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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

Clinical Study Protocol

Drug Name:	K-321
Study Number:	K-321-302
U.S. IND Number:	123413
Protocol Version Date:	February 16, 2022 (Original Protocol) July 12, 2022 (Amendment No. 1) September 29, 2022 (Amendment No. 2) NCT05528172
Name of Sponsor:	**Kowa Research Institute, Inc.**
Address:	430 Davis Drive, Suite 200 Morrisville, NC 27560 United States of America
Managing Contract Research Organization:	[redacted]
Address:	[redacted]
Contact Numbers:	[redacted]

INVESTIGATOR'S STATEMENT

I, the Investigator, understand that all information concerning the product supplied to me by Kowa Research Institute, Inc. (KRI) in connection with this study and not previously published is confidential information. This information includes the Investigators' Brochure, protocol, case report forms, assay methods, technical methodology and basic scientific data.

I understand that any changes to the protocol must be approved in writing by Kowa Research Institute (KRI) or representative and the Institutional Review Board/Independent Ethics Committee (IRB/IEC) before implementation, except where necessary to eliminate apparent immediate hazards to the subjects.

I confirm that I will report all Adverse Events following the regulations indicated in the protocol.

I confirm that I will conduct this study in conformance with the ethical principles that have their origin in the Declaration of Helsinki, Health Insurance Portability and Accountability Act (HIPAA), as applicable, and, as applicable, the International Council for Harmonisation (ICH) tripartite guideline E6 (R2): Good Clinical Practice (GCP). I will also conduct this study, as applicable, in compliance with the requirements of the United States (US) Food and Drug Administration (FDA) as outlined in Title 21 of the Code of Federal Regulations (CFR) (Parts 11, 50, 54, 56, and 312) and all other applicable regional or local regulatory requirements.

I confirm that I am informed of the need for record retention and that no data can be destroyed.

By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in this version of the protocol dated *September 29, 2022*.

Investigator's Signature: _____ Date: _____

mm/dd/yyyy

Investigator's Name: _____

SIGNATURE PAGE

[redacted]

Approved By:

[redacted]

[redacted]

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor Company:
Kowa Research Institute Inc.</td><td>Drug Under Study:
K-321</td></tr>
<tr><td colspan="3">Title of Protocol:
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</td></tr>
<tr><td>Protocol Number:
K-321-302</td><td>Phase:
3</td><td>Indication:
For the treatment of corneal edema after cataract surgery</td></tr>
<tr><td colspan="3">Study Design:
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</td></tr>
<tr><td colspan="3">Primary Objective:
• To investigate the effect of K-321 on central corneal endothelial cell density (ECD) in subjects after cataract surgery
Secondary Objectives:
• To investigate the effect of K-321 on central and peripheral (nasal and temporal) 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</td></tr>
<tr><td colspan="3">Subject Population:
Male and female subjects ≥ 18 years of age who have undergone cataract surgery</td></tr>
<tr><td colspan="2">Number of Subjects:
Total 330 subjects:
- 220 subjects assigned to K-321
o 150 subjects followed for 16 weeks
o 70 subjects followed for 26 weeks
- 110 assigned to placebo.
o 75 subjects followed for 16 weeks
o 35 subjects followed for 26 weeks</td><td>Number of Centers:
Approximately 45 sites in the United States</td></tr>
<tr><td colspan="2">Dose Levels:
0.4% ripasudil ophthalmic solution QID
Placebo ophthalmic solution QID</td><td>Route of Administration:
Eye drop</td></tr>
<tr><td colspan="3">Duration of Treatment:
The maximum total study duration for each enrolled subject is 30 weeks including the screening period</td></tr>
<tr><td colspan="3">Criteria for Evaluation:
The baseline for all efficacy and safety variables [redacted]
Primary Efficacy Endpoint:
• Change from baseline in central corneal ECD at Week 12

Secondary Efficacy Endpoints:
• 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 change at each visit</td></tr>
</table>

- Percent change in peripheral corneal ECD from baseline at each visit
- Change from baseline in parameters [redacted] at each visit
- Time to return of corneal thickness to less than or equal to the 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) domains and total score at each visit

[redacted]

Safety:

1) Primary Safety Endpoint:

- Adverse events

2) Secondary Safety Endpoints:

- Safety assessments by slit-lamp biomicroscopy (cornea, conjunctiva, anterior chamber, lens, lids and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), intraocular pressure (IOP)

Criteria for Inclusion:

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is at least 18 years old at the screening visit (Visit 1).
2. Is planning to undergo cataract surgery in the study eye, and has had cataract surgery at Visit 2.
3. Can understand the written informed consent, provides signed written informed consent, and agrees to comply with protocol requirements before any study-specific assessment is performed.

Criteria for Exclusion:

Subjects meeting any of the following criteria will be excluded from the study:

1. Is a female subject of childbearing potential and any of the following is true:
   a) is pregnant or lactating/breastfeeding, or
   b) has experienced menarche and is not surgically sterile, not post-menopausal (no menses for the previous 12 months), or not willing to practice an effective method of birth control during the study

period as determined by the Investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or partner with vasectomy).

c) has a positive urine pregnancy test result at Visit 2 before cataract surgery.

2. Had intraocular surgery (non-laser surgery) in the study eye within 6 months of Visit 1.
3. Had intraocular laser surgery in the study eye within 3 months of Visit 1.
4. Plans to receive any surgical treatment on the study eye, other than the cataract surgery, from Visit 1 to study exit. NOTE: Femtosecond laser for corneal incision, capsulotomy, and lens fragmentation is allowed. Femtosecond laser limbal relaxing incision (laser LRI), and treatment of postoperative ocular hypertension via aqueous release from the paracentesis is allowed.
5. Has known severe comorbidities that may interfere with cataract surgery (eg, a bacterial, viral, or fungal ophthalmic infection).
6. Has any clinically significant ocular condition in the study eye, other than cataract, glaucoma* or dry eye, that requires medication or ocular surgery (* Use of a single glaucoma medication except for any carbonic anhydrase inhibitor (CAI) or Rho kinase (ROCK) inhibitor is acceptable).
7. Has used either collagen shield or contact lens in either eye within the past 7 days of Visit 1.
8. Be unwilling to avoid wearing either collagen shield or contact lenses in either eye during the study period.
9. Has known hypersensitivity to any component of the study drugs or other study related procedures/medications.
10. Has previously used ripasudil in the study eye.
11. Has used netarsudil, eye drops, or ointments containing ≥2% sodium chloride in the study eye within 14 days of Visit 1.
12. Participated in any investigational drug or device clinical studies within 30 days of Visit 1 or planning to participate in any investigational drug or device clinical studies during the study period.
13. Has a positive urine test result for drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or alcohol (either urine or saliva test) at screening. If these drugs have been prescribed to treat current medical conditions, then these medications will be permitted during the study.
14. Is a member or a family member of the professional or ancillary personnel working at the study site or the Sponsor involved in the study.
15. Has a concomitant medical or psychological condition that could interfere with study participation or is otherwise not suitable for entry into the study in the opinion of the Investigator.
16. Is using prohibited prescription or over-the-counter (OTC) medications or devices and unwilling or unable to discontinue their use for the required period before entry into the study.

Sample Size Justification:

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. [redacted] The sample size of 330 randomized subjects in total is expected to provide safety data for the 12-week treatment period, and 105 out of 330 randomized subjects will provide safety data for the 12-week treatment period plus the 14-week follow-up period. [redacted]

Statistical Analysis:

Efficacy Analysis:

Primary Efficacy Analysis

The primary analysis of central corneal ECD will be performed on the study eye within the FAS via a Wilcoxon Rank Sum Test [redacted] Testing will be performed to compare K-321 versus placebo.

The following two-sided hypothesis will be tested:

$$Ho: \Delta = 0 \text{ versus } Ha: \Delta \neq 0$$

where Δ is the shift in location in central corneal endothelial densities change from baseline as measured at Week 12 between the active and placebo groups being compared: ie,

$$Xi = ei \text{ for } i = 1 \text{ to } n \text{ for the placebo subjects}$$

$$Yj = ej + \Delta \text{ for } j = 1 \text{ to } m \text{ for the K-321 subjects}$$

The Hodges-Lehmann estimate (Hodges and Lehmann 1963) for the shift in location (eg, the median of all differences d=Yj – Xi) and Moses 95% 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 confidence interval (CI) will be presented for supportive use.

This primary analysis using Wilcoxon Rank Sum Test to evaluate the superiority of K-321 versus placebo is 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 also 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.

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 shift in location (e.g., the median of all differences d=Yj – Xi)

Secondary Efficacy Analyses

All continuous efficacy endpoints will be summarized using basic summary statistics of observed value and change from baseline at each visit.

All categorical endpoints will be summarized by frequency and percentage at each visit.

All time-to-event endpoints will be summarized by treatment.

Pharmacokinetics Analysis:

[redacted]

The following are the defined major evaluations and statistical analyses. Additional evaluation and analyses will be considered on an as-needed basis.

Profile of Plasma Drug Concentration

[redacted]

Calculation Method of Pharmacokinetics Parameters

[redacted]

Plasma Pharmacokinetics Parameters

[redacted]

Safety:
AEs will be coded using the Medical Dictionary for Regulatory Activities dictionary (the most recent version, MedDRA ver. 24.1 or later). Frequencies, percentages, severity, and relationship to study drug of subjects with treatment-emergent AE (TEAEs), serious TEAEs, and TEAEs causing premature study discontinuation and study drug discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies of occurrence will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be additionally performed for ocular and non-ocular AEs.

Safety parameters will include monitoring of AEs, TEAEs, safety assessment by slit-lamp biomicroscopy (cornea, conjunctiva, anterior chamber, lens, lids and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), and IOP.

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[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	Adverse event(s)
AREDS	Age-Related Eye Disease Study
BCVA	Best corrected (distance) visual acuity
BID	Twice daily
BrdU	5-bromo-2'-deoxyuridine
CAI	Carbonic anhydrase inhibitor
CFR	Code of Federal Regulations
[redacted]	[redacted]
CRO	Clinical research organization
CS	Clinically significant
[redacted]	[redacted]
DMC	Data Monitoring Committee
DSO	Descemet Stripping Only
eCRF	Electronic case report form
ECD	Endothelial cell density
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCEC	Human Corneal Endothelial Cell
HIPAA	Health Insurance Portability and Accountability Act
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
KRI	Kowa Research Institute
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
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]
PMM	Predictive mean matching
QID	4 times daily
REC	Research Ethics Committee
[redacted]	[redacted]
ROCK	Rho kinase
SAE	Serious adverse event
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
US	United States
VFQ-25	Visual Field Questionnaire-25
WHODrug	World Health Organization Drug Dictionary

1.0 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

1.1 Background information

An estimated 95 million people globally have cataracts (Liu, 2017). It is the leading cause of blindness, reversible blindness, and impaired vision worldwide (Lam, 2015). Cataracts are particularly prevalent in middle- and low-income countries and in those with low socioeconomic status (Liu, 2017; Lam, 2015). Cataract extraction with insertion of an intraocular lens (IOL) is the most common eye surgery worldwide, with approximately 10 million procedures performed annually throughout the globe (Foster, 2000).

