Kowa Research Institute, Inc.

K-321-302

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

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Statistical Analysis Plan

Version 3.0

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SIGNATURE PAGE



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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AREDS	Age-Related Eye Disease Study
ATC	Anatomical therapeutic chemical
BCVA	Best corrected (distance) visual acuity
BID	Twice daily
BrdU	5-bromo-2'-deoxyuridine
CAI	Carbonic anhydrase inhibitor
CFR	Code of Federal Regulations
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CRO	Clinical research organization
CS	Clinically significant
[redacted]	[redacted]
DMC	Data Monitoring Committee
DSO	Descemet Stripping Only
ECD	Endothelial cell density
eCRF	Electronic case report form
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FAS12	Full Analysis Set in the 12-Week Period
FAS26	Full Analysis Set in the 26-Week Period
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCEC	Human Corneal Endothelial Cell
HIPAA	Health Insurance Portability and Accountability Act
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOL	Intraocular lens
IOP	Intraocular pressure
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KRI	Kowa Research Institute
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
NCS	Not clinically significant
OD	Oculus dextrus (right eye)

OS	Oculus sinister (left eye)
OTC	Over the counter
OU	Oculus uterque (both eyes)
PI	Principal Investigator
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred term
Q1	Quartile 1
Q3	Quartile 3
QID	4 times daily
REC	Research Ethics Committee
[redacted]	[redacted]
ROCK	Rho kinase
SAE	Serious adverse event
SD	Standard deviation
SOA	Schedule of (study site) activities
SP12	Safety Population in the 12-Week Period
SP26	Safety Population in the 26-Week Period
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
[redacted]	[redacted]
US	United States
VFQ-25	Visual Field Questionnaire-25
WHODrug	World Health Organization Drug Dictionary

1. Introduction

Ripasudil is a selective inhibitor of Rho-kinase (ROCK), a serine-threonine protein kinase which binds with low-molecular weight G protein Rho to form the Rho/Rho-kinase signaling system (Ishizaki, 1996). Ripasudil ophthalmic solution 0.4% has been marketed in Japan as Glanatec® for glaucoma and ocular hypertension since December 2014.

Two isoforms of Rho-kinase exist in humans, ROCK-1 and ROCK-2 (Nakagawa, 1996), and ripasudil has been shown to be an equipotent inhibitor of both. Inhibition of ROCK signaling has been reported to increase the drainage of aqueous humor through the trabecular meshwork and to have a stimulatory effect on corneal endothelial wound healing through the inhibition of apoptosis and increased proliferation of corneal endothelial cells (Meekins, 2016).

Okumura and colleagues tested the hypothesis that ripasudil could be repositioned for use as a treatment for corneal endothelial injuries (Okumura, 2011). They treated cultured human corneal endothelial cells (HCECs) with ripasudil and evaluated 5-bromo-2'-deoxyuridine (BrdU) incorporation by enzyme-linked immunosorbent assay (ELISA). They also created a rabbit model of mechanical endothelial damage by scraping the corneal endothelium, and then followed this by topical ripasudil application for 2 weeks. They evaluated the anterior segment by slit-lamp microscopy, and measured central corneal thickness by ultrasound pachymetry. They also used phalloidin staining and immunohistochemical analysis with antibodies against Ki67, N-cadherin, and Na+/K+ ATPase. They found that there were many more BrdU-positive cells in the HCECs treated with ripasudil (0.3-30 μM) than among the control cells. Notably, five of six corneas treated with ripasudil achieved corneal transparency, in contrast to zero of six corneas of the control eyes. The cell densities were higher in the eyes treated with ripasudil than in the control eyes. With regard to immunohistochemistry, the eyes treated with ripasudil had 91.5 ± 2.0% Ki67-positive cells after 48 hours and had expression of N-cadherin and Na+/K+ ATPase in almost all cells, in contrast to the control eyes which had 52.6 ± 1.3% Ki67-positive cells along with decreased expression of N cadherin and Na+/K+ ATPase. The Investigators concluded that "Ripasudil promoted corneal endothelial wound healing, supporting its development as eye drops for treating acute corneal endothelial damage due to eye surgeries, especially cataract surgery." In their discussion they note that "The World Health Organization reported that 51% of blindness is caused by cataracts on a global basis, therefore, it is reasonable to estimate that numerous subjects will undergo cataract surgery in the near future, and a certain percentage of those subjects will unfortunately experience severe corneal endothelial damage during their surgeries. The development of pharmaceutical treatments is urgently needed."

Fujimoto et al conducted a retrospective observational study in which they included 13 subjects (16 eyes) with glaucoma who had undergone cataract surgery with corneal

endothelial cell density (ECD) ≤1500 cells/mm2 (Fujimoto, 2021). Ripasudil was prescribed from the day after surgery for 6 months. The control group included 13 subjects (16 eyes) without glaucoma who had undergone cataract surgery with ECD ≤1500 cells/mm2 who were not treated with ripasudil. The mean rate of increase in the thinnest corneal thickness one week after surgery was significantly lower in the ripasudil group, at 1.25%, compared with the control group (5.97%; p = 0.0037). The mean ECD loss 90 to 120 days after surgery was also significantly lower in the ripasudil group (−4.5%) compared with the control group (14.1%; p = 0.0003).

Based on the above-mentioned studies of ripasudil for endothelial wound healing, Kowa proposes to evaluate the efficacy and safety of K-321 (ripasudil ophthalmic solution) in subjects after cataract surgery for the proposed indication of treatment after Descemet stripping only (DSO) in subjects with Fuchs endothelial corneal dystrophy.

This is a double-masked, randomized, Placebo-controlled, parallel-group, multi-center study after cataract surgery with a 12-week treatment period and a follow-up period of up to 14 weeks.

This statistical analysis plan for K-321-302 protocol (Amendment #2) dated 2022-09-29 will examine safety and efficacy endpoints at planned analysis time points.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to investigate the effect of K-321 on central ECD in subjects after cataract surgery.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To investigate the effect of K-321 on central and peripheral corneal ECD, [redacted] corneal thickness, corneal edema, visual acuity and vision-related quality of life after cataract surgery.
- To assess the safety of K-321 in subjects after cataract surgery.
- To evaluate the systemic exposure of K-321 in subjects after cataract surgery.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a double-masked, randomized, Placebo-controlled, parallel-group, multi-center study after cataract surgery with a 12-week treatment period and a follow-up period of up to 14 weeks. The study design is presented in Table 1 and the schedule of study site activities is presented in Table 3.

