# STATISTICAL ANALYSIS PLAN

Version 2.0

03-APR-2025

## A PHASE 2B RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ESTABLISH THE SAFETY AND EFFICACY OF ZIMURA™ (COMPLEMENT C5 INHIBITOR) COMPARED TO SHAM IN SUBJECTS WITH AUTOSOMAL RECESSIVE STARGARDT DISEASE

**Amendment B**

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## Version History

### SAP Version History Summary

The changes from the prior approved SAP that impact analyses are listed with the rationale in the table below.

| SAP Version | Approval Date | SAP Section(s) | Change | Rationale |
|---|---|---|---|---|
| 1.0 | See the signature page | Not Applicable | Not Applicable | Original Version |
| 2.0 | See the signature page | | | |
| 2.0 | See the signature page | 1.1, 4.4.1, 4.4.2, 4.5 | 1). Differentiated secondary endpoints, supportive endpoints, and safety endpoints.<br><br>2). Removed the secondary endpoint "Mean rate of change in the horizontal width of undetectable ellipsoid zone measured by a horizontal scan through the foveal center with SD-OCT over 18 months".<br><br>3). Added the supportive endpoint "Rate of change in the square root transformed area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18". | Updated according to Protocol Amendment C.<br><br>An additional supportive endpoint based on applying the square root transformation to the primary endpoint was added to reduce the impact of outliers and further understand the treatment effect on ellipsoid zone defect. |
| 2.0 | See the signature page | 1.2 | Removed sentence "that will obtain evidence regarding the effect of ACP on the mean rate of change in the area of ellipsoid zone defect measured by en face SD-OCT over 18 months, | The removed sentence is not needed in the study design section and has already been mentioned in Section 1.1. |

| SAP Version | Approval Date | SAP Section(s) | Change | Rationale |
|---|---|---|---|---|
| | | | when compared with Sham." | |
| 2.0 | See the signature page | 1.3, 5.1 | Details of the randomization procedure have been added. | To improve clarity on the randomization procedure. |
| 2.0 | See the signature page | 2, 2.1 | 1). Added statistical hypotheses to secondary endpoints "Change in BCVA (ETDRS letters) from Baseline at Month 18" and "Change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18".<br><br>2). Updated the multiplicity adjustment to the fixed sequence testing procedure. | Updated multiplicity adjustment procedure to include the endpoint "Change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18". |
| 2.0 | | 3.2 | Added sentence "The SAF population will be used for the summary of medical history, concomitant medications and analyses of all safety endpoints." | Provided a clearer description of the use of SAF. |
| 2.0 | | 4.1 | Updated the SAS version to "SAS® Enterprise Guide Version 7.15 HF8." | Updated the SAS version to reflect the current version in use. |
| 2.0 | | 4.2.3 | Removed SAF population. | Clarify that only the ITT population is used to summarize demographics and other baseline characteristics. |
| 2.0 | | 4.2.5 | Added "in the SAF population". | Updated to reflect the analysis set. |
| 2.0 | | 2.1, 4.3.2, 4.4.2 | Changed the definition of the mean difference | The order reflected the difference of ACP minus sham in a way |

| SAP Version | Approval Date | SAP Section(s) | Change | Rationale |
|---|---|---|---|---|
| | | | between ACP and Sham to ACP minus Sham. | that interprets the treatment effect more naturally. |
| 2.0 | | 4.3.2 | Added sentence "The treatment effect estimate is taken to be the estimated regression coefficient for the interaction between treatment and time multiplied by 547.875 days (i.e. 18 months × 30.4375 days/month)." | Added details of the treatment effect estimate. |
| | | 4.3.3, 4.4.3 | 1). Changed the title to "Supplementary Analysis: Jump to Reference Multiple Imputation".<br><br>2). Updated language of methodology description. | Updated to reflect the contents more clearly. |
| 2.0 | | 4.3.4, 4.4.4 | Added sections for sensitivity analysis: re-randomization test. | Added re-randomization test as additional sensitivity analysis to assess the robustness of results to misspecification of the distribution of the test statistics. |
| 2.0 | | 4.5 | 1). Added the paragraph "The MMRM model will include all observed…will be provided."<br><br>2). Added "The 5$^{th}$ percentile and … complementary log-log transformation."<br><br>3). Added "The odds ratio and its corresponding 95% confidence interval will be reported for ACP vs. Sham." and "participants | Added more detailed descriptions of analysis methods. |

| SAP Version | Approval Date | SAP Section(s) | Change | Rationale |
|---|---|---|---|---|
| | | | who do not have any atrophic lesion (DDAF) through Month 18 will be excluded from the analysis." | |
| 2.0 | | 4.6.3 | Updated Month 18/EW to Month 18. | Updated due to the use of analysis window. |
| 2.0 | | 4.6.5.1.1 | For shift tables from Baseline to Month 18, it is clarified that the pre-injection assessment will be used, and that these tables will be produced for all ophthalmic examinations.<br><br>Shift tables from Baseline through Month 18 have been removed. | Using the pre-injection assessment will allow more assessments to be included because not all patients will have a post-injection assessment.<br><br>The information in shift tables from Baseline to Month 18 will already be captured in the shift tables from pre-injection to post-injection. |
| 2.0 | | 4.10.1 | Lab and ECG analysis window rules have been updated to differentiate between assessments occurring at early termination visit if the study day is < 534 days or Month 18 if the study day is ≥ 534 days. | Provides a cleaner interpretation of the assessments at Month 18. |
| 2.0 | | 4.10.1 | Relaxed the condition for when IOP assessments can contribute to the analysis. Specifically, IOP assessments will now be included if either a pre or post injection record, but not necessarily both, is | Ensures more IOP assessments are included in the analysis. |

| SAP Version | Approval Date | SAP Section(s) | Change | Rationale |
|---|---|---|---|---|
| | | | present on the same day as the IOP assessment. | |
| 2.0 | | 5.1 | Expanded the definition of Ocular AEs to include the lower-level term: INTRAOCULAR LENS SUBLUXATION.<br><br>Additionally, the requirement for AE location to be right/left or both eyes, or AE term to contain eye or ocular has been added. | The exclusion of the lower-level term was a topographic error.<br><br>The additional requirement is to ensure that the AE either occurred in the eye(s) or its description includes eye or ocular. |
| 2.0 | | Throughout SAP | Corrected topographic errors without changing contents. | To improve clarity and correct errors. |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfil the objectives of the study.