The standard of care for cataract removal is phacoemulsification with intraocular lens implantation, which uses energy from ultrasound to break up the eye's innate lens into smaller pieces, which are then aspirated from the eye. The energy introduced into the eye during phacoemulsification has been demonstrated to result in undesirable endothelial injury resulting in corneal edema and endothelial cell loss. Thus, longer phacoemulsification duration has been found to be a risk factor for endothelial cell loss after surgery. In addition to the effects of the ultrasound energy, many other factors can contribute to endothelial cell loss during phacoemulsification, including anterior chamber depth; phaco power and duration; hard and large nucleus; endothelial contact from nuclear fragments, IOL, air bubbles, or surgical tools; irrigation fluid; implantation technique or the type of IOL; short axial length; free radical release; small pupil; and toxicity of the medications given during surgery (Tsorbatzoglou, 2007; Yeniad, 2010). Endothelial cell loss has been widely studied in the literature with mean percentages varying from 0.4 to 27.7% depending on the surgical technique (Tsorbatzoglou, 2007).

The corneal endothelium is a single layer of hexagonal cells that sit on a modified basement membrane (Descemet membrane) which lines the inner surface of the cornea. This monolayer forms a barrier between the aqueous humor of the anterior chamber of the eye and the cornea. The endothelial cells contain Na+/K+ pumps that return water to the aqueous humor, causing the corneal stroma to remain in a state of relative dehydration, thereby maintaining corneal transparency.

Corneal endothelial cells do not undergo mitosis in vivo in postnatal humans and are maintained in a state of mitotic arrest due to contact inhibition from neighboring cells. At birth endothelial cell density (ECD) is high at about 6,000 cells/mm^2. The ECD falls as the eye grows during childhood but then stabilizes, with average ECD of the human adult cornea in the range of 2,000 to 3,500 cells/mm^2 (Ianchulev, 2018). During adulthood there is a continuous attrition of endothelial cells at the rate of about 0.6% per year. Since the number of endothelial cells cannot increase due to mitotic arrest, gaps caused by apoptosis are filled by the migration of adjacent

cells which increase in size and change shape. The function of the corneal endothelium can be maintained, however, as long as the ECD is maintained above a threshold value, which is thought to be 300-500 cells/mm^2. If the ECD decreases to below the threshold due to disease, trauma, or increased age, the pump function starts to decrease, the cornea thickens, and the resultant corneal edema leads to a visual haze due to impairment of corneal transparency (Van den Bogerd, 2018). Thus, endothelial damage due to intraocular surgery or implants can cause endothelial failure, ultimately necessitating corneal transplantation.

1.2 Rationale

1.2.1 Rationale for use of ripasudil in the post-cataract setting

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 signalling 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 signalling 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 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 ECD ≤ 1500 cells/mm^2 (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/mm^2 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 endothelial cell density 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).

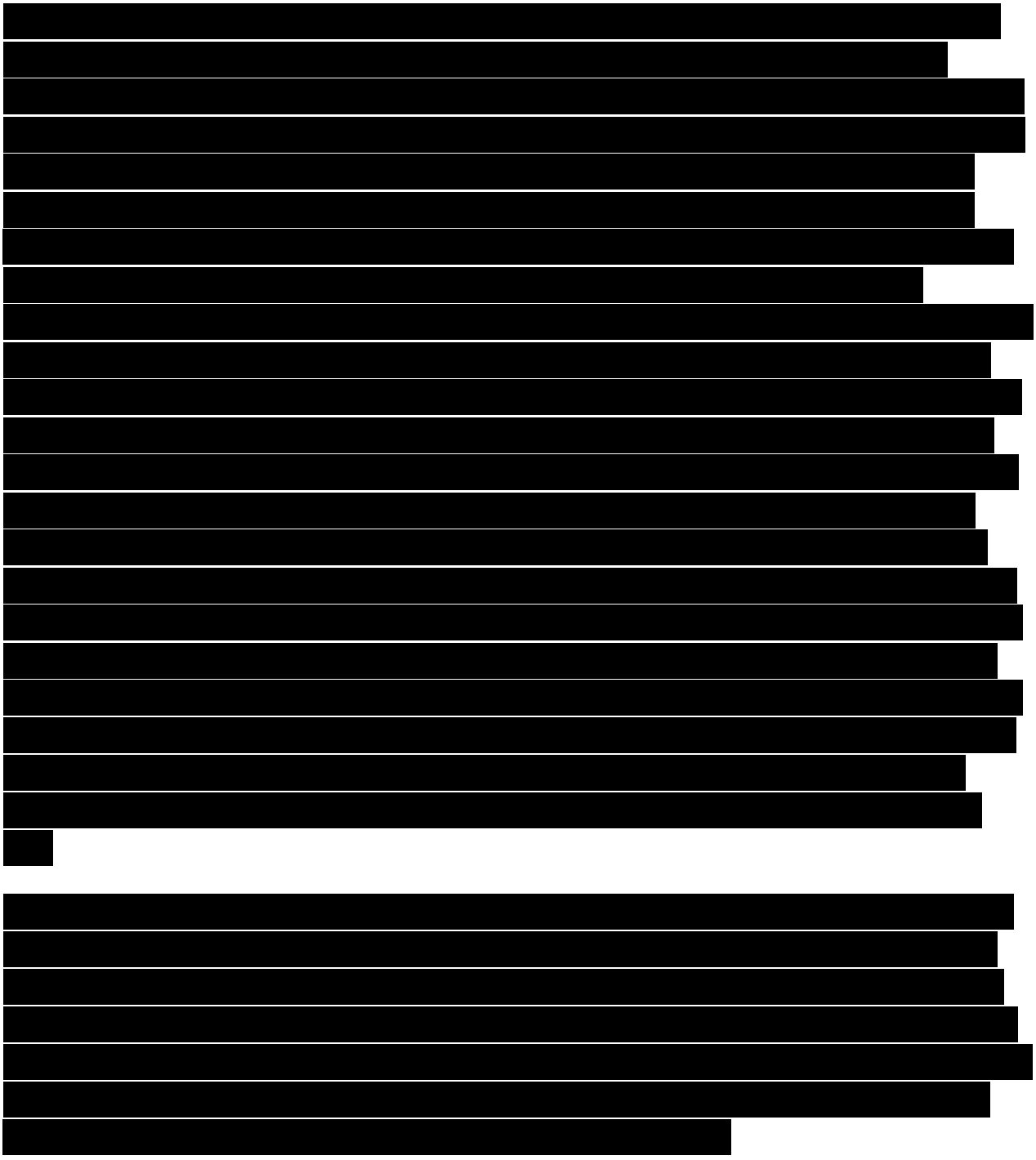
Based on the above-mentioned studies of ripasudil for endothelial wound healing, Kowa proposes to evaluate the efficacy and safety of K-321 (ripasudil ophthalmic solution) in subjects after cataract surgery for the proposed indication of treatment after Descemet stripping only (DSO) in patients with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

1.2.2 Rationale for Selection of Dose

Planned clinical studies will include instillation of K-321 ophthalmic solution at concentrations of 0.4% four times daily (QID), justified by the results above in the nonclinical toxicity studies.

Ripasudil is considered to induce the changes in the lens, because the changes were observed in the 1.0% four times daily or 2.0% twice daily (BID) (4.0% daily dose) and higher instillation groups in the 13 week or 26 week repeated-dose instillation toxicity study in rabbits. However, these changes were observed only in rabbits in the nonclinical toxicity studies. The factor of the species difference regarding the onset of the changes in the lens is considered to be the intraocular concentration after instillation of the ripasudil ophthalmic solution, because it is confirmed that the ripasudil concentration in rabbits is higher than in dogs or monkeys. No changes in the lens were observed in monkeys, who have similar anatomical eye structures to humans, at the dose of 2.0% four times daily (8.0% daily dose).

Therefore, 0.4% four times daily (1.6% daily dose) was set as the highest dose for the ongoing Investigational New Drug Application (IND) opening Phase 2 study to secure at least 5 times safety margins based on the results in monkeys dosed at 2.0% four times daily (8.0% daily dose).



[redacted]

Given the higher efficacy seen in nearly all parameters for K-321 administered at the QID dose compared to BID, Kowa has selected the QID dose for the planned Phase 3 study.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to investigate the effect of K-321 on central corneal endothelial cell density (ECD) in subjects after cataract surgery.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To investigate the effect of K-321 on central and peripheral corneal endothelial cell density (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.

2.2 Study Endpoints

[redacted]

2.2.1 Primary Efficacy Endpoint:

The primary efficacy endpoint is:

- Change from baseline in central corneal ECD at Week 12

2.2.2 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 change 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

2.2.3 [redacted]

- [redacted]
- [redacted]

[redacted]

2.2.4 Safety Endpoints

2.2.4.1 Primary Safety Endpoint

Adverse events (AEs)

2.2.4.2 Secondary Safety Endpoints

Safety assessments by slit-lamp biomicroscopy (cornea, conjunctiva, anterior chamber, lens, lids and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), intraocular pressure (IOP)

3.0 STUDY DESCRIPTION

3.1 Study Design

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 2 and Section 5.0.

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 (Visit 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.

Table 1 Study Design



3.2 Number of Sites

Approximately 45 sites in the United States

Table 2 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
Drug, alcohol 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

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**
[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 study drug [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 study drug [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 labeled.

[redacted]

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

4.0 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is at least 18 years old at the screening visit (Visit 1).

2. Is planning to undergo cataract surgery in the study eye, and has had cataract surgery at Visit 2.

3. Can understand the written informed consent, provides signed written informed consent, and agrees to comply with protocol requirements before any study-specific assessment is performed.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Is a female subject of childbearing potential and any of the following is true:

    a. is pregnant or lactating/breastfeeding, or

    b. has experienced menarche and is not surgically sterile, not post-menopausal (no menses for the previous 12 months), or not willing to practice an effective method of birth control during the study period as determined by the Investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or partner with vasectomy).

    c. has a positive urine pregnancy test result at Visit 2 before cataract surgery.

2. Had intraocular surgery (non-laser surgery) in the study eye within 6 months of Visit 1.

3. Had intraocular laser surgery in the study eye within 3 months of Visit 1.

4. Plans to receive any surgical treatment on the study eye, other than the cataract surgery, from Visit 1 to study exit. NOTE: Femtosecond laser for corneal incision, capsulotomy, and lens fragmentation is allowed. Femtosecond laser limbal relaxing incision (laser LRI), and treatment of postoperative ocular hypertension via aqueous release from the paracentesis is allowed.

5. Has known severe comorbidities that may interfere with cataract surgery (eg, a bacterial, viral, or fungal ophthalmic infection).

6. Has any clinically significant ocular condition in the study eye, other than cataract, glaucoma* or dry eye, that requires medication or ocular surgery.

   (Use of a single glaucoma medication except for any carbonic anhydrase inhibitor (CAI) or Rho kinase (ROCK) inhibitor is acceptable).*

7. Has used either collagen shield or contact lens in either eye within the past 7 days of Visit 1.

8. Be unwilling to avoid wearing either collagen shield or contact lenses in either eye during the study period.

9. Has known hypersensitivity to any component of the study drugs or other study related procedures/medications.

10. Has previously used ripasudil in the study eye.

11. Has used netarsudil, eye drops, or ointments containing $\geq$2% sodium chloride in the study eye within 14 days of Visit 1.