At Visit 1, subjects will complete an informed consent process and will be screened for preliminary eligibility. At Visit 2, subjects will have cataract surgery, will be assessed for study eligibility, and will be randomly assigned to one of four treatment groups using 2:1 ratio of active or Placebo:

- Group A: Treatment with K-321 four times per day (QID) for 12 weeks followed by a 4-week follow-up period with no treatment. These subjects will exit the study after Visit 9 (Week 16) (n = 150 subjects).
- Group B: Treatment with K-321 QID for 12 weeks followed by a 14-week follow-up period with no treatment. These subjects will exit the study after Visit 11 (Week 26) (n = 70 subjects).
- Group C: Treatment with Placebo QID for 12 weeks followed by a 4-week follow-up period with no treatment. These subjects will exit the study after Visit 9 (Week 16) (n = 75 subjects).
- Group D: Treatment with Placebo QID for 12 weeks followed by a 14-week follow-up period with no treatment. These subjects will exit the study after Visit 11 (Week 26) (n = 35 subjects).

Subjects eligible for randomization will be [redacted].

At Visit 3, eligible subjects in Groups A (K-321) and C (Placebo) will be dispensed their randomly assigned study drug for use in the study eye QID for 12 weeks. Subjects will be scheduled for five study visits (Visits 4, 5, 6, 7, and 8) during the 12-week treatment period

followed by a 4-week period without treatment. End of Study (EOS) visit will occur at the end of the 4-week follow-up period (Visit 9). In these two groups, the total duration on the study will be 16 weeks following cataract surgery.

At Visit 3, eligible subjects in Groups B (K-321) and D (Placebo) will be dispensed their randomly assigned study drug in the study eye QID for 12 weeks. Subjects will be scheduled for five study visits (Visit 4, 5, 6, 7, and 8) during the 12-week treatment period followed by a 14-week period without treatment. Plasma samples from subjects who participate and consent at selected sites will be collected predose and at 5, 15, and 30 minutes postdose on Day 1 (Visit 3) and at Week 12 (Visit 8). During the 14-week follow-up period, the subjects will receive two telephone calls (Visits 9 and 10) and will be required to return for an additional study visit as EOS (Visit 11). In these two groups, the total duration of the study will be 26 weeks after cataract surgery.



3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in central corneal ECD at Week 12.

3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Central corneal ECD at each visit
- Change from baseline in central corneal ECD at each visit (other than Week 12)

- Percent change in central corneal ECD from baseline at each visit
- Peripheral corneal ECD at each visit
- Change from baseline in peripheral corneal ECD at each visit
- Percent change in peripheral corneal ECD from baseline at each visit
- Change from baseline in [redacted]
- Time to return of corneal thickness to less than or equal to baseline level
- Time to complete clearance of corneal edema after cataract surgery
- Number and percentage of subjects who achieve corneal clearance at each visit, where corneal clearance is defined as achieving a central corneal thickness less than or equal to baseline central corneal thickness without any corneal edema
- Number and percentage of subjects who achieve central corneal thickness less than or equal to baseline central corneal thickness at each visit
- Number and percentage of subjects without any evidence of corneal edema at each visit
- Change from baseline in central corneal thickness at each visit
- Percent change from baseline in central corneal thickness at each visit
- Change from baseline in best corrected distance visual acuity (BCVA) (letters) by Early Treatment Diabetic Retinopathy Study (ETDRS) score at each visit
- Time to achieve BCVA by ETDRS letter score >70 letters (Snellen equivalent better than 20/40) after cataract surgery
- Number and percentage of subjects from baseline with improvement in BCVA by ETDRS of [redacted] or more at each visit

- Change from baseline in Visual Function Questionnaire-25 (VFQ-25) domain and total score at each visit

3.2.3. Pharmacokinetics Endpoints

[redacted]

3.2.4. Safety Endpoints

The primary safety endpoint includes the incidence of Adverse Events (AEs), treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs).

Secondary safety endpoints include changes in slit-lamp biomicroscopy (cornea, conjunctiva, sclera, anterior chamber, lens, lids, and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), and intraocular pressure (IOP).

3.3. Study Procedures and Baseline

Prior to the implementation of study procedures, subjects and persons conducting the consent discussion will be required to sign and date the Institutional Review Board (IRB)/Independent Ethnics Committee (IEC)–approved informed consent form (ICF), and each subject will be given a copy. In addition, this information will be recorded in the subject's medical record (i.e., source document).

After obtaining informed consent at Visit 1, the investigator will select one eye as the study eye, and the subject will come back for the cataract surgery and random assignment to treatment. At Visit 2, each subject's eligibility for study participation will be confirmed, including a successful cataract surgery that meets the inclusion criteria. After eligibility is confirmed, subjects will be randomly assigned to the 4 treatment groups (in a 2:1 ratio of K-321 to Placebo). All subjects will be instructed to apply the study drug only to the study eye.

Day 1 (Visit 3) is considered to be the day when first dose of study drug is administered. Randomization is scheduled to be performed on Day -1 (Visit 2).

Baseline for all efficacy and safety variables [redacted] Change from baseline is defined as the post baseline value minus the baseline value for the given assessment.

The EOT (Week 12 or ET [Early Termination]) visit is defined as the visit occurring at the end of the 12-week treatment period (Week 12) or the final visit at which the subject is prematurely discontinued/withdrawn from study drug administration.

The EOS (Week 16 or ET) visit for Groups A/C is defined as the visit occurring at the end of the 16-week study period (Week 16) or the final visit at which the subject is prematurely discontinued/withdrawn from participation in the study. A similar definition applies to subjects in Groups B/D though with extended untreated follow-up through Week 26.

The schedule of study site activities (SOA) is presented in Table 3 in the Appendix.