The final SAP will be approved prior to study unmasking.

If there are any changes from the planned analyses in the final version of the SAP that impact the statistical analyses, it will be documented in the Clinical Study Report (CSR).

## 1.1 Objective(s) and Endpoints

The objectives of this study are to evaluate the safety and efficacy of avacincaptad pegol/Zimura™ (ACP) intravitreal injection compared to sham in participants with autosomal recessive Stargardt disease 1 (STGD1).

Primary Efficacy Endpoint

- Rate of change in the area of ellipsoid zone defect measured by en face spectral domain-optical coherence tomography (SD-OCT) from Baseline through Month 18.

Secondary Endpoints

- Change in best corrected visual acuity (BCVA) [Early Treatment Diabetic Retinopathy Study [ETDRS] letters] from Baseline at Month 18.
- Change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18.

Supportive Endpoints

- Rate of change in the area of atrophic lesion (definite decrease in autofluorescence, DDAF) measured by fundus autofluorescence (FAF) from Baseline through Month 18.
- Rate of change in the thickness of the outer nuclear layer measured by a horizontal scan through the foveal center using SD-OCT from Baseline through Month 18.
- Rate of change in the square root transformed area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18
- Time to persistent vision loss (defined as BCVA loss ≥10, 15 or 20 letters from Baseline at two or more consecutive visits through Month 18).
- Emergence of at least one new atrophic lesion (DDAF) measured by FAF through Month 18.

Safety Endpoints:

- Adverse events, vital signs, ophthalmic variables [ophthalmic examination, intraocular pressure (IOP), fluorescein angiogram (FA), FAF, SD-OCT, microperimetry], electrocardiogram (ECG), and laboratory variables.

## 1.2 Study Design

This is a randomized, double masked, sham controlled, Phase 2b trial.

Details of the schedule of clinical assessments are available in the protocol.

## 1.3 Randomization

Participants will be randomized in a 1:1 ratio to the following two treatment groups: ACP and Sham.

Participants will be centrally allocated to one of the two treatment groups by a dynamic minimization procedure (see Section 5.1 Appendix 1 for details). Randomization will be stratified by site and performed using an IRT system based on the stratification information to randomize each participant and assign a treatment group. Details of the randomization procedure can be found in Appendix 1.

All participants will be treated as follows:

**Induction Phase:** Administered starting on Day 1, 14 days apart for a total of 6 administrations (Day 1 – Month 2):

- ACP 2mg/eye or Sham

**Maintenance Phase**: Administered monthly (Month 3 – Month 17):

- ACP group continued with ACP 4 mg/eye (administered as two injections of ACP 2 mg)
- Sham group continued with Sham + Sham to maintain the masking

# 2 STATISTICAL HYPOTHESES

The fixed sequence testing procedure, as described in Section 2.1., will be used to test the treatment effect on the primary and secondary endpoints.

For the primary endpoint, let $\mu_1$ and $\mu_2$ be the mean rate of change in the area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18 for Sham group and ACP group, respectively.

Let $\Delta$ be the mean difference between ACP and Sham, defined as $\Delta = \mu_2 - \mu_1$. The primary hypothesis of the study is:

$$H_0 \text{ (null hypothesis): } \Delta = 0 \text{ vs. } H_1 \text{ (alternative hypothesis): } \Delta \neq 0,$$

where negative values of $\Delta$ indicates favorable outcomes for ACP.

For the secondary endpoint of change in BCVA from Baseline at Month 18, let $\mu_1$ and $\mu_2$ be the mean change in BCVA (ETDRS letters) at Month 18 for Sham group and ACP group, respectively. Let $\Delta$ be the mean difference between ACP and Sham, defined as $\Delta = \mu_2 - \mu_1$. The hypothesis for the secondary endpoint of change in BCVA (ETDRS letters) from Baseline at Month 18 is:

$$H_0: \Delta = 0 \text{ vs. } H_1: \Delta \neq 0,$$

where positive values of $\Delta$ indicates favorable outcomes for ACP.

For the secondary endpoint of change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18, let $\mu_1$ and $\mu_2$ be the mean change in photopic and/or mesopic macular sensitivity measured by microperimetry at Month 18 for Sham group and ACP group, respectively. Let $\Delta$ be the mean difference between ACP and Sham, defined as $\Delta = \mu_2 - \mu_1$. The hypothesis for the secondary endpoint of change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18 is:

$$H_0: \Delta = 0 \text{ vs. } H_1: \Delta \neq 0,$$

where positive values of $\Delta$ indicates favorable outcomes for ACP.

## 2.1 Multiplicity Adjustment

A fixed sequence testing procedure will be used to control the family-wise error rate at 0.05 by testing hypotheses in a predefined order. The testing procedure begins with testing the treatment effect on the primary endpoint of rate of change in the area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18. Then, only if the treatment effect estimate on the primary endpoint is statistically significant, a test of the treatment effect on the secondary endpoint of change in BCVA from Baseline at Month 18 will be performed. Lastly, if the treatment effect on the secondary BCVA endpoint is also statistically significant, then a test of the treatment effect on the secondary endpoint of change in photopic and/or mesopic macular sensitivity measured by microperimetry (optional assessment) from Baseline at Month 18 will be performed. For each endpoint, a two-sided test of the treatment effect on the endpoint will be conducted at a significance level of 0.05.

# 3 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

## 3.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all participants who are randomized. Participants will be analyzed according to the treatment to which they have been assigned at the time of randomization regardless of the actual study drug the participant might receive during his/her participation in the study. The Intent-to-Treat (ITT) population will include all participants who are randomized. Participants will be analyzed according to the treatment that they have been assigned at the time of randomization regardless of the actual treatment that the participant received during his/her participation in the study. The ITT population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy endpoints.