12. Participated in any investigational drug or device clinical studies within 30 days of Visit 1 or planning to participate in any investigational drug or device clinical studies during the study period.

13. Has a positive urine test result for drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or alcohol (either urine or saliva test) at screening. If these drugs have been prescribed to treat current medical conditions, then these medications will be permitted during the study.

14. Is a member or a family member of the professional or ancillary personnel working at the study site or the Sponsor involved in the study.

15. Has a concomitant medical or psychological condition that could interfere with study participation or is otherwise not suitable for entry into the study in the opinion of the Investigator.

16. Is using prohibited prescription or over-the-counter (OTC) medications or devices and unwilling or unable to discontinue their use for the required period before entry into the study.

4.3 Study Drug Discontinuation Criteria

It will be necessary to make a distinction between subjects who prematurely discontinue study drug treatment and those who withdraw from the study for any reason. Subjects who discontinue study drug are not required to withdraw from the study and will be encouraged to remain in the study and will be asked to attend all of the remaining study visits through Visit 9 for Groups A and C, and through Visit 11 for Groups B and D.

All study drug discontinuations should be considered to be temporary interruptions because subjects are allowed to restart medication at any time if the condition leading to study drug interruption has resolved and, in the opinion of the Investigator, the subject is not put at undue risk by restarting the study drug.

If the subject discontinues study drug, the reason should be captured and could include the following:

1. The subject requests discontinuation of the study drug
2. The subject develops an AE that, in the opinion of the Investigator, would compromise the subject's safety to continue the study drug
3. Violation of the protocol inclusion or exclusion criteria is discovered, and if, in the opinion of the Investigator or the Sponsor, the violation will significantly compromise data interpretation or safety
4. The female subject becomes pregnant during the study (Section 9.3)
5. In the Investigator's judgment, it is in the subject's best interest
6. Lost to follow-up
7. Sponsor termination of study
8. Other

Although a subject is not obligated to give his/her reason for discontinuing study drug, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. The reason for discontinuation of study drug must be documented in the electronic case report form (eCRF).

4.4 Withdrawal Criteria

The subject has the right to withdraw from the study at any time and for any reason without prejudice to the subject's future medical care. Nevertheless, every attempt will be made to prevent missing data and to obtain complete follow-up for all subjects.

Subjects who meet study drug discontinuation criteria described in Section 4.3 will be discontinued from study drug; however, these subjects are not required to withdraw from the study unless they choose to withdraw complete consent. These subjects will be encouraged to remain in the study and asked to attend all of the remaining study visits through Visit 9 for Group A and C, or through Visit 11 for Group B and D (Table 1). Subjects who choose to withdraw from the study will be asked if they will be willing to complete a final visit. If a subject withdraws from the study during the treatment period, the same evaluations required at the Visit 8 (EOT) should be performed. For Group A and C, in the case that the subjects withdraw during the 4-week follow-up period, the same evaluations required at Visit 9 (EOS) should be performed. For Group B and D, in the case that the subjects withdraw during the 14-week follow-up period, the same evaluations required at Visit 11 (EOS) should be performed. If a subject fails to actively maintain contact with the Investigator, reasonable efforts (telephone calls to family members or friends, email contacts, etc.) will be made in order to encourage the subject to complete the study visits.

If the subject withdraws from the study, the reason should be captured.

The subject will be withdrawn from the study if:

1. The subject withdraws consent to attend the remaining study visits
2. Lost to follow-up
3. Sponsor termination of study
4. AEs
5. Other

Although a subject is not obligated to give his/her reason for withdrawing from the study, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. Unless revoked, further contact in the case of withdrawal from the study will occur consistent with methods listed in the informed consent form (ICF). The reason for withdrawal from the study must be documented in the eCRF.

If a subject withdraws from the study due to an AE, the subject will be asked to return to the clinic for, at a minimum, the evaluations scheduled for post-dose assessments. If the

AE has still not recovered/resolved, additional follow-up will be performed, as appropriate. Every effort will be made by the Investigator or delegate to contact the subject until the AE is recovered/resolved or stabilized, or the medical monitor and Investigator agree that further follow-up is not necessary. If subjects are lost to follow-up, the Investigator will make 3 reasonable attempts to contact the subject via telephone, US postal service, or certified mail. All attempts to contact them must be made and documented in the study records.

4.5 Rescreening and Retesting

4.5.1 Rescreening

Subjects who fail to satisfy inclusion and exclusion criteria at screening may be rescreened 1 additional time at the discretion of the Sponsor. Screen failures due to inclusion and/or exclusion criteria that could transiently change and do not compromise the subject's safety, as judged by the Investigator, may be rescreened once. All eligibility assessments will be repeated, regardless of the reason for the initial screen failure, and a new subject number will be assigned. The rescreening decision must be confirmed by the Sponsor's medical monitor.

Subjects who are screened for the study and receive cataract surgery in one eye may be replaced by using the fellow eye if they have not yet undergone cataract surgery in the fellow eye and they were never randomly assigned study drug or were withdrawn from the study before they were administered any study drug. The reason for not enrolling the subjects with the initial study eye must be clearly documented in the Screening Log or appropriate electronic record. In this situation, the replaced fellow eye will receive a new randomly assigned treatment and will not receive the treatment assignment of the initial study eye.

4.5.2 Retesting

Drug, alcohol test (either urine or saliva test) indicating positive can be retested one time within the screening period. Unscheduled visits are allowed within screening period.

5.0 PROCEDURES FOR PHARMACOKINETICS, SAFETY, AND EFFICACY EVALUATIONS

5.1 Examination Procedures

The timing of subject visits and examinations should be consistent throughout the study. The schedule of required assessments is provided in Table 2. This section describes the study site procedures required at each visit. Questionnaires and ocular examination procedures that do not touch the eye should be performed prior to assessments that require the eyes to be touched or that require the use of anesthetics. When dilated fundoscopy is required, it should be the last ocular examination procedure (except Ocular characteristics) performed due to the use of mydriatics.

5.1.1 Scheduled Visits

5.1.1.1 Visit 1 (Range: 1 to 27 days prior to Cataract Surgery)

All subjects will undergo the following screening assessments. All ocular assessments should be done in both eyes. The recommended order of the procedures is shown below. Dilated fundoscopy must be the last ocular examination procedure performed (except Ocular characteristics):

1. Informed consent/ Health Insurance Portability and Accountability Act (HIPAA)
2. Medical history, surgical history and demographics
3. Review the list of medications (See Section 8.1)
4. Abbreviated physical examination
5. VFQ-25
6. Drug, alcohol screen
7. BCVA (ETDRS scale)
8. Slit-lamp Biomicroscopy (safety evaluation)
9. Corneal edema (Slit-lamp Biomicroscopy)
10. Photo-documentation of ocular findings (if any meaningful finding is observed)
11. Capture of Corneal Endothelial Cell Images by Specular Microscopy (non-contact type) (If site has a qualified Specular Microscopy)
12. IOP (contact or non-contact type tonometer)
13. Corneal thickness (pachymetry)
14. Dilated fundoscopy
15. Ocular characteristics

16. AE documentation (this is being done after dilated fundoscopy at this visit because all AEs during this visit will be events that occur during the screening visit itself, since all pre-existing conditions will be collected as Medical history)
17. Eligibility evaluation
18. Subjects will be scheduled for Visit 2 (within 1 to 27 days).

5.1.1.2 Visit 2: Day - 1 / Cataract Surgery – Randomization

All subjects will undergo the following assessments. The recommended order of the procedures is shown below:

1. Review the list of medications (See Section 8.1)
2. AE documentation
3. Abbreviated physical examination (pre-operative)
4. Urine pregnancy test (pre-operative, if applicable)
5. Cataract surgery (see Section 5.1.7)
    - Photo-documentation of the phacoemulsification information. Pictures should be printed and filed with the source documentation.
6. Eligibility evaluation (following cataract surgery)
7. Randomization (following cataract surgery)
8. Subjects will be scheduled for Visit 3 (the day immediately following Visit 2) within [redacted] after the end of the cataract procedure

5.1.1.3 Visit 3: Day 1

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. Review the list of medications (See Section 8.1)
2. AE documentation
3. BCVA (ETDRS scale)
4. Slit-lamp Biomicroscopy (safety evaluation)
5. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
6. Photo-documentation of ocular findings (if any meaningful finding is observed)
7. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type); (If site has a qualified Specular Microscopy)
8. IOP (contact or non-contact type tonometer)
9. Corneal thickness (pachymetry)

10. Schedule subject for Visit 4
11. Instruct subject to bring used study drug for drug accountability at Visit 4
12. Instruct subjects not to apply study drug on their next visit (Visit 4) until all study measurements are completed
13. Dispense study drug
14. [redacted]
15. Study drug administration

    Note: On Visit 3 (Day 1), subjects must first apply study drug within [redacted] after the end of the cataract procedure on Visit 2 (Day –1) and begin a QID regimen.

    During the Visit 4 (Week 1) through Visit 8 (Week 12) period, on those days when a study visit is scheduled, subjects will not apply any study drug until after all study measurements have been completed. After completion of the study visit, subjects will instill their assigned study drug at the closest time point coinciding with their normal daily dosing schedule and continue with the remaining doses for the day. Remind subjects, that they may need to bring study drug for remaining doses of the day since some subjects are far away from study sites.
16. [redacted]

5.1.1.4 Visit 4: Week 1 (Range: Day 6 to Day 10)

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. [redacted] used study drug
2. Review the list of medications (See Section 8.1)
3. AE documentation
4. BCVA (ETDRS scale)
5. Slit-lamp Biomicroscopy (safety evaluation)
6. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
7. Photo-documentation of ocular findings (if any meaningful finding is observed)
8. Corneal Capture of Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)
9. IOP (contact or non-contact type tonometer)
10. Corneal thickness (pachymetry)
11. Schedule subject for Visit 5
12. Instruct subject to bring used study drug for drug accountability at Visit 5

13. Instruct subjects not to apply study drug on their next visit (Visit 5) until all study measurements are completed.
14. Study drug administration

    NOTE: During the Visit 4 (Week 1) through Visit 8 (Week 12) period, on those days when a study visit is scheduled, subjects will not apply any study drug until after all study measurements have been completed. After completion of the study visit, subjects will instill their assigned study drug at the closest time point coinciding with their normal daily dosing schedule and continue with the remaining doses for the day. Remind subjects, that they may need to bring study drug for remaining doses of the day since some subjects are far away from study sites.

