A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12 Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy

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K-321-201

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Statistical Analysis Plan

Version *2.0*

Prepared by:

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Significant Changes from Previous Authorized Version
1.0	09 Feb, 2021	Not applicable – First version
2.0	25 Aug, 2021	1. Updated the imputation on [redacted] images. 2. Added the exploratory analysis on primary endpoint based on van Elteren test, an extension of the Wilcoxon rank sum test in a stratified experiment. 3. Modified the permutation test to be based on the two-sample rank-sum statistics 4. Modified the disposition section on patients who 'provided informed consent' to patients who 'screened' 5. Modified the inclusion and exclusion criteria section on 'informed consent patients' to 'screened patients' 6. Specified that the analysis visit window is for FAS and PPS only. 7. Specified in the primary analysis section that the p values from Wilcoxon rank sum test will be presented.

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANOVA	Analysis of Variance
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
CFR	Code of Federal Regulations
CI	Confidence Interval
[redacted]	[redacted]
CTMS	Clinical Trial Management System
CRO	Contract Research Organisation
CS	Clinically Significant
CV	Curriculum Vitae
ECD	Endothelial Cell Density
eCRF	electronic Case Report Form
EOS	End-Of-Study
EOT	End-Of-Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full-Analysis Set
FDA	US Food and Drug Administration
FECD	Fuchs endothelial corneal dystrophy
HRT	Heidelberg retina tomography
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intra-Ocular Pressure
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LOCF	Last-Observation-Carried-Forward
M/N	Morning and Night
MD/E	Mid-Day and Evening
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NCS	Not Clinically Significant
PPS	Per Protocol Set

Abbreviation	Definition
Q1	Quartile 1
Q3	Quartile 3
QID	4 Times Daily
ROCK	Rho-associated Protein Kinase
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFS	Safety Set
SOA	Schedule Of study site Activities
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
[redacted]	[redacted]

1. Introduction

In the early 20th century, Ernst Fuchs described a bilateral corneal dystrophy now referred to as Fuchs endothelial corneal dystrophy (FECD). The primary defect in FECD seems to be related to the endothelial cells that normally sit on a modified basement membrane (Descemet's membrane) that lines the inner surface of the cornea.

Ripasudil ophthalmic solution 0.4% (K-321) is a Rho-associated protein kinase (ROCK) inhibitor that has been marketed in Japan since December 2014 as Glanatec®, with twice daily (BID) dosing for glaucoma and ocular hypertension. Studies in endothelial cells have indicated that K-321 can lead to reduction of apoptosis, enhancement of cell proliferation, and increased rates of migration, all of which may support endothelial healing (Kowa Company Ltd 2019). Moloney et al (2017) first reported use of a ROCK inhibitor to promote healing in patients with FECD treated with Descemet stripping only (DSO). More recently, Macsai et al (2019) reported results from a small study of 18 patients with FECD and central confluent guttae of up to 5 mm diameter who underwent DSO and were subsequently treated with either ripasudil ophthalmic solution 0.4% four times daily (QID) or no ripasudil for 2 months. Overall, patients who underwent DSO with ripasudil recovered vision more quickly [redacted] The patients in the no-ripasudil group had a [redacted] while in the ripasudil group there was [redacted]. In the short-term studies (8 weeks duration and less) for the development of Glanatec, there were no [redacted] (Kowa Company Ltd 2019).

Kowa proposes to pursue development of K-321 for the following indication: "the treatment of Fuchs endothelial corneal dystrophy after descemetorhexis." This will be the first Kowa-sponsored study in patients for this indication.

This is a multi-centre, double-masked, randomised, parallel-group, placebo-controlled, 2-period study of patients with FECD after descemetorhexis.

This statistical analysis plan for K-321-201 protocol v1.0 (United States and Australia) dated 16-August-2019 and protocol v2.0 (European Union) dated 31-December-2019 will examine efficacy and safety endpoints (described in Section 8 and 9) at planned analysis time points (described in Section 13.3). Protocol Version v2.0 has the addition of vital signs and physical examinations at Visit 9. Statistical

analysis based on two protocol versions will be the same but will have the protocol version information added on the vital signs and physical examinations related table and listings.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to investigate the effect of K-321 dosed for 12 weeks on central ECD in patients with FECD after descemetorhexis.

2.2. Secondary Objective

The secondary objectives of this study are the following:

- to investigate the effect of K-321 on central ECD, corneal thickness, and corneal clarity in patients with FECD at each visit after descemetorhexis out to 52 weeks
- to assess the safety and tolerability of K-321 in patients with FECD at each visit after descemetorhexis out to 52 weeks

2.3. Exploratory Objective

[redacted]

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multi-centre, double-masked, randomised, parallel-group, placebo-controlled, 2-period study of patients with FECD after descemetorhexis. Approximately 60 patients will be enrolled at approximately 30 sites in the United States, Europe, and Australia. The study design is presented in Figure 1, and the schedule of study site activities (SOA) is presented in Table 5.