## 3.2 Safety Analysis Set

The Safety Analysis Set (SAF) population will include all participants that received at least one dose of study drug. Participants will be analyzed in the ACP group if they ever received ACP at any time during the study. Otherwise, participants that received Sham and never received ACP will be analyzed in the Sham group.

The SAF population will be used for the summary of medical history, concomitant medications, and analyses of all safety endpoints.

The determination of whether participants are included or excluded from the ITT and safety analysis sets will be made prior to database lock.

# 4 STATISTICAL ANALYSES

## 4.1 General Considerations

Continuous data will be summarized descriptively including the number of participants (n), mean, standard deviation (SD), median, minimum, 1st quartile (Q1), 3rd quartile (Q3), and maximum. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of participants with no missing data, i.e., the percentages for the non-missing categories will add up to 100%.

All statistical comparisons will be conducted using 2-sided tests at the 5% significance level.

All data summarization and analyses will be performed using SAS® Version 9.4 and Enterprise Guide 7.15 HF8. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

Baseline values will be defined as the last available value prior to the first dose of study drug. Unless otherwise specified, where multiple measurements are taken on the same day, the baseline value will be taken to be the average of the multiple measurements. Specifically:

- For BCVA, the baseline value will be taken as the average of the last two pre-treatment values for the study eye. This will typically be the Screening and Day 1 (D0) values. If there is only one pre-treatment value present, then this will be the baseline value. The baseline value for the fellow eye will be the last pre-treatment value. This will typically be the value at Screening.
- For area of ellipsoid zone defect, the baseline value will be the last pre-treatment value. This will typically be the measurement at Screening.
- For intraocular pressure (IOP), the baseline value will be taken as the average of the last two pre-treatment values for the study eye. This will typically be the Screening and Day 1 (D0) pre-injection values. If there is only one pre-treatment value present, then this will be the baseline value. The baseline value for the fellow eye will be the last pre-treatment value. This will typically be the value at Screening.

Change from baseline to post-baseline will be calculated as: post-baseline value – baseline value.

## 4.2 Study Participants

Participant disposition, demographics and baseline characteristics will be summarized for ITT population.

### 4.2.1 Participant Disposition

Disposition of participants will be summarized for ITT and SAF populations. Number of participants who complete or prematurely discontinue from the treatment or study (i.e., follow up period) will be summarized by treatment group and overall. For discontinuation, the primary reason reported by the investigator will be summarized.

Number and percentage of participants for each analysis set will be summarized by treatment group and overall.

### 4.2.2 Protocol Deviations

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

The major protocol deviations will be summarized for the ITT population, by treatment group and overall. In the summary table, participants deviating from a criterion more than once will be counted once for the corresponding criterion. The details will be provided in a participant listing.

### 4.2.3 Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized descriptively by treatment group and overall, for the ITT population.

The variables to be summarized are:

- Gender, ethnicity, race, age, age group (18 to <65 years, >=65 years), current smoking status, iris color, study eye, height, weight, intraocular pressure (study/fellow eye)
- FAF imaging assessments for study eye
- BCVA (ETDRS letters) for study/fellow eye
- Ophthalmic exam for study/fellow eye (motility, lids/lacrimal/lashes, conjunctiva/sclera, cornea, anterior chamber activity: cells, iris, pupils, lens status, vitreous haze, vitreous hemorrhage, posterior vitreous detachment, optic nerve, macula, retinal vessels, peripheral retina)

Prior ocular history as coded by MedDRA for study eye and fellow eye will be summarized by Preferred Term (PT), by treatment group and overall, in the SAF population.

Medical history as coded by MedDRA (excluding ocular history) will be summarized by System Organ Class (SOC) and PT, by treatment group and overall, in the SAF population.

Prior surgeries/procedures as coded by MedDRA will be summarized by SOC and PT, by treatment group and overall, in the SAF population.

### 4.2.4 Previous and Concomitant Medications

Previous and concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name (active ingredients for combination drugs) by treatment group for the SAF population. Participants taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

The summaries will include the number and percentage of all participants with at least one prior or concomitant medication, respectively.

Previous medications are defined as medications that participants started prior to first administration of study drug. Concomitant medications are defined as any medications that a participant took after the first dose of study drug and through the last follow-up visit, or 30 days after the last dose of study drug, whichever comes later. Medications that started prior to and continued after first administration of study drug will be counted in both previous and concomitant medications.

### 4.2.5 Extent of Exposure

Exposure to study medication will be evaluated for each treatment group in the SAF population with respect to treatment duration = (Last injection date - First injection date + 31)/30.4357, in months. Number of participants treated at each planned visit, total injections received, using descriptive statistics (N, mean, SD, median, Q1, Q3, minimum, maximum).

## 4.3 Primary Endpoint Analysis

### 4.3.1 Primary Estimand

The primary objective is to assess efficacy of ACP versus Sham in reducing the rate of change in the area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18 in participants with STGD1.

The following 5 attributes define the primary estimand for the primary objective evaluation:

1. Population: Participants with STGD1 that satisfy the inclusion/exclusion criteria specified in the protocol. The analysis will be performed in the ITT population.
2. Interventions: ACP versus Sham.
3. Variable: The area of ellipsoid zone defect ($mm^2$) measured by en face SD-OCT from Baseline through Month 18.
4. Intercurrent events (ICE's) and strategies:
    a. Study drug discontinuation: A hypothetical strategy will be adopted, as if all participants would continue treatment.
    b. Any other interruption or change to treatment that does not result in study drug discontinuation: A treatment policy strategy will be adopted, i.e., all data pre and post ICE will contribute to the analysis.

c. COVID-19: A treatment policy strategy will be adopted, i.e., all data pre and post ICE will contribute to the analysis.

5. Population-level summary: Difference between ACP group and Sham group in rate of change in the area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18.

