Kowa Research Institute, Inc.

A Double-Masked, Randomized, Placebo-Controlled, Parallel-Group, 12-Week Treatment and 14-week Extension, Phase 3 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Cataract Surgery

Statistical Analysis Plan

Compound Number(s): K-321
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Signatures

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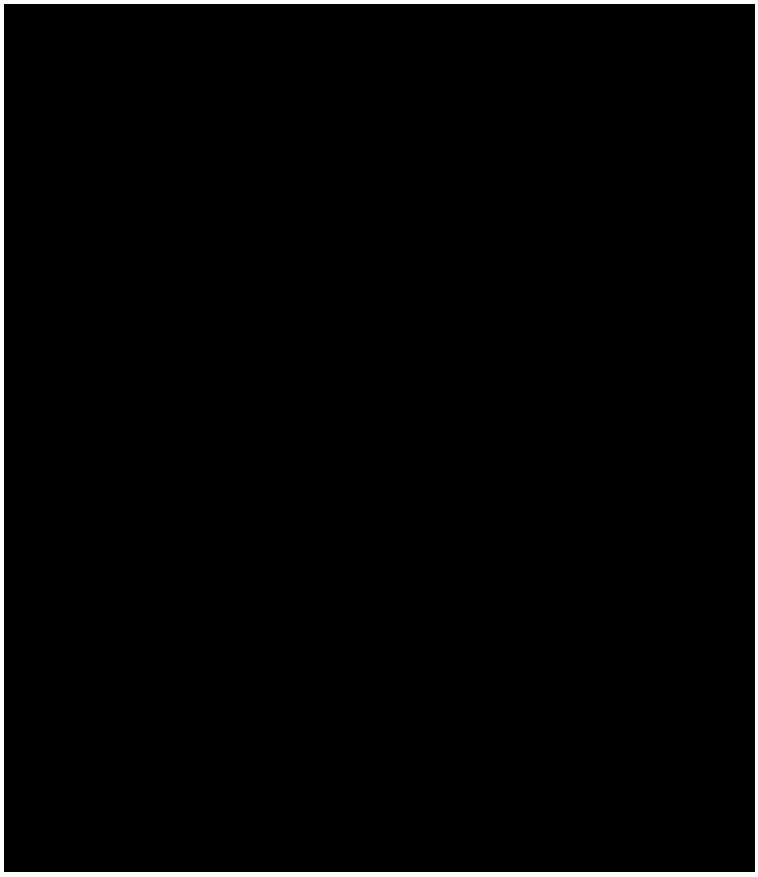

Revision history

Version	Version date	Summary of changes
1.0	January 9th, 2024	Initial version

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1. Introduction

The objective of this statistical analysis plan (SAP) addendum is to specify the statistical analyses to be precise enough to serve as a guideline for creation of tables and figures of ad-hoc analysis.

This SAP is an addendum for SAP ver3.0, dated September 7th, 2023, and was created after unmasking processes. SAP ver3.0 is based on the clinical study protocol (Amendment #2), dated September 29th, 2022.

2. Objectives

Same as SAP ver3.0, dated September 7th, 2023.

3. Investigational Plan

3.1 Overall Study Design and Plan

Same as SAP ver3.0, dated September 7th, 2023.

3.2 Study Endpoints

This SAP describes the analysis plan for the following secondary efficacy endpoints:

- Time to complete clearance of corneal edema after cataract surgery
- Time to return of corneal thickness to less than or equal to baseline level
- Time to achieve BCVA by ETDRS letter score ≥70 letters (Snellen equivalent better than 20/40) after cataract surgery

3.3 Study Procedures and Baseline

For all time-to-event endpoints, the date of the first dose of study drug (Visit 3 [Day 1]) is defined as the start date for calculating event time.

3.4 Treatments

Same as SAP ver3.0, dated September 7th, 2023.

4. General Statistical Considerations

Same as SAP ver3.0, dated September 7th, 2023.

5. Analysis Plans

5.1 Subject Disposition

The counts and percentages of withdrawals from the study will be presented. Withdrawals from the study will also be summarized separately for those who withdrew from the study prior to week 12 and withdrew from the study from week 12 to week 26. Subjects who withdrew from study on or before Day 99 will be regarded as "withdrawal from the study prior to week 12". Other subjects who withdrew from the study will be regarded as "withdrawal from the study from week 12 to week 26". Reasons for withdrawal from the study will be summarized separately for those who withdrew from the study prior to week 12 and withdrew from the study from week 12 to week 26. Percentages within the subject disposition summary will be based on the number of subjects randomized. For reasons for withdrawal from the study, percentages will be based on the number of subjects who "withdrew from the study prior to week 12" or "withdrew from the study from week 12 to week 26".

5.2 Secondary efficacy endpoints

For all time to event endpoints, time to event is defined as the following:

(Date of the first event or censoring after Day 1) - (Day 1 date) + 1

Subjects who achieve the event on Day 1 date are excluded from analysis.

- The analysis of time to complete clearance of corneal edema in the study eye will be performed for the FAS based on slit-lamp biomicroscopy assessments performed during the treatment period. Complete clearance of corneal edema will be determined when a subject is simultaneously normal for epithelial, stromal, and endothelial regions during slit-lamp review. Subjects who do not experience complete clearance during the treatment period will be censored at their last available slit-lamp examination. The Log-rank test will be used to compare the probability of having an event between two groups at any time point. The Kaplan-Meier method will be used to estimate the median time to event and its two-sided 95% confidence intervals when estimable. Kaplan-Meier plots will also be plotted for each treatment group. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time to event will be presented. These

estimates will be summarized by treatment group.

- The analysis of time to return of corneal thickness to less than or equal to baseline level in the study eye will be performed for the FAS based on measurements of corneal thickness performed during the treatment period. Subjects who do not experience complete clearance during the treatment period will be censored at their last available measurement of corneal thickness. The Log-rank test will be used to compare the probability of having an event between two groups at any time point. The Kaplan-Meier method will be used to estimate the median time to event and its two-sided 95% confidence intervals when estimable. Kaplan-Meier plots will also be plotted for each treatment group. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time to event will be presented. These estimates will be summarized by treatment group.

- The analysis of time to achieve BCVA by ETDRS letter score ≥70 letters in the study eye will be performed within the FAS based on BCVA assessments performed during the treatment period. Subjects who do not achieve BCVA by ETDRS letter score ≥70 letters during the treatment period will be censored at their last available BCVA assessment. The Log-rank test will be used to compare the probability of having an event between two groups at any time point. The Kaplan-Meier method will be used to estimate the median time to event and its two-sided 95% confidence intervals when estimable. Kaplan-Meier plots will also be plotted for each treatment group. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time to event will be presented. These estimates will be summarized by treatment group.

6. Changes from the Protocol

All analyses described in this SAP are based on the clinical study protocol (Amendment #2), dated September 29th, 2022, with changes in tabulation method or definition of endpoint. Outline of changes are following:

- Tabulate the subject disposition separately for those who completed study drug and discontinued study drug during treatment period.

- Change the start date of time to event from Day -1 (Visit 2) date to Day 1 (Visit 3) date.

All analyses described in this SAP are planned after unmasking.