.9%)	22 (20.0%)
2	3 (11.5%)	1 (4.0%)	1 (3.8%)	1 (2.4%)	10 (12.0%)	4 (4.8%)	2 (3.0%)	5 (4.5%)
3	0	0	0	1 (2.4%)	0	0	1 (1.5%)	0
4	0	0	0	0	0	0	0	0
Posterior subcapsular cataract								
0	7 (26.9%)	9 (36.0%)	9 (34.6%)	12 (28.6%)	22 (26.5%)	19 (22.6%)	21 (31.3%)	28 (25.5%)
1	1 (3.8%)	1 (4.0%)	0	1 (2.4%)	5 (6.0%)	3 (3.6%)	2 (3.0%)	3 (2.7%)
2	1 (3.8%)	0	1 (3.8%)	0	0	0	0	1 (0.9%)
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
Cortical								
0	6 (23.1%)	8 (32.0%)	6 (23.1%)	10 (23.8%)	17 (20.5%)	14 (16.7%)	18 (26.9%)	20 (18.2%)
1	2 (7.7%)	2 (8.0%)	3 (11.5%)	2 (4.8%)	9 (10.8%)	5 (6.0%)	4 (6.0%)	8 (7.3%)
2	1 (3.8%)	0	1 (3.8%)	1 (2.4%)	1 (1.2%)	3 (3.6%)	1 (1.5%)	4 (3.6%)
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

Source: Table 11 of the Applicant's study reports.

Table 9: Baseline and Demographic Characteristics (ISEE2008: ITT)

Number of patients (%)	**Zimura 2mg N=225**	**Sham N=222**	**Total N=447**
Sex, n (%)			
Male	71 (31.6%)	66 (29.7%)	137 (30.6%)
Female	154 (68.4%)	156 (70.3%)	310 (69.4%)
Ethnicity, n (%)			
Not Hispanic or Latino	168 (74.7%)	178 (80.2%)	346 (77.4%)
Hispanic or Latino	27 (12.0%)	23 (10.4%)	50 (11.2%)
Not reported	30 (13.3%)	21 (9.5%)	51 (11.4%)
Race, n (%)			
American Indian/Alaska Native	1 (0.4%)	0	1 (0.2%)
Black or African American	0	1 (0.5%)	1 (0.2%)
Asian	1 (0.4%)	1 (0.5%)	2 (0.4%)
Native Hawaiian/Pacific Islander	0	0	0
White	182 (80.9%)	186 (83.8%)	368 (82.3%)
Other	10 (4.4%)	13 (5.9%)	23 (5.1%)
Not reported	31 (13.8%)	21 (9.5%)	52 (11.6%)
Age (years)			
Mean	76.3	76.7	76.5

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Standard deviation	8.61	8.82	8.71
Median	77.0	77.0	77.0
Q1; Q3	71.0; 83.0	71.0; 83.0	71.0; 83.0
Range	51; 93	51; 96	51; 96
Age group (years), n (%)			
<65	19 (8.4%)	20 (9.0%)	39 (8.7%)
65 to 74	72 (32.0%)	65 (29.3%)	137 (30.6%)
75 to 84	91 (40.4%)	91 (41.0%)	182 (40.7%)
≥85	43 (19.1%)	46 (20.7%)	89 (19.9%)
Current smoking status, n (%)			
Non-active	119 (52.9%)	115 (51.8%)	234 (52.3%)
Active	106 (47.1%)	107 (48.2%)	213 (47.7%)
Lens status, n (%)			
Aphakic	0	0	0
Pseudophakic	123 (54.7%)	128 (57.7%)	251 (56.2%)
Phakic	102 (45.3%)	94 (42.3%)	196 (43.8%)
Not done	0	0	0
If Phakic, Grade:			
Nuclear			
0	12 (5.3%)	8 (3.6%)	20 (4.5%)
1	62 (27.6%)	61 (27.5%)	123 (27.5%)
2	25 (11.1%)	24 (10.8%)	49 (11.0%)
3	3 (1.3%)	1 (0.5%)	4 (0.9%)
4	0	0	0
Posterior subcapsular cataract			
0	87 (38.7%)	82 (36.9%)	169 (37.8%)
1	12 (5.3%)	9 (4.1%)	21 (4.7%)
2	3 (1.3%)	3 (1.4%)	6 (1.3%)
3	0	0	0
4	0	0	0
Cortical			
0	57 (25.3%)	49 (22.1%)	106 (23.7%)
1	38 (16.9%)	40 (18.0%)	78 (17.4%)
2	7 (3.1%)	5 (2.3%)	12 (2.7%)
3	0	0	0
4	0	0	0

Source: Table 8 of the Applicant's study reports.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

A. Primary Efficacy Analysis

Recall, the protocol defined primary efficacy endpoint for Study OPH2003 was the mean change from baseline in total GA area at Month 12; while the mean rate of GA growth (Slope) at Month 12 was the primary endpoint for ISEE28. In both studies, the primary efficacy analysis was conducted based on the ITT population using the square root transformed GA outcome. In both studies, the treatment differences in the protocol defined primary efficacy endpoints between each Zimura arm and the sham are statistically significant in favor of Zimura.

For Study OPH2003, the least squares mean change from baseline at Month 12 (standard error: SE) is 0.292 (0.077), 0.402 (0.075), 0.321 (0.074) and 0.444 (0.072) for the Zimura 2mg, sham (combined Part 1 and Part 2), Zimura 4mg, and sham (Part 2), respectively. The estimated treatment difference (95% CI) between sham (combined Part 1 and Part 2) and Zimura 2mg is 0.110 (0.030, 0.190). Similarly, the treatment difference (95% CI) between sham (Part 2) and Zimura 4mg is 0.124 (0.038, 0.209; Table 10). Recall, Study OPH2003 was an 18-month study. Per the Applicant's results, the differences in the mean change from baseline at Month 18 were favorable to the Zimura arms and were nominally statistically significant (Table 11).

For Study ISEE2008, the least squares estimate of the mean rate of GA growth (Slope) at Month 12 (SE) is 0.336 (0.032), and 0.392 (0.033) for the Zimura 2mg and sham arms, respectively. The estimated treatment difference (95% CI) between Zimura 2mg and sham arm is 0.056 (0.016, 0.096; Table 12).

Table 10: Summary of Mean Change from Baseline in Total GA Area at Month 12 (Study OPH2003)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)[c]	
	Zimura 2mg [a] N=67	Sham [a] N=110	Zimura 4mg N=82	Sham [b] N=84	Zimura 2mg vs Sham	Zimura 4mg vs Sham
Mean Change[1]	0.292 (0.077)	0.402 (0.075)	0.321 (0.074)	0.444 (0.072)	0.110 (0.030, 0.190)	0.124 (0.038, 0.209)
Slope[2]	0.283 (0.070)	0.392 (0.068)	0.307 (0.069)	0.416 (0.066)	0.109 (0.031, 0.186)	0.109 (0.027, 0.192)

Source: [1]Table 18 of the Applicant's study report. [2]Table 14.2.1.5 and Table 14.2.1.2 of the Applicant's integrated summary of efficacy (ISE.)
[a] Combination of Part 1 and Part 2 patients. [b] Sham from part 2 only. [c] Differecnes are taken as sham-zimura.

Table 11: Summary of Efficacy Month 18 (Study OPH2003)

Parameters	LS mean (SE)				Difference (95% Confidence Interval)[c]	
	Zimura 2mg [a] N=67	Sham [a] N=110	Zimura 4mg N=82	Sham [b] N=84	Zimura 2mg vs Sham	Zimura 4mg vs Sham
Mean Change[1]	0.430 (0.092)	0.599 (0.089)	0.391 (0.087)	0.559 (0.083)	0.168 (0.066, 0.271)	0.167 (0.062, 0.273)
Slope[2]	0.451 (0.089)	0.607 (0.086)	0.373 (0.084)	0.512 (0.079)	0.156 (0.055, 0.258)	0.139 (0.036, 0.242)

Source: [1]Table 18 and 19 of the Applicant's study report. [2]Table 14.2.1.1of Applicant response to an IR submitted on 1/27/23.
[a] Combination of Part 1 and Part 2 patients. b Sham from part 2 only. [c] Differecnes are taken as sham-zimura.