5.1.1.5 Visit 5: Week 2 (Range: Day 13 to Day 17)

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. [redacted] used study drug
2. Review the list of medications (See Section 8.1)
3. AE documentation
4. BCVA (ETDRS scale)
5. Slit-lamp Biomicroscopy (safety evaluation)
6. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
7. Photo-documentation of ocular findings (if any meaningful finding is observed)
8. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)
9. IOP (contact or non-contact type tonometer)
10. Corneal thickness (pachymetry)
11. Schedule subject for Visit 6
12. Instruct subject to bring used study drug for drug accountability at Visit 6
13. Instruct subjects not to apply study drug on their next visit (Visit 6) until all study measurements are completed
14. Study drug administration

    NOTE: During the Visit 4 (Week 1) through Visit 8 (Week 12) period, on those days when a study visit is scheduled, subjects will not apply any study drug until after all study measurements have been completed. After completion of the study visit, subjects will instill their assigned study drug at the closest time point coinciding with their normal daily dosing schedule and continue with the remaining doses for the day. Remind subjects, that they may need to bring study drug for remaining doses of the day since some subjects are far away from study sites.

5.1.1.6 Visit 6: Week 3 (Range: Day 19 to Day 25)

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. [redacted] used study drug
2. Review the list of medications (See Section 8.1)
3. AE documentation
4. VFQ-25
5. BCVA (ETDRS scale)
6. Slit-lamp Biomicroscopy (safety evaluation)
7. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
8. Photo-documentation of ocular findings (if any meaningful finding is observed)
9. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type)
10. IOP (contact or non-contact type tonometer)
11. Corneal thickness (pachymetry)
12. Schedule subject for Visit 7
13. Instruct subject to bring used study drug for drug accountability at Visit 7
14. Instruct subjects not to apply study drug on their next visit (Visit 7) until all study measurements are completed
15. Study drug administration

    NOTE: During the Visit 4 (Week 1) through Visit 8 (Week 12) period, on those days when a study visit is scheduled, subjects will not apply any study drug until after all study measurements have been completed. After completion of the study visit, subjects will instill their assigned study drug at the closest time point coinciding with their normal daily dosing schedule and continue with the remaining doses for the day. Remind subjects, that they may need to bring study drug for remaining doses of the day since some subjects are far away from study sites.

5.1.1.7 Visit 7: Week 7 (Range: Day 47 to Day 53)

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. [redacted] used study drug
2. Review the list of medications (See Section 8.1)
3. AE documentation
4. BCVA (ETDRS scale)

5. Slit-lamp Biomicroscopy (safety evaluation)
6. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
7. Photo-documentation of ocular findings (if any meaningful finding is observed)
8. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)
9. IOP (contact or non-contact type tonometer)
10. Corneal thickness (pachymetry)
11. Schedule subject for Visit 8
12. Instruct subject to bring all used and unused study drug for drug accountability at Visit 8
13. Instruct subjects not to apply study drug on their next visit (Visit 8) until all study measurements are completed
14. Study drug administration

    NOTE: During the Visit 4 (Week 1) through Visit 8 (Week 12) period, on those days when a study visit is scheduled, subjects will not apply any study drug until after all study measurements have been completed. After completion of the study visit, subjects will instill their assigned study drug at the closest time point coinciding with their normal daily dosing schedule and continue with the remaining doses for the day. Instruct subjects to bring ALL used and unused study drugs to the study site at the next scheduled visit.

5.1.1.8 Visit 8: Week 12 (Range: Day 82 to Day 88)

All subjects will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. [redacted] used and unused study drug
2. Review the list of medications (See Section 8.1)
3. AE documentation
4. Abbreviated physical examination
5. VFQ-25
6. Urine pregnancy test (if applicable)
7. BCVA (ETDRS scale)
8. Slit-lamp Biomicroscopy (safety evaluation)
9. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
10. Photo-documentation of ocular findings (if any meaningful finding is observed)
11. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)

12. IOP (contact or non-contact type tonometer)
13. Corneal thickness (pachymetry)
14. Dilated fundoscopy
15. [redacted]
16. [redacted]
17. [redacted]
18. Schedule all subjects for Visit 9 (telephone only for subjects in groups B and D)

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.

5.1.1.9 Visit 9: Week 16 (Range: Day 106 to Day 120) (EOS for Groups A/C)

Subjects who are in Group A and C will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. Review the list of medications (See Section 8.1)
2. AE documentation
3. Abbreviated physical examination
4. VFQ-25
5. BCVA (ETDRS scale)
6. Slit-lamp Biomicroscopy (safety evaluation)
7. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
8. Photo-documentation of ocular findings (if any meaningful finding is observed)
9. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)
10. IOP (contact or non-contact type tonometer)
11. Corneal thickness (pachymetery)
12. Dilated fundoscopy

5.1.1.10 Visit 9: Week 16 (Range: Day 106 to Day 120) / telephone only (for Groups B/D)

1. Review the list of medications (See Section 8.1)
2. AE documentation
3. Schedule subjects in Groups B and D for Visit 10 (telephone only)

5.1.1.11 Visit 10: Week 21 (Range: Day 141 to Day 155) / telephone only (for Groups B/D)

1. Review the list of medications (See Section 8.1)
2. AE Documentation
3. Schedule subjects in Groups B and D for Visit 11

5.1.1.12 Visit 11: Week 26 (Range: Day 176 to Day 190) (EOS for Groups B/D)

Subjects who are in Group B and D will undergo the following assessments. Ocular assessments should be done in both eyes unless noted otherwise. The recommended order of the procedures is shown below:

1. Review the list of medications (See Section 8.1)
2. AE documentation
3. Abbreviated physical examination
4. VFQ-25
5. BCVA (ETDRS scale)
6. Slit-lamp Biomicroscopy (safety evaluation)
7. Corneal edema (Slit-lamp Biomicroscopy) in the study eye only
8. Photo-documentation of ocular findings (if any meaningful finding is observed)
9. Capture of Corneal Endothelial Cell Images by Specular Microscopy in the study eye (non-contact type) (If site has a qualified Specular Microscopy)
10. IOP (contact or non-contact type tonometer)
11. Corneal thickness (pachymetery)
12. Dilated fundoscopy

5.1.2 Unscheduled Visits

These visits may be performed in order to ensure subject safety, address study supply issues or other reasons. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed during the unscheduled visit should be indicated as “Not done.”

5.1.3 Demographics

At Visit 1 (Screening), demographic information (eg, birth year, age, iris color (study eye), sex, race, ethnicity, smoking history, history of diabetes (whether type I or type II and HbA1c) will be collected.

5.1.4 Ocular Characteristics

At Visit 1 (Screening) ocular characteristics of lens characterization will be collected.

- Lens characteristics: The nuclear sclerosis, posterior subcapsular, and cortical opacification should be graded at the slit-lamp after dilation. The grading of the lens locations should be as follows:

- Nuclear sclerosis
  a. No opacity
  b. Nuclear Standard 1
  c. Nuclear Standard 2
  d. Nuclear Standard 3

- Posterior Subcapsular, Cortical Opacification
  a. No opacity
  b. Less than image Standard 2 on the Age-Related Eye Disease Study (AREDS) severity scale
  c. Equal to or more than image Standard 2 on the AREDS scale

Technique for each assessments are below:

- Nuclear assessment: Slit-lamp beam at 0.3mm width, 8mm height, at a 45 degree angle
- Posterior Subcapsular assessment: Using the red reflex with retroillumination
- Cortical opacification: Using the red reflex with retroillumination the total of both the anterior and posterior cortical opacities will be graded with one value that represents the sum of the anterior and posterior opacification.

5.1.5 Medical History and Surgical History

At Visit 1 (Screening), medical history and surgical history will be collected to assess eligibility to participate in the study:

- History of prior study eye surgical procedures
- All surgical procedures within the previous 30 days (any body part)
- All medications used within the previous 30 days

For ocular medical and surgical history, involvement of the right eye (OD), left eye (OS) , or both eyes (OU) should be clearly documented in the eCRF. Medical history will be coded by the most recent version of MedDRA.

5.1.6 Screening for Drugs of Abuse and Pregnancy Screening

At Visit 1 (Screening), screening for drugs of abuse and alcohol (either urine or saliva test) will be conducted to assess eligibility to participate in the study.

At Visit 2 (Day-1) and at the Visit 8 (EOT), urine pregnancy screening will be conducted for subjects of childbearing potential.

5.1.7 Cataract Surgery

Each subject will undergo cataract surgery of the investigator-selected study eye at Visit 2 (Day-1). We recommend that the study eye be the eye with the lower BCVA score. However, the ultimate decision as to the selection of the study eye will be at the discretion of the Investigator. After surgery, subject eligibility for enrollment in the study must be confirmed, including cataract surgery (see Section 4.0 for all eligibility criteria).

We ask that, prior to the first cataract procedure done at each site for this study, the site send [redacted] a copy of the cataract surgery equipment metrics, from a recently completed subject that is not from this study, in order to identify the specific phacoemulsification machine metrics that will be collected.

The following information should be collected for the cataract surgery:

1. Total Case Time (total time cataract surgery occurs with anesthesia)
   - this is reported in the metrics recorded by the phaco machine. For the ALCON equipment this is the Total Case Time.

2. Principal Investigator's assessment of the level of difficulty of the cataract surgery procedure. This should be graded as follows:
   1. Difficulty less than average
   2. Average difficulty
   3. Difficulty more than average

3. Phacoemulsification Information
   (i) Total cumulative dissipated energy (CDE) or the equivalent parameter for the specific instrument used
      - This is reported in the metrics recorded by the phaco machine. For the ALCON equipment this is the CDE.
   (ii) Total ultrasound time, which is the same as total phaco time.
      - This is reported in the metrics recorded by the phaco machine.

   All of the above Phacoemulsification Information will be collected by taking a picture or downloading a PDF of the surgical metrics from the phacoemulsification equipment. Pictures should be printed and filed with the source documentation. Phacoemulsification data should be entered in the EDC.

Use of topical antibiotic and anti-inflammatory medications is suggested as the standard of care treatment regimen for post-cataract surgery.

5.2 Pharmacokinetics Evaluations

5.2.1 Pharmacokinetics Sample Collection and Processing

Blood will be collected via venipuncture at the specified time points from the vein of participating subjects who consent at selected sites, when applicable (until the required number of subjects is met), at the volume of 6 mL in each collection using a blood collection tube containing sodium heparin. The blood will be mixed immediately after collection and iced. The sampled blood will be centrifuged at 4°C, 3000 rpm (approximately 1700-2000 × g) for 10 minutes, and the plasma obtained will be dispensed into two tubes (including one for reserve measurement) and stored in a freezer at or below -20°C. The exact time of blood collection will be recorded.

All sample collection and freezing tubes will be clearly labeled with a subject identification number, the study visit, and the collection time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. Plasma samples should be immediately stored at approximately -20°C.

A time window is allowed of 1 hour prior to dosing, ±2 minutes for 5 and 15 minutes postdose, and ±5 minutes for 30 minutes postdose.

Serial blood samples from subjects who participate and consent at selected sites will be collected, when applicable, predose and at 5, 15, and 30 minutes postdose on Day 1 (Visit 3) and at Week 12 (Visit 8).

5.2.2 Pharmacokinetics Sample Shipment

Samples will be grouped and shipped frozen (on dry ice).

The plasma samples will be sent from the sites directly to the central lab. The two aliquots of plasma obtained for each collection time point, per subject, will be shipped separately. The second set of aliquots will be shipped only after confirmation of the arrival of the first set of aliquots. A list of the samples shipped per subject will be included in each shipment. The plasma samples will then be sent from the central lab to the PK measurement vendor.



