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

| | |
|---|---|
| **BLA/Serial #:** | 215352 |
| **Drug Name:** | MydCombi (Tropicamide 1%/ Phenylephrine HCl 2.5%) Ophthalmic Spray |
| **Indication(s):** | For mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired. |
| **Applicant:** | Eyenovia, Inc. |
| **Date(s):** | Stamp Date: December 28, 2020<br>PDUFA Date: October 26, 2021<br>Review Date: August 10, 2021 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | IV |
| **Statistical Reviewer:** | Solomon Chefo, Ph.D. |
| **Concurring Reviewers:** | Guoxing Soon, Ph.D., Team Leader |
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**Keywords:** Mydriasis, Crossover Design

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# 1 EXECUTIVE SUMMARY

In this New Drug Application (NDA), the applicant seeks approval of MydCombi for mydriasis (dilation of the pupil of the eye) in routine diagnostic procedures and in conditions where short term pupil dilation is desired. MydCombi is a fixed-dose combination of tropicamide 1% - phenylephrine 2.5% ophthalmic solution (hereafter referred to as TR-PH) administered in microdroplet multi-dose spray (two sprays within 5 minutes). Of note, the individual components of MydCombi, phenylephrine 2.5% (hereafter referred to as PH) and tropicamide 1% (hereafter referred to as TR) ophthalmic solutions, are indicated for dilation of the pupil.

This NDA is based on data from two pivotal Phase 3, prospective, double-masked, controlled, crossover superiority studies: EYN-MYD-TP-31 (hereafter referred to as MIST-1) and EYN-MYD-TP-32 (here after referred to as MIST-2). MIST-1 was designed to evaluate the efficacy and safety of TR-PH compared to the individual components, TR and PH. In MIST-1 study, a total of 64 healthy volunteers of any age with screening photopic pupil diameter of ≤3.5 mm in each eye were randomized in equal ratio to one of the six sequences (ABC, BCA, CAB, ACB, BAC, CBA; where A is TR-PH, B is TR, and C is PH) and were to receive all three study drugs in a 3-treatment, 3-period (separated by 2-7 days), and 2-block balanced crossover design. Similarly, MIST-2 was designed to evaluate the efficacy and safety of TR-PH against Placebo (artificial tears). In MIST-2 study, a total of 70 healthy volunteers of any age with screening photopic pupil diameter of ≤3.5 mm in each eye were randomized in equal ratio to one of the two sequences (ABB or BAA; where A is TR-PH and B is placebo) and were to receive both study drugs in a 2-treatment, 3-period (separated by 2-7 days) crossover design. Randomization in both studies was stratified by iris color (dark versus light).

A total of 62 subjects in MIST-1 and 69 subjects in MIST-2 received at least one dose of the study drug and were evaluable for efficacy. In both studies, most subjects completed the study - only two subjects in MIST-1 and one subject in MIST-2 withdrew consent after their first treatment visit. A majority of subjects in both studies were male (58% in MIST-1 and 53% in MIST-2), white (55% in MIST-1 and 87% in MIST-2) and had dark iris color (84% in MIST-1 and 71% in MIST-2). The average age of subjects in MIST-1 was about 39 years (range: 12 – 64) and in MIST-2 was about 35 years (range: 13 – 66).

In both studies, efficacy evaluation for pupil dilation was based on pupil diameter (in mm) measured at each of the three treatment visits (periods) at baseline (pre-dose) and at times 20-, 35-, 50-, 65-, 80-, 120-, and 180-minute post-dose in both eyes. The mean change in pupil diameter from baseline at 35-minute post-dose was the primary efficacy endpoint and the proportion of eyes achieving a pupil diameter of ≥ 6.0 mm at 35-minute post-dose was the secondary efficacy endpoint in both studies.

In both studies, subjects treated with the combination product, TR-PH, demonstrated a statistically superior increase in pupil diameter at 35-minute post-dose compared to both the individual components, TR and PH, in MIST-1 and compared to placebo in MIST-2 (Figure 1 and Figure 2). For example, as shown in Table 4 and Table 5, the average pupil diameter increase at 35-minute post-dose in the TR-PH group in MIST-1 study was higher than in the TR group by 0.6 mm (95% CI: 0.4 to 0.8; p<0.001) and in the PH group by 3.9 mm (95% CI: 3.7 to 4.1; p<0.001) and in MIST-2 was higher than in the placebo group by 4.7 mm (95% CI: 4.5 to 4.8 mm; p-value < 0.001). Additionally, as shown in Figure 3 and Table 6, more subjects in TR-PH achieved a pupil diameter of ≥ 6 mm at

35-minute post-dose (95% in MIST-1 and 94% in MIST-2) compared to TR (79%) and PH (2%) in MIST-1 and compared to placebo (0%) in MIST-2.

Most subjects in the TR-PH group that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post-dose compared to the individual components in MIST-1 and to placebo in MIST-2 (Table 7). Additionally, in both studies, the time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time from baseline (time 0) to 180-minute post-dose was shorter in the TR-PH group than in the TR or PH groups in MIST-1 and in the placebo group in MIST-2. As shown in Table 8 and Table 9, the average time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time (0 to 180 minutes) was about 30 minutes in the TR-PH group compared to 44-50 minutes in TR and 155-163 minutes in PH in MIST-1 and compared to 178 minutes in placebo in MIST-2.

In summary, based on the collective efficacy evidence from the two adequate and well controlled trials of MIST-1 and MIST-2 studies, the reviewer concludes that the application provided substantial evidence of efficacy of TR-PH administered in microdroplet multi-dose spray (two sprays within 5 minutes) for dilation of the pupil.

# 2 INTRODUCTION

## 2.1 Overview

The applicant submitted this NDA for the use of MydCombi, a fixed-dose combination of tropicamide 1% - phenylephrine 2.5% ophthalmic solution for mydriasis in routine diagnostic procedures and in conditions where short term pupil dilation is desired.

This NDA contains two pivotal Phase 3, prospective, double-masked, controlled, crossover superiority studies: EYN-MYD-TP-31 (MIST-1) and EYN-MYD-TP-32 (MIST-2). A summary of these studies is outlined in **Error! Reference source not found.** below.

Table 1: Summaries of Studies Included in the Efficacy and Safety Analyses

| Phase 3 Study | Design | Key Entry Criteria | Planned number of subjects | Duration |
|---|---|---|---|---|
| EYN-MYD-TP-31 (MIST-1) | DOUBLE-MASKED, ACTIVE-CONTROLLED | • Male or female of any age.<br>• History of closed-angle glaucoma or anatomically narrow anterior chamber angles<br>• Iris or pupil abnormality | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at least 65 subjects to complete follow-up on 54 subjects | Study drug was administered at 3 treatment visits occurring over a 5 to 15-day period. At each treatment visit, one of the study drugs was administered to both eyes. |
| EYN-MYD-TP-32 (MIST-2) | DOUBLE-MASKED, PLACEBO-CONTROLLED | Same as MIST-1 | Up to 90 volunteer participants will be enrolled and drug administration will be initiated on at least 65 subjects to complete follow-up on 54 subjects | Same as MIST-1 |

Source: Table 1 of Applicant's Summary of Efficacy Report

## 2.2 Data Sources

The primary data source for this review were the clinical study reports, study protocols, statistical analysis plans, and the analyses and tabulation datasets. These were provided in an electronic submission located at \\CDSESUB1\evsprod\NDA215352\0001\. The primary analysis datasets are located at \\CDSESUB1\evsprod\NDA215352\0001\m5\datasets\ .

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

The reviewer found the quality of the submitted data and analysis acceptable.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

Study Design

Efficacy and safety support for MydCombi for mydriasis was based on data from two pivotal Phase 3, prospective, double-masked, controlled, crossover superiority studies: MIST-1 and MIST-2.

MIST-1 was designed to evaluate the efficacy and safety of the combination product (TR-PH) against the individual components (TR and PH). In this study, the sponsor enrolled a total of 64 healthy volunteers of any age with screening photopic pupil diameter of ≤3.5 mm in each eye. Eligible subjects were randomized in equal ratio to one of the six sequences (ABC, BCA, CAB, ACB, BAC, CBA; where A is TR-PH, B is TR, and C is PH) and received all three study drugs in a 3-treatment, 3-period, and 2-block balanced crossover design. MIST-1 was initiated on October 31, 2018 and completed on December 13, 2018.

MIST-2 was designed to evaluate the efficacy and safety of the combination product (TR-PH) against Placebo (artificial tears). In this study, the sponsor enrolled a total of 70 healthy volunteers of any age with screening photopic pupil diameter of ≤3.5 mm in each eye. Eligible subjects were randomized in equal ratio to one of the two sequences (ABB or BAA; where A is TR-PH and B is placebo) and received both study drugs in a 2-treatment, 3-period crossover design. MIST-2 was initiated on November 19, 2018 and completed on December 21, 2018.

Randomization in both studies was stratified by iris color (dark – either black or brown versus light – all other colors).

In both studies, study drugs were administered in microdroplet multi-dose spray (two sprays within 5 minutes) at three treatment visits (periods): Visit 1 (Day 1), Visit 2 (Day +3 to Day +8), and Visit 3 (Day +5 to Day +15); visits were separated by at least 2 days up to 7 days apart for wash-out. At each of the three treatment visits, baseline measurements were taken prior to study drug administration and then two doses of the study drug (separated by 5 minutes) were administered in both eyes.

Efficacy Evaluation

Efficacy evaluation in both studies was based on pupil dilation as measured by pupil diameter (in mm) using digital pupillometry in highly photopic condition. At each of the three treatment visits, pupil diameter in both studies was measured pre-treatment (baseline) and post-treatment at times 20-, 35-, 50-, 65-, 80-, 120-, and 180-minute from completion of the first of two study medications was administered. **The mean change in pupil diameter from baseline at 35 minutes was the primary efficacy endpoint** in both studies and **the proportion of eyes achieving pupil diameter of ≥ 6.0 mm at 35 minutes in the PP population was the secondary efficacy endpoint**.

Other exploratory efficacy endpoints defined in both studies include:

- Proportion of eyes achieving pupil size of ≥ 7.0 mm at 35 minutes
- Mean change in pupil diameter at other timepoints (20, 50, 65, 80, 120, and 180 minutes)
- Distribution of pupil diameters at 20, 35, 50, 65, 80, 120, and 180 minutes
- Time from baseline to maximal pupil dilation
- Pupillary light reflex (PLR) at each treatment visit

All primary analyses were performed using data from both eyes. To claim success, the combination product should be superior to both components in MIST-1 study and to placebo in MIST-2 study in the primary efficacy endpoint.

### 3.2.2 Statistical Methodology

*Primary Efficacy Analysis*

The applicant's primary efficacy analysis was an evaluation of superiority of TR-PH to TR and to PH in MIST-1 study and to placebo in MIST-2 study in the primary efficacy variable using a fixed-effects analysis of variance (ANOVA) model.

The model included an effect due to SUBJECT, EYE, SUBJECT x EYE, PERIOD (1, 2, or 3), TREATMENT, BASELINE PUPIL DIAMETER, IRIS COLOR CATEGORY (Dark vs Light), CROSS-TREATMENT CARRYOVER EFFECT (AB, AC, BA, BC, CA, CB) in MIST-1 and FIRST ORDER CARRYOVER EFFECT (A, B) in MIST-2. Within-subject correlation between eyes was accounted in the model in both studies.