Table 12: Summary of Efficacy at Month 12 (Study ISE2008)

Study	LS mean (SE)		Difference (95% Confidence Interval)[c]
	Zimura 2mg	Sham	

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Slope[1]	0.336 (0.032)	0.392 (0.033)	0.056 (0.016, 0.096)
Mean Change[2]	0.333 (0.034)	0.392 (0.035)	0.059 (0.017, 0.100)

Source: [1]Table 24 of the Applicant's study reports. [2]Table 14.2.3.6 of the Applicant's study report. [c] Differecnes are taken as sham-zimura

B. Sensitivity and Additional Analyses

❑ Sensitivity Analysis for Missing Data

Recall, the analyses of the protocol defined primary efficacy endpoints were conducted assuming missing data were missing at random (MAR). To evaluate the impact of deviation from this assumption, the Applicant conducted sensitivity analyses using different approaches including a pattern-mixture-model imputation approach and a tipping point analysis. The results of these analyses are supportive of the primary efficacy analyses results (See Section 3.2.2.3 for details of the sensitivity analyses methods).

❑ Pattern-mixture-model imputation

Table 13: Sensitivity Analysis: Pattern-Mixture: Month 12

Approaches	Difference (Sham-Zimura 2mg) [95% CI]		
	OPH2003 (Mean Change)	**OPH2003 (Slope)**	**ISEE2008 (Slope)**
CCMV [1]	0.114 (0.035, 0.192)	0.114 (0.034, 0.195)	0.055 (0.015, 0.096)
NCMV [2]	0.113 (0.034, 0.191)	0.114 (0.022, 0.207)	0.059 (0.019, 0.099)
Sham Controlled [3]	0.096 (0.016, 0.177)	0.094 (0.016, 0.173)	0.050 (0.009, 0.090)
Trimmed mean [4]	0.112 (0.030, 0.195)	0.110 (0.029, 0.191)	0.045 (0.0008, 0.088)
Trimmed mean [5]	0.110 (0.033, 0.186)	0.107 (0.030, 0.184)	0.054 (0.014, 0.095)

Source: Table 14.2.3.2 of the Applicant's study reports and the Applicant's response to IR submitted on 4/3/23. [1] Complete Case Missing Values (CCMV); [2] Neighboring Case Missing Values (NCMV); [3] Missing data are imputed using sham control multiple imputation, [4] All patients with any missing visit are trimmed in the analysis; [5] Patients discontinued due to AE are trimmed in the analyses. All other missing data are imputed using multiple imputations.

❑ Imputation based on Miller 2012 paper

Table 14: Sensitivity Analysis: Miller: Mean Change from Baseline at Month 12 (Study OPH2003)

Approaches	LS mean (SE)		Difference (95% Confidence Interval)
	Zimura 2mg [a] N=67	**Sham [a] N=110**	
Miller [1]	0.245 (0.061)	0.364 (0.059)	0.119 (0.053, 0.185)
Miller [2]	0.265 (0.063)	0.340 (0.061)	0.075 (0.007, 0.142)
Miller [3]	0.255 (0.062)	0.352 (0.060)	0.097 (0.030, 0.163)
Miller [4]	0.277 (0.061)	0.370 (0.059)	0.093 (0.028, 0.159)

Source: Table 06.01.01 of the Applicant's response to IR submitted on 4/3/23. [1]The observed means from the active arm and the Sham arm were to be imputed for patients with missing data in the arm they were allocated to. [2]The observed means from the active arm and the Sham arm were imputed for 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 was imputed for all patients with missing data. [4]The observed mean from the Sham arm was imputed for all patients with missing data.

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Table 15: Sensitivity Analysis: Miller: Mean Rate of GA Growth (Slope) at Month 12 (Study OPH2003)

Approaches	LS mean (SE)		Difference (95% Confidence Interval)
	Zimura 2mg [a] N=67	Sham [a] N=110	
Miller [1]	0.276 (0.058)	0.386 (0.056)	0.111 (0.046, 0.175)
Miller [2]	0.282 (0.058)	0.376 (0.057)	0.094 (0.029, 0.159)
Miller [3]	0.295 (0.058)	0.388 (0.056)	0.093 (0.028, 0.157)
Miller [4]	0.287 (0.059)	0.366 (0.057)	0.078 (0.012, 0.144)

Source: Table 14.2.4.3.2 of the Applicant's response to IR submitted on 4/3/23. [1]The observed means from the active arm and the Sham arm were to be imputed for patients with missing data in the arm they were allocated to. [2]The observed means from the active arm and the Sham arm were imputed for 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 was imputed for all patients with missing data. [4]The observed mean from the Sham arm was imputed for all patients with missing data.

Table 16: Sensitivity Analysis Miller: Mean Rate of GA (Slope) at Month 12 (Study ISEE2008)

Approaches	LS mean (SE)		Difference (95% Confidence Interval)
	Zimura 2mg N=225	Sham N=222	
Miller [1]	0.342 (0.029)	0.396 (0.03)	0.055 (0.018, 0.091)
Miller [2]	0.344 (0.029)	0.392 (0.029)	0.049 (0.012, 0.085)
Miller [3]	0.347 (0.029)	0.395 (0.029)	0.048 (0.012, 0.084)
Miller [4]	0.346 (0.029)	0.399 (0.029)	0.043 (0.006, 0.079)

Source: Table 14.2.3.3 of the Applicant's study reports. [1]The observed means from the active arm and the Sham arm were to be imputed for patients with missing data in the arm they were allocated to. [2]The observed means from the active arm and the Sham arm were imputed for 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 was imputed for all patients with missing data. [4]The observed mean from the Sham arm was imputed for all patients with missing data.

❑ Tipping Point Analysis Results

A tipping point analysis was conducted by applying a set of shifting parameters to the multiply imputed data for subjects in the Zimura arms who discontinued the study. For Study OPH2003, the tipping point, the shift that led to the treatment difference to no longer be statistically significant, was reached for a shift parameter of 0.07 for the comparison of Zimura 2mg versus sham and 0.05 for Zimura 4mg vs sham. For Study ISEE2008, the tipping point was reached for a shift parameter of 0.032. This quantity is approximately half of the effect size observed for the treatment arm (Table 17 and Table 18).

Table 17: Tipping Point Analyses of Mean Change from Baseline at Month 12 (OPH2003)

Treatment Comparison	Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
Zimura 2mg vs Sham	0	0.11	0.03; 0.19	0.0054
	0.01	0.1	0.03; 0.18	0.008
	0.02	0.1	0.02; 0.18	0.0118
	0.03	0.09	0.02; 0.17	0.0172
	0.04	0.09	0.01; 0.17	0.0247
	0.05	0.08	0.01; 0.16	0.0348
	0.06	0.08	0.00; 0.16	0.0483
	0.07	0.07	-0.00; 0.15	0.066
Zimura 4mg vs Sham	0	0.13	0.03; 0.22	0.0074
	0.01	0.12	0.03; 0.21	0.012
	0.02	0.11	0.02; 0.20	0.0193
	0.03	0.1	0.01; 0.20	0.0301
	0.04	0.09	0.00; 0.19	0.0459

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	0.05	0.09	-0.01; 0.18	0.0681

Source: Table 14.2.3.1 of the Applicant's study report. A shift value is added to the imputed value for subjects with missing data at Month 12 in the Zimura group.

Table 18: Tipping Point Analyses of Mean Rate of GA growth (Slope) at Month 12 [ISEE2008]

Shift Parameter	Estimate of LS Mean Difference	95% CI	P-value
0	0.0565	0.0172; 0.0958	0.0048
0.002	0.0555	0.0161; 0.0948	0.0057
0.004	0.0544	0.0151; 0.0937	0.0067
0.006	0.0533	0.0140; 0.0926	0.0079
0.008	0.0522	0.0129; 0.0916	0.0092
0.01	0.0512	0.0118; 0.0905	0.0108
0.012	0.0501	0.0107; 0.0895	0.0126
0.014	0.049	0.0096; 0.0884	0.0147
0.016	0.048	0.0085; 0.0874	0.0171
0.018	0.0469	0.0074; 0.0864	0.0199
0.02	0.0458	0.0063; 0.0853	0.023
0.022	0.0448	0.0052; 0.0843	0.0266
0.024	0.0437	0.0041; 0.0833	0.0306
0.026	0.0426	0.0030; 0.0823	0.0352
0.028	0.0416	0.0018; 0.0813	0.0403
0.03	0.0405	0.0007; 0.0803	0.0461
0.032	0.0394	0.0004; 0.0793	0.0525

Source: Table 14.2.3.1 of the Applicant's study report. A shift value is added to the imputed value for subjects with missing data at Month 12 in the ARC1905 group. The shift applied at month 6 is half of the shift at month 12.