The first period is the treatment period, consisting of a screening visit within a 1- to 4-week screening period, a descemetorhexis and randomisation visit, a 12-week full treatment period containing 7 interim visits (including 1 optional visit at Week 2) and an end-of-treatment (EOT) visit scheduled for Week 12. During the 2 weeks

immediately following the EOT visit, each enrolled patient will taper dosing of study drug to zero (Section 3.4).

The second period is a follow-up observation period of 40 weeks, including the tapering phase and containing 4 interim visits and an end-of-study (EOS) visit. Patients are not to self-administer study drug after approximately Week 14. The maximum total study period for each enrolled patient is 56 weeks, with a maximum of 15 visits (including the 1 optional visit). Patients will be considered to have completed the study with the completion of their EOS visit (scheduled for Week 52). The duration of the study is defined for each patient as the date signed written informed consent is provided through the last follow-up visit.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the central corneal ECD at Week 12 as assessed by the Central

3.2.2 Secondary Efficacy Endpoint

Secondary efficacy endpoints include:

- Central corneal thickness change from baseline to each subsequent visit
- Percent change of central corneal thickness from baseline to each subsequent visit
- Central corneal ECD at each visit
- Number and percentage of patients who achieve central corneal ECD of [redacted] cells/mm2 or more at each visit
- Time to achieve central corneal ECD [redacted] cells/mm2 or more
- Number and percentage of patients who achieve cornea clearance at each visit where corneal clearance is defined as patients achieving a cornea thickness less than or equal to baseline cornea thickness and who have no corneal oedema
  - Number and percentage of patients who achieve cornea thickness less than or equal to baseline cornea thickness
  - Number and percentage of patients who achieve no corneal oedema, i.e. absent of oedema in all three layers of cornea, including epithelial, stromal, and endothelial
- Time to cornea clearance
  - Time to return of cornea thickness to less than or equal to baseline cornea thickness
  - Time to no corneal oedema

3.2.3 Exploratory Endpoints

Exploratory endpoints include the following:

- Best Corrected Visual Acuity (BCVA) (letters) by Early Treatment Diabetic Retinopathy Study (ETDRS) change from [redacted] to [redacted]
- Time to achieve BCVA by ETDRS letter score [redacted]
- Number and percentage of patients who achieve [redacted] or more improvement (BCVA by ETDRS)
- [redacted] corneal ECD at [redacted]
- [redacted] corneal ECD change from [redacted] at [redacted]
- Percent change of [redacted] corneal ECD from [redacted] at [redacted]
- Changes in [redacted] parameters from [redacted] by [redacted]
- Contrast sensitivity change (log values) from [redacted] by [redacted]
- [redacted] ([redacted] domain and total scores change from [redacted] by [redacted]

3.2.4 Safety Endpoints

Safety parameters include monitoring of Adverse Events (AEs), treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs), physical examination findings, vital sign measurements, laboratory tests, slit-lamp biomicroscopy, measurement of intraocular pressure (IOP), and ophthalmoscopy.

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

3.3. Study Procedures and Baseline

Before performing any study procedures, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

After obtaining informed consent at Visit 1, the investigator will select one eye as the study eye, and the patient will come back for the descemetorhexis operation and random assignment to treatment after 1 to 4 weeks (Visit 2). At Visit 2, each patient's eligibility for study participation will be confirmed, including a successful descemetorhexis operation that meets the inclusion criteria. After eligibility is confirmed, patients will be randomly assigned to the 3 treatment groups (in a 1:1:1 ratio). All patients will be instructed to apply the study drug only to the study eye.

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

Baseline is defined as the last non-missing measurement including unscheduled assessments prior to the administration of first dose of study drug. Change from baseline is defined as the post baseline value minus the baseline value for the given assessment.

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

The EOS (Week 52 or ET) visit is defined as the visit occurring at the end of the 52-week study period (Week 52) or the final visit at which the patient is prematurely discontinued/withdrawn from participation in the study.

The schedule of study site activities (SOA) is presented in Section 13 (Table 5).

3.4. Treatments

There are 3 treatment groups: K-321 ophthalmic solution 0.4% dosed QID (K-321 QID), K-321 ophthalmic solution 0.4% dosed BID (K-321 BID); and placebo. To preserve masking, all patients will self-administer assigned study drug QID and will dose from [redacted] of assigned [redacted] one to be used M/N (morning and night) and the other to be used MD/E (mid-day and evening), as presented in Table 1.