The primary efficacy analysis in both studies was based on the per-protocol (PP) population including all randomized subjects who received at least one dose of study medication and completed all planned assessments (related to the primary endpoint) without major protocol violations. Subjects who did not receive each study drug were excluded from the PP population - two subjects in MIST-1 and one subject in MIST-2 who withdrew consent after their first treatment visit were not included in the PP populations which resulted in 62 completed subjects in MIST-1 and 69 completed subject in MIST-2 comprised the PP populations.

As a sensitivity analysis, the primary efficacy analysis was also performed on the modified per-protocol (mPP) population including all randomized subjects who completed all planned assessments without major protocol deviations for the given treatment visit. That is, unlike in the PP population, subjects who only complete 1 or 2 of the 3 treatment visits were included in the mPP population.

Additional sensitivity analysis was performed based on the intent-to-treat (ITT) population including all randomized subjects to a study drug treatment sequence who received a dose of study drug. In this analysis, missing data for the two subjects in MIST-1 and the one subject in MIST-2 that were excluded from the PP population were imputed using multiple imputation approach. See detail below (*RE: Handling of Missing Data*).

***Reviewer's Remark:***

*For the superiority evaluation in both studies, the Applicant used the following SAS code:*

(b) (4)

[redacted]

*However, for the MIST-1 study, the SAS Log file displayed the following message "**Convergence criteria met but final Hessian is not positive definite**". Because the final Hessian was not positive definite, the reliability of the standard errors for the treatment comparisons were questionable. As a result, on April 14, 2021, an information request (IR) with the following concerns and recommendations regarding the model specification was submitted to the Applicant:*

i) *The model is likely overparameterized due to the specification of **SUBJID*PARAMCD** as a fixed effect in the model. To mitigate the potential model overparameterization, the Agency requested that SUBJID alone (not SUBJID*PARAMCD) be specified as a fixed effect or as a random effect in the model. See sample SAS code below.*

   *Additionally, the inclusion of a cross-treatment carryover effect variable in the model (TRTC in table below) with 7- level (AB, AC, BA, BC, CA, CB, and 1 for Period 1) instead of the first-order carryover effect (TRTCS in table below) with 4- level (A, B, C, 1 for period 1) further overparameterized the model. In the 7-level carryover effect, the Applicant considered the treatment received at the prior period plus the treatment at the current period as carryover effect. However, it is unclear why the treatment at the current period was considered as part of the carryover effect. In the 4-level carryover effect, the Applicant defined only the treatment received in the prior period as a carryover effect but did not use this variable in the model. Thus, to mitigate the possible model overparameterization and limited sample size, the Agency recommended using TRTCS with 4-levels in the model to account for the carryover effect.*

(b) (4)

[redacted]

ii) *In the Applicant model specification above (**RE: repeated paramcd/subject = subjid type=cs**), the Applicant assumed the same variance for the two eyes within a given period. In the absence of a reasonable justification, the Agency requested that the variances for the two eyes be assumed different in the model specification.*

*To address the above issues, the Agency recommended the following two options:*


*In their response to the Agency's IR, the Applicant acknowledged the Agency's concern and accepted the recommendation. Additionally, to further mitigate the model overparameterization, the Applicant proposed to exclude the carryover effect from the model because the recovery time after treatment administration is between 3-8 hours and subjects in both studies had at least two days between visits. The Agency agreed with the Applicant's proposal on the condition that no subject had less than 3 days between visits. The reviewer confirmed that no subject in MIST-1 study had less than 3-days between visits and some subjects in the MIST-2 study had a minimum of 2-days between visits.*

*The Applicant also proposed to exclude non-significant fixed effects from the model to further mitigate the model overparameterization. In MIST-1 study, the effect of PERIOD (VISIT), VISIT-by-TREATMENT interaction, CARRYOVER EFFECT, and IRIS COLOR were not significant and in MIST-2 study the effect of VISIT, VISIT-by-TREATMENT interaction, and IRIS COLOR were not significant. The Agency agreed with the Applicant's proposed approach. Thus, the final model for MIST-1 study included EYE, TREATMENT GROUP, and BASELINE PUPIL DIAMETER and for MIST-2 study included EYE, TREATMENT GROUP, BASELINE PUPIL DIAMETER and CARRYOVER EFFECT. In both studies, within-subject correlation between eyes was accounted in the model.*

*Secondary Efficacy Analysis*

The Applicant's secondary efficacy analysis was an evaluation of superiority of TR-PH to TR and to PH in MIST-1 study and to placebo in MIST-2 study in the proportion of eyes achieving a pupil diameter of $\geq$ 6.0 mm at 35 minutes in the PP population. Treatment comparison was based on Generalized Estimating Equation (GEE) approach accounting for the within-subject correlation between eyes. In addition to the results from the GEE model, the reviewer presented two-sided 95% confidence interval estimates for the treatment differences in proportions based on 1000 bootstrap samples.

*Type I Error Control (Plan for Multiplicity Adjustment):*

The overall study-wise Type I error rate for superiority testing was controlled at a two-sided significance level of 5%. To claim success, the combination product should be superior to both components in MIST-1 study and to placebo in MIST-2 study in the primary efficacy endpoint and hence no multiplicity adjustment needed.

*Handling of Missing Data*

The Applicant performed the primary efficacy analyses in both studies using the PP population including all randomized subjects who received at least one dose of study medication and completed all planned assessments without major protocol violations. Thus, there was no missing data issue in the primary analysis. Overall, only two subjects in MIST-1 study and one subject in MIST-2 study who withdrew consent after their first treatment visit were not included in the PP populations. To assess the impact of excluding these subjects in the primary analysis, sensitivity analyses were performed in both studies using multiple imputation approach using the worse treatment arm in MIST-1 and using the placebo arm in MIST-2. Except for minor numerical differences, the sensitivity analysis results provided similar conclusion.

### 3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

Table 2 below shows the summary of subject disposition in both studies. As shown, a total of 64 and 70 subjects were enrolled in MIST-1 and MIST-2 studies, respectively. In both studies, most subjects completed the study. Only two subjects in MIST-1 and one subject in MIST-2 withdrew consent after their first treatment visit. These subjects were excluded in the primary efficacy analysis based on the PP analysis population but were included in the mPP population intended for sensitivity analysis. No subject was lost to follow-up or terminated early due to a safety event.

Table 2:Subject Disposition

| | MIST-1 | MIST-2 |
|---|---|---|
| Number of randomized subjects | 64 | 70 |
| Completed | 62 (96.9%) | 69 (98.6%) |
| Discontinued | 2 (3.1%) | 1 (1.4%) |
| Analysis Populations | | |
| ITT | 64 (100%) | 70 (100%) |
| PP | 62 (96.9%) | 69 (98.6%) |
| mPP | | |
| TR-PH | 62 (96.9%) | 69 (98.6%) |
| TR | 64 (100%) | -- |
| PH | 62 (96.9%) | -- |
| Placebo | -- | 70 (100%) |
| Safety | | |
| TR-PH | 62 (96.9%) | 69 (98.6%) |
| TR | 64 (100%) | -- |
| PH | 62 (96.9%) | -- |
| Placebo | -- | 70 (100%) |

TR-PH: a fixed-dose combination of Tropicamide 1% - Phenylephrine 2.5% Ophthalmic Solution; PH: Phenylephrine 2.5%; TR: Tropicamide 1%

Demographic Characteristics

The summaries of the demographic characteristics for all randomized subjects in MIST-1 and MIST-2 studies are shown in Table 3. As shown, a majority of subjects in both studies were male (58% in MIST-1 and 53% in MIST-2), white (55% in MIST-1 and 87% in MIST-2) and had dark iris color (84% in MIST-1 and 71% in MIST-2). The average age of subjects in MIST-1 was about 39 years (range: 12 – 64) and in MIST-2 was about 35 years (range: 13 – 66).

Table 3: Summary of Demographic and Baseline Disease Characteristics (Randomized Subjects)

| | MIST-1 (N = 64) | MIST-2 (N = 70) |
|---|---|---|
| Age (Years) | | |
| Mean (SD) | 39.4 (12.00) | 35.4 (14.55) |
| Median | 36.5 | 33.5 |
| Range | 12 – 64 | 13 – 66 |
| Age Categories | | |
| < 30 | 15 (23.4%) | 27 (38.6%) |
| 30-40 | 22 (34.4%) | 18 (25.7%) |
| ≥ 40 | 27 (42.2%) | 25 (35.7%) |
| Sex | | |
| Male | 37 (57.8%) | 37 (52.9%) |
| Female | 27 (42.2%) | 33 (47.1%) |
| Race | | |
| Asian | 8 (12.5%) | 1 (1.4%) |
| Black or African | 19 (29.7%) | 7 (10.0%) |
| White | 35 (54.7%) | 62 (88.6%) |
| Multi-Race | 2 (65.6%) | -- |
| Ethnicity | | |
| Hispanic or Latino | 22 (34.4%) | 35 (50.0%) |
| Not Hispanic or Latino | 42 (65.6%) | 35 (50.0%) |
| Iris Color Strata; n (%) | | |
| Light | 10 (15.6%) | 20 (28.6%) |
| Dark | 54 (84.4%) | 50 (71.4%) |

Source: Table 3 of MIST-1 and MIST-2 Clinical Study Reports.
Note: Iris color 'Dark' included brown and black; 'Light' included blue, gray, green, and hazel.

### 3.2.4 Efficacy Results and Conclusions

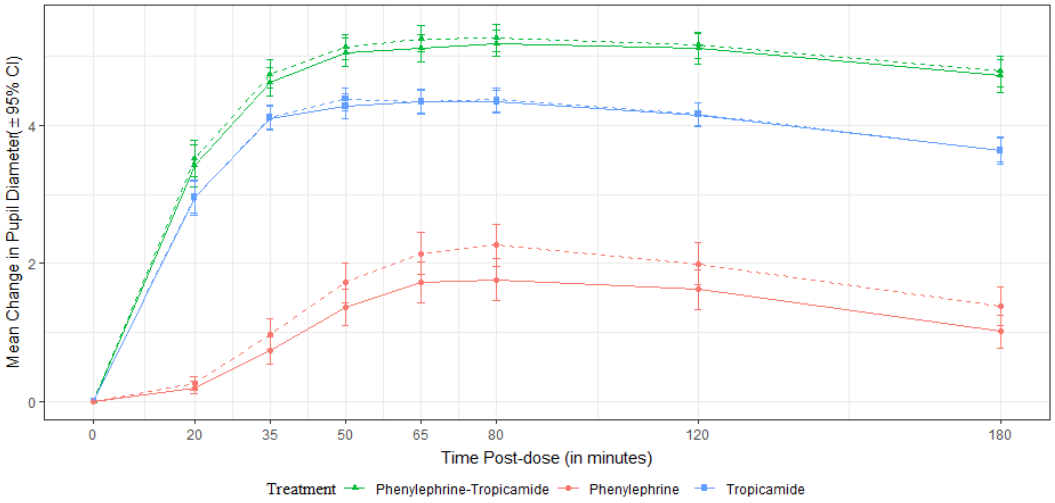
In this section, results of the primary and secondary efficacy variables in both studies are presented and discussed.

**Analysis of Primary Efficacy Variable: Change in Pupil Diameter from Baseline at 35-minute**

In both studies, pupil diameter was measured in both eyes at each of the three treatment visits at pre-treatment (baseline) and post-treatment at times 20-, 35-, 50-, 65-, 80-, 120-, and 180-minute from completion of the first of two study medications was administered at baseline. The change in pupil diameter from baseline at 35-minutepost-dose was the primary efficacy variable in both studies. The efficacy criterion was demonstration of superiority of TR-PH to TR and to PH in MIST-1 study and to placebo in MIST-2 study in the primary efficacy variable. Figure 1 and Figure 2 below show the mean change in pupil diameter over time in both eyes (dashed lines: left eye [OS], solid lines: right eye [OD]) in the MIST-1 and MIST-2 studies, respectively.