### 4.3.2 Main Analytical Approach

The treatment effect on the primary efficacy endpoint, rate of change (slope) in the area of ellipsoid zone defect ($mm^2$/18 months) measured by en face SD-OCT from Baseline through Month 18, will be estimated using a mixed model for repeated measures (MMRM). The model will include all observed area of ellipsoid zone defect at each scheduled visit from Baseline through Month 18 in the response variable. The fixed effects will include treatment group (ACP or Sham), time, pooled geographic region (North America or Rest of World), and treatment by time interaction. Time is defined as a continuous variable in number of study days since randomization (calculated as: visit date – randomization date +1). The model will include an unstructured modeling of within-participant correlations, induced by random effects at the participant-level. The MMRM model will be fitted using restricted maximum likelihood (REML) estimation. If this analysis fails to converge, alternative correlation structures (e.g., heterogeneous autoregressive, heterogeneous compound symmetry, autoregressive, or compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate the degrees of freedom. Comparison between ACP group and Sham group will be performed at a 2-sided 0.05 significance level. The difference between ACP group and Sham group (ACP – Sham) in the growth rate (slope) of the area of ellipsoid zone defect from Baseline through Month 18, i.e. the treatment effect, and the associated standard error and 95% confidence interval (CI) will be provided. The treatment effect estimate is taken to be the estimated regression coefficient for the interaction between treatment and time multiplied by 547.875 days (i.e. 18 months × 30.4375 days/month).

### 4.3.3 Supplementary Analysis: Jump to Reference Multiple Imputation

A supplementary analysis will be performed to estimate a slight modification of the Primary Estimand in Section 4.3.1, where instead of the hypothetical strategy, the treatment policy strategy is specified for the ICE of study drug discontinuation. To estimate this estimand, missing outcome data will be imputed using Jump to reference (J2R) multiple imputation (MI) under a missing not at random assumption. J2R MI will result in multiple data sets with complete outcome data. Then, the MMRM model described in Section 4.3.2 will be used to estimate the treatment effect in the multiple imputed data sets. Finally, Rubin's combination rules will be used to obtain a single estimate of the treatment effect and corresponding standard error.

It is worth noting that Rubin's rules can provide conservative inferences (Seaman et al. 2014, Bartlett 2021), e.g., CIs may have significantly greater than 95% coverage probability.

Therefore, jackknife resampling (Wolbers et al. 2022) may also be applied to obtain more accurate frequentist inferences.

The J2R assumption stipulates that the mean outcome trajectory in participants who discontinue study drug in the ACP group will follow the mean outcome trajectory of the Sham group, after the point of discontinuation. This J2R assumption will be used to impute missing outcome data for participants in the ACP group post study drug discontinuation. For participants in the Sham group at all time points and participants in the ACP group up to the time of study drug discontinuation, missing outcome data will be imputed under the missing at random assumption (MAR). The overall MI analysis will be implemented as follows:

1. Parameter estimation model: Let $\mathbf{Y}_{Oi}$ denote the vector of all observed data, and $\mathbf{Y}_{Mi}$ denote the vector of missing observations after the time point of the ICE (denoted by $D_i$), for participant $i$.
    1) Fit a multivariate normal (MVN) model using $\mathbf{Y}_{Oi}$, assuming MAR, to data up to the occurrence of the ICE. The MVN model will include pooled geographic region, treatment group, visit (categorical variable), and treatment-visit interaction in the mean function and have a common unstructured variance-covariance matrix across treatment groups.
    2) Draw a mean vector and a covariance matrix from the posterior distribution of the fitted MVN model parameters.
    3) In Sham group, for each participant with $\mathbf{Y}_{Mi}$, use the draw from 2) to form the joint distribution of $\mathbf{Y}_{Oi}$ and $\mathbf{Y}_{Mi}$ following an MVN with mean and covariance corresponding to the Sham group estimates.

       In ACP group, for each participant with $\mathbf{Y}_{Mi}$, use the draw from 2) to form the joint distribution of $\mathbf{Y}_{Oi}$ and $\mathbf{Y}_{Mi}$ following an MVN with mean parameters from the ACP group until $D_i$ and from the Sham group thereafter. The covariance matrix corresponds to the parameters from ACP group until $D_i$ and to the Sham group for the conditional components of the post-ICE variables, given the pre-ICE measurement.
    4) For each participant, use the joint distribution to construct the conditional distribution of $\mathbf{Y}_{Mi}$ given $\mathbf{Y}_{Oi}$ and draw random values from the conditional distribution to impute $\mathbf{Y}_{Mi}$.
    5) Repeat Steps 1) - 4) to construct 100 imputed datasets (including both observed and imputed data), using a pre-specified random number seed.
2. Fit the MMRM model as described in Section 4.3.2 to each imputed data set.
3. Use Rubin's rules to combine point and standard error estimates from the analysis results of each of the 100 imputed datasets.

### 4.3.4 Sensitivity Analysis: Re-Randomization Test

To assess the robustness of the results to misspecification of the distribution of the test statistic, defined as treatment effect estimate divided by standard error, when using a dynamic minimization randomization procedure, a sensitivity analysis applying re-randomization will be performed. In this analysis, the treatment allocation process will be simulated 1000 times to generate different randomization schedules using the same randomization procedure. Denote the observed test statistics as t* from the actual original randomization schedule, and the values of the test statistics estimated using the same MMRM model as in Section 4.3.2 from each simulated randomization schedule as ti, $i \in \{1, \ldots, 1000\}$. Recall that negative values of the test statistic indicate that the results are in favor of ACP. The 2-sided re-randomization p-value associated with the observed t* based on the empirical distribution of ti, $i \in \{1, \ldots, 1000\}$ is calculated as: $p = 2 \times P(t_i \leq t^* | H_0) = \frac{\sum_{i=1}^{1000} I\{t_i \leq t^*\}}{1000}$, where $I(\cdot)$ is an indicator function. If $p > 1$, the re-randomization p-value will be set to 1.

## 4.4 Secondary Endpoints Analysis

### 4.4.1 Secondary Estimands

The secondary endpoints of this study are:

- Change in BCVA (ETDRS letters) from Baseline at Month 18
- Change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18.

The following 5 attributes define the Secondary Estimand for change in BCVA from Baseline at Month 18:

1. Population: Participants with STGD1 that satisfy the inclusion/exclusion criteria specified in the protocol. The analysis will be performed in the ITT population.
2. Interventions: ACP versus Sham.
3. Variable: Change in BCVA from Baseline at Month 18.
4. Intercurrent events (ICE's) and strategies: Same as for Primary Estimand in Section 4.3.1.
5. Population-level summary: Mean difference between ACP group and Sham group in change from Baseline in BCVA at Month 18.