3.4. Treatments

Groups A/B receive K-321 ophthalmic solution 0.4% dosed QID (K-321 QID) and Groups C/D receive Placebo QID for 12 weeks. Groups A/C have 4 weeks of untreated follow-up whereas Groups B/D have 14 weeks of untreated follow-up. To preserve masking, all subjects will self-administer assigned study drug QID from [redacted].

During the 12-week treatment period, subjects will administer study drug [redacted] on Day 1 through Week 12. On days when a study visit occurs, subjects must visit their study sites without administering any topical ophthalmic preparations prior to the visit, including study drug, and must not administer topical ophthalmic preparations except examination purpose (e.g., topical anesthesia and mydriatics) until all examinations have been completed. Thereafter on those days, subjects will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day.

If a dose is missed, the subject is recommended to not administer the study drug if the next dosing is in less than 2 hours.

If a subject applies any study drug on the day of Visit 8 (EOT) before all study measurements have been completed, that subject's Visit 8 (EOT) should be rescheduled within the visit window allowance (e.g., the next day). For visits other than Visit 8 (EOT) during the

treatment period, a subject who applies study drug before all study measurements have been completed will be assessed as planned, and a protocol deviation must be recorded.

4. General Statistical Considerations

Statistical analysis will be performed using SAS software (Version 9.4, SAS/STAT 15.2). Continuous variables will be summarized using the mean, the standard deviation (SD), median, Quartile 1 (Q1), Quartile 3 (Q3), minimum value, and maximum value. [redacted] Categorical variables will be summarized using frequency and percentages. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Selected ordinal data may be summarized using both descriptive statistics and frequencies and percentages of participants in each category, as appropriate. Data will be listed in data listings.

The study eye is the eye receiving cataract surgery. Unless otherwise specified, efficacy analyses will be summarized for the study eye only. Ocular safety summaries will be presented separately for the study eye and the non-study eye.

Numeric data may be recorded at limits of detection (with a '<' or '>' sign, i.e., < 0.1 or > 0.1). To summarize the blood drug concentration data, the original value below the limit of detection will be converted as 0. Values above the limit of detection will be reported at the limit. The actual values will be presented in the data listings.

4.1. Sample Size

To compare Week 12 central corneal ECD change from baseline of K-321 QID to Placebo [redacted] A secondary objective of this study is to evaluate the safety of K-321. The sample size of 330 randomized subjects in total will provide safety data for a 12-week treatment period and 105 out of 330 randomized subjects will provide safety data for a 12-week treatment period plus a 14-week follow-up period. [redacted]

4.2. Randomization, Stratification and Masking

Subjects will be randomly assigned at Visit 2 to Group A, B, C, or D. Groups A/B receive K-321 ophthalmic solution 0.4% dosed QID (K-321 QID) and Groups C/D receive Placebo QID for 12 weeks. Groups A/C have 4 weeks of untreated follow-up whereas Groups B/D have 14 weeks of untreated follow-up. Allocation to K-321 and Placebo will be in a 2:1 ratio. Randomization will be stratified by [redacted]

Study drug will be double-masked. All study drug will be supplied in identical packaging, color, smell, and appearance to enable double-masked conditions. K-321 and matching Placebo will be provided in identical packaging so that all investigators, study site staff, subjects, and clinical monitors will remain masked throughout the study. The Electronic Data Capture (EDC) system will assign study drug to subjects at the time of randomization. Only personnel in randomization and clinical supplies will be unmasked and will have access to treatment assignments; all other parties involved in the study will be fully masked.

A subject's treatment assignment will not be unmasked for the investigator or study site staff until the EOS unless medical treatment of the subject depends on knowing the study treatment the subject received. In the rare event that unmasking is needed because of a medical emergency, the investigator may unmask an individual subject through the Interactive Web Response System (IWRS). Reasons for treatment unmasking must be clearly explained and justified in the electronic case report form (eCRF). The date on which the code was broken together with the identity of the person responsible must also be documented.

Subjects who are unmasked will be allowed to continue their participation in the study.

4.3. Analysis Sets

4.3.1 Full Analysis Set (FAS) in the 12-Week Period

FAS in the 12-Week Period (FAS12) will include all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed according to their randomized treatment group.

4.3.2 PK Analysis Set

The PK Analysis Set (PKAS) will include all subjects who have received at least one dose of study treatment and have at least one time point of PK measurement. Analyses will be presented by actual treatment received.

4.3.3 Safety Population in the 12-Week Period

Safety Population in the 12-Week Period (SP12) will include all subjects who have received at least 1 dose of study treatment. Analyses will be presented by actual treatment received.

4.3.4 FAS in the 26-Week Overall Period

FAS in the 26-Week Period (FAS26) will include the randomized subjects who are assigned into the 26-week Overall Period (Groups B and D) and received at least one dose of study treatment. Subjects will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment. .

4.3.5 Safety Population in the 26-Week Overall Period

Safety Population in the 26-Week Period (SP26) will include subjects for the 26-week Overall Period (Groups B and D) and who had at least 1 dose of study treatment. Analyses will be presented by actual treatment received.

4.4. Assessment Windows

4.4.1 Study Day

When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of assessment - Day 1 +1, if date of assessment ≥ Day 1.
- study day = date of assessment - Day 1, if date of assessment < Day 1.

Note that the day before Day 1 is Day -1 (for analysis, there is no Day 0 for study day).

4.4.2 Visit Windows for Analysis

Visit windows will be defined for by-visit summary and analysis purposes. Summary data (such as AEs and concomitant medications) that are not reported by visit will not use visit windows.

Scheduled, unscheduled, and early termination visits will all be considered as valid assessments for analysis. Visit labels will be assigned to each post baseline record based on the windows for study day relative to the date of first dose of double-masked study drug. [redacted] All analyses will be based on the analysis visit windows in Table 2. If there are multiple valid assessments within a time window, the assessment that occurs closest to the target day will be used in the analysis. If there are multiple valid assessments with the same difference from the target day, the latest assessment will be used in the analysis.