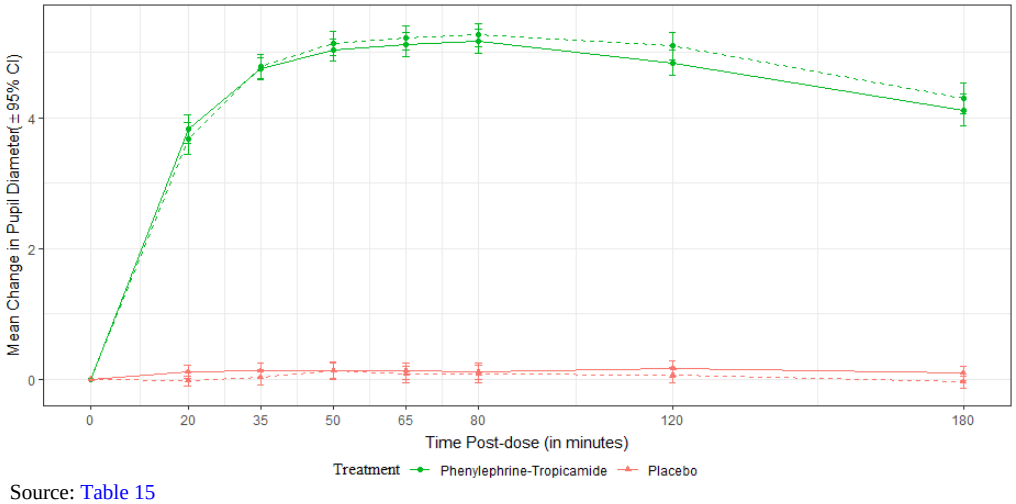
As shown, the combination product (TR-PH) displayed a greater gain in pupil diameter from baseline over time than the individual components (TR or PH) in MIST-1 and the placebo group in MIST-2 did. In both studies, the TR-PH group had a sharp gain during the first 35 to 50 minutes followed by a stable gain through 120 minutes and a slight decline through 180 minutes. Eyes in MIST-1 study achieved a maximal average pupil diameter of about 8 mm in TR-PH, 7mm in TR, and 5 mm in PH at median times of 80, 65, and 80 minutes, respectively (Table 13). Similarly, eyes in MIST-2 study achieved a maximal average pupil diameter of about 8 mm in TR-PH and 3 mm in placebo at median times of 65-80 minutes and 65 minutes, respectively.

Figure 1: Mean Change in Pupil Diameter from Baseline over Time Post-dose – MIST-1 (Per-protocol Population)




Source: Table 14

Figure 2: Mean Change in Pupil Diameter from Baseline over Time Post-dose – MIST-2 (Per-protocol Population)




Source: Table 15

Clearly, in MIST-1 study, the greater gain achieved in pupil diameter in the combination product TR-PH was mainly attributed to the individual component of TR than to PH.

Treatment comparison in the mean change in pupil diameter between the treatment groups at 35-minute post-dose was made using ANOVA model using treatment as factor, baseline pupil diameter

as a covariate, and carryover effect as a factor (only in MIST-2). An unstructured covariance structure was used to account for the within-subject correlation between eyes. In both studies, the effects of period, iris color, treatment-by-period interaction, and carryover effect (only in MIST-1) were determined statistically non-significant and excluded from the model.

Table 4 and Table 5 below display the summary of the pupil diameter at baseline and that of the mean change in pupil diameter from baseline at 35-minute post-dose in the MIST-1 and MIST-2 studies, respectively. The tables also display the treatment differences in the least squares (LS) means based on the model including the corresponding 95% confidence interval (CI) estimates and p-values (*TR-PH minus PH and TR-PH minus TR in MIST-1 study and TR-PH minus Placebo in MIST-2 study*).

Table 4: Summary of Mean Change in Pupil Diameter from Baseline at 35-Minute Post-Dose (MIST-1 Study) (Per-Protocol Population)

| | | TR-PH | | TR | | PH | |
|---|---|---|---|---|---|---|---|
| Visit | Summary | Right Eye (N = 62) | Left Eye (N = 62) | Right Eye (N = 62) | Left Eye (N = 62) | Right Eye (N = 62) | Left Eye (N = 62) |
| Baseline | Mean (SD) | 2.7 (0.57) | 2.6 (0.47) | 2.7 (0.60) | 2.6 (0.52) | 2.7 (0.57) | 2.6 (0.53) |
| | Median | 2.7 | 2.6 | 2.6 | 2.6 | 2.6 | 2.6 |
| | Range | 1.5 - 4.7 | 1.6 - 3.6 | 1.5 - 4.6 | 1.4 - 3.8 | 1.4 - 4.3 | 1.6 - 3.8 |
| 35-Minutes Post-dose | Mean (SD) | 7.3 (0.89) | 7.3 (0.98) | 6.8 (0.86) | 6.7 (0.87) | 3.4 (0.90) | 3.6 (0.93) |
| | Median | 7.4 | 7.5 | 6.8 | 6.9 | 3.2 | 3.3 |
| | Range | 3.3 - 9.0 | 3.7 - 9.0 | 5.0 - 8.8 | 4.4 - 8.6 | 1.7 - 6.2 | 2.0 - 6.1 |
| Change from Baseline | Mean (SD) | 4.6 (0.83) | 4.7 (0.82) | 4.1 (0.72) | 4.1 (0.68) | 0.7 (0.79) | 1.0 (0.89) |
| | Median | 4.7 | 4.9 | 4.2 | 4.2 | 0.6 | 0.7 |
| | Range | 0.8 - 6.2 | 1.3 - 6.3 | 2.4 - 5.4 | 2.2 - 5.9 | -0.5 - 3.8 | -0.1 - 3.5 |
| Treatment comparison: Combination product (TR-PH) versus Individual components (TR and PH) | | | | | | | |
| Difference in LS Means from TR-PH (95% CI)<br>p-value | | -- | | 0.57 (0.36, 0.77)<br><0.001 | | 3.86 (3.65, 4.06)<br><0.001 | |

Source: Reviewer analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA215352\0001\m5\datasets\eyn-myd-tp-31\analysis\adam\datasets.

In MIST-1 study, as shown in Table 4, the combination product (TR-PH) displayed a statistically superior increase in the mean pupil diameter from baseline at 35-minutes post-dose compared to each of the individual components (TR or PH). For example, the average pupil diameters increase at 35-minute post-dose in the TR-PH group was higher than in the TR group by 0.6 mm (95% CI: 0.4 to 0.8; p<0.001) and in the PH group by 3.9 mm (95% CI: 3.7 to 4.1; p<0.001). Analyses performed within each period separately provided consistent efficacy results (See Table 16 and Figure 6 in the Appendix).

Similarly, as shown in Table 5, the combination product in MIST-2 study showed a statistically superior increase in pupil diameter compared to placebo. For example, the average pupil diameters increase at 35-minutes post-dose in the TR-PH group was higher than in the placebo group by 4.7 mm (95% CI: 4.5 to 4.8 mm; p-value < 0.001). Analyses performed within each period separately provided consistent efficacy results.

Table 5: Summary of Mean Change in Pupil Diameter from Baseline at 35-Minute Post-Dose - MIST-2 (Per-protocol Population)

| | | TR-PH | | Placebo | |
|---|---|---|---|---|---|
| Visit | Summary | Right Eye (N = 69) | Left Eye (N = 69) | Right Eye (N = 69) | Left Eye (N = 69) |
| Baseline | Mean (SD) | 2.6 (0.48) | 2.5 (0.48) | 2.6 (0.52) | 2.6 (0.47) |
| | Median | 2.6 | 2.5 | 2.5 | 2.5 |
| | Range | 1.6 - 3.5 | 1.5 - 3.9 | 1.5 - 4.2 | 1.5 - 4.0 |
| 35-Minutes Post-dose | Mean (SD) | 7.3 (0.80) | 7.3 (0.83) | 2.8 (0.66) | 2.6 (0.59) |
| | Median | 7.3 | 7.4 | 2.6 | 2.5 |
| | Range | 5.2 - 9.0 | 4.9 - 8.9 | 1.7 - 5.3 | 1.7 - 5.5 |
| Change from Baseline | Mean (SD) | 4.7 (0.73) | 4.8 (0.80) | 0.1 (0.50) | 0.0 (0.50) |
| | Median | 4.7 | 4.8 | 0.1 | 0.0 |
| | Range | 3.1 - 6.1 | 2.5 - 6.5 | -0.5 - 3.1 | -1.0 - 3.2 |
| Treatment comparison: Combination product (PH-TR) versus Placebo | | | | | |
| Difference in LS Means from PH-TR (95% CI) | | | -- | | 4.65 (4.51, 4.79) |
| p-value | | | | | <0.001 |

Source: Reviewer analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA215352\0001\m5\datasets\eyn-myd-tp-32\analysis\adam\datasets.

Additionally, more subjects in the combination product (TR-PH) achieved ≥ 6 mm or ≥ 7 mm of pupil diameter at 35-minute post-dose compared to TR or to PH in MIST-1 and compared to placebo in MIST-2 (Table 6 and Figure 3). For example, the proportion of eyes achieving ≥ 6 mm of pupil diameter at 35-minute post-dose was 95% in TR-PH, 79% in TR, and about 2% in PH in MIST-1 study and was 94% in TR-PH and 0% in placebo in MIST-2 study. Based on the average of the two eyes data, the response rates in the TR-PH group were superior to each of the individual components in MIST-1 and to Placebo in MIST-2.