❑ Additional Analyses

Sensitivity Analysis to Evaluate Combining Part 1 and 2 (OPH2003)

Recall, Study OPH2003 was conducted in two parts. In Part 1, subjects were randomized to Zimura 1mg, Zimura 2mg and sham in a 1:1:1 ratio. In Part 2, subjects were randomized to Zimura 2mg, Zimura 4mg and Sham in a 1:2:2 ratio. For the analysis of safety and efficacy, the Applicant combined the subjects from the two parts, i.e., for the comparison of Zimura 2mg versus sham, subjects randomized to the Zimura 2mg in Parts 1 and 2 combined were compared to sham randomized subjects from the two parts combined. In addition, the Applicant did not conduct any formal treatment comparison between Zimura 1mg and sham.

This reviewer identifies two issues: (1) potential multiplicity issue if the decision not to conduct treatment comparison between Zimura 1mg and sham was made after the study was conducted, and (2) issue with combining data from the two parts when the randomization ratios are different. In response to this reviewer's information request on why formal treatment comparison was not conducted between Zimura 1mg and sham, and if there is a need to adjust for multiplicity, the Applicant provided the following response:

"The Sponsor clarifies that, in Part 1 of Study OPH2003, the treatment comparison was neither conducted between avacincaptad pegol 2mg and Sham nor conducted between avacincaptad pegol 1mg and Sham. In October 2017, the Sponsor revised clinical protocol OPH2003 and the SAP upon considering the results from a phase 2 study for a C3 inhibitor (pegcetacoplan). The results of this study indicated that a statistically significant reduction in the rate of GA growth can be achieved with a smaller patient population and shorter trial duration. In addition, after

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conducting a masked review of the safety data, it was found that there were no tolerability concerns associated with the avacincaptad pegol doses tested in Part 1 (i.e., 1mg and 2mg). Therefore, the protocol was revised under Protocol Amendment B to investigate safety and efficacy of higher doses in Part 2 (i.e., 2mg and 4mg). At the time, the Sponsor believed that focusing on safety and efficacy of higher doses was appropriate to establish efficacy and safety for Study OPH2003 and future confirmatory pivotal studies. As a result of the Protocol amendment and revision to the SAP, the 1mg comparison was not powered for formal statistical comparison per study design, and therefore, no formal statistical comparison, or multiplicity adjustment was warranted. Rather, the SAP specified statistical comparisons between: (1) combined avacincaptad pegol 2mg and combined Sham from Part 1 and Part 2, and (2) avacincaptad pegol 4mg and Sham from Part 2."

Per the Applicant's response above, the decision to proceed with treatment comparisons between the two higher doses, Zimura 2mg and Zimura 4mg (from Part 2 only) versus sham was made based on results from a Phase 2 study. If this indeed was the case, the multiplicity issue might not be critical. However, the treatment comparison was conducted combining the two parts with Part (1 and 2) included in the model as a fixed effect. To evaluate the impact of treating Part as a fixed effect in the model, two additional analyses were conducted. The first analysis was done for each part separately, and in the second analysis, Part was included in the model as a random effect. For the analysis by part, the treatment difference was not nominally significant in Part 1.

Table 19: Analysis of Mean Change from Baseline at Month 12: Adjusting for Part (OPH2003)

	LS mean (SE)		
	Zimura 2mg	Sham	Difference (95% Confidence Interval)
Part 1	0.329 (0.041)	0.423 (0.042)	0.093 (-0.023, 0.209)
Part 2	0.308 (0.082)	0.423 (0.077)	0.114 (0.012, 0.216)
Combined [1]	0.292 (0.077)	0.402 (0.075	0.110 (0.030, 0.190)
Combined [2]	0.308 (0.082)	0.423 (0.077)	0.114 (0.012, 0.216)

Source: Reviewer's Analysis. [1] Part is included as a fixed effect. [2] Part is included as random effect in the model.

Sensitivity Analyses to Evaluate Stratification Error

Per the Applicant, they have identified stratification errors for some subjects in Study OPH2003. To assess the impact of a stratification error, the Applicant conducted two sensitivity analyses. The two analyses were done by performing analyses that stratify by 3-level covariates for the Baseline GA size. The first analysis was stratified by: < 4 mm^2 vs. ≥ 4 mm^2 to < 10 mm^2 vs. ≥ 10 mm^2, and the second analysis was stratified by: patients randomized prior to 16 Nov 2020 vs. < 4 mm^2 vs. ≥ 4 mm^2. These analyses provided results that are consistent with the Applicant's primary efficacy analysis result.

- **Identifying Potential Factors That Led to Difference in Magnitude of Treatment Effects Between Zimura 2mg Arms Across the Two Studies**

Per the study results, the treatment difference between sham and the Zimura 2mg arm is roughly 50% lower in Study ISEE2008 compared to Study OPH2003. This appears mainly because of

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the difference in the growth rate in subjects treated with Zimura 2mg arms across the two studies. Subjects treated with Zimura 2mg in Study OPH2003 appear to have slower GA growth rate compared to similar subjects in Study ISEE2008.

Although there does not appear to be noticeable difference in the demographic characteristics of age, sex and ethnicity among subjects randomized to the Zimura 2mg arms across the two studies, there were some notable differences in missing data rate, treatment compliance rate and in some baseline and disease characteristics between subjects randomized to the Zimura 2mg arms across the two studies. Therefore, the difference in GA progression across the Zimura 2mg arms of the two studies could be partly attributed to the differences above. The most notable differences between the Zimura 2mg arms across the two studies are presented below:

- In Study OPH2003, patients who developed CNV in the study eye were withdrawn from the clinical trial whereas similar subjects in Study ISEE2008 remained in the clinical trial and were treated with concomitant anti-VEGF therapy. Based on the summary provided below, it appears that slightly more subjects had CNV in the Zimura randomized subjects in Study OPH2003 compared to similar subjects in Study ISEE2008. The proportion of subjects who received anti-VEGF therapy after developing CNV was 11 (4.9%) in the Zimura 2mg arm and 8 (3.6%) in the sham arm.

	OPH2003				**ISEE2008**	
Timeframe	**Month 12**		**Month 18**		**Month 12**	
CNV Rate	Zimura 2mg (n=67)	Sham (n=110)	Zimura 2mg (n=67)	Sham (n=110)	Zimura 2mg (n=225)	Sham (n=222)
	9%	2.7%	11.9%	2.7%	6.7%	4.1%

- More subjects had missing data in study OPH2003 than in Study ISEE2008. For example, at Month 12, 27% of subjects in the Zimura 2mg arm of Study OPH2003 had missing GA data compared to 20% subjects in the Zimura 2mg arm of Study ISEE2008.

- Subjects in Study OPH2003 were slightly older (median age: 82 years) than those in ISEE2008 (median age: 77 years). Besides, the proportion of subjects older than 85 years was 34.3% in Study OPH2003 compared to 19.1% in Study ISEE2008. Note, the subgroup analysis by age group shows that, the treatment difference between Zimura 2mg and sham in both studies is higher for subjects over the age of 85 years old. The difference for this subgroup was higher (favorable to Zimura) in Study OPH2003 compared to Study ISEE2008.

- All subjects (100%) in Study ISEE2008 had extrafoveal GA while 92.5% subjects in study OPH2003 had extrafoveal GA with the remaining 7.5% having foveal GA. Per the medical literature, extrafoveal GA lesions progress faster than foveal lesions.

- The proportion of subjects with temporal peripapillary atrophy and temporal peripapillary atrophy with macular GA was slightly higher in Study OPH2003 (92.5%, 9.7%) compared to (85.3%, 6.3%) in Study ISEE2008.

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- The overall proportion of subjects who had concomitant surgery was higher in Study ISEE2008 (10.2%) versus 3% in OPH2003. Besides, a higher proportion of subjects in Study ISEE2008 (82%) had cataract compared to Study OPH2003 (69%).

- Subjects in Study OPH2003 had slightly lower baseline low luminous visual acuity (LLVA) compared to subjects in Study ISEEE2008. The median LLVA was 42 letters in Study ISEE2008 compared to 37.5 letters in Study OPH2003. In addition, the proportion of subjects who could read >50 letters was 42% in Study ISEE2008 compared to 32% in Study OPH2003.

- There is also a slightly better treatment compliance in Study OPH2003 compared to in Study ISEE2008. The proportion of subjects who completed the 12 injections is 69% in Study ISEE2008 compared to 71% in Study OPH2003.