Table 2 Analysis Visit Windows

Analysis Visit	Analysis Visit Window
Screening Visit (Visit1) [redacted]	-28 to -2 Day
Day-1 (Visit 2) [redacted]	-1 Day
Day1	1 Day (Target1)
Week 1	2 to 11 Days (Target 8)
Week 2	12 to 18 Days (Target 15)
Week 3	19 to 36 Days (Target 22)
Week 7	37 to 67 Days (Target 50)
Week 12	68 to 99 Days (Target 85)
Week 16	100 to 130 Days (Target 113)
Week 21	131 to 165 Days (Target 148)
Week 26	166 to 200 Days (Target 183)

[redacted]

5. Subject Disposition

5.1. Disposition

Enrollment by site will be presented.

The counts and percentages of screened subjects, subjects who are randomized, and subjects who receive study treatment will be presented overall and by treatment period. Withdrawals from the study will be presented based on the number of subjects in each treatment group and overall for all randomized subjects. Reasons for study drug discontinuation during the treatment period and reasons for withdrawal from the study will be summarized for each treatment group as treatment disposition and subject disposition, respectively. All percentages within the subject disposition summary will be based on the number of subjects randomized. All percentages within the treatment disposition summary will be based on the number of subjects randomized who received at least 1 dose of study therapy. For reason for study withdrawal, percentages will be based on the number of subjects who withdrew from the study. For treatment completion status, percentages will be based on the number of subjects randomized who received at least one dose of study therapy. For reason for study drug discontinuation, percentages will be based on the number of subjects who discontinued study drug.

Subject and treatment disposition data will be listed. Screen failures will also be listed in the data listing.

5.2. Protocol Deviations

Protocol deviations will be tracked by the clinical team on an ongoing basis and will be recorded within the EDC. Subjects with protocol deviations will be tabulated for each treatment group and overall. All percentages will be based on the number of subjects randomized. All deviations, including critical and major protocol deviations, will be listed by subject.

5.3. Intercurrent Events

Intercurrent events (ICEs) will be summarized by treatment and overall. Possible ICEs include:

- Discontinuation of the study treatment due to an adverse event;
- Discontinuation of the study treatment due to lack of efficacy.

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information and baseline characteristics collected at Screening will be summarized for the FAS12, FAS26, SP12, SP26, and [redacted]. Continuous variables including age (years) will be summarized using descriptive statistics for each treatment group and overall. The following categorical variables will be summarized by reporting the number and percentage of subjects in each category for each treatment group and overall by treatment.

- Sex (Male, Female)
- Age (<65, ≥65 years) and (<65, 65-84, ≥85 years)
- Femtosecond laser × Age (Yes <65 years, Yes ≥65 years, No <65 years, No ≥65 years)
- Ethnicity (Hispanic, Latino/a, or Spanish origin, Not Hispanic, Latino/a, or Spanish origin, Not Reported, Unknown)
- Hispanic, Latino/a, or Spanish origin (Mexican, Mexican American, Chicana/o; Puerto Rican; Cuban; Other; Multiple)
- Race (White, Black or African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander, Not Reported, Unknown, Other, and Multiple)
- Color of Study Eye (Brown, Blue, Hazel, Grey, Green, Black, Other)
- Study Eye (OD or OS)
- History of Diabetes (Yes, Type I, Type II, No)

- Specular Microscopy Assessment (Yes, No)

Percentages will be based on the total number of subjects in the FAS12, FAS26, SP12, and SP26. Percentages of individual ethnicities will be based on total number of subjects of Hispanic, Latino/a, or Spanish origin.

Treatment comparisons will be performed; age will be compared using a Wilcoxon Rank Sum Test (based on Z-approximation with continuity correction of 0.5) and categorical variables will be compared using a chi-square test.

All demographic and baseline characteristics will be listed.

6.2 Cataract Surgery

Continuous descriptive variables for the cataract surgery (total case time, cumulative dissipated energy, total ultrasound time) will be summarized for FAS12 and FAS26 using descriptive statistics for each treatment group and overall. The following categorical variables will be summarized by reporting the number and percentage of subjects in each category for each treatment group and overall.

- Femtosecond Laser (Yes, No)
- Surgery Difficulty (Difficulty less than average, Average difficulty, Difficulty more than average)
- Measured Energy Parameter (Cumulative Dissipated Energy, Other)

6.3 Medical History

6.3.1 Medical History

Ocular and non-ocular medical histories will be captured in the eCRF. The investigator will record the verbatim term, start date, and stop date (or continuing). For ocular medical history, the investigator will also record the eye [right eye (OD), left eye (OS), both eyes (OU)]. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

The frequency and percentage of subjects with any medical history will be summarized by treatment group using the FAS12 and FAS26. System organ class (SOC) will be sorted alphabetically, and preferred term (PT) within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-321;
- Descending frequency within Placebo;

- PT in alphabetical order.

The medical history will include both the ocular and the general (non-ocular) history. Ocular medical history and general (non-ocular) medical history will be summarized separately. Ocular and non-ocular medical history will be identified according to whether eye is specified or not. Ocular medical history will be summarized separately for study eye and non-study eye.

6.3.2 Surgical History

Ocular and non-ocular surgical histories will be captured in the eCRF. The investigator will record the verbatim term, and surgical date. For ocular surgical history, the investigator will also record the eye (OD, OS, OU). Surgical history will be coded using MedDRA Version 25.0.

The frequency and percentage of subjects with any surgical history will be summarized by treatment group using the FAS12 and FAS26. SOC will be sorted alphabetically, and PT within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-321;
- Descending frequency within Placebo;
- PT in alphabetical order.

The surgical history will include both the ocular and the general (non-ocular) history. Ocular surgical history and general (non-ocular) surgical history will be summarized separately. Ocular and non-ocular surgical history will be identified according to whether eye is specified or not. Ocular surgical history will be summarized separately for study eye and non-study eye.

6.4 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented in a data listing. A summary table of inclusion and exclusion criteria that were not met will be presented for screen failures.

7. Treatments and Medications

7.1 Prior Medications and Concomitant Medications

At Screening, all subjects' prior medications used, and surgical procedures undergone within the previous 30 days will be recorded in the eCRF. Any medicinal product prescribed or

over-the-counter (OTC), including herbal products, vitamins, and minerals is considered a prior or concomitant medication.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) (B3 WHO Drug Global March 2022) for anatomical therapeutic chemical (ATC) classification and preferred drug name.