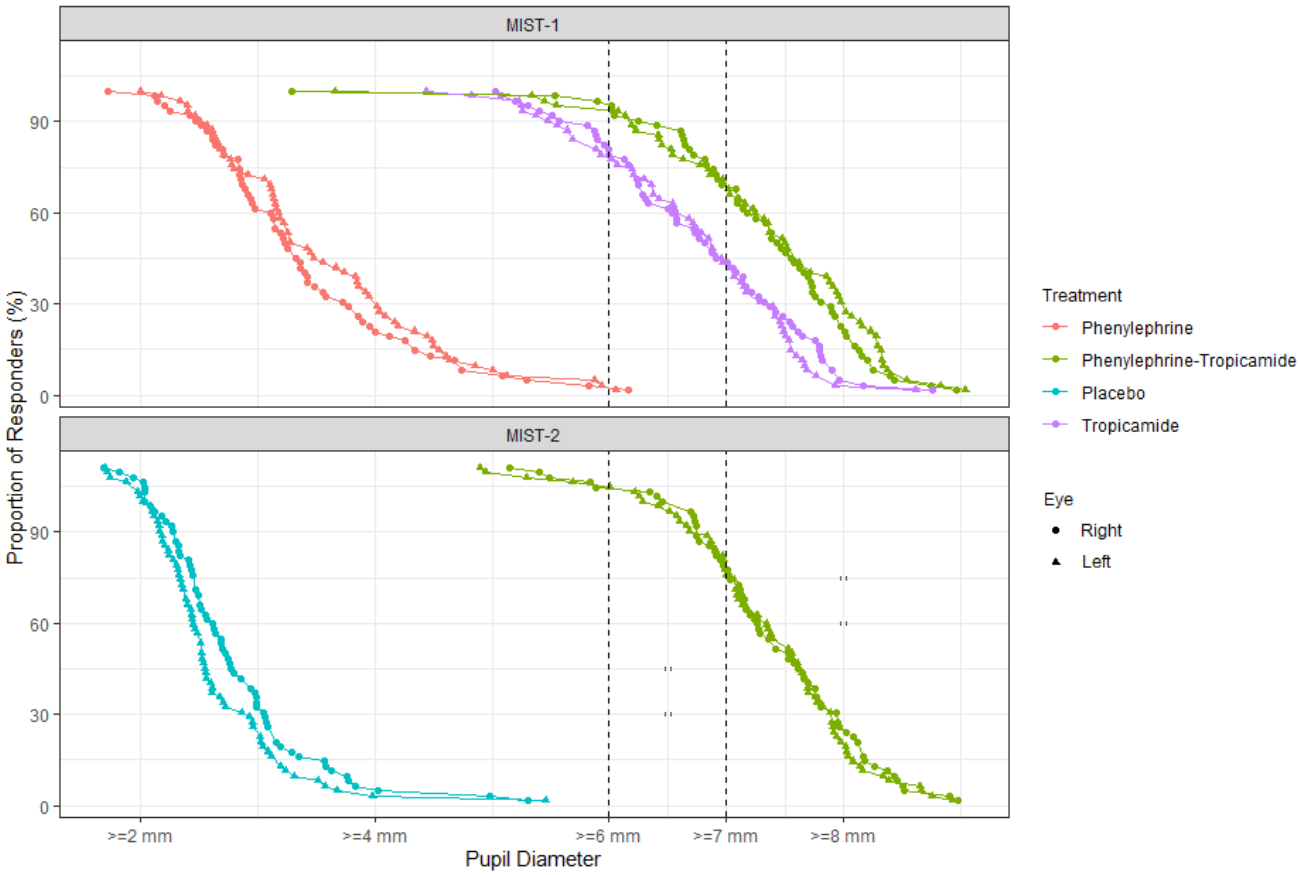
Table 6: Proportion of Subjects Who Achieved a Pupil Diameter of ≥6 mm and ≥7 mm at 35-Minute Post-Dose (Per-protocol Population)

| | | MIST-1 | | | MIST-2 | |
|---|---|---|---|---|---|---|
| Pupil Diameter | Eye | PH-TR (N = 62) | TR (N = 62) | PH (N = 62) | PH-TR (N = 69) | Placebo (N = 69) |
| >= 6.0 mm | Right | 59 (95.2%) | 49 (79.0%) | 1 (1.6%) | 64 (92.8%) | 0 |
| | Left | 58 (93.5%) | 48 (77.4%) | 1 (1.6%) | 65 (94.2%) | 0 |
| | Average | 59 (95.2%) | 49 (79.0%) | 1 (1.6%) | 65 (94.2) | 0 |
| Difference in proportion from PH-TR (95% CI) [1] | | -- | 16.2 (8.1, 25.8) | 93.6 (87.1, 98.4) | -- | 94.2 (88.4, 97.5) |
| >= 7.0 mm | Left | 42 (67.7%) | 27 (43.5%) | 0 | 48 (69.6%) | 0 |
| | Right | 42 (67.7%) | 26 (41.9%) | 0 | 47 (68.1%) | 0 |
| | Average | 42 (67.7%) | 25 (40.3%) | 0 | 47 (68.1%) | 0 |
| Difference in proportion from PH-TR (95% CI) [1] | | -- | 27.4 (16.1, 40.3) | 67.7 (56.5, 79.0) | -- | 68.1 (56.5, 78.3) |

Source: Reviewer analysis based on ADEFF.xpt dataset

[1] Difference and confidence intervals were based on average of two eyes. Confidence intervals were based on 1000 bootstrap samples.

Figure 3: Cumulative Distribution of Pupil Diameter at 35-Minute Post-Dose
(Per-Protocol Population)




Source: Reviewer analysis based on ADEFF.xpt dataset and Figure 7 of MIST-1 and Figure 10 of MIST-2 Clinical Study Reports.

Most of the subjects in the TR-PH group that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post-dose.

As shown in Table 7, 87% of subjects in TR-PH group (in both eyes) that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post-dose compared to 61% in the right eye and 66% in the left eye in TR and about 2% in both eyes in PH. In MIST-2, 75% of subjects in the right eye and 81% in the left eye in TR-PH that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post dose compared to 0% in the placebo group.

Table 7: Proportion of Subjects Who Achieved a Pupil Diameter of ≥6 mm at 35-Minute Post-Dose and Maintained through 180-Minute Post-Dose
(Per-protocol Population)

| | | MIST-1 | | | MIST-2 | |
|---|---|---|---|---|---|---|
| | Eye | TR-PH (N = 62) | TR (N = 62) | PH (N = 62) | PH-TR (N = 69) | Placebo (N = 69) |
| Achieved >= 6.0 mm at 35 minutes and maintained through 180 minutes | Right | 54 (87.1%) | 38 (61.3%) | 1 (1.6%) | 52 (75.4%) | 0 |
| | Left | 54 (87.1%) | 41 (66.1%) | 1 (1.6%) | 56 (81.2%) | 0 |

Source: Reviewer analysis based on ADEFF.xpt dataset.

Additionally, in both studies, the time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time from baseline (time 0) to 180 minutes post-dose was shorter in the TR-PH group than in the TR or PH groups in MIST-1 and in the placebo group in MIST-2.

Table 8 and Table 9 below display a summary of the time to a pupil diameter of ≥ 6 mm was achieved first during the observation time in each treatment group in the MIST-1 and MIST-2 studies, respectively. In this summary, subjects who did not achieve a pupil diameter of ≥ 6 mm across the observation time was censored at the last observation time of 180 minutes.

As shown, in MIST-1, almost all eyes (61 right and left eyes) in TR-PH, 57 right and 54 left eyes in TR, and 9 right and 13 left eyes in PH achieved a pupil diameter of ≥ 6 mm at some time during the observation time through 180-minute. The average time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time was shorter in the TR-PH group than in the individual components. For example, it took an average of about 30 minutes in both eyes in the TR-PH group, 44 minutes in the right eye and 50 minutes in the left eye in the TR group, and 163 minutes in the right eye and 155 minutes in the left eye in the PH group to achieve a pupil diameter of ≥ 6 mm for the first time.

Table 8: Summary of the Time to a Pupil Diameter of ≥ 6 mm Achieved First – MIST-1 Study (Per-protocol Population)

| | TR-PH (n=62) | | TR (n=62) | | PH (n=62) | |
|---|---|---|---|---|---|---|
| Summary | OD | OS | OD | OS | OD | OS |
| Achieved >= 6mm | 61 (98.4) | 61 (98.4) | 57 (91.9) | 54 (87.0) | 9 (14.5) | 13 (21.0) |
| Censored | 1 (1.6%) | 1 (1.6) | 5 (8.1) | 8 (13.0) | 53 (85.5) | 49 (79.0) |
| Median (95% CI) | 20 (20, 35) | 20 (20, 35) | 35 (20, 35) | 35 (n/a, n/a) | n/a | n/a |
| Mean (SE) [1] | 29.4 (2.78) | 30.3 (2.78) | 43.8 (5.38) | 50.3 (6.49) | 162.6 (5.40) | 154.7 (6.29) |

Source: Reviewer analysis based on ADEFF.xpt dataset.
[1] Based on the area under the survival curves (Figure 4) from the beginning of follow-up time (time=0) to the minimum of the largest observed time on each of the groups (time=180).
Abbreviation: OD: Right Eye; OS: Left Eye

In the MIST-2 study (Table 9), the time it took to achieve a pupil diameter of ≥ 6 mm for the first time in the TR-PH group (28 minutes in the right eye and 30 minutes in the left eye) is similar to what has been observed in MIST-1. In the placebo group in MIST-2, only one subject in the left eye achieved a pupil diameter of ≥ 6 mm for the first time at an average of 178 minutes.

Table 9: Summary of the Time to a Pupil Diameter of ≥ 6 mm Achieved First - MIST-2 Study (Per-protocol Population)

| | TR-PH (n=62) | | Placebo (n=62) | |
|---|---|---|---|---|
| Summary | OD | OS | OD | OS |
| Achieved >= 6mm | 68 (99.0) | 67 (97.1) | 0 | 1 (1.0) |
| Censored | 1 (1.0) | 2 (2.9) | 69 (100) | 68 (99.0) |
| Median (95% CI) | 20 (n/a, n/a) | 20 (n/a, n/a) | n/a | n/a |
| RMST (SE) [1] | 27.8 (2.48) | 30.3 (3.29) | 180 (n/a) | 178.3 (1.66) |

Source: Reviewer analysis based on ADEFF.xpt dataset.
[1] Based on the area under the survival curves (Figure 5) from the beginning of follow-up time (time=0) to the minimum of the largest observed time on each of the groups (time=180).
Abbreviation: OD: Right Eye; OS: Left Eye

### 3.2.5 Efficacy Conclusion

Based on the collective efficacy evidence from the two adequate and well controlled trials of MIST-1 and MIST-2 studies, the reviewer concluded that the combination product displayed a statistically superior improvement in pupil diameter from baseline at 35-minute post-dose compared to each of the individual components in MIST-1 and to placebo in MIST-2.

At 35 minutes post-dose, 95% (or 68%) of eyes treated with the combination product (TR-PH) in MIST-1 study achieved ≥ 6 mm (or ≥ 7 mm) pupil diameter compared to 79% (or 40%) and about 2% (or 0%) of eyes treated with the individual components of TR and PH, respectively. Similarly, in MIST-2 study, about 94% and 68% of treated eyes with the combination product achieved ≥ 6 mm and ≥ 7 mm in pupil diameter, respectively, compared to 0% of placebo treated eyes. Moreover, most subjects in the TR-PH group that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post-dose compared to the individual components in MIST-1 and to placebo in MIST-2.

The average time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time from baseline (time 0) to 180-minute post-dose was shorter in the TR-PH group (about 30 minutes) than in the individual components (44-50 minutes in TR and 155-163 minutes in PH) in MIST-1 and in the placebo group (about 178 minutes in the left eye) in MIST-2.

Additional analyses performed on the modified PP population and reference based multiple imputation (for two subjects excluded in the PP population) provided similar conclusion except for minor numerical differences.

### 3.3 Safety Evaluation

In this section, a high-level summary of the safety data is presented and discussed. For a comprehensive safety evaluation, the reviewer defers to the FDA medical review.

Summary of Treatment Exposure

In both MIST-1 and MIST-2 studies, all subjects except for two subjects in MIST-1 and one subject in MIST-2 who withdrew consent after their first treatment visit, had received at least one successful administration of study drug in both eyes at all three treatment visits. Table below shows the treatment exposure for each of the treatment sequences across all visits in the two studies:

Treatment Exposure Across All Visits (Safety Analysis Set)

MIST-1

| | Sequence ABC (N=10) | Sequence ACB (N=11) | Sequence BAC (N=11) | Sequence BCA (N=11) | Sequence CAB (N=10) | Sequence CBA (N=11) | All Subjects (N=64) |
|---|---|---|---|---|---|---|---|
| Received At Least One Successful Spray for All 3 Treatments: n (%) | | | | | | | |
| Yes in OD | 10 (100.0%) | 11 (100.0%) | 10 ( 90.9%) | 10 ( 90.9%) | 10 (100.0%) | 11 (100.0%) | 62 ( 96.9%) |
| Yes in OS | 10 (100.0%) | 11 (100.0%) | 10 ( 90.9%) | 10 ( 90.9%) | 10 (100.0%) | 11 (100.0%) | 62 ( 96.9%) |
| Received At Least Two Successful Sprays for All 3 Treatments: n (%) | | | | | | | |
| Yes in OD | 10 (100.0%) | 10 ( 90.9%) | 10 ( 90.9%) | 10 ( 90.9%) | 10 (100.0%) | 11 (100.0%) | 61 ( 95.3%) |
| Yes in OS | 10 (100.0%) | 11 (100.0%) | 10 ( 90.9%) | 10 ( 90.9%) | 10 (100.0%) | 11 (100.0%) | 62 ( 96.9%) |

Source: Table 29 of MIST-1 Clinical Study Report.