5.3 Efficacy Evaluations

The following efficacy assessments will be performed to assess efficacy in this study:

- Capture of Corneal Endothelial Cell Images by Specular Microscopy (non-contact type) (If site has a qualified Specular Microscopy)
  - Central and peripheral corneal ECD measurement (specular microscopy, non-contact type)
  - [redacted]
- Corneal thickness (pachymetry)
- Corneal edema (slit-lamp evaluation)
- BCVA (ETDRS scale)
- VFQ-25

5.3.1 Corneal Endothelial Cell Images Capturing by Specular Microscopy

Central and peripheral (nasal and temporal) corneal endothelial cell images of the **study eye** will be captured by non-contact specular microscopy at study visits indicated in Table 2: [redacted] ([redacted] images total), whereas images of the **non-study eye** will be captured only at Visit 1. 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.

The same specular microscopy instrument must be used for all study visits for a given subject throughout the study. All reasonable efforts should be made to have the same evaluator perform the measurements for all study visits for a given subject throughout the study. All specular microscope images taken will be sent to the [redacted] for analysis via a designated portal site. The original image data should be kept at each site. It is possible that for the first few follow-up visits the specular microscope may not be able to successfully capture central images; however, even if the images that are captured are completely black, the site still should submit all the images, in all locations, that are obtained at each visit. Thus, we do not want sites to decide not to take images based on the presence of [redacted]. On the contrary, images must be taken, and submitted, at all visits, regardless of image quality. In case all [redacted] images are not captured, this will be a deviation and should be recorded in the source document.

Sites must submit images to [redacted] promptly. Prior to submission, please confirm the following:

- Correct data export
- Accurate and complete study labelling

- Complete image submission, including any blank images, and provide comments on the [redacted] web portal if image capture issues prevented imaging according to the study protocol.
- Review all the images captured (correct # of images, analyzability, quality) and try to obtain the best images possible (central, nasal, and temporal images) at each visit while the subject is still present. Re-capture the images at that same visit if you believe it is possible to get better quality imaging.
- In the event that a subject cannot remain at the study site until all images are reviewed and any additional images that are needed are obtained, or if re-imaging is recommended per [redacted] the site should schedule the subject to come back for re-imaging.

Contact [redacted] with any questions or issues regarding image capture, export or submission.

5.3.2 Corneal Thickness

Corneal thickness of both eyes (**study eye and non-study eye)** will be measured by contact ultrasound pachymetry, or optical pachymetry with topical anesthesia on the central cornea at study visits indicated in Table 2. If both contact ultrasound pachymetry and optical pachymetry are available, contact ultrasound pachymetry should be used. (i.e. If only optical pachymetry is available, optical pachymetry will be used.) The same pachymetry should be used throughout study.

Three readings will be recorded in micrometers (μm) in each eye and will be averaged for analysis per eye. The same instrument must be used for all study visits for a given subject throughout the study. All reasonable efforts should be made to have the same evaluator conduct the measurements for all study visits for a given subject throughout the study.

5.3.3 Corneal Edema

Corneal edema of the **study eye** will be categorized according to location (whether it is epithelial, stromal, or endothelial) and assessed by the Investigator as either being present or absent during slit-lamp examination at study visits indicated in Table 2, whereas images of the **non-study eye** will be categorized and assessed only at Visit 1. The same instrument must be used for all study visits for a given subject throughout the study. All reasonable efforts should be made to have the same evaluator perform the assessments for all study visits for a given subject throughout the study.

The grading is as follows:

- Epithelial:
  - Normal (none)
  - Abnormal
    - Mild

- ✧ Moderate
- ✧ Severe

- Stromal: Without the use of pachymetry–- grade the stromal thickness.
  - ➢ Normal (none)
  - ➢ Abnormal
    - ✧ Mild
    - ✧ Moderate
    - ✧ Severe
- Endothelial: Assess posterior corneal edema by folds in Descemet's Membrane
  - ➢ Normal (none)
  - ➢ Abnormal
    - ✧ Mild
    - ✧ Moderate
    - ✧ Severe

5.3.4 BCVA (ETDRS scale)

The BCVA of both eyes (**study eye and non-study eye**) will be assessed by ETDRS testing without pupil dilation at study visits indicated in Table 2. For all measurements, the BCVA letter score should be recorded using the worksheet provided by [redacted] BCVA will be calculated by the sum of 1-meter and 4-meter tests. The measurement must be assessed only by a [redacted] Please refer to procedure manual provided by [redacted] for more information. The same instrument must be used for all study visits for a given subject throughout the study. All reasonable efforts should be made to have the same evaluator perform the assessments for all study visits for a given subject throughout the study.

5.3.5 VFQ-25

The subjects' visual function will be assessed using the Interviewer Administrated Format of National Eye Institute Visual Functioning Questionnarie-25 (VFQ 25, Version 2000), a quality-of-life instrument at study visits indicated in Table 2. All reasonable efforts should be made to have the same evaluator conduct the assessments for all study visits for a given subject throughout the study. The Interviewer should ensure that the subject understands that each question should be answered as though the subject is wearing their eyeglasses. The Interviewer should read each question and answer slowly and clearly and should allow the subject to have ample time to answer each question.

5.4 Safety Evaluations

The following safety assessments will be performed:

- AEs
- Treatment-emergent AEs (TEAEs)

- Slit-lamp Biomicroscopy (safety evaluation) (cornea, conjunctiva, anterior chamber, lid, lens, external exam of the lids and lashes)
- Dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery)
- IOP

5.4.1 AEs

Refer to Section 9.1 for further information regarding AEs, TEAEs and Serious AEs.

5.4.2 Slit-lamp Biomicroscopy (Safety Evaluation)

Slit-lamp biomicroscopic observations for both eyes without pupillary dilation will be graded as being Normal or Abnormal at the study visits indicated in Table 2. Abnormal findings will be categorized as clinically significant (CS) (findings that may interfere with study parameters or otherwise confound the data as determined by the Investigator) or not clinically significant (NCS). The following will be examined:

- Cornea (Normal, Abnormal NCS, Abnormal CS)
- Conjunctiva
    - Bulbar Conjunctival Injection (Normal, Abnormal NCS, Abnormal CS)
    - Sclera - Ciliary Flush (Normal, Abnormal NCS, Abnormal CS)
- Anterior Chamber
    - Cells:

      The anterior chamber examination will be performed with the slit-lamp. Anterior chamber cells should be counted using the high light intensity level and the high magnification (Haag-Streit 16 X or comparable), with the slit beam set at an oblique angle, and the height and width of the beam setto 1.0 X 1.0 mm. The cells should be counted over an approximate 3 second time interval at all visits. The anterior chamber cell count will be converted to a grade count.

        - Grade 0: 0 Cells
        - Grade 1: 1-5 Cells
        - Grade 2: 6-15 Cells
        - Grade 3: 16-30 Cells
        - Grade 4: > 30 Cells

    - Flare: Using the investigator's usual technique, the flare will be assessed as described below

Grade	Description
0	None
1	Faint
2	Moderate (iris and lens details clear)
3	Marked (iris and lens details hazy)
4	Intense (fibrin or plastic aqueous)

- Lens (Normal, Abnormal NCS, Abnormal CS)
- Lids and Lashes (Normal, Abnormal NCS, Abnormal CS)

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice and the subject will be seated. All reasonable efforts should be made to have the same evaluator and the same instrument perform the assessments for a given subject throughout the study. Digital photographs of both eyes should be taken during the slit-lamp examination in case any clinically meaningful ocular findings such as AEs are observed, per PI's discretion. All personal identification information for subjects, such as name, initials, gender, and specific dates of birth, must be anonymized. Please refer to Appendix A for additional guidance on images storage and transfer.

5.4.3 Dilated Fundoscopy

Dilated fundus exams for both eyes (**study eye and non-study eye**) will be performed with pupillary dilation using an indirect ophthalmoscope according to current standard of care to evaluate the condition of the vitreous, retina, macula, choroid, optic nerve, and retinal periphery at study visits indicated in Table 2.

Observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the Investigator) or NCS. All reasonable efforts should be made to have the same evaluator and the same instrument.

- Vitreous: Examination must emphasize the visual axis.
- Retina, Retinal periphery, Macula, Choroid: Include an observation of the retina/retinal periphery and its blood vessels. Eyes must be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve must be noted.

5.4.4 IOP

IOP will be measured for both eyes (the **study eye and the non-study eye**) by either contact or non-contact tonometry by the examiner and the results will be recorded in

mm Hg at study visits indicated in Table 2. A single measurement will be made to determine IOP. The same tonometer employing the Investigator's standard technique should be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject throughout the study. For contact tonometry, the eye must be anesthetized and thus this should be done after all other eye assessments have been completed (with the exception of pachymetry, which should be done after IOP measurement, and fundoscopy (if it requires pupillary dilatation, which can affect IOP).

5.4.5 Abbreviated Physical Examinations and Review the list of medications

At Visit 1 (Screening), Visit 2 (Day-1), Visit 8 (EOT), Visit 9 (EOS for groups A/C) and at Visit 11 (EOS for groups B/D), an abbreviated physical examination and an assessment of concomitant disease will be conducted to assess eligibility to participate in the study and changes in any conditions. The limited physical examination includes a review of the subject's medical and medication history and subsequent evaluation of relevant body system complaints. If clinically significant abnormal findings are noted the PI should be assess if they meet AE criteria and report as appropriate (see Section 9.1.1).The specific nature of the physical exam will be left to the judgement of the Investigator. In case of relevant findings, full evaluation of the condition needs to be conducted. Review of the list of medications will be conducted at each visit (see Section 8.1).

5.5 Clinical laboratory

No clinical laboratory testing will occur except screening for pregnancy, drugs of abuse and alcohol (see Section 5.1.6).

5.6 Data Monitoring Committee

No Data Monitoring Committee (DMC) is planned for this study.

6.0 CONDUCT OF STUDY

6.1 Study Masking and Randomization

Subjects, Sponsor, clinical research organization (CRO), and site personnel will all be masked to treatment assignment except for unmasked individuals within the CRO who are independent from study conduct. Before the initiation of Visit 1, each subject who provides written informed consent will be assigned a subject number. All subject numbers will be assigned in strict numerical sequence at a site and no numbers will skipped or omitted. If a subject is retested for the drug and alcohol screen, the same subject number will be used (Section 4.5.2). If a subject is rescreened, the subject will be assigned with a new subject number (Section 4.5.1). Subjects who have signed informed consent and subsequently fail to satisfy inclusion and exclusion criteria are defined as screen failures. For all screen failures, the reason(s) for screen failure will be recorded on the subject's source document and eCRF. At the time of randomization, subjects will be informed whether they will be enrolled for a total of 16 or 26 weeks and their office visit schedule. However, subjects, and both the site and appropriate Sponsor/CRO personnel, will remain masked as to the assignment of active or placebo treatment. K-321 PK information that would unmask the study will not be reported to investigative sites or masked personnel until the study has been unmasked.