Categories	**ISEE2008**	**OPH2003**
Missing GA data at Month 12	20%	27%
Median Age	77 years	82 years
Subjects older than 85 years	19%	34%
Extrafoveal	100%	92.5%
Temporal peripapillary atrophy	85.3%	92.5%
Temporal peripapillary atrophy with macular GA	6.3%	9.7%
concomitant surgery	10%	3%
Cataract	82%	69%
lower low luminous visual acuity (LLVA)	42	37.5
>50 letter read	42%	32%
Received all 12 injections	69.3%	71.4%

C. Analysis of Key Secondary Efficacy Endpoints

This section presents the results of two key secondary efficacy endpoints evaluated in the two studies. For each endpoint, the analysis was conducted using a similar MRM model that was used for the protocol defined primary efficacy endpoints based on the ITT population. From each model, the least squares mean change from baseline for each treatment arm, the differences between treatment arms and the associated 2-sided 95% confidence intervals are provided. Per the Applicant, no clinically meaningful changes were observed in the two endpoints. The treatment differences between Zimura and sham are not statistically significant in either study. Detailed results for each endpoint are provided below.

- Best-Corrected Visual Acuity (BCVA

For Study OPH2003, the least squares estimate (standard error: SE) of the mean change from baseline BCVA at Month 12 is -7.90 (2.66), -9.29 (2.59), -3.79 (3.11) and -3.51 (2.99) for the Zimura 2mg, sham (combined Part 1 and Part 2), Zimura 4mg, and sham (Part 2), respectively. The estimated treatment difference (95% CI) between sham (combined Part 1 and Part 2) and Zimura 2mg is 1.39 (-1.52, 4.30). Similarly, the treatment difference (95% CI) between sham (Part 2) and Zimura 4mg is -0.28 (-4.01, 3.46). There is a further decline in BCVA between Month 12 and 18. For example, the mean change from baseline in BCVA for the Zimura 2mg arm changed from -7.90 letters to -12.7 letters, for an average decline of 5 letters (Table 20).

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For Study ISEE2008, the least squares estimate of the mean change from baseline BCVA at Month 12 (SE) is 1.34 (1.483), and 0.96 (1.513) for the Zimura 2mg and sham arms, respectively. The estimated treatment difference (95% CI) between Zimura 2mg and sham arm is 0.38 (-1.43, 2.199; Table 21).

Table 20: Mean Change from Baseline in BCVA Score (Study OPH2003)

	LS mean (SE)				Difference (95% Confidence Interval)	
Visits	**Zimura 2mg [a] N=67**	**Sham [a] N=110**	**Zimura 4mg N=82**	**Sham N=84**	**Zimura 2mg vs Sham**	**Zimura 4mg vs Sham**
Month 12	-7.90 (2.66)	-9.29 (2.59)	-3.79 (3.11)	-3.51 (2.99)	1.39 (-1.52, 4.30)	0.124 (4.01, 3.46)
Month 18	-12.7 (4.29)	-15.1 (4.12)	-4.27 (4.24)	-7.07 (4.06)	2.37 (-2.23, 6.96)	2.80 (-2.29, 7.88)

Source: Table 20 and 21 of the Applicant's study report. [a] Combination of Part 1 and Part 2 patients.

Table 21: Mean Change from Baseline in BCVA Score at Month 12 (Study ISE2008)

	LS mean (SE)		
Visit	**Zimura 2mg**	**Sham**	**Difference (95% Confidence Interval)**
Month 12	1.34 (1.483)	0.96 (1.513)	0.38 (-1.43, 2.199)

Source: Table 15 of the Applicant's study reports.

- Low-Luminance Best-Corrected Visual Acuity (LL-BCVA)

In both studies, the estimated mean change from baseline in LL-BCVA scores were negative for the Zimura 2mg arm. This implies that subjects in this arm had a decline in the number of letters read from baseline at Month 12. For Study OPH2003, the least squares estimate (standard error: SE) of the mean change from baseline LL-BCVA at Month 12 is -1.03 (3.40), -1.41 (3.30), 1.53 (3.53) and 2.97 (3.39) for the Zimura 2mg, sham (combined Part 1 and Part 2), Zimura 4mg, and sham (Part 2), respectively. The estimated treatment difference (95% CI) between sham (combined Part 1 and Part 2) and Zimura 2mg is 0.38 (-3.34; 4.10). Similarly, the treatment difference (95% CI) between sham (Part 2) and Zimura 4mg is -1.44 (-5.66, 2.78). There is a further decline in LL-BCVA between Month 12 and 18. For example, the mean change from baseline in LL-BCVA for the Zimura 2mg arm changed from -1.03 letters to -2.72 letters (Table 22). For Study ISEE2008, the least squares estimate of the mean change from baseline LL-BCVA at Month 12 (SE) is -4.35 (2.301), and -2.29 (2.356) for the Zimura 2mg and sham arms, respectively. The estimated treatment difference (95% CI) between Zimura 2mg and sham arm is -2.06 (-4.86, 0.75; Table 23).

Table 22: Mean Change from Baseline in LL-BCVA Score (Study OPH2003)

	LS mean (SE)				Difference (95% Confidence Interval)	
Visits	**Zimura 2mg [a] N=67**	**Sham [a] N=110**	**Zimura 4mg N=82**	**Sham N=84**	**Zimura 2mg vs Sham**	**Zimura 4mg vs Sham**
Month 12	-1.03 (3.40)	-1.41(3.30)	1.53 (3.53)	2.97 (3.39)	0.38 (-3.34, 4.10)	-1.44 (-5.66, 2.78)
Month 18	-2.72 (4.21)	-3.10 (4.03)	2.85 (3.86)	1.68 (3.70)	0.37 (-4.10, 4.84)	1.17 (-3.43, 5.77)

Source: Table 22 and 23 of the Applicant's study report. [a] Combination of Part 1 and Part 2 patients.

Table 23: Mean Change from Baseline in LL-BCVA Score at Month 12 (Study ISE2008)

	LS mean (SE)		
Visit	**Zimura 2mg**	**Sham**	**Difference (95% Confidence Interval)**
Month 12	-4.35 (2.301)	-2.29 (2.356)	-2.06 (-4.86, 0.75)

Source: Table 16 of the Applicant's study reports.

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3.3 Evaluation of Safety

This section presents treatment exposure and descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs), using MedDRA 20.1 dictionary derived term, from Study OPH2003 and Study ISEE2008. These summaries are provided for the safety analysis population, which is defined in the SAPs as all randomized patients who receive at least 1 dose of study medication.

The safety analysis population is comprised of 260 subjects in Study OPH2003 [Zimura 2mg (67); Zimura 4mg (83); sham (110)], and 447 subjects in Study ISEE2008 [Zimura 2mg (225) and Sham (222)].

3.3.1 Extent of Treatment Exposure

Per the study protocol, during the first 12/18 months, subjects were to receive up to 12/18 injections. In both studies, the percentage of subjects who received the maximum number of planned injections during the first 12/18 months was relatively low. This appears to be more pronounced in the Zimura 2mg arm raising the issue of treatment compliance for the to-be-marketed dose. Detailed exposure summary is provided below.

- **Month 12 cut-off**

In Study OPH2003, there is a difference in extent of treatment exposure between Part 1 and Part 2. For example, in Part 1, 60% of subjects randomized to the Zimura 2mg arm received the maximum allowed number of 12 injections (with an average injection of 10.1). The corresponding figure in Part 2 for this same arm was 71.4% (average injection of 10.6). The proportion of subjects randomized to the sham arm who received the maximum allowed number of 12 injections was 65.4% in Part 1 and 71.4% in Part 2.

In Study ISEE2008, 69.3% of subjects randomized to the Zimura 2mg arm received the maximum allowed number of 12 injections (with an average injection of 10.9). The corresponding figure for sham randomized subjects was 77.9% (average injection of 11.9).

- **Month 18 cut-off (Study OPH2003 only)**

In Study OPH2003, in Part 1, the percentage of subjects who received the maximum allowed number of 18 injections (did not miss any injection) was (Zimura 2mg: 52.0%), (Zimura 1mg: 61.5%), and (Sham: 53.8%). The corresponding figures in Part 2 of this same study were (Zimura 2mg: 52.4%), (Zimura 4mg: 47.0%), and (Sham: 61.9%).

At month 18, in Part 1, the [Mean (SD), min, max] number of injections of was [16.0 (4.06), 1, 18], [14.3 (5.60), 1, 18], and [14.0 (6.06), 1, 18] for the Zimura 1mg, Zimura 2mg, and Sham groups, respectively. In Part 2, the [Mean (SD), min, max] number of injections of was [15.1 (4.89), 1, 18], [13.4 (5.83), 1, 18], and [15.9 (4.38), 1, 18] for the Zimura 2mg, Zimura 4mg, and Sham groups, respectively.