The frequency and percentage of subjects with coded medications will be summarized by treatment group using SP12 and SP26. A subject who used multiple medications will be counted only once for each ATC and preferred drug name. Therapeutic Subgroup will be sorted alphabetically, and Pt will be sorted by descending frequency overall within each Level 3 term in order:

- Descending frequency within K-321;
- Descending frequency within Placebo;
- PT in alphabetical order.

Prior medications are defined as any medications that started and stopped prior to the first dose of double-masked study drug. Concomitant medications are defined as any medications that (1) start prior to the first dose of double-masked study drug and stop or are ongoing at or after the date of first dose of double-masked study drug; or (2) start at or after the first dose of double-masked study drug. Medications taken after a subject's last visit or withdrawal from the study are not considered concomitant.

Partial or missing medication stop dates for medications that are not ongoing will be handled as follows:

- Partial stop dates of prior and concomitant medications and procedures will be assumed to be the latest possible date consistent with the partial date.
- If the year is present and the month is missing, then the month is set to December.
- If the month and year are present and the day is missing, then the day is set to the last day of the month.
- For subjects who are treated, if the year is missing and the month or day are not missing, then the year will be assumed to be the year part of the subject's last recorded study visit date.
- For subjects who are not treated, if the year is missing and the month or day is not missing, then the year will be assumed to be the year part of the subject's discontinuation date.
- If the complete stop date is missing, the stop date will be considered to be either the subject's last recorded visit date for treated subjects or the subject's discontinuation date for non-treated subjects.

The above imputations are for tabulations of study data. Data will be presented as obtained in listings. Prior and concomitant medications will be summarized separately. Ocular and non-ocular medications will be identified according to whether eye is specified or not and will be summarized separately. Ocular prior and concomitant medications will be summarized for study-eye and non-study eye.

7.2 Rescue Medications

The subset of concomitant medications that are determined to be rescue medications will be summarized in a manner similar to concomitant medications.

7.3 Concomitant Surgeries/Procedures

Concomitant surgeries/procedures will be captured in the EDC in a similar manner to what is described in Section 6.3.2 Surgical History. Concomitant surgeries/procedures are defined as any surgery/procedure that starts at or after the first dose of double-masked study drug. Date imputation will be performed in a manner consistent with what is described in Section 7.1 Prior Medications and Concomitant Medications. Concomitant surgeries/procedures will be presented for FAS12 and FAS26.

7.4 Rescue Surgeries/Procedures

The subset of concomitant surgeries/procedures that are determined to be rescue will be summarized in a manner similar to concomitant surgeries/procedures.

7.5 Concomitant Devices

Concomitant devices will be presented in a listing.

7.6 Study Treatments

7.6.1 Extent of Exposure

Descriptive statistics including the number of subjects, mean, SD, median, Q1, Q3, minimum, and maximum for the study treatment exposure (number of instillations and duration of treatment) and compliance will be provided by treatment group using SP12. Duration of exposure will be calculated in days as the (date of last dose minus date of first dose + 1).

Frequency and percentages of subjects in the following exposure categories will be summarized:

- <1 week;
- 1 to ≤ 4 weeks;

- >4 to ≤ 8 weeks;
- >8 to ≤ 12 weeks;
- > 12 weeks.

7.6.2 Treatment Compliance and Modifications

Percent compliance will be calculated as:

$$\frac{\text{total assumed number of study drug instillations}}{\text{planned number of instillations}} \times 100$$

for SP12.

To calculate the planned number of instillations, the following scenarios are considered:

- For all study days, the total assumed number of study drug instillations is the number of dispensed vials minus the number of unused vials minus the number of missing vials reported on the Study Drug Dispensation and Drug Accountability eCRFs.
- For all study visits during the treatment period, the planned number of instillations will be adjusted based on the time all planned study visit assessments are completed on the respective study visit days, as activities on these days may reduce the number of doses that can be given. Thus, on the study visit days, the number of planned instillations will be based on the time of the dose in the clinic (e.g., if the first dose of the day is taken [redacted], then the planned instillation will be considered to be 4 doses; if the first dose of the day is taken [redacted], then the planned instillation will be considered to be 3 doses).
- Planned number of instillations for Visit 8 (Week 12) should be 0 for subjects not in the PKAS. The planned number of instillations should be 1 for subjects in the PKAS. [redacted]
- For all other study days, the number of planned instillations will be 4 doses.
- If the first and last doses are administered on the same day, the number of planned instillations will be based on the time of the first dose.
- Subjects will be considered compliant with study treatment if the calculated compliance is between 80% and 125%, inclusive.

A by-subject listing will be presented for the study treatment exposure and compliance, as well as drug accountability.

8. Efficacy Analysis

The FAS12 will be the primary analysis set for efficacy analyses. Separate efficacy analyses will be presented by the FAS26. Efficacy analyses will be presented for the study eye and the non-study eye, where available. Regarding ECD, the analysis set is limited to subjects enrolled at the site which has a qualified Specular Microscope.

8.1. Primary Efficacy Endpoint

The primary analysis of central corneal ECD will be performed on the study eye within the FAS12 via a Wilcoxon Rank Sum Test (based on Z-approximation with continuity correction of 0.5) [redacted] Testing will be performed to compare K-321 versus Placebo.

The following 2-sided hypothesis will be tested:

Ho: $\Delta = 0$ versus Ha: $\Delta \neq 0$

where Δ is the shift in location in central corneal ECD change from baseline as measured at Week 12 between the active and Placebo groups being compared: i.e.,

$X_i = e_i$ for i = 1 to n for the Placebo subjects

$Y_j = e_j + \Delta$ for j = 1 to m for the K-321 subjects

The Hodges-Lehmann estimate (Hodges and Lehmann 1963) for the shift in location (e.g., the median of all differences d=Yj – Xi) and Moses 95% confidence interval (CI) (Moses 1965) will also be presented. Exact test will also be performed, and the p-values from the exact Wilcoxon Rank Sum Test and the Hodges-Lehmann exact CI will be presented for supportive use, and an asymptotic stratified Wilcoxon (Van Elteren) test will be performed as a secondary analysis.