A: Phenylephrine 2.5% - Tropicamide 1% Ophthalmic Solution; B = Tropicamide 1% Ophthalmic Solution; and C = Phenylephrine 2.5% Ophthalmic Solution

MIST-2

| | Sequence ABB (N=37) | Sequence BAA (N=33) | All Subjects (N=70) |
|---|---|---|---|
| Received At Least One Successful Spray for All 3 Treatments: n (%) | | | |
| Yes in OD | 37 (100.0%) | 32 ( 97.0%) | 69 ( 98.6%) |
| Yes in OS | 37 (100.0%) | 32 ( 97.0%) | 69 ( 98.6%) |
| Received At Least Two Successful Sprays for All 3 Treatments: n (%) | | | |
| Yes in OD | 37 (100.0%) | 32 ( 97.0%) | 69 ( 98.6%) |
| Yes in OS | 37 (100.0%) | 32 ( 97.0%) | 69 ( 98.6%) |

Source: Table 31 of MIST-2 Clinical Study Report.

A: Phenylephrine 2.5% - Tropicamide 1% Ophthalmic Solution and B = Placebo

Summary of Treatment Emergent Adverse Events (TEAEs)

In both studies, the rate of TEAEs was low and all events were ocular in nature. A total of 10 TEAEs in MIST-1 (2 in TR-PH, 4 each in TR and PH) and two TEAEs both in TR-PH in MIST-2 were reported. In both studies, there were no serious TEAEs and no TEAEs leading to early treatment discontinuation and/or death.

Table below shows the summary of ocular TEAEs reported in the two studies.

Summary of Ocular TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)

MIST-1

| System Organ Class (SOC) Preferred Term (PT) | Phenylephrine 2.5%-tropicamide 1% (N=62) | | Tropicamide 1% (N=64) | | Phenylephrine 2.5% (N=62) | | All Subjects (N=64) | |
|---|---|---|---|---|---|---|---|---|
| | Events | Subjects n (%) | Events | Subjects n (%) | Events | Subjects n (%) | Events | Subjects n (%) |
| Number of Subjects with Ocular TEAEs | 2 | 2 ( 3.2%) | 4 | 4 ( 6.3%) | 4 | 4 ( 6.5%) | 10 | 6 ( 9.4%) |
| | | | | | | | | |
| Eye disorders | 2 | 2 ( 3.2%) | 4 | 4 ( 6.3%) | 3 | 3 ( 4.8%) | 9 | 5 ( 7.8%) |
| Vision blurred | 1 | 1 ( 1.6%) | 3 | 3 ( 4.7%) | 1 | 1 ( 1.6%) | 5 | 3 ( 4.7%) |
| Visual acuity reduced | 1 | 1 ( 1.6%) | 1 | 1 ( 1.6%) | 1 | 1 ( 1.6%) | 3 | 1 ( 1.6%) |
| Eye pain | 0 | 0 | 0 | 0 | 1 | 1 ( 1.6%) | 1 | 1 ( 1.6%) |
| | | | | | | | | |
| Investigations | 0 | 0 | 0 | 0 | 1 | 1 ( 1.6%) | 1 | 1 ( 1.6%) |
| Vital dye staining cornea present | 0 | 0 | 0 | 0 | 1 | 1 ( 1.6%) | 1 | 1 ( 1.6%) |

Source: Table 25 of MIST-1 Clinical Study Report

MIST-2

| System Organ Class (SOC) Preferred Term (PT) | Phenylephrine 2.5%-tropicamide 1% (N=69) | | Placebo (N=70) | | All Subjects (N=70) | |
|---|---|---|---|---|---|---|
| | Events | Subjects n (%) | Events | Subjects n (%) | Events | Subjects n (%) |
| Number of Subjects with Ocular TEAEs | 2 | 2 ( 2.9%) | 0 | 0 | 2 | 2 ( 2.9%) |
| | | | | | | |
| Eye disorders | 1 | 1 ( 1.4%) | 0 | 0 | 1 | 1 ( 1.4%) |
| Photophobia | 1 | 1 ( 1.4%) | 0 | 0 | 1 | 1 ( 1.4%) |
| | | | | | | |
| General disorders and administration site conditions | 1 | 1 ( 1.4%) | 0 | 0 | 1 | 1 ( 1.4%) |
| Instillation site pain | 1 | 1 ( 1.4%) | 0 | 0 | 1 | 1 ( 1.4%) |

Source: Table 27 of MIST-2 Clinical Study Report

Based on the overall safety evaluation, MydCombi, a fixed-dose combination of tropicamide 1% - phenylephrine 2.5% ophthalmic solution administered in microdroplet multi-dose spray (two sprays within 5 minutes), appeared to be well tolerated.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the primary efficacy variable of the mean change in pupil diameter from baseline at 35-minutes post-dose was summarized by the subgroups of Age, Gender, Race, and Iris Color. It should be noted that some categories of race were pooled as 'Others' due to small sample size.

Table 10 and Table 11 below shows summary of the mean change in pupil diameter from baseline at 35-minutes post-dose by the subgroups of Age, Gender, Race, and Iris Color. As shown below, within the levels of each subgroup variables, subjects in the TR-PH group displayed greater gain in pupil diameter from baseline at 35-minutes post-dose compared to TR and PH in MIST-1 and compared to placebo in MIST-2. In both studies, the efficacy results in the levels of these subgroup variables were consistent with the overall population (See Table 4 and Table 5). It should be noted that in some subgroups (example 'Race: Others') there were only few subjects (See Table 3) and results for these subgroup levels may not be indicative of the overall treatment effects.

Table 10: Mean change in Pupil Diameter from Baseline at 35-Minute Post-Dose by Subgroup – MIST-1 (Per-Protocol Population)

| Subgroup | Labels | TR-PH | TR | PH | Difference in LS Means (95% CI) | |
|---|---|---|---|---|---|---|
| | | | | | PH-TR vs TR | PH-TR vs PH |
| Age | <30 | 4.7 (0.55) | 4.0 (0.63) | 0.6 (0.40) | 0.7 (0.3, 1.1) | 4.2 (3.8, 4.5) |
| | 30-40 | 4.5 (1.02) | 4.1 (0.77) | 0.6 (0.51) | 0.5 (0.1, 0.9) | 3.9 (3.5, 4.3) |
| | >=40 | 4.8 (0.65) | 4.2 (0.50) | 1.2 (0.99) | 0.6 (0.3, 0.9) | 3.6 (3.2, 3.9) |
| Sex | Male | 4.7 (0.65) | 4.1 (0.65) | 0.8 (0.67) | 0.6 (0.4, 0.8) | 3.9, (3.7, 4.2) |
| | Female | 4.6 (0.94) | 4.1 (0.62) | 0.9 (0.93) | 0.6 (0.2, 1.0) | 3.7 (3.3, 4.1) |
| Race | White | 4.6 (0.90) | 4.1 (0.61) | 0.8 (0.70) | 0.6 (0.2, 0.9) | 3.8 (3.5, 4.1) |
| | Black or African | 4.6 (0.58) | 4.1 (0.64) | 0.8 (0.81) | 0.6 (0.2, 0.9) | 3.9 (3.5, 4.3) |
| | Others | 4.9 (0.71) | 4.2 (0.74) | 1.1 (1.01) | 0.7 (0.2, 1.3) | 3.8 (3.3, 4.4) |
| Iris Color | Dark | 4.6 (0.80) | 4.1 (0.65) | 0.8 (0.82) | 0.5 (0.3, 0.8) | 3.8 (3.6, 4.0) |
| | Light | 5.0 (0.59) | 4.2 (0.54) | 1.1 (0.53) | 0.8 (0.3, 1.3) | 3.9 (3.4, 4.5) |

Source: Reviewer analysis based on ADEFF xpt dataset
Race = 'Others' include Asian (N=8) and Multi-Race group (N = 2)
Note: Iris color 'Dark' included brown and black; 'Light' included blue, gray, green, and hazel.

Table 11: Mean change in Pupil Diameter from Baseline at 35-Minute Post-Dose by Subgroup – MIST-2 (Per-Protocol Population)

| Subgroup | Labels | TR-PH | Placebo | Difference in LS Means (95% CI) |
|---|---|---|---|---|
| Age (years) | <30 | 4.9 (0.64) | 0.2 (0.70) | 4.7 (4.2, 5.2) |
| | 30-40 | 4.5 (0.70) | 0.0 (0.27) | 4.6 (4.1, 5.2) |
| | >=40 | 4.8 (0.75) | 0.0 (0.25) | 4.7 (4.3, 5.2) |
| Sex | Male | 4.8 (0.76) | 0.0 (0.34) | 4.7 (4.3, 5.1) |
| | Female | 4.7 (0.64) | 0.1 (0.60) | 4.5 (4.1, 4.9) |
| Race | White | 4.9 (0.66) | 0.1 (0.50) | 4.7 (4.4, 5.0) |
| | Others | 4.0 (0.59) | -0.0 (0.24) | 4.4 (3.7, 5.1) |
| Iris Color | Dark | 4.8 (0.68) | 0.1 (0.55) | 4.6 (4.3, 5.0) |
| | Light | 4.7 (0.76) | 0.1 (0.22) | 4.6 (4.0, 5.1) |

Source: Reviewer analysis based on ADEFF xpt dataset
Race = 'Others' include Asian (N=1) and Black or African American (N = 7)
Note: Iris color 'Dark' included brown and black; 'Light' included blue, gray, green, and hazel.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

The Applicant's primary efficacy analysis in both studies was based on a fixed-effect analysis of variance (ANOVA) model. The model included an effect due to SUBJECT, EYE, SUBJECT x EYE, PERIOD (1, 2, or 3), TREATMENT, BASELINE PUPIL DAIMETER, IRIS COLOR, and CROSS-TREATMENT CARRYOVER EFFECT (AB, AC, BA, BC, CA, CB) in MIST-1 and FIRST ORDER CARRYOVER EFFECT (A, B) in MIST-2. Within-subject correlation between eyes was accounted in the model. However, in the SAS Log file, the Applicant analysis for the MIST-1 study displayed the following message: "*Convergence criteria met but final Hessian is not positive definite*". Because the final Hessian was not positive definite, the reliability of the standard errors for the treatment comparisons were questionable for this study.

The issue was likely due to overparameterization of the Applicant's model specification and the limited sample size. Specifically, the overparameterization was mainly due to the specification of each eyes of a subject (SUBJECT X EYE) as a fixed effect in the model and due to the specification of cross-treatment carryover effect using 7-level. To mitigate the issue, the reviewer requested that SUBJID alone (not SUBJID X EYE) be specified as a fixed or as a random effect in the model. The Applicant concurred with the reviewer's recommendation.