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3.3.2 Adverse Events

The overall adverse event summary for each study separately (up to Month 18 for Study OPH2003 and up to Month 12 for Study ISEE2008) is presented in Table 24 and Table 25. By Month 18, a higher percentage of subjects in the two Zimura arms of Study OPH2003 reported at least one ocular adverse event compared to the sham arms: Part 1: [46.2% (Zimura 1mg], 44.0% (Zimura 2) mg, and 23.1% (Sham)]; and Part 2: [66.7% (Zimura 2mg], 73.5% (Zimura 4) mg, and 46.4% (Sham)]. Similarly, in Study ISEE2008, a higher percentage of subjects in the Zimura 2mg arm reported at least one ocular adverse event compared to the sham arm by Month 12 [48.9% (Zimura 2mg) and 37.4% (sham)]. The most frequently reported ocular adverse events in subjects randomized to the Zimura arms in the two studies were conjunctival hemorrhage, conjunctival hyperemia, punctate keratitis, CNV and visual acuity reduced.

The proportion of subjects in both studies who reported at least one serious adverse event was comparable between the Zimura and sham arms. In both studies, slightly higher percentage of subjects discontinued the study drug in the Zimura arms compared to the sham arm (Table 26 and Table 27).

- ❑ Adverse Events of Special Interest

The Applicant provided summaries of adverse events of special interest, namely, endophthalmitis, intraocular inflammation (IOI), and intraocular pressure (IOP).

Study OPH2003

Per the study results, no subject reported endophthalmitis, and only two subjects, one in the Zimura 1mg and one in Zimura 2mg, reported IOI in the study eye. The percentage of subjects with IOP ≥ 35 mmHg 30 minutes after the first injection was 5.7% in the Zimura 2mg and 18.1% in the Zimura 4mg arm. Additionally, over the 18-month treatment period, increased IOP was reported twice as many times in the Zimura 4mg group compared to the combined to the Zimura 2mg group (22.9% vs 9.5%, respectively).

Study ISEE2008

Per the study results, no subject reported endophthalmitis or IOI in the study eye. The percentage of subjects with IOP ≥ 35 mmHg 30 minutes after the first injection was 5.3% in the Zimura 2mg arm. Additionally, over the 12-month treatment period, significantly higher proportion of subjects reported increased IOP in the Zimura 2mg group compared to the sham group (9.3% vs 0.9%, respectively).

Table 24: Overall Summary of Adverse Events (Up to Month 18: OPH2003)

	Part 1			**Part 2**		
	Zimura 1mg N=26	**Zimura 2mg N=25**	**Sham N=26**	**Zimura 2mg N=42**	**Zimura 4mg N=83**	**Sham N=84**
All AE	19 (73.1%)	16 (64.0%)	17 (65.4%)	38 (90.5%)	74 (89.2%)	65 (77.4%)
Ocular AE	12 (46.2%)	11 (44.0%)	6 (23.1%)	28 (66.7%)	61 (73.5%)	39 (46.4%)
All Serious AE (SAE)	116 (27.7)	89 (21.2)	205 (24.4)	52 (25.1)	39 (18.6)	91 (21.8)

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Ocular SAE	3 (11.5%)	4 (16.0%)	7 (26.9%)	8 (19.0%)	21 (25.3%)	21 (25.0%)
Death	0	0	0	1 (2.4%)	1 (1.2%)	0
AEs leading to treatment discontinuation	0	0	1 (3.8%)	2 (4.8%)	3 (3.6%)	1 (1.2%)

Source: Adapted from Table 33 of the Applicant's study reports. AE: Adverse event.

Table 25: Overall Summary of Adverse Events (Up to Month 12: ISEE2008)

	Treatments		
	Zimura 2mg N=225	**Sham N=222**	**Total N=447**
All AE	178 (79.1%)	157 (70.7%)	335 (74.9%)
Ocular AE	110 (48.9%)	83 (37.4%)	193 (43.2%)
All Serious AE (SAE)	30 (13.3%)	37 (16.7%)	67 (15.0%)
Ocular SAE	2 (0.9%)	2 (0.9%)	4 (0.9%)
Death	3 (1.3%)	1 (0.4%)[a]	4 (0.9%)
AEs leading to treatment discontinuation	6 (2.7%)	2 (0.9%)	8 (1.8%)

Source: Adapted from Table 19 of the Applicant's study reports. AE: Adverse event. [a] The Applicant did not include this subject in this table because the subject died 30 days after the last drug administration.

Table 26: Summary of Ocular Adverse Events in the Study Eye (Up to Month 18: Study OPH2003)

	Part 1			Part 2			Combined	
	Zimura 1mg N=26	**Zimura 1mg N=25**	**Sham N=26**	**Zimura 2mg N=42**	**Zimura 4mg N=83**	**Sham N=84**	**Zimura N=176**	**Sham N=110**
At least one TEAE	12 (46 2%)	11 (44 0%)	6 (23 1%)	28 (66 7%)	61 (73 5%)	39 (46 4%)	112 (63 6%)	45 (40 9%)
Eye disorders	12 (46 2%)	9 (36 0%)	5 (19 2%)	26 (61 9%)	56 (67 5%)	37 (44 0%)	103 (58 5%)	42 (38 2%)
Conjunctival hemorrhage	2 (7 7%)	2 (8 0%)	1 (3 8%)	9 (21 4%)	27 (32 5%)	12 (14 3%)	40 (22 7%)	13 (11 8%)
CNV[b]	2 (7 7%)	2 (8 0%)	1 (3 8%)	6 (14 3%)	13 (15 7%)	2 (2 4%)	23 (13 1%)	3 (2 7%)
Conjunctival hyperemia	0	0	0	3 (7 1%)	9 (10 8%)	4 (4 8%)	12 (6 8%)	4 (3 6%)
Eye pain	0	1 (4 0%)	0	1 (2 4%)	8 (9 6%)	3 (3 6%)	10 (5 7%)	3 (2 7%)
Punctate keratitis	0	0	0	4 (9 5%)	6 (7 2%)	8 (9 5%)	10 (5 7%)	8 (7 3%)
Vitreous detachment	3 (11 5%)	0	0	2 (4 8%)	4 (4 8%)	6 (7 1%)	9 (5 1%)	6 (5 5%)
Cataract	2 (7 7%)	0	1 (3 8%)	4 (9 5%)	2 (2 4%)	3 (3 6%)	8 (4 5%)	4 (3 6%)
Conjunctival oedema	0	0	0	2 (4 8%)	5 (6 0%)	4 (4 8%)	7 (4 0%)	4 (3 6%)
Visual acuity reduced	0	2 (8 0%)	0	1 (2 4%)	3 (3 6%)	5 (6 0%)	6 (3 4%)	5 (4 5%)
Eye irritation	0	0	1 (3 8%)	3 (7 1%)	2 (2 4%)	3 (3 6%)	5 (2 8%)	4 (3 6%)
Lacrimation increased	0	0	0	2 (4 8%)	3 (3 6%)	0	5 (2 8%)	0
Retinal artery occlusion[c]	0	1 (4 0%)	0	0	3 (3 6%)	0	4 (2 3%)	0
Vision blurred	0	0	0	1 (2 4%)	3 (3 6%)	2 (2 4%)	4 (2 3%)	2 (1 8%)
Photopsia	0	0	0	2 (4 8%)	1 (1 2%)	0	3 (1 7%)	0
Retinal hemorrhage	0	0	1 (3 8%)	0	3 (3 6%)	1 (1 2%)	3 (1 7%)	2 (1 8%)
Vitreous floaters	0	0	0	1 (2 4%)	2 (2 4%)	3 (3 6%)	3 (1 7%)	3 (2 7%)
Blepharitis	0	0	0	0	2 (2 4%)	1 (1 2%)	2 (1 1%)	1 (0 9%)
Corneal oedema	0	0	0	1 (2 4%)	1 (1 2%)	0	2 (1 1%)	0
Dry eye	0	0	0	0	2 (2 4%)	2 (2 4%)	2 (1 1%)	2 (1 8%)
Eyelid dermatochalasis	0	0	1 (3 8%)	0	2 (2 4%)	2 (2 4%)	2 (1 1%)	3 (2 7%)
Keratitis	0	1 (4 0%)	0	0	1 (1 2%)	0	2 (1 1%)	0
Meibomian gland dysfunction	1 (3 8%)	0	0	0	1 (1 2%)	0	2 (1 1%)	0
Ocular discomfort	0	0	0	1 (2 4%)	1 (1 2%)	1 (1 2%)	2 (1 1%)	1 (0 9%)
Visual impairment	0	0	0	0	2 (2 4%)	0	2 (1 1%)	0
Blepharospasm	0	1 (4 0%)	0	0	0	0	1 (0 6%)	0
Eye pruritus	1 (3 8%)	0	0	0	0	1 (1 2%)	1 (0 6%)	1 (0 9%)
Eyelid oedema	0	0	0	0	1 (1 2%)	2 (2 4%)	1 (0 6%)	2 (1 8%)
Iritis	1 (3 8%)	0	0	0	0	0	1 (0 6%)	0
Lacrimal disorder	0	0	0	1 (2 4%)	0	0	1 (0 6%)	0
Narrow anterior chamber angle	1 (3 8%)	0	0	0	0	0	1 (0 6%)	0
Optic ischemic neuropathy	0	0	0	1 (2 4%)	0	0	1 (0 6%)	0
Retinal pigment epitheliopathy	0	0	0	1 (2 4%)	0	0	1 (0 6%)	0
Vitreous hemorrhage	1 (3 8%)	0	0	0	0	0	1 (0 6%)	0
Vitreous opacities	1 (3 8%)	0	0	0	0	0	1 (0 6%)	0
Vitritis	0	0	0	1 (2 4%)	0	0	1 (0 6%)	0
Conjunctival disorder	0	0	1 (3 8%)	0	0	0	0	1 (0 9%)
Infections and infestations	0	1 (4 0%)	1 (3 8%)	0	5 (6 0%)	1 (1 2%)	6 (3 4%)	2 (1 8%)
Conjunctivitis	0	1 (4 0%)	1 (3 8%)	0	2 (2 4%)	0	3 (1 7%)	1 (0 9%)
Conjunctivitis viral	0	0	0	0	2 (2 4%)	0	2 (1 1%)	0
Injury, poisoning and procedural	1 (3 8%)	0	0	3 (7 1%)	1 (1 2%)	3 (3 6%)	5 (2 8%)	3 (2 7%)