Sample code for analysis:

```
proc npar1way wilcoxon hl data = dsnin;
   [redacted]
   class trtpn;
   var ECD_CFB;
   exact wilcoxon hl / mc n = 1000000;
run;
```

The primary analysis using the Wilcoxon Rank Sum Test to evaluate the superiority of K-321 versus Placebo will be performed under the assumption that the underling central corneal

ECD distribution in the treatment groups is the same except for a location shift. However, since the shape of the assumed central corneal ECD distribution in the treatment groups may likely differ, as a supporting analysis, a permutation test will be performed to evaluate the median of the differences between the treatment groups. If deemed necessary, an additional analysis to evaluate central corneal ECD change from baseline at Week 12 by adjusting for the baseline peripheral corneal ECD data will also be provided.

Sample code to generate the permutation test:

```
proc multtest data = dsnin outsamp = dsnout permutation
                        seed = 321302 nsample = 1000000;
   class trtpn;
   test mean(ECD_CFB);
run;

proc means data= dsnout median;
       by _sample_ ;
       class _class_ ;
       var ECD_CFB ;
run;
```

8.2. Data Imputation Rules and Estimands for Primary Analysis

Central corneal ECD will be based on scores that are provided for up to [redacted] for each subject and visit combination. [redacted] Scores for individual images will be provided in listings.

[redacted]

Targeted Estimands

The following targeted estimands will be used for primary analysis:

Treatment Condition:
- Treatment condition based on the assigned treatment group.

Population:
- Subjects based on the Inclusion and Exclusion criteria of the study.

Variable:
- Central corneal ECD Week 12 assessment (change from baseline) performed by specular microscopy [redacted]

Intercurrent events are as follows:
- Discontinuation of the study treatment due to an adverse event
- Discontinuation of the study treatment due to lack of efficacy

Population-level Summary:
- The Hodges-Lehmann estimate (Hodges and Lehmann 1963) for the difference in median between two groups

8.3. Secondary Efficacy Endpoints

Descriptive summaries of continuous outcomes by visit and treatment will be presented by study eye and non-study eye for the following efficacy endpoints. Comparisons between treatments will be performed.

- Change from baseline in central and peripheral corneal ECD;
- Change from baseline in central and peripheral corneal ECD within Subgroups
  - Central ECD: < 2000 cells/mm^2 and ≥ 2000 cells/mm^2 at baseline
  - Nasal ECD: < 2000 cells/mm^2 and ≥ 2000 cells/mm^2 at baseline
  - Temporal ECD: < 2000 cells/mm^2 and ≥ 2000 cells/mm^2 at baseline
  - Minimum ECD at baseline < 2000 cells/mm^2 and ≥ 2000 cells/mm^2
- Percent change from baseline for central and peripheral corneal ECD;
- Change from baseline in [redacted]
- Change from baseline for central corneal thickness;
- Change from baseline for IOP;
- Percent change from baseline for central corneal thickness;

- Change from baseline in BCVA;
- Change from baseline in VFQ-25 domain and total scores.

Summaries of central and peripheral corneal ECD [redacted] Scores for individual images will be provided in listings.

The NEI-VFQ-25 consists of 25 questions. Mangione (2000) describes the scoring of the instrument into 12 subscales and an overall composite scale. The 12 subscales and their component questions include:

1. General Health (1)
2. General Vision (2)
3. Ocular Pain (4, 19)
4. Near Activities (5, 6, 7)
5. Distance Activities (8, 9, 14)
6. Vision Specific
    a. Social Functioning (11, 13)
    b. Mental Health (3, 21, 22, 25)
    c. Role Difficulties (17, 18)
    d. Dependency (20, 23, 24)
7. Driving (15c, 16, 16a)
8. Color Vision (12)
9. Peripheral Vision (10)

The scores within each subscale are the average of the available recoded scores according to Table 2 of Mangione (2000). The overall composite is the average of the available subscales in 2-9 above.

Change from baseline for continuous secondary endpoints will be analyzed using mixed-model repeated measures (MMRM) with an unstructured covariance assumed with fixed effects for baseline measurement, [redacted] visit, treatment, and visit by treatment interaction. If the model fails to converge using this covariance structure, heterogenous Toeplitz or compound symmetry will be implemented in this order until convergence is reached.

```
PROC MIXED DATA = indata;
   CLASS subject [redacted] visit treatment;
   MODEL CFB = baseline [redacted] visit treatment visit*treatment / solution
      DDFM = KR;
   REPEATED visit / SUBJECT=subject TYPE=UN;
   LSMEANS visit*treatment / slice = visit CL diff OM;
RUN;
```

Subgroup tables will analyze data through Week 12, though only Week 12 inference will be summarized.

The frequency and percentage of the following efficacy endpoints will be presented for each windowed visit by eye:

- Corneal clearance, defined as central corneal thickness less than or equal to baseline central corneal thickness with corneal edema simultaneously normal for epithelial, stromal, and endothelial regions during slit-lamp review;
- Central corneal thickness less than or equal to baseline central corneal thickness;
- Corneal edema simultaneously normal for epithelial, stromal, and endothelial regions during slit-lamp review;
- Improvement in BCVA by at least [redacted]

The Cochran-Mantel-Haenszel (CMH) correlation statistic using standardized midrank scores will be used to assess the difference between treatments.

Time to complete clearance of corneal edema will be analyzed using Kaplan-Meier time-to-event analyses. 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 will be censored at their last slit-lamp biomicroscopy where these assessments are performed within the double-masked treatment period. A Kaplan-Meier plot will summarize the probability that an event occurs. Median follow-up time, measured from Visit 2 date until date of the earliest event or censoring, its 95% confidence interval, and log-rank p-value will be provided. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time-to-event will be presented.

Time to return of corneal thickness to less than or equal to baseline level will be analyzed using Kaplan-Meier time-to-event analyses. Subjects who do not experience a return to baseline level will be censored at their last available measurement of corneal thickness within the double-masked treatment period. A Kaplan-Meier plot will summarize the probability that an event occurs. Median follow-up time, measured from Visit 2 date until date of the earliest event or censoring, its 95% confidence interval, and log-rank p-value will be provided. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time-to-event will be presented.