The following 5 attributes define the Secondary Estimand for change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18:

1. Population: Participants with STGD1 that satisfy the inclusion/exclusion criteria specified in the protocol and were enrolled at sites where microperimetry could be performed. The analysis will be performed in the subset of the ITT population with a baseline and at least one post-baseline microperimetry assessment.
2. Interventions: ACP versus Sham.

3. Variable: Change in photopic and/or mesopic macular sensitivity measured by microperimetry from Baseline at Month 18.
4. Intercurrent events (ICE's) and strategies: Same as for Primary Estimand in Section 4.3.1.
5. Population-level summary: Difference between ACP group and Sham group in mean change from Baseline in photopic and/or mesopic macular sensitivity measured by microperimetry at Month 18.

### 4.4.2 Main Analytical Approach

For analyses of both secondary endpoints, the treatment effect will be estimated using MMRM with the following fixed effects: treatment group (ACP or Sham), visit (categorical variable), pooled geographic region (North America or Rest of World), treatment by visit interaction and baseline value of BCVA or photopic and/or mesopic macular sensitivity. The response variable will be the change from Baseline in BCVA or photopic and/or mesopic macular sensitivity measured by microperimetry at each scheduled post-baseline visit through Month 18. An unstructured (co)variance structure will be used to model the within-participant errors. The model will be fitted using REML estimation. If this analysis fails to converge, alternative correlation structures (e.g., heterogeneous autoregressive or heterogeneous compound symmetry, in this order) will be considered. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Statistical testing of the mean difference in change from Baseline in BCVA between ACP group and Sham group (defined as ACP minus Sham) at Month 18 from the MMRM will be performed at a 2-sided significance level of 5% only if the null hypothesis for the primary efficacy endpoint is rejected. The statistical testing of the difference for mean change from Baseline in photopic and/or mesopic macular sensitivity measured by microperimetry will be performed at a 2-sided significance level of 5% only if the null hypothesis for the primary efficacy endpoint and the secondary endpoint of change in BCVA at Month 18 are rejected, according to the fixed sequence procedure specified in Section 2.1.

### 4.4.3 Supplementary Analysis: Jump to Reference Multiple Imputation

Similar supplementary analyses to that described in Section 4.3.3 will also be performed for both secondary endpoints. The imputation of missing observations will proceed as described in Section 4.3.3, with the exception that baseline value (i.e. BCVA or photopic and/or mesopic macular sensitivity) will also be included in the mean function of the imputation model. Additionally, following J2R MI, an analysis of covariance (ANCOVA) with treatment group, pooled geographic region and baseline value will be performed in each of the 100 imputed data sets for change in BCVA and photopic and/or mesopic macular sensitivity from Baseline at Month 18. Finally, Rubin's rules will be used to combine treatment effect and standard error estimates from applying ANCOVA to the 100 imputed data sets.

### 4.4.4 Sensitivity Analysis: Re-Randomization Test

The same rerandomization test, as described in Section 4.3.4 will be performed for both secondary endpoints, with the exception that the 2-sided re-randomization p-value is calculated as: $p = 2 \times P(t_i \geq t^* | H_0) = \frac{\sum_{i=1}^{1000} I\{t_i \geq t^*\}}{1000}$, where $I(\cdot)$ is an indicator function. If $p > 1$, the re-randomization p-value will be set to 1. The difference in the calculation of the p-value is required to reflect that positive values of the test statistic for the secondary endpoints indicate favorable results for ACP, unlike for the primary endpoint.

## 4.5 Supportive Endpoint(s) Analysis

The supportive endpoints are:

- Rate of change in the area of atrophic lesion (DDAF) measured by FAF from Baseline through Month 18
- Rate of change in the thickness of the outer nuclear layer measured by a horizontal scan through the foveal center using SD-OCT from Baseline through Month 18
- Rate of change in the square root transformed area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18
- Time to persistent vision loss (defined as BCVA loss ≥ 10, 15 or 20 letters from Baseline at two or more consecutive visits through Month 18).
- Emergence of at least one new atrophic lesion (DDAF) measured by FAF through Month 18.

The supportive endpoints of the rate of change in the area of atrophic lesion (DDAF) measured by FAF from Baseline through Month 18, the rate of change in the thickness of the outer nuclear layer measured by a horizontal scan through the foveal center using SD-OCT from Baseline through Month 18, and the rate of change in the square root transformed area of ellipsoid zone defect measured by en face SD-OCT from Baseline through Month 18 will be analyzed similarly to the primary endpoint using the analysis method in Section 4.3.2. The MMRM model will include all observed outcomes for these endpoints at each scheduled visit from Baseline through Month 18. Fixed effects will include treatment group (ACP or Sham), time, pooled geographic region (North America or Rest of World), and treatment by time interaction. The random effects will be at the participant-level. The model will be fitted using REML estimation with unstructured (co)variance matrix. Comparison between ACP group and Sham group will be performed at a 2-sided 0.05 significance level. The difference between ACP group and Sham group (ACP – Sham) in the treatment effect, and the associated standard error and 95% CI will be provided.

Time to persistent vision loss is defined for each participant as the first study day (in months) where the participant experiences a BCVA loss ≥10, 15 or 20 letters from Baseline at two or more consecutive visits through Month 18. Participants without a vision loss event have their time to event censored at the last assessment of BCVA prior to the end of the study, or at 0.03285 months (i.e. day 1) if no post-baseline BCVA assessments are available. The hazard ratio for ACP vs. Sham on time to persistent vision loss, along with its corresponding 95% CI, will be calculated using a stratified Cox proportional hazards regression model with

pooled geographic region (North America or Rest of World) as the stratification factor. The two-sided p-value will be derived using the stratified log-rank test with pooled geographic region as the stratification factor. The 5$^{th}$ percentile and median time to the first occurrence of persistent vision loss will be analysed using the Kaplan-Meier method without stratification. Additionally, the event rate at Month 6, 9, 12, 15 and 18, and corresponding 95% CIs will be estimated using the Kaplan-Meier method without stratification and Greenwood formula with complementary log-log transformation.