To further mitigate the overparameterization, the Applicant proposed to exclude the carryover effect from the model because the recovery time after treatment administration was between 3-8 hours. The Agency agreed with the Applicant proposal on the condition that no subject had less than 3 days between visits. Since all subjects in MIST-1 study had at least 3 days between visits, the carryover effect was excluded from the model in MIST-1 but was included in MIST-2 because some subjects in this study had a minimum of 2-days between visits.

Additionally, the Applicant proposed to exclude non-significant fixed effects such as visit, visit-by-treatment interaction, and iris color from the model to further mitigate the overparameterization. The Agency agreed to the Applicant's approach. Thus, the final model to assess superiority of TR-PH to the individual components in the mean change in pupil diameter from baseline at 35-minute post-dose in MIST-1 study included EYE, TREATMENT GROUP, and BASELINE PUPIL DIAMETER in the model and to placebo in MIST-2 study included EYE, TREATMENT GROUP, BASELINE PUPIL DIAMETER, and CARRYOVER EFFECT.

## 5.2 Collective Evidence

In the pivotal Phase 3 efficacy and safety studies (MIST-1 and MIST-2), the Applicant assessed the improvement in pupil diameter from baseline over time between the combination product (TR-PH) versus the individual components (TR and PH), in MIST-1, and versus placebo in MIST-2.

In both studies, subjects treated with the combination product, TR-PH, demonstrated a statistically superior increase in pupil diameter at 35-minutes post-dose compared to both the individual components, TR and PH, in MIST-1 and compared to placebo in MIST-2 (Figure 1 and Figure 2). Additionally, more subjects in TR-PH achieved a pupil diameter of ≥ 6 mm at 35-minutes post-dose

compared to TR and PH in MIST-1 and compared to placebo in MIST-2 (Figure 3). Most subjects in the TR-PH group that achieved a pupil diameter of ≥6 mm at 35-minute post-dose maintained it through 180-minute post-dose compared to the individual components in MIST-1 and to placebo in MIST-2 (Table 7).

In both studies, the time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time from baseline (time 0) to 180-minute post-dose was shorter in the TR-PH group than in the TR or PH groups in MIST-1 and in the placebo group in MIST-2. For example, the average time to achieve a pupil diameter of ≥ 6 mm for the first time during the observation time from baseline (time 0) to 180-minute post-dose was about 30 minutes in the TR-PH group compared to 44-50 minutes in TR and 155-163 minutes in PH in MIST-1 and compared to 178 minutes in placebo in MIST-2.

### 5.3 Conclusion and Recommendation

Based on the totality of evidence from the two adequate and well controlled trials of MIST-1 and MIST-2 studies, the reviewer concludes that the application provided substantial evidence of efficacy of TR-PH administered in microdroplet multi-dose spray (two sprays within 5 minutes) for dilation of the pupil.

## 5.4 Labeling Recommendation

In Section 14 of the draft labeling, the Applicant proposed to include the text below (RE: 14 Clinical Studies) including the (b) (4) efficacy results from MIST-1 and MIST-2 (RE: Table 1 below) and plot of the mean pupil diameter over time by treatment group.

**14. CLINICAL STUDIES**

(b) (4)


***Reviewer's Remark:***

*Overall, the Applicant's proposed text included in Section 14 of the draft label appear acceptable. However, the reviewer recommend that Table 1 and Figure 1 above be presented for each study separately and Table 1 should include the treatment differences and the corresponding 95% confidence interval estimates as shown below. Additionally, all the efficacy results reported in Section 14 should be based on the individual study results.*

**Table 1 Pupil Size and Change in Diameter from Baseline at 35 Minutes Post-Dose (MIST-1 and MIST-2) (Per-Protocol Population [1])**

| | MIST-1 | | | MIST-2 | |
|---|---|---|---|---|---|
| Visit | MYDCOMBI (N = 124) | Tropicamide Alone (N = 124) | Phenylephrine Alone (N = 124) | MYDCOMBI (N = 138) | Placebo (N = 138) |
| Baseline | 2.6 (0.05) | 2.6 (0.05) | 2.6 (0.05) | 2.6 (0.04) | 2.6 (0.04) |
| 35-Minutes Post-Dose | 7.3 (0.08) | 6.7 (0.08) | 3.5 (0.08) | 7.3 (0.07) | 2.7 (0.05) |
| Change from Baseline | 4.7 (0.07) | 4.1 (0.06) | 0.9 (0.08) | 4.8 (0.07) | 0.1 (0.04) |
| Difference from MYDCOMBI (95% CI) [2] | -- | 0.6 (0.4, 0.8) | 3.9 (3.7, 4.1) | -- | 4.7 (4.5, 4.8) |

[1] The per-protocol (PP) population included all randomized subjects who received at least one dose of study medication and completed all planned assessments (related to the primary endpoint) without major protocol violations. Two subjects in MIST-1 and one subject in MIST-2 who withdrew

consent after their first treatment visit were not included in the PP populations which resulted in 62 completed subjects (124 eyes) in MIST-1 and 69 completed subjects (138 eyes) in MIST-2 comprised the PP populations. Sensitivity analysis performed on the intent-to-treat (ITT) population including all randomized subjects resulted in consistent efficacy results.

[2] Treatment differences and 95% confidence interval estimates were based on a mixed model including treatment, eye, baseline diameter, and carryover effect (for MIST-2 study only). In both studies, an unstructured covariance structure was used to account for within-subject correlation between eyes.

*In the Table 1 above, the Applicant should clarify the number of eyes, (b) (4) (124 from MIST-1 and 138 from MIST-2) and for placebo should be 138.*

# Appendix:

Table 12: Summary of Mean Change in Pupil Diameter from Baseline at 35-Minute Post-Dose: Analyses Based on Average of Two Eyes
(Per-protocol Population)

**MIST-1**

| Visit | Summary | TR-PH (N = 62) | TR (N = 62) | PH (N = 62) |
|---|---|---|---|---|
| Baseline | Mean (SD) | 2.6 (0.50) | 2.6 (0.54) | 2.6 (0.54) |
| | Median | 2.6 | 2.6 | 2.6 |
| | Range | 1.6 – 4.1 | 1.5 – 4.0 | 1.5 – 4.1 |
| 35-Minutes Post-dose | Mean (SD) | 7.3 (0.90) | 6.7 (0.82) | 3.5 (0.86) |
| | Median | 7.4 | 6.8 | 3.3 |
| | Range | 3.5 – 9.0 | 4.9 – 8.7 | 2.1 – 6.0 |
| Change from Baseline | Mean (SD) | 4.7 (0.78) | 4.1 (0.63) | 0.9 (0.78) |
| | Median | 4.7 | 4.2 | -0.6 |
| | Range | 1.1 – 6.2 | 2.3 – 5.3 | -0.2 – 0.6 |
| Treatment comparison: Combination product (PH-TR) versus Individual components (TR and PH) | | | | |
| Difference in LS Means from TR-PH (95% CI) | | -- | 0.58 (0.37, 0.79) | 3.84 (3.63, 4.05) |
| p-value | | | <0.001 | <0.001 |

**MIST-2**

| Visit | Summary | TR-PH (N = 69) | Placebo (N = 69) |
|---|---|---|---|
| Baseline | Mean (SD) | 2.6 (0.46) | 2.6 (0.48) |
| | Median | 2.6 | 2.5 |
| | Range | 1.7 – 3.6 | 1.5 – 4.1 |
| 35-Minutes Post-dose | Mean (SD) | 7.3 (0.76) | 2.7 (0.61) |
| | Median | 7.3 | 2.6 |
| | Range | 5.2 – 9.0 | 1.7 – 5.4 |
| Change from Baseline | Mean (SD) | 4.8 (0.70) | 0.1 (0.48) |
| | Median | 4.7 | 0.1 |
| | Range | 3.4 – 6.2 | -0.7 – 3.2 |
| Treatment comparison: Combination product (PH-TR) versus Placebo | | | |
| Difference in LS Means from TR-PH (95% CI) | | | 4.66 (4.52, 4.80) |
| p-value | | | <0.001 |

Source: Reviewer analysis based on ADEFF.xpt dataset

Table 13: Summary of the Time to Maximal Pupil Diameter Achieved in each Treatment Group (Per-protocol Population)

MIST-1

| | | TR-PH | | TR | | PH | |
|---|---|---|---|---|---|---|---|
| | | Maximal Diameter | Time (Hours) | Maximal Diameter | Time (Hours) | Maximal Diameter | Time (Hours) |
| OD | Mean (SD) | 8.0 (0.89) | 89.3 (31.18) | 7.2 (0.80) | 64.7 (21.54) | 4.6 (1.28) | 83.1 (23.60) |
| | Median | 8.1 | 80 | 7.2 | 65 | 4.4 | 80 |
| | 25 - 75 Percentile | 7.4 - 8.6 | 65 - 120 | 6.6 - 7.8 | 50 -80 | 3.7 - 5.4 | 65 - 80 |
| | Range | 4.9 - 10.0 | 50 - 180 | 5.7 - 9.1 | 20 - 120 | 2.3 - 7.9 | 20 -120 |
| OS | Mean (SD) | 8.1 (0.92) | 87.1 (31.26) | 7.1 (0.91) | 67.2 (23.39) | 5.0 (1.25) | 84.0 (21.24) |
| | Median | 8.2 | 80 | 7.2 | 65 | 5.2 | 80 |
| | 25 - 75 Percentile | 7.4 - 8.7 | 65 - 120 | 6.6 - 7.8 | 50 - 80 | 3.9 - 5.9 | 65 - 80 |
| | Range | 5.3 - 10.0 | 35 - 180 | 5.0 - 9.4 | 35 - 120 | 2.7 - 7.7 | 50 -120 |

OD: Right Eye; OS: Left Eye

MIST-2

| | | TR-PH | | Placebo | |
|---|---|---|---|---|---|
| | | Maximal Diameter | Time (Hours) | Maximal Diameter | Time (Hours) |
| OD | Mean (SD) | 7.9 (0.80) | 74.6 (24.89) | 3.1 (0.75) | 75.9 (48.35) |
| | Median | 7.92 | 65 | 3.01 | 65 |
| | 25 - 75 Percentile | 7.4 -8.4 | 65 -80 | 2.5 -3.4 | 35 -120 |
| | Range | 5.6 – 10.0 | 35 - 180 | 1.7 - 5.7 | 20 - 180 |
| OS | Mean (SD) | 8.0 (0.76) | 75.7 (21.23) | 2.9 (0.71) | 77.8 (40.01) |
| | Median | 7.97 | 80 | 2.72 | 65 |
| | 25 - 75 Percentile | 7.5 – 8.5 | 65 - 80 | 2.4 – 3.2 | 50 -120 |
| | Range | 5.8 - 9.6 | 35 -120 | 2.0 – 6.2 | 20 -180 |