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complications								
Corneal abrasion	1 (3 8%)	0	0	2 (4 8%)	1 (1 2%)	3 (3 6%)	4 (2 3%)	3 (2 7%)
Chemical burns of eye	0	0	0	1 (2 4%)	0	0	1 (0 6%)	0
Investigations	1 (3 8%)	2 (8 0%)	0	4 (9 5%)	19 (22 9%)	1 (1 2%)	26 (14 8%)	1 (0 9%)
IOP increased	1 (3 8%)	2 (8 0%)	0	4 (9 5%)	19 (22 9%)	1 (1 2%)	26 (14 8%)	1 (0 9%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	0	1 (3 8%)	0	0	0	0	1 (0 9%)
Blepharal papilloma	0	0	1 (3 8%)	0	0	0	0	1 (0 9%)

Source: Table 38 of the Applicant's study reports
AE = adverse event; CNV = choroidal neovascularization; IOP = intraocular pressure; nvAMD = neovascular age-related macular degeneration; PT = preferred term; SOC = system organ class; TEAE = Treatment-Emergent Adverse Event
Note: TEAEs are AEs occurring after the first injection on Day 1 up to the Month 17 injection + 30 days or 30 days after the last dose of study drug if no Month 17 injection is given However, all occurrences of nvAMD and CNV are collected as treatment-emergent events, even if the last study visit occurred more than 30 days after the last dose of the study
[a]Both Zimura (1, 2, 4mg) and Sham groups are a combination of Part 1 and Part 2
[b]Includes AEs with the synonymous term of nvAMD (neovascular age-related macular degeneration)
[c]The AEs of retinal artery occlusion reflect transient injection related events and are further described in Section 12 2 4 1 2 2 and Section 12 2 4 1 2 5

Table 27: Summary of Ocular Adverse Events in the Study Eye (Up to Month 12: Study ISEE2008)

	Zimura 2mg N=225	**Sham N=222**	**Total N=447**
Patients (%) with at least one TEAE	110 (48.9%)	83 (37.4%)	193 (43.2%)
Eye disorders	104 (46.2%)	80 (36.0%)	184 (41.2%)
Conjunctival hemorrhage	27 (12.0%)	17 (7.7%)	44 (9.8%)
Conjunctival hyperemia	12 (5.3%)	13 (5.9%)	25 (5.6%)
Punctate keratitis	11 (4.9%)	14 (6.3%)	25 (5.6%)
CNV[a]	15 (6.7%)	9 (4.1%)	24 (5.4%)
Dry eye	8 (3.6%)	8 (3.6%)	16 (3.6%)
Eye pain	9 (4.0%)	6 (2.7%)	15 (3.4%)
Vitreous detachment	7 (3.1%)	6 (2.7%)	13 (2.9%)
Cataract	4 (1.8%)	7 (3.2%)	11 (2.5%)
Retinal hemorrhage	4 (1.8%)	5 (2.3%)	9 (2.0%)
Eye irritation	3 (1.3%)	5 (2.3%)	8 (1.8%)
Lacrimation increased	2 (0.9%)	6 (2.7%)	8 (1.8%)
Vision blurred	6 (2.7%)	2 (0.9%)	8 (1.8%)
Visual acuity reduced	3 (1.3%)	5 (2.3%)	8 (1.8%)
Visual impairment	6 (2.7%)	2 (0.9%)	8 (1.8%)
Visual acuity reduced transiently	6 (2.7%)	1 (0.5%)	7 (1.6%)
Vitreous floaters	6 (2.7%)	1 (0.5%)	7 (1.6%)
Blepharitis	6 (2.7%)	0	6 (1.3%)
Ocular hypertension	5 (2.2%)	0	5 (1.1%)
Investigations	21 (9.3%)	2 (0.9%)	23 (5.1%)
IOP increased	21 (9.3%)	2 (0.9%)	23 (5.1%)

Source: Adapted from Table 22 of the Applicant's study reports.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses for each individual study are presented in Figure 4--Figure 7. The subgroup analyses are conducted using the same methodology used for the analysis of the primary efficacy endpoint. The subgroup results are generally consistent with the Applicant's primary efficacy analysis results. Note, because of the low number of subjects enrolled in the studies across some races, subgroup analyses by race are not conducted.

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In this review, the main issue is related to missing data. For both studies, the amount of missing data, i.e., subjects who did not have efficacy measurements reported at the primary analysis time points, i.e., Month 12, is relatively very high. Specifically, approximately 27% of subjects in Study OPH2003 and approximately 20% subjects in Study ISEE2008 randomized to the Zimura 2mg had missing GA data at Month 12. The missing data rate is even higher in the Zimura 4mg arm of Study OPH2003 with approximately 45% of the subjects having missing GA data at Month 12. Note, the Applicant is planning to request marketing approval for Zimura 2mg.

5.2 Collective Evidence

The Applicant's analyses of the protocol defined primary efficacy endpoints provided statistically significant results in favor of Zimura. The analyses of the protocol defined as well as DOP's primary efficacy endpoints under different missing data handling methods are generally consistent with the primary analysis findings, providing credence to the results of the primary efficacy analyses. Treatment comparisons with respect to secondary efficacy endpoints did not result in any meaningful differences between the two Zimura arms and the sham arm.

The incidence of adverse events including some adverse events of special interest was higher in the Zimura arms especially in the 4mg arm, compared to the sham arm. The most frequently reported ocular adverse events in subjects randomized to the Zimura arms in the two studies were conjunctival hemorrhage, conjunctival hyperemia, punctate keratitis, CNV and visual acuity reduced. In both studies, approximately less than 71% of the subjects randomized to the Zimura groups received the maximum allowed number of injections during the study period. This raises potential treatment compliance issues in the real world, and the potential for underestimation of incidence of adverse events with a full treatment regimen.

5.3 Conclusions and Recommendation

Overall, the results of in this review provide evidence to support the efficacy of Zimura for the treatment of GA secondary to AMD. Safety wise, incidence of adverse events, including some adverse events of special interest, were higher in the Zimura arms; with more adverse events reported for the 4mg arm than the 2mg arm. Therefore, the final determination for the approval of this drug should be made based on the totality of evidence, taking the potential safety issues into account.