For the emergence of at least one new atrophic lesion (DDAF) through Month 18, participants who do not have any atrophic lesion (DDAF) assessments through Month 18 will be excluded from the analysis. A dichotomized response (yes or no new atrophic lesion) will be evaluated and tested using Cochran-Mantel-Haenszel $\chi^2$ test for risk difference between ACP and Sham adjusting for the stratification factor of pooled geographic region (North America or Rest of World). The odds ratio and its corresponding 95% CI will be reported for ACP vs. Sham.

## 4.6 Safety Analyses

All safety analyses will be performed on the SAF population. Missing values of safety data will not be imputed, and safety summaries will be based on the observed cases.

### 4.6.1 Adverse Events

A TEAE is defined as an AE that started after the first dose of study drug until 30 days after the last dose of study drug or until the last follow-up visit required by the protocol, whichever comes later.

All AEs will be coded using MedDRA terms. The number and percentage of participants with TEAEs will be tabulated for each treatment group and in total by system organ class (SOC) and preferred term (PT). The number and percentage of the participants who experienced at least one TEAE will be included. Participants will only be counted once for each preferred term. In case that a participant experienced the same event more than once, the worst severity will be presented.

An overview of TEAEs will be provided. A second overview of TEAEs will be provided which displays the overall summary of TEAEs by the categories ‘Study Eye’, ‘Non-Study Eye’, and ‘Non-Ocular’.

Tabular summaries of the following AEs will be provided by SOC and PT:

- All TEAEs regardless of the relationship to study drug
- All TEAEs regardless of the relationship to study drug with frequency of ≥ 5% in any treatment group
- TEAEs related to injection procedure
- TEAEs related to study drug
- TEAEs by the maximum severity grade
- TEAEs related to injection procedure by the maximum severity grade
- TEAEs related to study drug by the maximum severity grade

- All ocular TEAEs for study (see Appendix B for the definition of ocular AEs)
- Ocular TEAEs related to injection procedure for study eye
- Ocular TEAEs related to study drug for study eye
- Ocular TEAEs by the maximum severity grade for study eye
- Ocular TEAEs related to injection procedure by the maximum severity grade for study eye
- Ocular TEAEs related to study drug by the maximum severity grade for study eye
- TEAEs leading to study drug discontinuation
- TEAEs leading to study drug discontinuation related to injection procedure
- TEAEs leading to study drug discontinuation related to study drug
- Ocular TEAEs leading to study drug discontinuation for study eye
- Ocular TEAEs leading to study drug discontinuation related to injection procedure for study eye
- Ocular TEAEs leading to study drug discontinuation related to study drug for study eye
- TEAEs with high level term of cataract conditions for phakic participants for study eye
- TEAEs with high level term of cataract conditions for phakic participants for fellow eye
- All treatment-emergent serious AEs (SAEs)
- Treatment-emergent SAEs related to injection procedure
- Treatment-emergent SAEs related to study treatment
- All ocular treatment-emergent SAEs for study eye
- Ocular treatment-emergent SAEs related to injection procedure for study eye
- Ocular treatment-emergent SAEs related to study treatment for study eye
- All ocular treatment-emergent SAEs for fellow eye
- Ocular treatment-emergent SAEs related to injection procedure for fellow eye

All AEs, including non-TEAEs, will be included in individual participant listings.

The listings will include the participant identifier, age, sex, verbatim term, SOC/PT, eye (NA/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, onset before injection, after first injection or after second injection, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study drug/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/not resolved/fatal).

The same listings will be provided separately for SAEs, AEs leading to permanent discontinuation of the study treatment, AEs leading to death and deaths.

### 4.6.2 Clinical Laboratory Evaluation & Liver Safety Assessment

The baseline value will be the last non-missing value taken prior to the first dose of study drug.

Quantitative values evaluated by the central laboratory including hematology, biochemistry, and urinalysis will be summarized using mean, SD, minimum, maximum and median by treatment group at each analysis visit. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

The incidence of participants with "Notable Laboratory Values" after the first dose of study drug will be evaluated using the criteria for Notable Laboratory Values given below. Only data collected after the first dose of study drug, up to the laboratory data taken at the Month 18 visit or 30 days after last dose of study drug will be included.

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

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

Laboratory analytes and primary criteria used for Notable Laboratory Values:

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

i. UN > 1.3xULN
ii. Creatinine > 1.3xULN

d. ELECTROLYTES
i. Potassium < 0.9xLLN or > 1.1xULN
ii. Sodium < 0.9xLLN or > 1.1xULN
iii. Chloride < 0.9xLLN or > 1.1xULN
iv. Bicarbonate < 0.9xLLN or > 1.1xULN
v. Calcium < 0.9xLLN or > 1.1xULN
vi. Phosphate < 0.9xLLN or > 1.1xULN

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

a. HEMATOLOGY
i. Hemoglobin < 0.75x Baseline (same as primary criterion)
ii. Platelets < 0.75x Baseline or > 1.25x Baseline
iii. WBC count < 0.75x Baseline or > 1.25x Baseline
iv. Neutrophils (absolute) < 0.5x Baseline or > 1.5x Baseline
v. Eosinophils (absolute) > 1.5x Baseline
vi. Lymphocytes (absolute) < 0.5x Baseline or >1.5x Baseline

b. LIVER FUNCTION
i. Total bilirubin > 1.5x Baseline
ii. Alkaline phosphatase > 1.5x Baseline
iii. ASAT (SGOT) > 1.5x Baseline
iv. ALAT (SGPT) > 1.5x Baseline
v. GGT > 1.5x Baseline

c. RENAL FUNCTION
i. UN > 1.3x Baseline
ii. Creatinine > 1.3x Baseline

d. ELECTROLYTES
i. Potassium < 0.9x Baseline or > 1.1x Baseline
ii. Sodium < 0.9x Baseline or > 1.1x Baseline
iii. Chloride < 0.9x Baseline or > 1.1x Baseline
iv. Bicarbonate < 0.9x Baseline or >1.1x Baseline
v. Calcium < 0.9x Baseline or >1.1x Baseline

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

### 4.6.3 Vital Signs

The baseline value will be the last non-missing value taken prior to first dose of study drug. This will typically be at Screening. Any participant without a Screening value for any, or all, vital sign parameters will be considered to have a missing baseline value.