OD: Right Eye; OS: Left Eye
Source: Reviewer analysis based on ADEFF.xpt dataset

Table 14: Summary of the Change in Pupil Diameter from Baseline at each Post-Dose Time Point – MIST-1
(Per-Protocol Population)

| | | TR-PH (N = 62) | | | TR (N = 62) | | | PH (N = 62) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time | Eye | Mean (SD) | Median | 95% CI | Mean (SD) | Median | 95% CI | Mean (SD) | Median | 95% CI |
| Baseline | OD | 2.7 (0.57) | 2.7 | (2.5, 2.8) | 2.7 (0.60) | 2.6 | (2.5, 2.8) | 2.7 (0.57) | 2.6 | (2.5, 2.8) |
| | OS | 2.6 (0.47) | 2.6 | (2.5, 2.7) | 2.6 (0.52) | 2.6 | (2.4, 2.7) | 2.6 (0.53) | 2.6 | (2.4, 2.7) |
| 20 Minutes | OD | 3.4 (1.23) | 3.8 | (3.1, 3.7) | 3.0 (0.94) | 3.0 | (2.7, 3.2) | 0.2 (0.37) | 0.1 | (0.1, 0.3) |
| | OS | 3.5 (1.07) | 3.7 | (3.3, 3.8) | 3.0 (1.01) | 3.1 | (2.7, 3.2) | 0.3 (0.40) | 0.2 | (0.2, 0.4) |
| 35 Minutes | OD | 4.6 (0.83) | 4.7 | (4.4, 4.8) | 4.1 (0.72) | 4.2 | (3.9, 4.3) | 0.7 (0.79) | 0.6 | (0.5, 0.9) |
| | OS | 4.7 (0.82) | 4.9 | (4.5, 5.0) | 4.1 (0.68) | 4.2 | (3.9, 4.3) | 1.0 (0.89) | 0.7 | (0.7, 1.2) |
| 50 Minutes | OD | 5.1 (0.82) | 5.2 | (4.9, 5.3) | 4.3 (0.76) | 4.3 | (4.1, 4.5) | 1.4 (1.06) | 1.2 | (1.1, 1.6) |
| | OS | 5.1 (0.75) | 5.2 | (4.9, 5.3) | 4.4 (0.66) | 4.5 | (4.2, 4.5) | 1.7 (1.17) | 1.4 | (1.4, 2.0) |
| 65 Minutes | OD | 5.1 (0.77) | 5.2 | (4.9, 5.3) | 4.3 (0.68) | 4.4 | (4.2, 4.5) | 1.7 (1.21) | 1.6 | (1.4, 2.0) |
| | OS | 5.3 (0.78) | 5.4 | (5.1, 5.5) | 4.4 (0.71) | 4.4 | (4.2, 4.5) | 2.1 (1.25) | 1.9 | (1.8, 2.5) |
| 80 Minutes | OD | 5.2 (0.77) | 5.3 | (5.0, 5.4) | 4.3 (0.68) | 4.4 | (4.2, 4.5) | 1.8 (1.21) | 1.7 | (1.5, 2.1) |
| | OS | 5.3 (0.79) | 5.3 | (5.1, 5.5) | 4.4 (0.69) | 4.5 | (4.2, 4.5) | 2.3 (1.23) | 2.1 | (2.0, 2.6) |
| 120 Minutes | OD | 5.1 (0.89) | 5.3 | (4.9, 5.3) | 4.2 (0.69) | 4.2 | (4.0, 4.3) | 1.6 (1.13) | 1.4 | (1.3, 1.9) |
| | OS | 5.2 (0.76) | 5.3 | (5.0, 5.4) | 4.2 (0.65) | 4.2 | (4.0, 4.3) | 2.0 (1.23) | 1.8 | (1.7, 2.3) |
| 180 Minutes | OD | 4.7 (0.95) | 4.9 | (4.5, 5.0) | 3.6 (0.79) | 3.8 | (3.4, 3.8) | 1.0 (0.96) | 0.8 | (0.8, 1.3) |
| | OS | 4.8 (0.89) | 4.8 | (4.6, 5.0) | 3.6 (0.71) | 3.8 | (3.5, 3.8) | 1.4 (1.10) | 1.3 | (1.1, 1.7) |

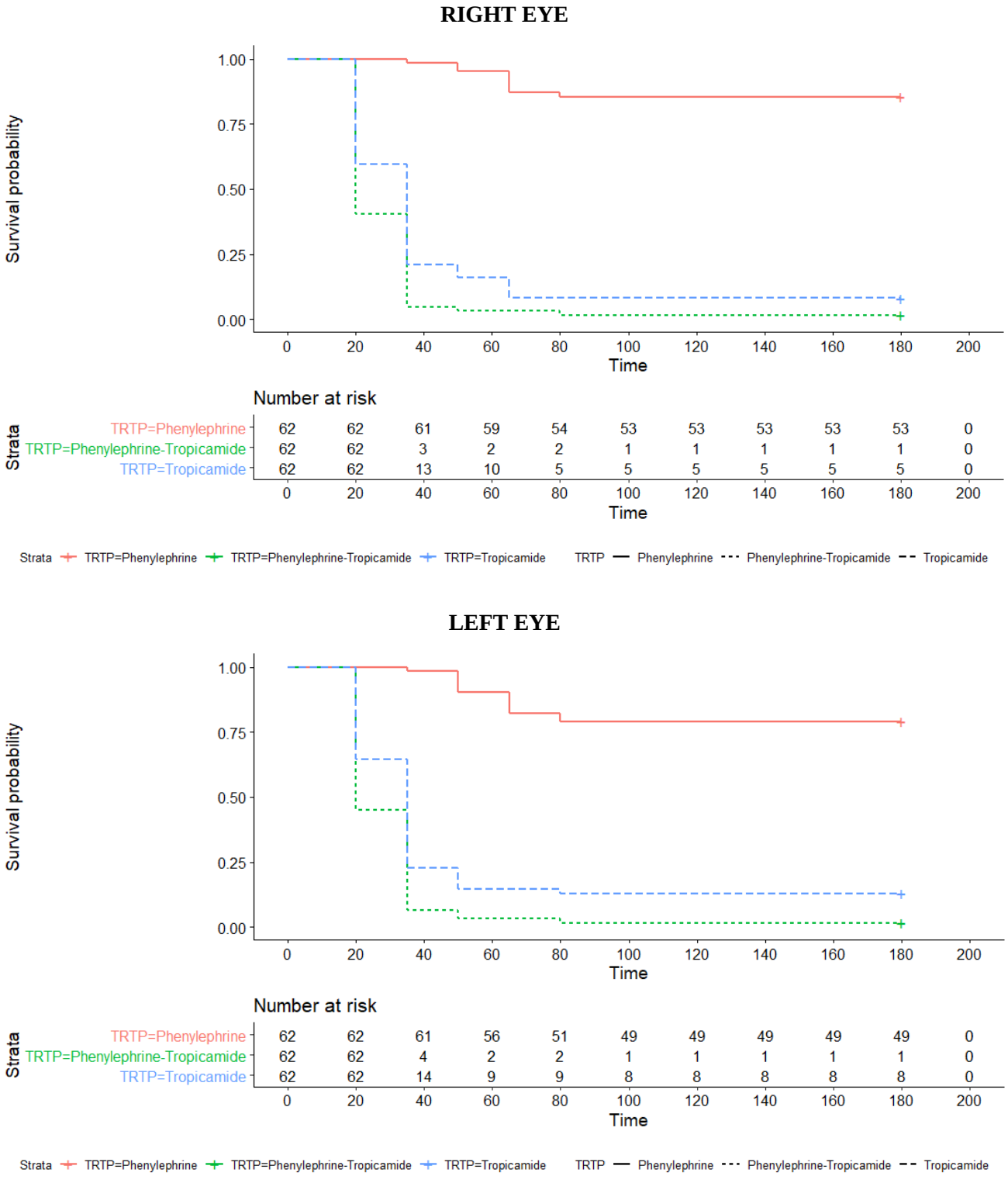
OD: Right Eye; OS: Left Eye
Source: Reviewer analysis based on ADEFF.xpt dataset

Table 15: Summary of the Change in Pupil Diameter from Baseline at each Post-Dose Time Point – MIST-2 (Per-protocol Population)

| | | TR-PH (N = 69) | | | Placebo (N=69) | | |
|---|---|---|---|---|---|---|---|
| Time | Eye | Mean (SD) | Median | 95% CI | Mean (SD) | Median | 95% CI |
| Baseline | OD | 2.6 (0.48) | 2.6 | (2.5, 2.7) | 2.6 (0.52) | 2.5 | (2.5, 2.8) |
| | OS | 2.5 (0.48) | 2.5 | (2.4, 2.6) | 2.6 (0.47) | 2.5 | (2.4, 2.7) |
| 20 Minutes | OD | 3.8 (0.94) | 3.8 | (3.6, 4.0) | 0.1 (0.40) | 0.0 | (0.0, 0.2) |
| | OS | 3.7 (1.01) | 3.6 | (3.4, 3.9) | -0.0 (0.31) | 0.0 | (-0.1, 0.1) |
| 35 Minutes | OD | 4.7 (0.73) | 4.7 | (4.6, 4.9) | 0.1 (0.50) | 0.1 | (0.0, 0.3) |
| | OS | 4.8 (0.80) | 4.8 | (4.6, 5.0) | 0.0 (0.50) | 0.0 | (-0.1, 0.2) |
| 50 Minutes | OD | 5.0 (0.73) | 5.0 | (4.9, 5.2) | 0.1 (0.52) | 0.0 | (0.0, 0.3) |
| | OS | 5.1 (0.78) | 5.1 | (5.0, 5.3) | 0.1 (0.56) | 0.0 | (-0.0, 0.3) |
| 65 Minutes | OD | 5.1 (0.77) | 5.1 | (4.9, 5.3) | 0.1 (0.52) | 0.1 | (0.0, 0.3) |
| | OS | 5.2 (0.77) | 5.3 | (5.0, 5.4) | 0.1 (0.56) | 0.0 | (-0.1, 0.2) |
| 80 Minutes | OD | 5.2 (0.78) | 5.2 | (5.0, 5.3) | 0.1 (0.53) | 0.1 | (-0.0, 0.2) |
| | OS | 5.3 (0.74) | 5.3 | (5.1, 5.4) | 0.1 (0.57) | 0.0 | (-0.1, 0.2) |
| 120 Minutes | OD | 4.8 (0.83) | 4.9 | (4.6, 5.0) | 0.2 (0.52) | 0.1 | (0.0, 0.3) |
| | OS | 5.1 (0.88) | 5.1 | (4.9, 5.3) | 0.1 (0.50) | 0.0 | (-0.0, 0.2) |
| 180 Minutes | OD | 4.1 (1.03) | 4.2 | (3.9, 4.4) | 0.1 (0.44) | 0.1 | (-0.0, 0.2) |
| | OS | 4.3 (0.98) | 4.3 | (4.1, 4.5) | -0.0 (0.38) | -0.1 | (-0.1, 0.1) |