Subject number and study drug kit numbers will be assigned automatically to each subject by IBM Clinical Development EDC System. Following cataract surgery, all eligible subjects will be randomized into one of the two active groups (Groups A and B) or one of the two vehicle groups (Groups C and D) using 2:1 ratio of active or placebo.

Subjects who are eligible for randomization will be [redacted]

- Group A will instill K-321 QID in the study eye for 12 weeks followed by a 4-week period with no treatment. These subjects will exit the study on Visit 9 (Week 16) (n = 150 subjects).
- Group B will instill K-321 QID in the study eye for 12 weeks followed by a 14 week period with no treatment. These subjects will exit the study following Visit 11 (Week 26) (n = 70 subjects).
- Group C will instill placebo QID in the study eye for 12 weeks followed by a 4 week period with no treatment. These subjects will exit the study following Visit 9 (Week 16) (n = 75 subjects).

- Group D will instill placebo QID in the study eye for 12 weeks followed by a 14 week period with no treatment. These subjects will exit the study following Visit 11 (Week 26) (n = 35 subjects).

The site staff will dispense the required kit(s). Both the subject number and the dispensed study drug kit number(s) will be recorded on the subject's source document and eCRF.

6.2 Study Visits

For each subject, 9 to 11 scheduled visits will occur, depending on the assigned treatment group:

- All subjects (Groups A, B, C and D)
  - Visit 1 (1 to 27 days prior to Visit 2)
    - Screening may take place anytime within this time period.
  - Visit 2 at Day -1 (1 to 27 days after Visit 1)
    - Cataract surgery - Randomization
  - Visit 3 at Day 1 (day immediately after Visit 2)
  - Visit 4 at Day 8 ± 2 days
  - Visit 5 at Day 15 ± 2 days
  - Visit 6 at Day 22 ± 3 days
  - Visit 7 at Day 50 ± 3 days
  - Visit 8 at Day 85 ± 3 days (EOT)
- Subjects in Groups A and C
  - Visit 9 at Day 113 ± 7 days (EOS)
- Subjects in Groups B and D
  - Visit 9 at Day 113 ± 7 days (telephone only)
  - Visit 10 at Day 148 ± 7 days (telephone only)
  - Visit 11 at Day 183 ± 7 days (EOS)

The procedures and assessments to be performed at each visit are indicated in Table 2.

6.3 Compliance with the Protocol

The Investigator must agree to implement the study protocol as written and adhere to the guidelines given in the "Investigator's Statement", which will be signed prior to the start of the study. The study will be performed in accordance with Health Insurance Portability and Accountability Act, Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, local laws, Food and

Drug Administration (FDA) GCP regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312), and other applicable guidance documents.

Protocol noncompliance must be reported to the sponsor or its representatives. Each deviation and the reason for its occurrence must be documented. The Sponsor retains the right to require the withdrawal of any subject who violates the protocol.

6.4 Termination of the Study

If, in the opinion of an Investigator, the clinical observations in the study suggest that it may be unwise to continue, the study may be terminated after consultation with the Sponsor. A written statement fully documenting the reason(s) for the termination will be provided to the Sponsor. In addition, the Sponsor may terminate the study at any time.

If it becomes apparent that subject enrollment is unsatisfactory with respect to quality or quantity, or data recording is inaccurate or incomplete on a chronic basis, the Sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities, if required. In the event of any serious or non-serious AEs having occurred at a site, all documentation relating to the event(s) must be obtained.

6.5 Contingency Plan due to Pandemics or Endemics

To help ensure subject safety and to minimize potential disruption of clinical study data in the event of a pandemic or endemic, such as COVID-19, sites may follow local and regional guidelines and regulations in modifying in-person study visits where subject safety may be placed at risk.

To minimize subject risk, sites may implement the following safety contingency plans provided IRB/IEC approval and regulatory authorization has been granted:

- Clinical sites may be permitted to send study drug to subjects via a traceable courier and/or shipping provider. Prior to doing this, sites must acquire verbal consent from the subjects, verification of correct shipping address, and subject's availability to receive the shipment. Confirmation of receipt and the subject's consent will be documented in the site source.
    - Subjects will be instructed to safely store the study drug at home and not destroy the study drug. All study drug packaging and unused study drug

should either be returned to the site via courier at the next scheduled visit or at the next available in-person visit depending on the length of the interruption in in-person visits.

- Clinical sites may be permitted to perform telephone visits with subjects in lieu of onsite face to face visits. Subjects will be brought back for an onsite visit as soon as the site and subject determine it is appropriate.

In any case, confidentiality of study participation will still be maintained by the site, and the continuous monitoring of safety assessments should be conducted in accordance with the schedule of events.

7.0 STUDY MEDICATION

7.1 Description of Study Medication

K-321 investigational medicinal product will [redacted].

- Active constituents: ripasudil hydrochloride dihydrate
- Other constituents: sodium dihydrogen phosphate dihydrate, glycerol 100%, sodium hydroxide, water for injections

A matching [redacted] placebo product (Vehicle) will be provided using the same excipient formulation as the active K-321 product.

7.2 Drug Packaging

Study drug will be packaged in [redacted] Each subject will receive all study kits at Visit 3.

7.3 Drug Labeling

Study drug will be labeled according to country/state/province specific requirements, with the following information:

1) Name and address of Sponsor (eg, KRI)
2) Drug name, dosage form, and quantity of dosage units
3) Lot number (as required)
4) Caution - New Drug - Limited by Federal (US) Law to Investigational Use
5) The storage conditions
6) "Keep out of reach of children"
7) Expiration date (as required)

7.4 Drug Storage

The study drug must be stored in a secure area accessible only to the Investigator and his/her designees. K-321 and Placebo must be stored at [redacted]

7.5 Dispensing and Administration Of Treatment

All arms will be double-masked. The treatments administered will be:

- 0.4% K-321; QID
- Placebo Ophthalmic Solution (Vehicle); QID

7.5.1 Dosing Regimen

Subjects will begin a 12-week treatment period with QID dosing with their assigned study drug within [redacted] after the end of the cataract surgery on Day –1 (Visit 2).

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 dose is missed, the subject is recommended 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.

7.5.2 Subject Use Instructions

Subjects will be instructed to not discuss any perceived treatment effects with other study subjects.

At Visit 3, subjects will be given instructions on how to administer their assigned ophthalmic solution and how to avoid contaminating the [redacted] solution, and they will be observed instilling their own drops by the site staff.

Re-education on the proper administration procedure will be given to subjects by study site staff throughout the treatment period at each visit. For each dose, subjects must instill 1 drop to the study eye only and then close the eyelids, pressing on the lacrimal punctum. Subjects will be advised to keep the eye closed for 1 to 5 minutes before opening the eye. Any other concurrent ocular medication(s) must be applied no earlier than 5 minutes following instillation of study drug. Subjects will be trained by site staff on the application of eye drops.

7.5.3 Diet and Physical Exercise

No special diets or activity restrictions are required for this study. Subjects are asked to not change their personal routines throughout the study.

7.6 Compliance with Dispensed Study Drug Dosing Regimen

Subjects will be instructed to bring all the used [redacted] from Visit 4 to Visit 7 and all the used/unused [redacted] on Visit 8 (EOT) for all subjects to assess dosing compliance. Duration of exposure will be calculated in days as the (date of last dose – date of first dose + 1). Percent compliance will be calculated as the total number of study drug instillations/planned number of instillations × 100. The planned number of instillations for Visit 3 (Day 1) will be adjusted based on the time the cataract surgery was completed on Visit 2 (Day –1) and the time by which all study visit assessments are completed on Visit 3. For all other study visits during the treatment period, the planned number of instillations will be adjusted based on the time by which 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. For all other study days, the number of planned instillations will be considered to 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. If the subject is less than 80% or more than 125% compliant with dosing during each visit interval based on the expected number of [redacted], then the subject will be deemed non-compliant, and a dosing deviation should be recorded in the source document. Dosing compliance will be calculated for all period of drug treatment. The Investigator will use these guidelines to determine subject study compliance and deviation.

7.7 Drug Accountability

The study drug is to only be dispensed by the Investigator or designated person and is to only be used in accordance with this protocol. The study drug must only be distributed to subjects properly qualified to receive study drug, as described in this protocol.

The Investigator must keep an accurate accounting of the study drug received from the supplier. This includes the amount of study drug dispensed to subjects, amount of study drug returned to the Investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

7.8 Procedure for Unmasking

A subject's treatment mask may be broken by the Investigator if needed to manage an urgent medical safety event. If possible, the Sponsor's Medical Monitor should be contacted to discuss the case before the code is broken.

If it becomes necessary to unmasked treatment information during the study, the reason for unmasking must be clearly documented in the eCRF. The Investigator must contact the Sponsor's Medical Monitor promptly to explain the reason for the premature unmasking [eg, unmasking due to a Serious Adverse Event (SAE)].

The unmasking for final analysis will be performed after database lock, and when all subjects in the 4 groups have completed all scheduled and follow-up visits or have withdrawn from the study.

8.0 MEDICATIONS/SURGERIES

8.1 Review the list of medications and Surgical History

The Investigator must record all medications used within the previous 30 days from Visit 1 (screening visit) (Section 5.1.5), all Current medications (which is defined as those medications used at the Visit 1 (screening visit) and used prior to the administration of the assigned study drugs, both dispensed and OTC) in the eCRF along with the reason the medication was taken. This includes drugs used on a chronic and as-needed basis. Subjects must be discouraged from starting any new medication, both dispensed and over-the-counter, without consulting the Investigator, unless the new medication is required for emergency use. Concomitant medications (defined as medications used to treat medical conditions after the administration of the assigned study drugs, including those used as part of the standard of care for cataract surgery and any medications required to treat AEs) need to be recorded in the eCRF. The Investigator must characterize the medication as ocular or non-ocular. Ocular medication must be designated as right eye (OD), left eye (OS) or both eyes (OU).

Drugs used for examination purpose (eg, topical anesthesia and mydriatics) can be used as needed and need not be recorded in eCRF. Medications will be coded with the most recent version of the World Health Organization Drug Dictionary (WHODrug).

The list of current medications and concomitant medications should be reviewed with each subject at every visit to ensure that all changes are documented.

Surgical history (Section 5.1.5) and all surgeries, except cataract surgery in the study eye, during the study need to be recorded in the eCRF. The Investigator must characterize the surgery as ocular or non-ocular. Ocular surgery must be designated as OD, OS or OU.

8.2 Enrollment in Other Studies

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.3 Prohibited and Restricted Surgical Intervention

Throughout the study, study eye must not undergo any surgical intervention other than the cataract surgery at Visit 2. A subject who is screened for the study and receives cataract surgery in one eye may be replaced by using the second eye if they have not yet undergone cataract surgery in the second eye and they were never randomly assigned study drug or were withdrawn from the study before they were administered any study

drug. In this case, if all other inclusion and exclusion criteria are met by the second eye, then the subject can be enrolled using the second eye. The reason for not enrolling the subject with the initial study eye must be clearly documented in the Screening Log or appropriate electronic record.

Punctal occlusion plugs are considered to be surgical interventions.