Vital sign parameters will be summarized using mean, SD, minimum, maximum and median by treatment group at each analysis visit. Additionally, a within-participant change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit. These visits will be Month 6, Month 12, and Month 18.

### 4.6.4 Electrocardiograms

Number and percent of participants with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by the investigator for the 12-lead ECG will be tabulated by treatment group at each analysis visit.

A by-participant listing will be provided for ECGs which are deemed abnormal.

### 4.6.5 Other Safety-Related Assessments

#### 4.6.5.1 Ophthalmic Variables

##### 4.6.5.1.1 Ophthalmic Examination

The following ophthalmic examination variables will be analysed by treatment group using shift table from Baseline (pre-injection examination) to Month 18 or last visit available (pre-injection examination) whichever comes later (normal/abnormal, unless otherwise specified below).:

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

The following ophthalmic examination variables will be analysed by treatment group using shift table from pre-injection assessment to post-injection assessment at each monthly injection visit.

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

#### 4.6.5.1.2 Intraocular Pressure

IOP will be summarized by treatment group and visit, including all pre-injection, "IOP after first injection", and "IOP after second injection" measurements for applicable visits. An additional tabular summary of the percentage of participants in categories of IOP will be presented by treatment group, visit, and injection time (pre-injection, IOP after first injection, IOP after second injection). Baseline IOP for the study eye will be taken as the average of the last two pre-treatment values, this will typically be the Screening and Day 1(D0) pre--injection values. If there is only one pre-treatment value present, then this will be the baseline value. Baseline IOP for the fellow eye will be the last pre-treatment value, this will typically be the value at Screening.

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

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

## 4.7 Other Analyses

N/A

## 4.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

There will be no interim analysis.

## 4.9 Sample Size Determination

The planned size of 120 participants for this phase 2b trial was determined based on the number of participants with STGD1 that could potentially be enrolled within a reasonable period of time. Based on the actual recruitment rate during the trial, this number may be increased or decreased. As STGD1 is an orphan indication, there is no natural history data currently available regarding the SD of rate of change in the area of ellipsoid zone defect over 18 months in the STGD1 patient population that we plan to enroll in this trial.

## 4.10 Additional Conventions

### 4.10.1 Analysis Windows

Scheduled Day (Study Day) for analysis windows will be calculated as: Date of visit/assessment – first dose of study drug in this study + 1.

The assignment of visits to analysis will be consistent across all by-visit analysis datasets, and will follow the respective step-by-step algorithm:

1. All assessment visits will be windowed, per the tables below, regardless of scheduled/unscheduled status, injection date, or pre/post-injection status.
2. Baseline derivations will follow the definitions as stated in the SAP.
3. Scheduled visits, that fall into their respective analysis window, will be prioritized over unscheduled visits for assignment to analysis, if multiple visits satisfy this criterion, then next priority will be given to the visit closest to the Scheduled Day as stated per the table will be used.
4. For ADPE/ADIOP only; Assessments flagged for analysis will first have the assessment date match with an exposure date (injection day) and have at least one pre-injection or one post-injection record present. The exceptions to this rule are if the analysis visit is Month 18 or if the analysis visit is Screening.
5. For ADPE/ADIOP only; If there are no scheduled assessments for a particular visit label present then any assessments which match an exposure date (injection day) may be used if there is at least one pre-injection or one post-injection measurement. Unscheduled data which do not match an injection day will not be used for replacement.

For any analysis visit for an assessment for Study Eye, the analysis visit windowing approach will follow that for visits occurring monthly. For any analysis visit for an assessment for Fellow Eye, the analysis visit windowing approach will follow that for visits occurring at either every 3 or 6 months, for further details see the tables below.

There are particular exceptions for ADLB and ADEG. These datasets will contain assessments that are only scheduled to occur twice, at Screening and Month 18. In these cases, all visits (scheduled, unscheduled, early termination) that occur after first study drug exposure will be windowed to either an early termination visit if the study day is < 534 days or Month 18 if the study day is ≥ 534 days.

Listings will include all scheduled, unscheduled, and early withdrawal data.

The definition of visit label and visit windows in reporting are described in the table below.

For visits occurring monthly (Tonometry (SE), Ophthalmic Examination (SE), Visual Acuity (SE)):

| Analysis Visit | Scheduled Day (Study Day) | Analysis Window |
|---|---|---|
| Day 1 (D0) | 1 | 1-1 |
| Day 1 (D14) | 15 | 2-23 |
| Month 1 (D0) | 30 | 24-37 |
| Month 1 (D14) | 44 | 38-53 |
| Month 2 (D0) | 61 | 54-68 |
| Month 2 (D14) | 75 | 69-83 |
| Month 3 | 91 | 84-107 |
| Month 4 | 122 | 108-137 |
| Month 5 | 152 | 138-168 |
| Month 6 | 183 | 169-198 |
| Month 7 | 213 | 199-229 |
| Month 8 | 244 | 230-259 |
| Month 9 | 274 | 260-289 |
| Month 10 | 304 | 290-320 |
| Month 11 | 335 | 321-350 |
| Month 12 | 365 | 351-381 |
| Month 13 | 396 | 382-411 |
| Month 14 | 426 | 412-442 |
| Month 15 | 457 | 443-472 |
| Month 16 | 487 | 473-502 |
| Month 17 | 517 | 503-533 |
| Month 18 | 548 | >=534 |

For visits occurring every 6 months (Vital Signs, Physical Examination):

| Analysis Visit | Scheduled Day (Study Day) | Analysis Window |
|---|---|---|
| Month 6 | 183 | 2-274 |
| Month 12 | 365 | 275-457 |
| Month 18 | 548 | >=458 |

For visits occurring every 9 months (SD-OCT, Microperimetry, FP, FA):

| Analysis Visit | Scheduled Day (Study Day) | Analysis Window |
|---|---|---|
| Month 9 | 274 | 2-411 |
| Month 18 | 548 | >=412 |

For visits occurring 3/6 months (Tonometry (FE), Ophthalmic Examination (FE), Visual Acuity (FE))

| Analysis Visit | Scheduled Day (Study Day) | Analysis Window |
|---|---|---|
| Month 6 | 183 | 2-229 |
| Month 9 | 274 | 230-320 |
| Month 12 | 365 | 321-457 |
| Month 18 | 548 | >=458 |

### 4.10.2 Handling Missing or Partially Missing Data

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

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

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

### 4.10.3 Pooling Algorithm

For analysis purposes all participants will be pooled by geographic region, with this same variable then used as a fixed effect in any statistical modeling. The pooling will occur according to the following rule:

Participants will be grouped into their geographic regions defined by the categories North America and Rest of World.