Table 1 Vial Contents by Dosing Regimen and Dosing Time for Each Treatment Group From Day 1 to Visit 9 (Week 12)

Treatment	Morning	Mid-day	Evening	Night
K-321 QID	K-321 0.4%	K-321 0.4%	K-321 0.4%	K-321 0.4%
K-321 BID	K-321 0.4%	Placebo	Placebo	K-321 0.4%
Placebo	Placebo	Placebo	Placebo	Placebo

Except on days of study visits on Day 1 through Week 12 (not including Visit 9) during the treatment period, study drug will be dosed by the patient QID: morning (9 AM ±1 hour), mid-day (1 PM ±1 hour), evening (5 PM ±1 hour), and night (9 PM ±1 hour). Each patient will be provided with [redacted] of colour-coded [redacted], one set to be applied M/N and the other to be applied MD/E.

On study visit days Visit 3 through Visit 9, patients will not apply any study drug until after all study measurements have been completed; thereafter on those days, patients will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day. Additionally, on Visit 3 they must first apply study drug within [redacted] after the end of the descemetorhexis procedure on Day –1 (Visit 2).

With the primary efficacy endpoint being assessed at Visit 9 (Week 12), if a patient applies any study drug on the day of Visit 9 before all study measurements have been completed, that patient's Visit 9 should be rescheduled within the visit window allowance (eg, the next day). For visits other than Visit 9 during the treatment period, a patient who applies study drug before all study measurements have been completed will be assessed as planned, and a protocol deviation must be recorded.

At Visit 9 (Week 12), patients will enter the drug-tapering phase of the follow-up period, and new study drug will be dispensed without M/N or MD/E colour coding. All patients will self-administer their tapering-phase study drug BID (9 AM ±1 hour and 9 PM ± 1 hour) for a week, then once daily (9 AM ± 1 hour) for a week, and then will discontinue study drug.

4. General Statistical Considerations

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarised using the mean, the Standard Deviation (SD), median, Quartile 1 (Q1), Quartile 3 (Q3), minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Selected ordinal data may be summarised using both descriptive statistics and counts and percentages of participants in each category, as appropriate. Data will be listed in data listings.

All statistical tests will be 2-sided and performed using a 0.05 significance level, leading to 95% (2-sided) Confidence Intervals (CIs).

A closed 2-step ordered testing procedure will be used to control overall type I error for the primary efficacy endpoint, central corneal ECD at Week 12. In step 1, the K-321 0.4% QID group will be statistically compared with the placebo group. If the step 1 comparison is significant, step 2 will be performed to statistically compare K-321 0.4% BID group with the placebo group. If the statistical comparison made during step 1 is not significant, testing will still be performed to compare the BID group to placebo; however, all p values will be considered nominal/descriptive only.

No other measures will be taken to control error for the multiple secondary and exploratory endpoints or multiple treatment comparisons.

A study eye will be identified for each patient. Unless otherwise specified, efficacy will be summarised for the study eye only. Ocular safety summaries by eye will be presented separately for the study eye and the non-study eye.

4.1. Sample Size

A sample size of 20 patients in each group will be needed to detect a difference of [redacted] in the measurement in the corneal ECD at Week 12 between K-321 0.4% QID/BID and placebo groups with a power of [redacted] for Step 1 and a power of [redacted] for Step 2 using a Wilcoxon rank sum test with a 0.050 two-sided significance level with closed testing procedures. Sample size was calculated by simulation. For the simulation, based on the existing literature, placebo was assumed to be distributed normally with a [redacted] and K-321 was assumed to be distributed normally with a [redacted]. Proportion of unmeasurable value of Week 12 due to corneal oedema and proportion of [redacted] value of Week 12 due to the withdrawal were assumed to be about 10% and about 5%, respectively.

4.2. Randomization, Stratification and Masking

Patients will be randomly assigned at Visit 2 to either placebo, K-321 BID, or K-321 QID treatment (Section 3.1) using a 1:1:1 allocation ratio. There is no stratification on the randomization for this study.

Study drug will be double-masked. All study drug will be supplied in identical packaging, colour, smell, and appearance to enable double-masked conditions. K-321 and matching placebo will be provided in identical packaging so that all investigators, study site staff, patients, and clinical monitors will remain masked throughout the study. The Interactive Web Response System (IWRS) will assign study drug to patients at the time of randomisation. Only personnel in IWRS, the independent randomisation team within [redacted] Biostatistics, and clinical supplies will be unmasked and will have access to treatment assignments; all other parties involved in the study will be fully masked.

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

Patients who are unmasked will be allowed to continue their participation in the study; however, their data may be excluded from per-protocol analyses.