8.4 Permitted Medication and Rescue Therapy

Use of a single glaucoma medication, except for any carbonic anhydrase inhibitor (CAI) or ROCK inhibitor, is acceptable, but dose changes are not acceptable during screening and treatment periods. Treatment of postoperative ocular hypertension is allowed via aqueous release from the paracentesis.

Artificial tears, over-the-counter anti-allergic ophthalmic products, drugs prescribed by the Investigator for post-cataract concomitant therapy, and drugs used for examination purposes are permitted (eg, topical anesthetics and mydriatics) with use of the assigned study drug (K-321 or placebo).

In case an Investigator decides that any surgery is necessary to protect subject health, the Investigator should perform the surgery and discontinue dosing with study drug at their discretion. In such a case, the subject should be instructed to attend all remaining, planned study visits, including those in the follow-up period, and this should be recorded as a protocol deviation in the source data. Consultation with the Sponsor's Medical Monitor is strongly encouraged.

All medications (OTC and prescription) used at the study site for diagnostic or treatment purposes and any surgical intervention must be recorded.

8.5 Prohibited and Restricted Medication

The following medications and drugs identified as exclusion criteria are prohibited for use by subjects throughout the study:

- Netarsudil or other ROCK inhibitors.
- Eye drops and ointments containing $\geq$2% sodium chloride.
- Devices to improve any ocular symptoms (eg, TrueTear®, LipiFlow®, etc).
- Drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or more than 2 standard drinks of alcohol per day. If these drugs

have been prescribed to treat current medical conditions, then these medications will be permitted during the study.

- Collagen shield or contact lenses in both eyes.
- Any ophthalmic solution other than those described in Section 8.4.
- Any investigational drug other than study drug (K-321 or placebo).

9.0 ADVERSE EVENTs (AEs) AND SERIOUS ADVERSE EVENTs (SAEs)

9.1 AEs

9.1.1 AE Definition

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the subject's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that subject.

Clinically meaningful (for a given subject) changes in physical examination findings and abnormal objective test findings are also recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1) Test result is associated with accompanying symptoms, and/or;
2) Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
3) Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or;
4) Test result leads to any of the outcomes included in the definition of an SAE (Section 9.2).

Merely repeating a test, in the absence of any of the above conditions, does not meet condition Number 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

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

9.1.2 Reporting of AEs

At each evaluation, the Investigator will determine whether any AEs have occurred. The subject will be questioned in a general way and no specific symptoms will be suggested. If any AEs have occurred, they will be recorded on the AE pages of the eCRF and in the

subject's medical record. If known, the diagnosis will be recorded, in preference to the listing of individual signs and symptoms.

AE reporting begins when informed consent is obtained and ends at the conclusion of the study, unless an unresolved/unrecovered AE is still being followed.

The severity of the AE will be graded as follows:

Mild The AE is easily tolerated and does not interfere with normal daily activities.

Moderate The AE causes some interference with daily activities.

Severe The AE causes all normal daily activities to be completely halted.

The Investigator must characterize AEs as ocular or non-ocular. Ocular AEs must be designated as OD, OS or OU. The Investigator must make a judgment regarding whether or not the AE was related to the study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE MUST be recorded in the eCRF. The relationship of each AE to the study drug will be determined by the Investigator using these explanations:

- ***Related*:** A reasonable possibility exists that the study drug caused the AE. A related AE can be further defined as follows:
  - Occurs within a reasonable temporal sequence to administration of study drug.
  - Cannot be explained by concurrent disease or other drugs or chemicals.
  - Improves or disappears on stopping or reducing study drug (de-challenge).
  - Reappears on repeated exposure to study drug (re-challenge).
  - Is an unusual event that is known to be associated with the drug or this class of compound, and cannot be explained by other therapy or the subject's physical condition.
  - Unlikely to be attributed to concurrent disease or other drugs or a clinically reasonable response on withdrawal (de-challenge).
- ***Not Related:*** A reasonable possibility does not exist that the study drug caused the AE. A not related AE can be further defined as follows:
  - Occurs with a temporal relationship to administration of study drug which makes a causal relationship improbable.
  - Other drugs, chemicals or underlying disease provide plausible explanations of causality.

- Is known to be associated with the subject's clinical condition, or with other medication taken by the subject.

The Investigator will record each action taken and outcome for each AE according to the following:

Action taken

- None
- Treatment required
- Hospitalization
- Study drug interrupted
- Study drug discontinued
- Subject withdrawn
- Other (specify)

Outcome

- Resolved/Recovered: The event has resolved.
  - Note: An SAE/AE stop date should be provided.
- Resolved/Recovered with sequelae: The study subject has recovered as much as may be expected but is left with sequelae of the event that are not expected to recover further.
  - Note: If the sequelae are severe enough to represent a significant disability or incapacity then the event should be reported as an SAE.
- Resolving/Recovering: Can be used in cases where study subject is known to be clearly recovering from the event at the end of a study, although the event is not yet resolved, and the Investigator and Medical Monitor agree that further follow-up is not necessary.
- Death: The study subject died as a result of the AE
  - Note: Death is considered an outcome of an AE rather than an AE in its own right, and the cause of death should be recorded as the AE. There may be rare circumstances where the cause of death is unknown and the death may have to be recorded as the event (e.g., "sudden cardiac death"). AEs resulting in death are SAEs.
- Not resolved/recovered: The subject has an AE that has not improved or recuperated at the time of the report.
  - Note: The decision not to continue follow-up must be discussed with Medical Monitor and recorded in the source documents.
- Unknown: The outcome of the event is genuinely unknown in spite of efforts to contact the subject.

Whether each AE is ocular or non-ocular will be determined by the Investigator for each AE and it will be recorded on the AE pages of the eCRF.

9.1.3 Follow-up of AEs

If any AEs are present when a subject completes the study, or if a subject is withdrawn from the study, the subject will be re-evaluated. At the Investigator's discretion, minor AEs can be reevaluated via telephone and documented. If the AE is still not resolved/recovered with sequelae, additional follow-up will be performed, as appropriate. Every effort will be made by the Investigator or delegate to contact the subject until the AE is resolved/recovered with sequelae or stabilized, or the Medical Monitor and Investigator agree that further follow-up is not necessary. The follow-up of AEs will be documented in the subject's medical records.

9.2 SAEs

9.2.1 SAE Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Events that require expedited reporting will also be considered to be SAEs.

9.2.1.1 Life-Threatening AEs

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

9.2.1.2 Hospitalization

Hospitalization is defined as the subject being admitted to hospital, or a preplanned hospital stay being prolonged for at least an additional overnight stay. Pre-planned

hospital stays for existing medical conditions or hospital stays for non-medical social reasons are not applicable. Hospitalizations of less than twenty-four (24) hours for observation will be discussed with the Medical Monitor to determine whether they are appropriate for SAE reporting.

9.2.2 Reporting of SAEs

All SAEs occurring from the time of informed consent until the completion of the study or early termination must be reported to the CRO safety personnel within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers to be related to study drug occurring after the follow-up period must be reported to the Sponsor.

To report the SAE, the site staff will complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, the CRO safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, site staff will send a completed paper SAE form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours

[redacted]

The Investigator must continue to follow-up with the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Pharmacovigilance vendor via email or fax. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs. Written confirmation that these serious, unexpected, and related AEs have been submitted to the IRB/IEC must be forwarded to the Sponsor and kept in the Investigator files.

9.2.3 Serious Unexpected Suspected Adverse Reactions

According to FDA CFR 312.32(a) and FDA Guidance "Safety Reporting Requirements for Investigational New Drugs (INDs) and BA/BE Studies" finalized December 2012, *suspected adverse reaction* means any AE for which there is a reasonable possibility that the medicinal product caused the AE. The phrase "reasonable possibility" means there is evidence to suggest a causal relationship between the AE and the medicinal product.

The following are examples of types of evidence that would suggest a causal relationship between the drug and the AE (i.e., *reasonable possibility*):

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event. The Investigator will initially classify the relatedness of an AE, but the final classification is subject to the Medical Monitor's determination unless revised by the Sponsor, which has the ultimate responsibility for judging relatedness.

A suspected adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information in Section 6 of the K-321 Investigator's Brochure or is not listed at the specificity or severity that has been described in the K-321 Investigator's Brochure.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening AE, subject hospitalization or prolongation of existing hospitalization as defined above, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (Section 9.2.1). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any AE meeting the definitions of suspected adverse reaction, unexpected, and serious is considered a serious unexpected suspected adverse reaction (SUSAR). In accordance with the FDA Guidance "Safety Reporting Requirements for INDs and BA/BE Studies", finalized December 2012, the Sponsor will unmask the study data for subjects experiencing SUSARs and will only report those SUSARs for subjects who are on the active K-321 product. All such reports will be submitted to the Investigator(s), FDA, and IRB/IEC in an expedited manner.

9.3 Pregnancy

Any subject who becomes pregnant must immediately discontinue study drug. The Investigator is required to report the pregnancy to the Sponsor's Medical Monitor within 24 hours of being notified of any subject becoming pregnant during the study. Pregnant subjects will require periodic follow-up with documentation of the outcome of the pregnancy in the study records.

9.4 Subject Withdrawal and Drug Discontinuation

If a subject experiences an AE that leads to discontinuation of study drug treatment, the eCRF should identify the AE as being the reason for drug discontinuation.

If a subject experiences an AE and withdraws informed consent and rejects the remaining scheduled visits, it is considered to be a subject withdrawal and the eCRF should identify the AE as being the reason for withdrawal.

10.0 STATISTICAL METHODS AND DATA ANALYSIS

Continuous variables will be summarized using N, mean, SD, median, minimum value, and maximum value, geometric mean, and coefficient of variation (CV%).

10.1 Sample Size Justification

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]

10.2 Study Populations

The following analysis populations will be considered:

Full Analysis Set (FAS) in the 12-week Period: will include all randomized subjects who received at least one dose of study treatment.

PK Analysis Set: will include all subjects who have received at least one dose of study treatment and have at least one time point of PK measurement.

Safety Population in the 12-week Period: will include all subjects who have received at least 1 dose of study treatment.

FAS in the 26-week Overall Period: will include the randomized subjects who are assigned into the 26-week Overall Period 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.

Safety Population in the 26-week Overall Period: will include subjects for the 26-week Overall Period and who had at least 1 dose of study treatment.

10.3 Analysis of Efficacy Parameters

10.3.1 Primary Efficacy Analysis

The primary analysis of central corneal ECD will be performed on the study eye within the FAS via a Wilcoxon Rank Sum Test [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 endothelial densities change from baseline as measured at Week 12 between the active and placebo groups being compared: ie,

$X_i = e_i$ 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 (eg, the median of all differences $d=Y_j - X_i$) and Moses 95% 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 confidence interval (CI) will be presented for supportive use.

This primary analysis using Wilcoxon Rank Sum Test to evaluate the superiority of K-321 versus placebo is 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 also 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.

10.3.2 Data Imputation Rules for Primary Variable in Primary Analysis

[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 shift in location (e.g., the median of all differences d=Yj – Xi)

10.3.3 Secondary Efficacy Analyses

All continuous efficacy endpoints will be summarized using basic summary statistics of observed value and change from baseline at each visit.