# 5 SUPPORTING DOCUMENTATION

## 5.1 Appendix 1 Randomization Approach

The dynamic minimization algorithm described in Pocock and Simon (Pocock et al. 1975) was used to allocate patients to either ACP or Sham in this study. This procedure consists of two steps. First, the level of balance in treatment assignments within 1) the strata of randomization stratification factors (i.e. site) and 2) the overall population are determined for the settings where a new participant is assigned to ACP or Sham. Then, the treatment assignment that would cause the least imbalance is attributed higher probability when assigning the actual treatment assignment to the new participant. Note that this allocation scheme helps balance the treatment assignment while maintaining a random component.

**Imbalance measures**

Let $X_{jk}$ be the number of participants already assigned to treatment $k$ ($k$ = ACP, Sham) within site $j$ ($j = 1, 2, .., S$) as the new participant to be assigned. That is, $X_{jACP}$ and $X_{jSham}$ are the number of participants already assigned to receive ACP and Sham within site $j$, respectively. Additionally, let $Y_{ACP}$ and $Y_{Sham}$ be the total number of participants already assigned to ACP and Sham across all sites, respectively.

Suppose a new participant is enrolled at Site $j$. Then, the imbalance in treatment assignments at the site-level is defined by:

$$D_{ACP} = |X_{jACP} - X_{jSham} + 1| \text{ if the new participant is assigned to ACP or}$$

$$D_{Sham} = |X_{jACP} - X_{jSham} - 1| \text{ if the new participant is assigned to Sham}$$

Where $|a|$ is the absolute value of $a$. Similarly, the imbalance in treatment assignments in the overall population is defined by:

$$T_{ACP} = |Y_{ACP} - Y_{Sham} + 1| \text{ if the new participant is assigned to ACP or}$$

$$T_{Sham} = |Y_{ACP} - Y_{Sham} - 1| \text{ if the new participant is assigned to Sham}$$

The overall imbalance measure is defined by:

$$I_t = W_1 D_t + W_2 T_t \ (t = ACP \ or \ Sham)$$

Where $W_1$ and $W_2$ are positive weights that sum to one and are prespecified before the second participant has been randomized. The weights will only be made available to the broader study team after database lock.

**Allocation**

The first participant will be assigned to ACP or Sham with equal chance. Then, for each subsequent participant, the participant will be assigned to ACP with probability $p$ or to Sham with probability $1 - p$, based on the following rules:

$$p = 0.5 \ if \ I_{ACP} = I_{Sham}$$

$$p = 0.2 \ if \ I_{ACP} > I_{Sham}$$

$$p = 0.8 \ if \ I_{ACP} < I_{Sham}$$

## 5.2 Appendix 2 Ocular AEs

Ocular AEs are defined as AEs that satisfy at least one of the following criteria:

1) The SOC is coded to EYE DISORDERS and (AE location is right and/or left eye or AE term contains Eye or Ocular) or
2) The LLT is coded to INTRAOCULAR LENS SUBLUXATION or
3) The PT is coded to either INTRAOCULAR PRESSURE INCREASED, INTRAOCULAR PRESSURE DECREASED, INTRAOCULAR PRESSURE ABNORMAL or INTRAOCULAR PRESSURE FLUCTUATED.

## 5.3 Appendix 3 List of Abbreviations

| Abbreviations | Description of abbreviations |
|---|---|
| ACP | Avacincaptad pegol |
| ADEG | Electrocardiogram Examinations Analysis Dataset |
| ADIOP | Tonometry Analysis Dataset |
| ADLB | Laboratory Test Results Analysis Dataset |
| ADPE | Ophthalmic Examinations Analysis Dataset |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ATC | Anatomic Therapeutic Chemical |
| BCVA | Best Corrected Visual Acuity |
| CSR | Clinical Study Report |
| DDAF | Definite Decrease in Autofluorescence |
| ECG | Electrocardiogram |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluorescein Angiography |
| FAF | Fundus Autofluorescence |
| FE | Fellow Eye |
| FP | Fundus Photography |
| GGT | Gamma-glutamyl Transferase |
| ICE | Intercurrent Event |
| ICH | International Conference on Harmonization |
| IOP | Intraocular Pressure |
| ITT | Intention-to-Treat |
| J2R | Jump to Reference |
| LLN | Lower Limit Normal |
| LLT | Lower-Level Term |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| MMRM | Mixed Model for Repeated Measures |
| MVN | Multivariate Normal Distribution |
| NA | Not Available / Not Applicable |
| OD | Oculus Dexter (Right Eye) |
| OS | Oculus Sinister (Left Eye) |
| OU | Oculus Uterque (Both Eyes) |
| REML | Restricted Maximum Likelihood |
| PSC | Posterior Subcapsular Cataract |
| PT | Preferred Term |
| Q1 | 1st Quartile |
| Q3 | 3rd Quartile |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD | Standard Deviation |
| SD-OCT | Spectral Domain-Optical Coherence Tomography |
| SE | Study Eye |
| SGOT/AST | Aspartate Aminotransferase |
| SGPT/ALT | Alanine Aminotransferase |
| SOC | System Organ Class |
| STGD1 | Stargardt Disease 1 |
| TEAE | Treatment Emergent AE |
| ULN | Upper Limit Normal |

| Abbreviations | Description of abbreviations |
|---|---|
| UN | Urea Nitrogen |
| VA | Visual Acuity |
| WBC | White Blood Cells |
| WHO | World Health Organization |

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# 7 SIGNATURE

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