5.4 Labeling Recommendations

The Applicant presented the results for the mean change from baseline GA area at Month 12 for Study OPH2003 and the slope at Month 12 for Study ISEE2003 using the untransformed GA outcome. We have the following recommendations:

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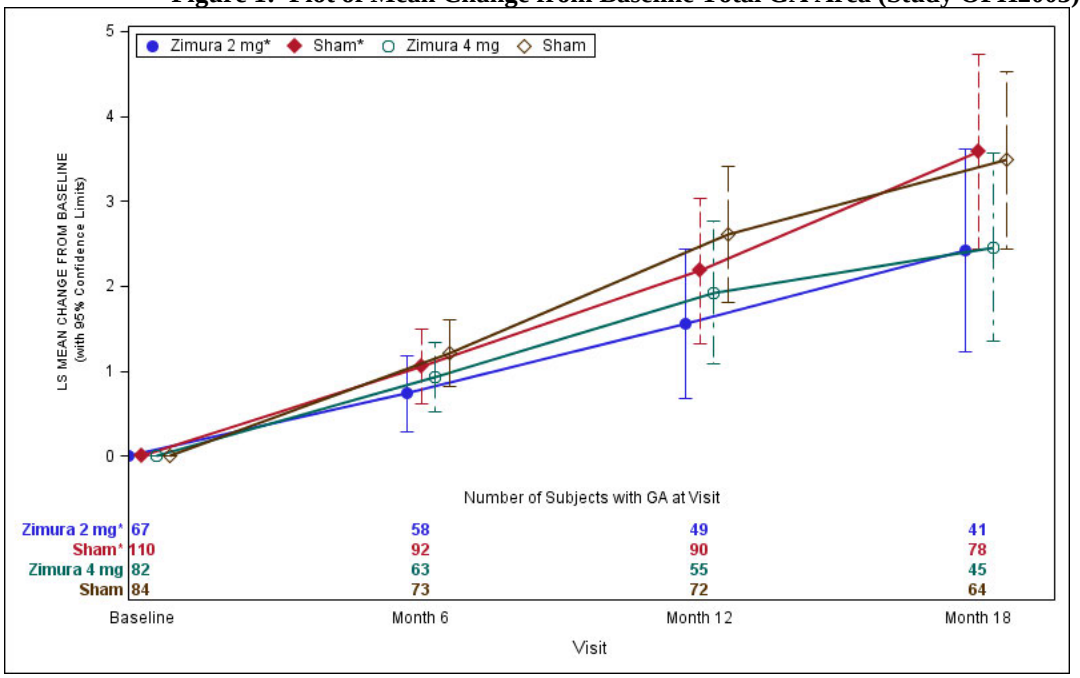
- As noted, first, the primary efficacy analysis was conducted based on the square root transformed GA area. Second, although the results are similar, the DOP's preferred primary efficacy endpoint is the mean rate of GA growth. Therefore, we request the Applicant to present the summary results based on the square root GA area and for the slope endpoint.

- The Applicant presented, the plot of the mean change from baseline GA area for GATHER 1 only. Given the observed differences in efficacy between the Zimura 2mg arms across the two studies, we request the Applicant to provide the plots for each study separately.

The Applicant's current draft label contains the following in Section 14.

6 Appendix A: Selected Efficacy and Safety Summaries (OPH2003 and ISEE2008)

Figure 1: Plot of Mean Change from Baseline Total GA Area (Study OPH2003)



Source: Figure 14.2.2.A of the Applicant's Study report

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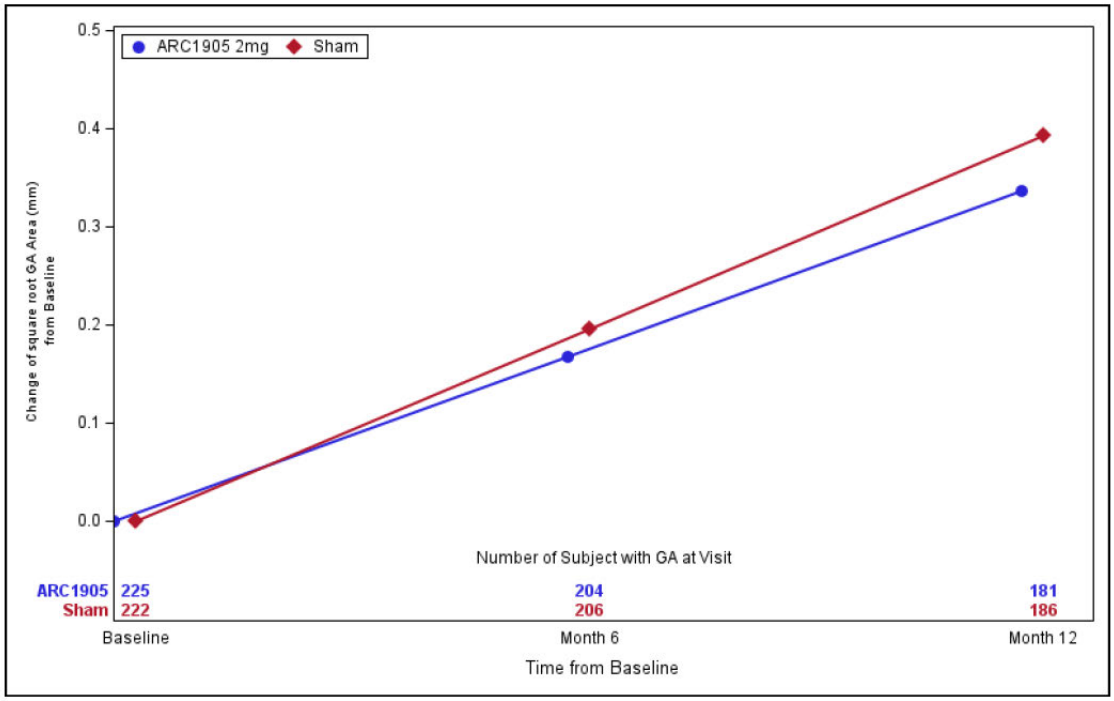
Figure 2: Plot of Mean Change from Baseline Total GA Area (Study ISEE2008)



Source: Figure 2 of the Applicant's study report

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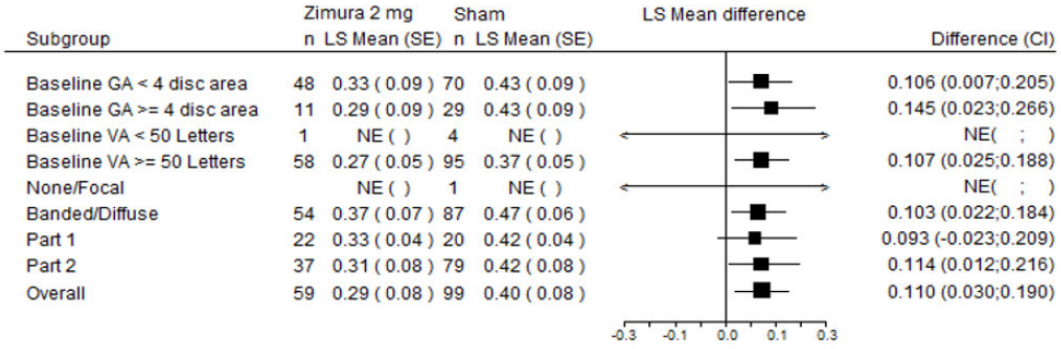
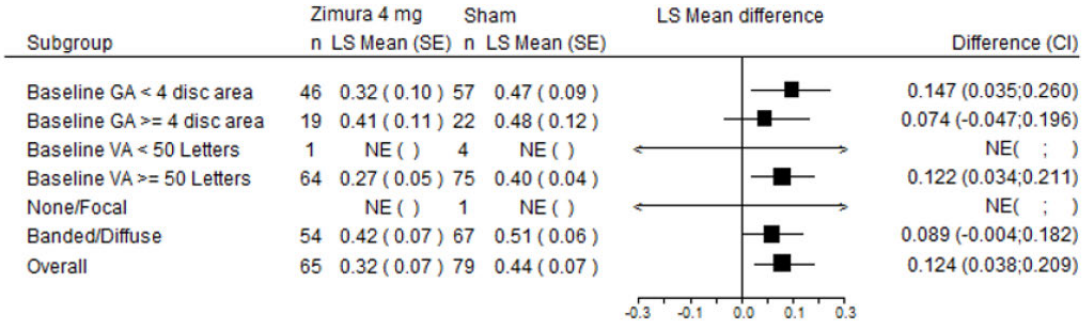
Figure 3: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (OPH2003: Zimura 2mg)



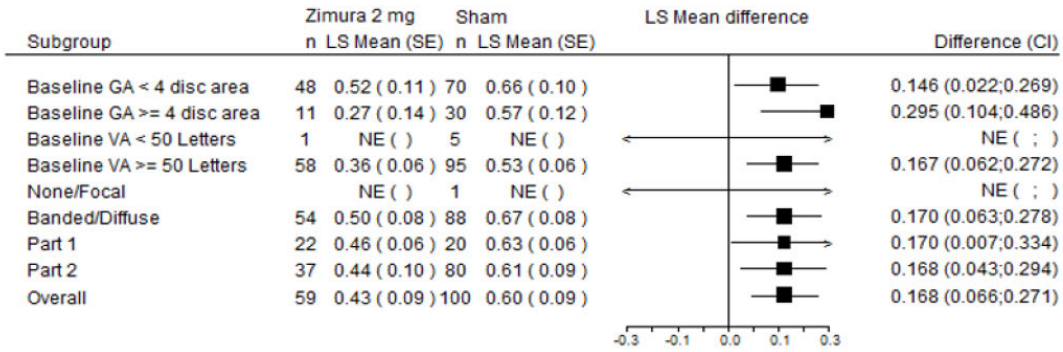
Source: Figure 10 of the Applicant's study report.

