Study Title:

A Single-Center, Open Label, Phase 4 Study of the Safety and Efficacy of Fixed combination Phenylephrine 2.5%-Tropicamide 1% Ophthalmic Solution (MydCombi®) Administered with the MydCombi Dispenser for Pupil Dilation (The MIST 2.1 Study)

Document Title:

Statistical Analysis Plan

NCT Number 06217796

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M E M O R A N D U M

To: Lucinda Marinus, Eyenovia, Inc.

From: George DeMuth, Stat One LLC
Allison Ross, Stat One LLC
Sam Galloway, Stat One LLC

Date: 20 March 2024

Re: EYN-MYD-TP-41 Statistical Analyses

This memo summarizes the statistical analyses for the EYN-MYD-TP-41 study in the evaluation of phenylephrine 2.5%-tropicamide 1% ophthalmic solution for pupil dilation.

Descriptive summaries for continuous endpoints will include the number of subjects (n), mean, standard deviation or standard error of the mean, median, maximum, and minimum. Descriptive summaries for categorical variables will include the frequency and percentage. Any confidence intervals provided will be two-sided 95% intervals. Analyses will be conducted on available data from the Per-Protocol (PP) population that includes treated subjects without imputation of missing data. Demographics information will be provided for subjects in the PP and modified Intent-to-Treat (mITT) populations with a descriptive summary for the subjects age, and a categorical summary for the subjects age quartile, sex, race, ethnicity, eye color and eye color strata (for OD and OS).

The primary efficacy endpoint of change from baseline (CFB) in pupil diameter 30 minutes after drug administration will be analyzed for the PP and mITT populations, along with the change from baseline at additional time points (15, 60, 90, 150, 210, and 360 minutes), will be summarized descriptively as described above for continuous endpoints and with two-sided 95% confidence intervals for the mean CFB. A bootstrap analysis approach resampling subjects will be used to construct confidence intervals for the change from baseline and, optionally, can be used to obtain p-values for any hypotheses of mean change. Time points other than the primary evaluation at 30 minutes will be considered supporting analyses, and thus there will be no adjustment for multiplicity for these summaries or any others. The mean pupil diameter and mean change in pupil diameter (+/- SE) will be displayed by time in figures. The same analysis for the CFB in pupil diameter will also be done by number of sprays in each eye for the PP population but without confidence intervals being provided.

The proportions of eyes achieving pupil diameter of 6.0 mm or greater and 7.0 mm or greater at 30 minutes will be summarized descriptively and with two-sided 95% confidence intervals obtained from a bootstrap analysis approach re-sampling on subjects. The time from baseline to maximal pupil dilation will be summarized descriptively, with a 95% CI for the mean based on the T-distribution. The proportion of eyes that have gone from their maximum pupil dilation to 4.0 mm or less and 5.0 mm or less within 150, 210, and 360 minutes will also be summarized descriptively.

Safety evaluations will be based on the percentage of subjects with events reported. For adverse events, the number and percentage of subjects with one or more events will be summarized, along with the number of individual events. For the slit lamp evaluation, the number and percentage of subjects with an abnormality present at baseline and the number of percentage of subjects with a new abnormality noted post-treatment will be reported. Similarly, individual slip lamp findings will be summarized as present at baseline or post-treatment, if any new findings are observed. For adverse events and slit lamp exam findings, similar terms may be combined using a common term although no coding library will be used. IOP measurements will be recorded prior to and at the end of treatment. These will be summarized by

eye and as the average IOP at each assessment. The change from baseline in IOP will be summarized at the post-treatment visit, and the 95% CI for the mean change will be provided based on a bootstrap analysis. Baseline visual acuity (VA) will be summarized by eye and for all eyes combined using counts and percentages along with the distribution of shifts (improved, same, worsened).