Time to achieve BCVA letter score > 70 letters in the study eye will be analyzed using Kaplan-Meier time-to-event analyses. Subjects who do not achieve a letter score > 70 will be censored at their last available BCVA assessment within the double-masked treatment period. A Kaplan-Meier plot will summarize the probability that an event occurs. Median follow-up time, measured from Visit 2 date until date of the earliest event or censoring, its

95% confidence interval, and log-rank p-value will be provided. The frequency and percentage of the number of individuals experiencing events will be summarized. Summary statistics of the time-to-event will be presented.

9. Pharmacokinetics Analysis

9.1. Pharmacokinetics Analysis

[redacted]

9.2. Profile of Plasma Drug Concentration

[redacted]

9.3. Plasma Pharmacokinetics Parameters

[redacted]

[redacted]

10. Safety Analysis

Safety will be assessed by adverse events, slit-lamp biomicroscopy (cornea, conjunctiva, sclera, anterior chamber, lens, lids, and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), and intraocular pressure (IOP).

Safety data will be summarized and listed with no statistical hypothesis testing performed. Continuous variables will be summarized using the mean, the SD, median, Q1, Q3, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

Safety analyses will be presented by SP12. Separate analyses will be presented by SP26.

10.1. Adverse Events

AEs will be coded using the MedDRA Version 25.0.

In general, all AEs will be listed, and all TEAEs and TESAEs will be summarized.

A TEAE is defined as an AE that begins after the start of the randomized study drug or an event that begins before the start of the randomized study drug and worsens in intensity after starting the randomized study treatment.

An overall summary of TEAEs and TESAEs will be provided, with number (percentage) of subjects and number of events for all TEAEs/TESAEs by the following categories: any TEAEs, any TESAEs, study drug-related TEAEs/TESAEs, TEAEs/TESAEs by worst severity, TEAEs/TESAEs leading to treatment discontinuation, TEAEs/TESAEs leading to study withdrawal, and TEAEs leading to death. The total number of TEAEs and TESAEs (overall and study drug-related) will be presented.

TEAEs and TESAEs will be summarized separately by ocular events for the study eye and non-study eye, ocular events at the subject level, and non-ocular events by:

- TEAEs/TESAEs during Treatment Period are defined as TEAEs/TESAEs with date on or after the first treatment date (Day 1) up to and including the Week 12 Visit date. For subjects who miss the Week 12 Visit and/or do not complete the Treatment Period, the end date for this definition will be the Week 12 (the imputation date (day 85)) or the date of the end of the study, respectively. This will be performed only for SP12.
- TEAEs/TESAEs during the 4-Week Follow-up are defined as TEAEs/TESAEs with a date after the Week 12 Visit date, up to and including the Week 16 Visit for Groups B and D. For subjects who miss the Week 16 Visit and/or do not complete tapering period, the end date for this definition will be the Week 16 (the imputation date (day 113)) or the date of the end of the study, respectively. This will be performed for SP12 and SP26.
- TEAEs/TESAEs in the extended Follow-up are defined as TEAEs/TESAEs with date after the Week 16 phone call date through the remainder of the study. For subjects who miss the Week 26 Visit, the end date for this definition will be date of the last available follow-up. This will be performed only for SP26.

SOC will be sorted alphabetically, and PT within each SOC will be sorted by overall descending order of frequency according to the following rules in order:

- Descending frequency within K-321;
- Descending frequency within Placebo;
- PT in alphabetical order.

Subjects will be counted only once for each SOC and PT. The percentages will be calculated based on the number of subjects in each treatment group.

Partial dates on AE start dates will be handled as follows:

- If the onset date is completely missing and the AE end date is not prior to the date of first dose of double-masked study drug, onset date is set to the date of first dose.
- If the year is present and the month is missing, then the month is set to January. If the year is the same as the year of the date of first dose of double-masked study drug and the AE end date is not prior to the date of first dose of double-masked study drug, then onset date is set to the date of first dose of double-masked study drug.
- If the month and year are present and the day is missing, then the day is set to the 1st day of the month. If the month and year are the same as the month and year of the date of first dose and the AE end date is not prior to the date of first dose of double-masked study drug, then onset date is set to the date of first dose of double-masked study drug.

- If the AE end date is present, then the imputed start date will be no later than the end date.

The above imputations are for tabulations of study data. Data will be presented as obtained in listings.

10.1.1. Incidence of Adverse Events

Both ocular and non-ocular TEAEs will be summarized by treatment group. The total number of TEAEs and the number and percentage of subjects with at least one TEAE in each SOC and having each individual TEAE based on the PT will be presented. All AEs will be listed.

10.1.2. Adverse Events Related to Study Drug

The relationship or association of the study drug in causing or contributing to the TEAE will be characterized as related or not related. A summary of TEAEs related to study drug will be presented in a table by total number of subjects with incidence of TEAE occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. TEAEs that are missing a relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship. Percentages will be calculated out of the number of subjects in the SP. The number of events under each SOC and PT will also be presented.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 10.1.1.

10.1.3. Severity of Adverse Event

A summary of TEAEs by maximum severity will be presented in a table by total number of subjects with incidence of TEAE occurrence. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are "Mild," "Moderate," and "Severe." If a subject reported multiple occurrences of the same TEAE, only the most severe will be presented in the incidence count. TEAEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the SP.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 10.1.1.

10.1.4. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

TEAEs leading to treatment discontinuation will be identified as TEAEs on the AE eCRF page, where the action taken with study drug is "Study Drug Discontinued". The TEAEs leading to study drug discontinuation will be categorized and presented by SOC and PT in a manner similar to that described in Section 10.1.1. All TEAEs leading to study drug discontinuation will be listed in a data listing.

10.1.5. Treatment-Emergent Adverse Events Leading to Study Withdrawal

TEAEs leading to study withdrawal will be identified as such if the study discontinuation page lists reason for discontinuation as adverse event, in the opinion of the investigator with the adverse event listed. The TEAEs leading to study withdrawal will be categorized and presented by SOC and PT in a manner similar to that described in Section 10.1.1. All TEAEs leading to study withdrawal will be listed in a data listing.