Figure 4: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 12 (OPH2003: Zimura 4mg)



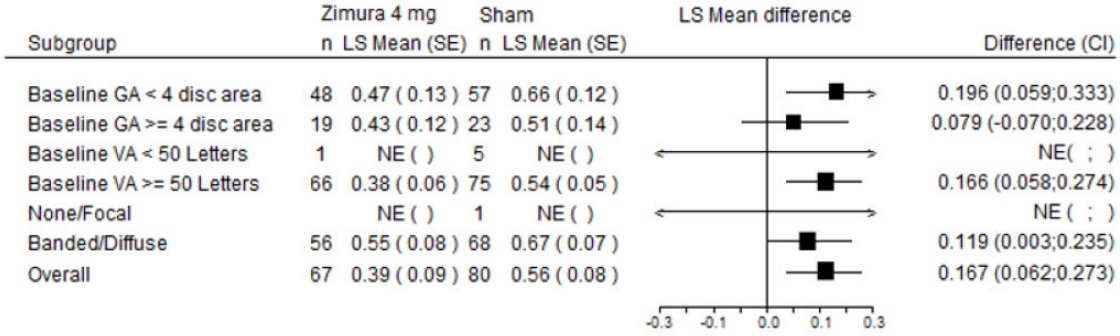
Source: Figure 11 of the Applicant's study report.

Figure 5: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (OPH2003: Zimura 2mg)



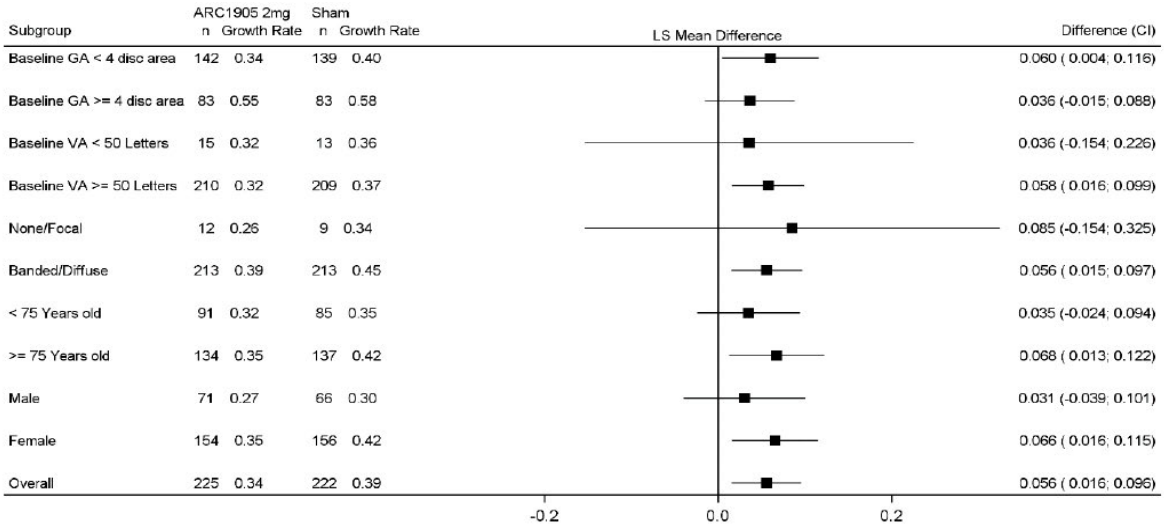
Source: Figure 12 of the Applicant's study report.

Figure 6: Subgroup Analysis: Mean Change from Baseline in GA Area at Month 18 (OPH2003: Zimura 4mg)



Source: Figure 12 of the Applicant's study report.

Figure 7: Subgroup Analysis: Mean Rate of GA growth (Slope) at Month 12 (ISEE2008)



Source: Figure 3 of the Applicant's study report.

Table 28: Safety Breakdown of Subjects Who Withdrew Consent (Study OPH2003: Month 12)

	Part 1			Part 2			Combined	
Number of subjects (%)	Zimura 1mg (N=26)	Zimura 2mg (N=25)	Sham (N=26)	Zimura 2mg (N=42)	Zimura 4mg (N=83)	Sham (N=84)	Zimura 2mg (N=67)	Sham (N=110)
Number of subjects withdraw per subject request	1 (3.8)	3 (12.0)	3 (11.5)	3 (7.1)	13 (15.7)	5 (6.0)	6 (9.0)	8 (7.3)
Any Serious Ocular TEAE-Study eye	0	0	0	0	0	0	0	0
Any Serious Ocular TEAE after last injection-Study eye	0	0	0	0	0	0	0	0
Any Ocular TEAE-Study eye	1 (3.8)	1 (4.0)	0	2 (4.8)	8 (9.6)	2 (2.4)	3 (4.5)	2 (1.8)
Any Ocular TEAE after last injection-Study eye	0	0	0	0	0	0	0	0
Any Serious non-Ocular TEAE	0	0	0	0	0	0	0	0
Any Serious non-Ocular TEAE after last injection	0	0	0	0	0	0	0	0
Any Non-Ocular TEAE	1 (3.8)	0	0	1 (2.4)	2 (2.4)	1 (1.2)	1 (1.5)	1 (0.9)
Any Non-Ocular TEAE after last injection	0	0	0	0	0	0	0	0

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Table 29: Safety Breakdown of Subjects Who Withdrew Consent (Study ISEE2008: Month 12)

	Treatments		
	Zimura 2mg N=225	**Sham N=222**	**Total N=447**
Total # withdrew consent	17 (7.6%)	13 (5.9%)	30 (6.7%)
Any Serious Ocular TEAE in the study eye	0	0	0
Any Serious Ocular TEAE after last injection in the study eye	0	0	0
Any Ocular TEAE in the study eye	8 (3.6%)	6 (2.7%)	14 (3.1%)
Any Ocular TEAE after last injection in the study eye	0	0	0
Any Serious Non-Ocular TEAE in the study eye	3 (1.3%)	4 (1.8%)	7 (1.6%)
Any Serious Non-Ocular TEAE after last injection in the study eye	2 (0.9%)	2 (0.9%)	4 (0.9%)
Any Non-Ocular TEAE in the study eye	9 (4.0%)	9 (4.1%)	18 (4.0%)
Any N0n-Ocular TEAE after last injection in the study eye	2 (0.9%)	3 (1.4%)	5 (1.1%)

Table 30: Number of Subjects Included in the Analyses Populations (OPH2003)

	PART 1			PART 2			Combined [a]	
	Zimura 1mg	**Zimura 2mg**	**Sham**	**Zimura 2mg**	**Zimura 4mg**	**Sham**	**Zimura 2mg**	**Sham**
Randomized subjects	26	25	26	42	83	84	67	110
Intent-to-treat (ITT)	26	25	26	42	83	84	67	110
Per protocol (PP) set	17	18	18	29	52	69	47	87
Safety Set	26	25	26	42	83	84	67	110

Source: Table 10 of the Applicant's study report. [a] combination of Part 1 and Part 2.

Table 31: Number of Subjects Included in the Analyses Populations (ISEE2008)

	Treatments	
	Zimura 2mg	**Sham**
Randomized subjects	225	223
Randomized not treated	0	1
Intent-to-treat (ITT)	225	222
Per protocol (PP) set	220	217
Safety Set	225	222

Source: Table 14.1.1.1of the Applicant's study report.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ABEL T ESHETE
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GUOXING SOON
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