All categorical endpoints will be summarized by frequency and percentage at each visit.

All time-to-event endpoints will be summarized by treatment.

Efficacy data will be presented for the study eye and for the non-study eye, if collected.

10.4 Analysis of Safety Data

AEs will be coded using the MedDRA dictionary (the most recent version, ver. 24.1 or later). Frequencies, percentages, severity, and relationship to study drug of subjects with TEAEs, serious TEAEs, and TEAEs causing premature study withdrawal and study drug discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Furthermore, frequencies of occurrence will be given of subjects with TEAEs by system organ class; by system organ class and preferred term; by system organ class, preferred term and maximal severity; by system organ class and preferred term for treatment-related TEAEs; and by system organ class, preferred term, and study day of onset. Separate summaries will be additionally performed for ocular and non-ocular AEs.

Other safety endpoints including slit-lamp biomicroscopy (cornea, conjunctiva, anterior chamber, lens, lids and lashes), dilated fundoscopy (vitreous, retina, macula, choroid, optic nerve, retinal periphery), and IOP will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed for the eye, Study Eye, and non-study eye will be summarized separately. No safety endpoints will be imputed.

10.5 Demographic/Baseline Information

Basic summary statistics will be provided by treatment group for demographics (e.g., age, gender, race, ethnicity, and eye color groups).

[redacted]

10.6 Interim Analysis

No interim analysis is planned for this study.

10.7 Pharmacokinetics/Pharmacodynamics Analysis

10.7.1 Pharmacokinetics Analysis

[redacted]

The following are the defined major evaluations and statistical analyses. Additional evaluation and analyses will be considered on an as-needed basis.

10.7.1.1 Profile of Plasma Drug Concentration

[redacted]

10.7.1.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.7.2 Pharmacodynamics Analysis

Not applicable.

11.0 STUDY MANAGEMENT AND DATA COLLECTION

11.1 Ethical Conduct of the Study

This study will be conducted according to the protocol, FDA Good Clinical Practice (GCP), as described in 21 CFR Parts 11, 50, 54, 56, and 312; the World Medical Association Declaration of Helsinki; the Health Insurance Portability and Accountability Act (HIPAA); and International Conference on Harmonisation (ICH) GCP (E6/R2), all applicable country and local regulatory requirements.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC must be constituted according to the applicable state, federal and local requirements of each participating location, and those of the ICH GCP guidance and FDA GCP regulations.

It is the responsibility of each investigational site to submit the protocol, Investigator's Brochure, subject informed consent, subject recruitment materials (if applicable), and other required documentation to the IRB/IEC for review and approval. Copies of the written approvals must be provided to the Sponsor. The documentation should clearly mention the approval/favorable opinion of the protocol, the subject informed consent form, and subject recruitment materials (if applicable). The respective version dates are to be included. The written approvals and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRB/IEC and provided to the Sponsor prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB/IEC has direct participation in the study, written notification regarding his or her abstinence from voting must also be obtained.

Sites must adhere to all requirements stipulated by the IRB/IEC. This includes notification to the IRB/IEC regarding protocol amendments; updates to the subject informed consent and recruitment materials intended for viewing by subjects; Investigational New Drug safety reports; serious and unexpected AEs; updates regarding the ongoing review of the study at intervals specified by the IRB/IEC; and final study reports or summaries.

It is the responsibility of each investigational site to submit information to the appropriate IRB/IEC for annual review and annual re-approval.

11.3 Subject Informed Consent

Written consent must be obtained from the subject prior to any study-specific procedure or investigation.

Prior to the implementation of study procedures, subjects and persons conducting the consent discussion will be required to sign and date the IRB/IEC-approved 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).

The written consent document will embody the elements of informed consent as described in the HIPAA, World Medical Association Declaration of Helsinki, FDA 21 CFR Part 50.25, ICH GCP, and in accordance with any local regulations. The Investigator is responsible for the preparation, content, and IRB/IEC/Research Ethics Committee (REC) approval of the ICF. The ICF must be approved by the clinical site-designated IRB/IEC/REC and be acceptable to the Sponsor or its designee prior to their use.

The ICF must be written in a language fully comprehensible to the prospective subject. The written subject ICF will explain the objectives of the study and its potential risks and benefits. The information included on the ICF must be provided to the subject both verbally and in writing whenever possible and in a manner deemed appropriate by the IRB/IEC/REC. Subjects should be given ample opportunity to read the information and inquire about details of the study. The Investigator must be satisfied that the subject has understood the information provided before written consent is obtained. If there is any doubt as to whether the subject has understood the written and verbal information, the subject must not be allowed to enter the study.

If a subject agrees to participate, he or she will be asked to sign and date an ICF, the original copy of which will be kept by the Investigator. A copy of the signed ICF will be given to the subject. Information documenting the informed consent procedure will be recorded in the subject's medical records (i.e., source document), and the original signed ICF must be made available to the study monitor for inspection.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by CRO and/or the Sponsor and provided in writing by CRO and/or the Sponsor prior to the consent process.

All ICFs must be approved for use by the Sponsor or designee and receive approval/favorable opinion from an IRB/IEC/REC prior to their use. If the ICF requires revision (e.g., due to a protocol amendment or significant new safety information), it is

the PI's responsibility to ensure that the amended form is reviewed and approved by the Sponsor prior to submission to the governing IRB/IEC/REC and that it is read, signed, and dated by all subjects or their designees currently and subsequently enrolled in the study.

11.4 Amendments to the Protocol

An amendment must be agreed to in writing by the Sponsor, submitted as an IND application amendment, and submitted to and approved by the respective IRB/IEC for each investigational site before it is implemented. Written approval of a protocol amendment is not required prior to implementation of changes to the protocol which are necessary to eliminate immediate hazard to the subject; however, approval must be obtained as soon as possible thereafter. Approved amendments must also be signed by the Investigator.

11.5 Study Initiation

The Investigator must not enroll any subjects prior to the completion of a formal meeting conducted by a representative of the Sponsor. This meeting will include a detailed review of the study protocol and eCRFs. Study drug will not be supplied to an Investigator until all the necessary pre-study requirements have been completed and essential signed documents are received by the Sponsor or its representative.

11.6 Study Monitoring

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH/FDA GCPs, applicable regulatory requirements, HIPAA, and the current Declaration of Helsinki. Valid data are to be entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of accurate, complete, legible, well-organized, and easily retrievable data. The monitor will review the protocol with the Investigator. In addition, the monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of the Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are acceptable. The eCRFs and related source documents will be reviewed in detail by the monitor at each visit, in accordance with relevant Standard

Operating Procedures (SOPs), ICH GCP guidance, and FDA GCP regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses. The Investigator and staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.7 Case Report Form

All subject data generated during the study will be recorded on the eCRF. Corneal ECD results and corneal endothelial cell parameters will be available in a [redacted] report.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs, designed specifically for this study and supplied by the representatives of the Sponsor for each subject.

The representatives of the Sponsor will only consider the eCRFs to be complete after they are reviewed and signed by the Investigator, indicating his/her assurance of the accuracy of all recorded data. It is expected that the Investigator and staff will cooperate with the monitoring team and provide missing data in a timely manner.

11.8 Verification Procedures

In fulfilment of their obligations to the Sponsor and to verify compliance with this protocol, ICH GCP guidance, and FDA GCP regulations, the Investigator will permit the representatives of the Sponsor, the IRBs/IECs, the monitor, and regulatory authorities to have direct access to the subject's medical records.

It is the Investigator's obligation to ensure documentation of all relevant data in the subject's medical record, eCRFs, and on study forms, when applicable, according to procedures provided in the protocol and / or supplemental instructions.

The Investigator will maintain a Subject Identification Code List to enable unambiguous identification of the subjects (subject names and corresponding subject numbers). The Subject Identification Code List is an essential document and as such it must be maintained according to the ICH GCP guidelines.

11.9 Retention of Records

All documentation pertaining to the study will be retained by the Sponsor in accordance with U.S. FDA regulations and the ICH GCP guidance document.

The representatives of the Sponsor will provide each Investigator with a study file, which will be used to file the Investigator's Brochure; protocol; drug accountability records; correspondence with the IRB/IEC and the Sponsor; and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and the Sponsor or its designees.

The Investigator will retain records required to be maintained under federal regulations for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, these documents will be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the Investigator must make provision for the subject's medical records to be kept for the same period of time.

Subjects' medical records and other original data will be archived in accordance with applicable regulations and requirements established by the investigational sites.

11.10 Insurance and Indemnity

The Sponsor's obligations regarding insurance and indemnification are described in other documents or agreements.

11.11 Audit and Inspection

The Investigator must permit study related quality oversight monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. It is important that the Investigator(s) and their relevant personnel are available during the monitoring, audit or inspection visits and that sufficient time is devoted to the process.

It is the responsibility of the Sponsor to perform Sponsor quality oversight, as part of the quality assurance and quality control programs. The purpose of a quality assurance audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, the principles of ICH-GCP, and other applicable regulatory requirements.

12.0 USE OF INFORMATION

12.1 General Aspects

All information concerning the Sponsor, such as patent applications, formula, manufacturing processes, basic scientific data or formulation information supplied by the Sponsor and not previously published, are considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of the Sponsor, except for official representatives, such as regulatory authorities.

It is understood by the Investigator that the information developed in this clinical study, in connection with the development of K-321 will be used by the Sponsor and, therefore, may be disclosed by the Sponsor as required to other clinical Investigators, other pharmaceutical companies and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to the Sponsor complete test results and all data compiled in this study.

12.2 Subject Confidentiality and Data Protection

The Sponsor and its designees affirm and uphold the principle of the subject’s right to protection against invasion of privacy. Throughout this study, all data will be linked to the eCRF via a unique identification number and the subject's initials. The data will be masked correspondingly in all data analyses.

However, in compliance with the guidelines and regulations of the US FDA concerning the acceptance of clinical studies in support of IND applications and the ICH GCP (whether performed in US or elsewhere), and in fulfilment of its obligations to the Sponsor to verify compliance with this protocol, the Sponsor’s designee requires that the Investigator to permit its monitor, representatives from the FDA, the Sponsor’s designated auditors, IRBs/IECs, and other governmental regulatory authorities to review the subject’s primary medical records (source data or documents) including, but not limited to laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject’s study participation, and autopsy reports related to deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the subject before the subject is entered into the study.

12.3 Final Report and Publication Policy

All information regarding this study will be kept strictly confidential. All data derived from the study will be the property of the Sponsor. The Investigator must undertake not to submit any part of the data from this study for publication without prior consent of the Sponsor. The sponsor may disclose data derived from the study to other Investigators and drug regulatory authorities.

After completion of the study, and as agreed by the Investigator and the Sponsor, the Investigator may send a draft manuscript to the Sponsor to be reviewed in order to reach an agreement regarding publication. The Investigator must receive written approval from the Sponsor before the final version of the manuscript is submitted for publication.

At the conclusion of the study, after the data are analyzed, the Sponsor or its designee will prepare a final clinical report.

13.0 REFERENCES

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APPENDICES

Appendix A: Guidance on images storage and transfer