10.1.6. Serious Adverse Events

The TESAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 10.1.1. TESAEs leading to study drug discontinuation and study withdrawal will be categorized and presented by SOC and PT in a manner similar to that described in Sections 10.1.4 and 10.1.5. For all TESAE summaries, the number of events under each SOC and PT will also be presented. All SAE data will be listed in a data listing.

10.1.7. Death

Deaths will be identified as AEs on the AE eCRF page. Subject deaths will be identified as AEs where the outcome is "Fatal". All deaths will be listed in a data listing.

10.2. Ophthalmological assessments

Ophthalmological assessments will be performed at the indicated visits in the SOA (Table 3).

10.2.1. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed at every visit using slit-lamp examination (cornea, conjunctiva, sclera, anterior chamber, lens, lids and lashes).

Except for anterior chamber findings, findings will be evaluated by the following criteria:

- Normal;

- Abnormal and not clinically significant (NCS);
- Abnormal and clinically significance (CS).

Anterior chamber cells will be graded 0 (0 cells), 1 (1-5 cells), 2 (6-15 cells), 3 (16-30 cells), or 4 (>30 cells). Anterior chamber flare will be graded none, faint, moderate (iris and lens details clear), marked (iris and lens details hazy), and intense (fibrin or plastic aqueous).

The frequency and percentage of subjects with observed values of normal, abnormal NCS, and abnormal CS as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes.

All slit-lamp biomicroscopy assessments will be listed.

10.2.2. Dilated Fundoscopy

Dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery) will be performed at Screening and Weeks 12, 16, 26.

Ocular findings will be evaluated by the following criteria:

- Normal;
- Abnormal and NCS;
- Abnormal and CS.

The frequency and percentage of subjects with observed values of normal, abnormal NCS, and abnormal CS as well as the categorical shift from baseline at each post-baseline visit will be tabulated at each scheduled visit for both eyes.

All dilated fundoscopy assessments will be listed.

10.2.3. Intraocular Pressure

IOP may be measured by either contact or non-contact tonometry, but the same method must be used for all study visits for a given subject throughout the study and all reasonable efforts must be made to have the same examiner obtain all IOP measurements for a given subject. At each study visit, a single IOP measurement will be made for each eye, with pressure recorded in millimeters of mercury (mm Hg).

Observed values at baseline and each subsequent study visit, as well as changes from baseline in IOP for each subsequent study visit, will be summarized descriptively by treatment group for the study eye and non-study eye. Statistical comparisons will be performed in a similar manner as for efficacy. All IOP data will be listed.

11. Interim Analysis

Not applicable.

12. Changes to Protocol Specified Analysis

1. Imputation rules were updated to fit K-321-302 requirements that do not involve DSO as in other K-321 studies.

2. Secondary analyses involving cornea edema were clarified to consider all zones simultaneously.

SAP (Version 2.0) was amended to modify the definition of study drug instillations for the treatment compliance.

13. References

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14. Appendix

Table 3: Schedule of Study Site Activities

Time Point	Day -28 to -2	Day -1	Day 1	Week 1 (Day 8)	Week 2 (Day 15)	Week 3 (Day 22)	Week 7 (Day 50)	Week 12 (Day 85) (EOT)[a]	Group A/C Week 16 (Day 113) (EOS) [b]	Group B/D Week 16 [c] (Day 113)	Group B/D Week 21 [c] (Day 148)	Group B/D Week 26 (Day 183) (EOS) [d]
Visit Window (Day)	-	-	-	± 2	± 2	± 3	± 3	± 3	± 7	±7	± 7	± 7
Visit No	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 9 (telephone)**	**Visit 10 (telephone)**	**Visit 11**
Informed consent / HIPAA	X											
Medical history and surgical history and demographic	X											
Abbreviated physical examination	X	X [e]						X	X			X
Urine drug screen	X											
Urine pregnancy test (if applicable)		X [e]						X				
Ocular characteristics	X											
Cataract surgery		X										
Eligibility evaluation	X	X [f]										
Randomization		X [f]										
Study drug administration [g]			X [g]	X [g]	X [g]	X [g]	X [g]	X [g]				
Dispense study drug			X									
[redacted]												
Capture of Corneal Endothelial Cell Images by Specular Microscopy (non-contact type) [j]	X [i]		X	X	X	X	X	X	X			X
Corneal thickness (pachymetry)	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]			X [i]
Corneal edema (slit-lamp biomicroscopy)	X [i]		X	X	X	X	X	X	X			X
BCVA (ETDRS scale)	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]			X [i]
Slit-lamp biomicroscopy (safety evaluation)	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]			X [i]
Photo Documentation of Ocular Findings [k]	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]			X [i]
IOP (contact or non-contact type tonometer)	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]			X [i]
Dilated fundoscopy	X [i]							X [i]	X [i]			X [i]
VFQ-25	X					X		X	X			X
[redacted]												
Review the list of medications [m]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event documentation	X	X	X	X	X	X	X	X	X	X	X	X

a EOT = End of Treatment

b EOS = End of Study for groups A/C

c Subjects who are in Groups B and D will have a follow-up phone call at Visit 9 (Week 16) and at Visit 10 (Week 21), and AE and concomitant medication will be recorded.

d EOS = End of Study for groups B/D

e Pre-operative

f Post-operative

g During Visit 3 (Day 1), **all assessments must occur prior to the administration of the assigned study drug**. During Visit 3, subjects must first apply study drug within [redacted] after the end of the cataract surgery. During Visits 4, 5, 6, and 7, subjects will not apply any study drug until after all study measurements have been completed; thereafter on those days, subjects will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day. During Visit 8 (Week 12), [redacted]

h Used [redacted] will be [redacted] and the numbers will be recorded in the electronic case report form (eCRF) during Visit 4 (Week 1) through Visit 7 (Week 7). Both used and unused [redacted] will be [redacted] and the numbers will be recorded in the eCRF during Visit 8 (Week 12).

i Both eyes

j If site has a qualified Specular Microscope, this assessment will be required. If site does not have a qualified Specular Microscope, this assessment is not mandatory.

k Photo-documentation of clinical meaningful slit-lamp findings, per Principal Investigator (PI) discretion, should be collected and labelled

l [redacted]

m Review the list of current and/or concomitant medications during each study visit