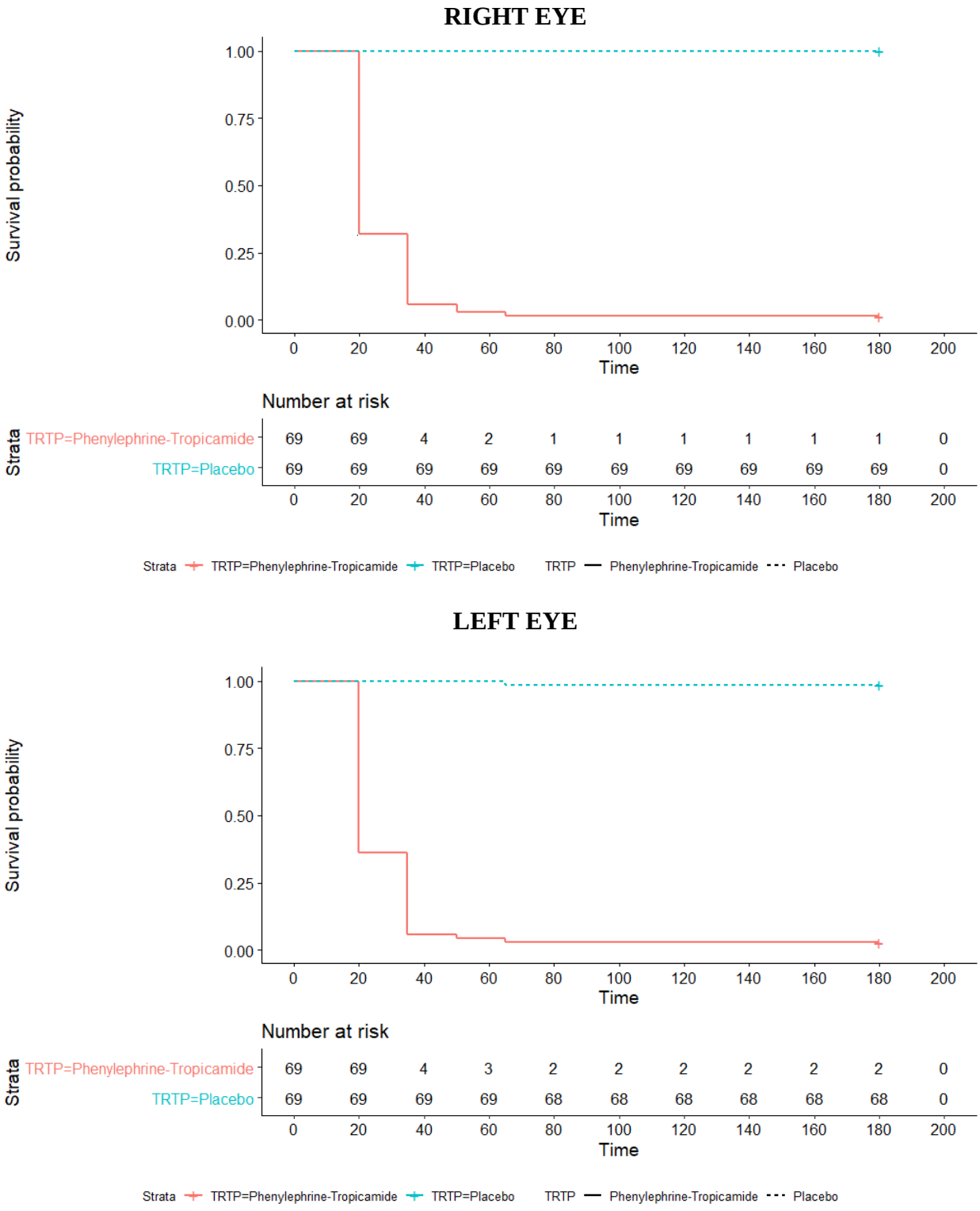
OD: Right Eye; OS: Left Eye
Source: Reviewer analysis based on ADEFF.xpt dataset

Figure 4: Time to a Pupil Diameter of ≥ 6 mm Achieved First - MIST-1
(Per-protocol Population)




Source: Reviewer analysis based on ADEFF.xpt dataset

Figure 5: Time to a Pupil Diameter of ≥ 6 mm Achieved First -MIST-2 (Per-Protocol Population)




Source: Reviewer analysis based on ADEFF.xpt dataset

Table 16: Summary of Mean Change in Pupil Diameter from Baseline at 35-Minutes Post-Dose by Period (MIST-1)
(Per-Protocol Population)

| | TR-PH | | TR | | PH | |
|---|---|---|---|---|---|---|
| Visit | OD | OS | OD | OS | OD | OS |
| Period 1 | 4.5 (0.18) | 4.5 (0.14) | 4.5 (0.16) | 4.4 (0.16) | 0.6 (0.17) | 0.9 (0.19) |
| Period 2 | 4.5 (0.23) | 4.7 (0.23) | 4.0 (0.17) | 4.0 (0.17) | 0.8 (0.16) | 1.1 (0.20) |
| Period 3 | 4.9 (0.13) | 5.0 (0.16) | 3.9 (0.13) | 4.0 (0.10) | 0.8 (0.20) | 0.9 (0.22) |
| Treatment comparison: Combination product (TR-PH) versus Individual components (TR and PH) Difference in LS Means from TR-PH | | | | | | |
| Period 1 | | | | | | |
| LS Mean (SE) | | | 0.09 (0.22) | | 3.8 (0.21) | |
| 95% CI | | | (-0.3, 0.5) | | (3.4, 4.2) | |
| p-value | | -- | p = 0.6861 | | p < 0.0001 | |
| Period 2 | | | | | | |
| LS Mean (SE) | | | 0.6 (0.26) | | 3.7 (0.26) | |
| 95% CI | | | (0.1, 1.1) | | (3.2, 4.2) | |
| p-value | | -- | p = 0.0196 | | p < 0.0001 | |
| Period 3 | | | | | | |
| LS Mean (SE) | | | 1.0 (0.21) | | 4.0 (0.21) | |
| 95% CI | | | (0.6, 1.4) | | (3.6, 4.4) | |
| p-value | | -- | p < 0.0001 | | p < 0.0001 | |
| Pooled (Period 1-3) [1] | | | | | | |
| LS Mean (SE) | | | 0.56 (0.13) | | 3.8 (0.13) | |
| 95% CI | | | (0.3, 0.8) | | (3.5, 4.1) | |
| p-value | | -- | p < 0.0001 | | p < 0.0001 | |

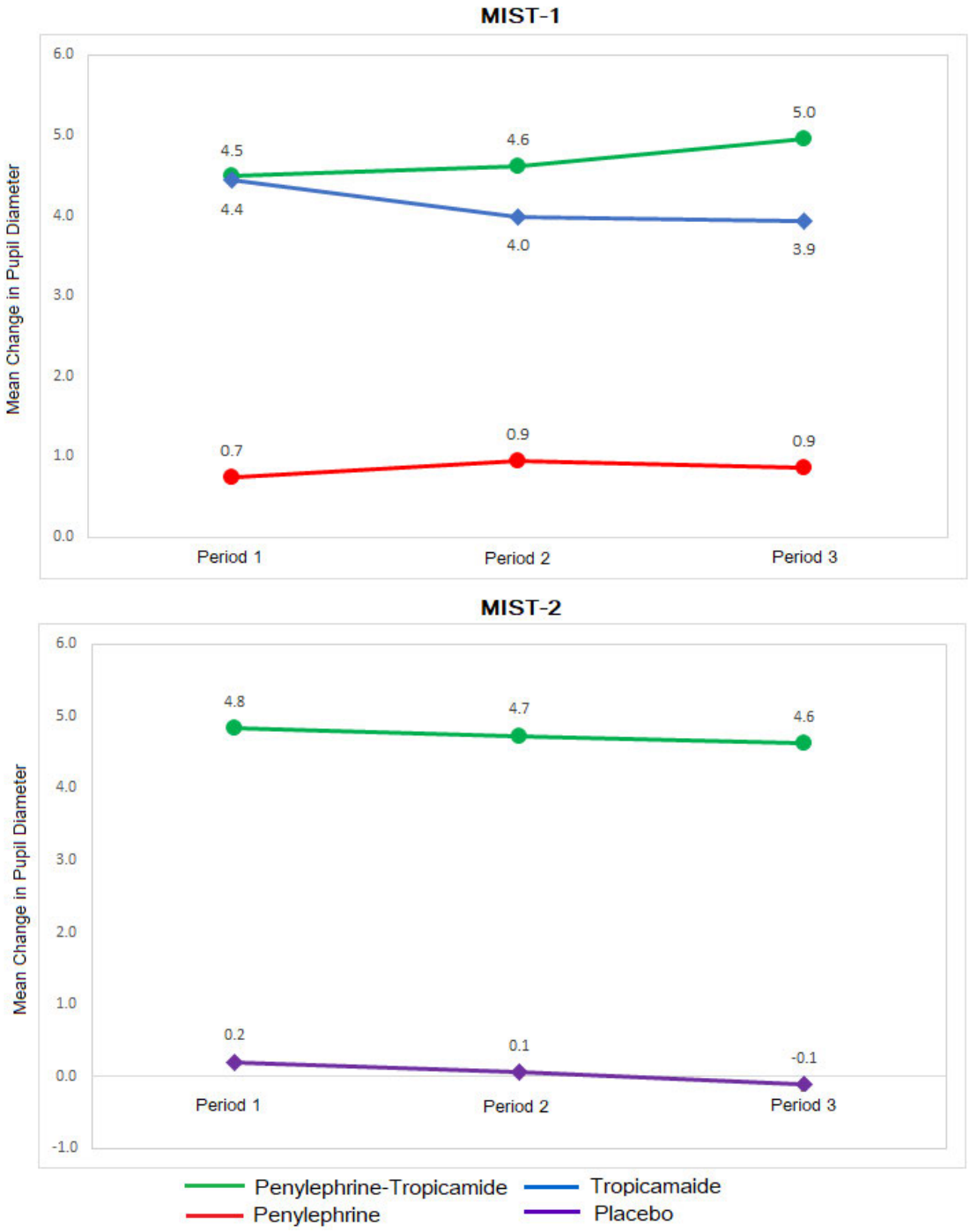
Source: Reviewer analysis based on ADEFF.xpt dataset
Abbreviation: LS Mean – Least Square Means; SE: Standard Error; CI: Confidence Interval; TR-PH - Tropicamide – Phenylephrine; TR – Tropicamide; PH – Phenylephrine; OD – Right Eye; OS – Left Eye
Note: LS Means (SE), 95% CI, and p-value were from mixed model accounting for the correlation between eyes within a subject.
[1] Pooled results assumed that the mean pupil diameters across periods are independent.

Table 17: Proportion of Subjects Who Achieved a Pupil Diameter of ≥6 mm and ≥7 mm at 35-Minute Post-Dose by Period (MIST-1 Study)
(Per-Protocol Population)

| | | TR-PH | | TR | | PH | |
|---|---|---|---|---|---|---|---|
| Pupil Diameter | Visit | OD | OS | OD | OS | OD | OS |
| >= 6 mm | Period 1 | 19 (90.5%) | 19 (90.5%) | 18 (90.0%) | 17 (85.0%) | 0 (0.0%) | 1 (4.8%) |
| | Period 2 | 19 (95.0%) | 18 (90.0%) | 17 (81.0%) | 17 (81.0%) | 0 (0.0%) | 0 (0.0%) |
| | Period 3 | 21 (100%) | 21 (100%) | 14 (66.7%) | 14 (66.7%) | 1 (5.0%) | 0 (0.0%) |
| >= 7 mm | Period 1 | 12 (57.1%) | 10 (47.6%) | 12 (60.0%) | 12 (60.0%) | 0 (0.0%) | 0 (0.0%) |
| | Period 2 | 14 (70.0%) | 15 (75.0%) | 7 (33.3%) | 6 (28.6%) | 0 (0.0%) | 0 (0.0%) |
| | Period 3 | 16 (76.2%) | 17 (81.0%) | 8 (38.1%) | 8 (38.1%) | 0 (0.0%) | 0 (0.0%) |

Source: Reviewer analysis based on ADEFF.xpt dataset.
Abbreviation: TR-PH - Tropicamide – Phenylephrine; TR – Tropicamide; PH – Phenylephrine; OD – Right Eye; OS – Left Eye

Figure 6: Mean change in Pupil Diameter from Baseline at 35-Minute Post-Dose by Period
(MIST-1 and MIST-2 Study)
(Per-Protocol Population)




Source: Reviewer analysis based on ADEFF.xpt datasets. Within each period, measurements within two eyes of a subjects were averaged.

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