4.3. Analysis Set

4.3.1 Full-analysis set (FAS)

The FAS will consist of all participants who have a successful descemetorhexis procedure performed, were randomly assigned to receive double-mask study drug, received at least one dose of study drug in the study eye, and have at least one assessment of central corneal ECD performed after the descemetorhexis procedure on the study eye. (An assessment of "cannot perform due to corneal oedema" is considered a valid assessment for inclusion in the FAS.) All analyses using the FAS will group participants according to randomised treatment.

4.3.2 Per-protocol set (PPS)

The PPS will consist of all FAS participants who complete the 12-week dosing treatment period for the study eye (for the primary analysis only), have at least 80% compliance and at most 125% compliance with study treatment for the study eye,

have not taken any prohibited medication and have no major protocol deviations. Patients who receive rescue therapy will be considered to have completed study treatment for inclusion in the PPS. All analyses using the PPS will group participants according to treatment actually received.

4.3.3 Safety Set (SFS)

The SFS will consist of all participants who received any study drug. All analyses using the safety set will group participants according to treatment actually received.

The FAS will be the primary analysis set for efficacy analyses. Selected efficacy analyses will be repeated for the PPS. Safety will be summarised using the SFS.

4.4 Assessment Windows

4.4.1 Study day

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

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

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

4.4.2 Visit Windows for Analysis

Visit windows will be defined for by-visit summary and analysis purposes. Summary data (such as AEs and concomitant medications) that are not reported by visit will not use visit windows. The EOT or EOS assessments will be summarized based on visit window of when the visit occurred (e.g., if the patient discontinued treatment at Week 7, the EOT assessment will be included in the Week 7 by-visit summaries).

Both scheduled and unscheduled assessments will be considered as valid assessments for analysis. Visit labels will be assigned to each post baseline record based on the windows for study day relative to the date of first dose. If an assessment at Day 1 is missing, the closest visit with non-missing assessment on or before the date of first dose will be used as baseline. All analyses for FAS and PPS be based on the analysis visit windows in Table 2. If there are multiple valid assessments within a time window, the assessment which occurs closest to the target day will be used in the analysis. If there are multiple valid assessments with same difference from the target day, the latest assessment will be used in the analysis.

Table 2 Analysis Visit Windows

Analysis Visit	Analysis Visit Window
Screening/Washout	NA
Baseline/Day 1	NA
Week 1	2 to 10 Days (Target 7)
Week 2	11 to 17 Days (Target 14)
Week 3	18 to 27 Days (Target 21)
Week 5	28 to 41 Days (Target 35)
Week 7	42 to 55 Days (Target 49)
Week 9	56 to 73 Days (Target 63)
Week 12	74 to 97 Days (Target 84)
Week 16	98to 125 Days (Target 112)
Week 20	126 to 153 Days (Target 140)
Week 24	154to 216 Days (Target 168)
Week 38	217 to 314 Days (Target 266)
Week 52	315 to 413 Days (Target 364)

5. Patient Disposition

5.1. Disposition

The counts of patients who screened and screen failed will be presented. The counts and percentages of patients who are randomized, receive study treatment, completed treatment period (12 week) as well as 12 week visit, completed treatment period (12 week) as well as 52 week visit, discontinued during treatment period (12 week) but completed 12 week visit, discontinued during treatment period (12 week) but completed 52 week visit. Withdrawn from the study will be presented based on the number of patients in each treatment group and overall for all randomized patients. Reasons for discontinuation during treatment period and reasons for withdrawn from the study will be summarized for each treatment group as treatment disposition and patient disposition, respectively. All percentages within the patient disposition summary will be based on the number of patients randomized. All percentages within the treatment disposition summary will be based on number of patients from SFS. Patient and treatment disposition data will be listed. Screen failures will also be listed in the data listing.

5.2. Protocol Deviations

Protocol deviations will be tracked by the clinical team on an ongoing basis. Major protocol deviations are the subset of deviations which are considered to have potential significant impact on primary analysis. Subjects with major protocol deviations will be excluded from the analysis based on PPS. Specific criteria for

what constitute a major protocol deviation will be determined by the clinical team and the following criteria may be considered:

- Eligibility criterion violation
- Not complete the 12-week dosing treatment period for the study eye (for the primary analysis only)
- Less than 80% or more than 125% compliance with study treatment in the study eye
- Taking prohibited medication or treatment listed in protocol section 5.8.3

Protocol deviations will be recorded within the [redacted] Clinical Trial Management System (CTMS) and will undergo a blinded review prior to database lock and unblinding. Significant protocol deviations are defined as the subset of deviations which are considered to affect primary efficacy and safety assessments, the safety or mental integrity of a subject, or the scientific value of the trial.

Patients with significant protocol deviations will be tabulated for each treatment group, and overall. All deviations, including significant and major protocol deviations, will be listed by-patient for all randomized patients. All percentages will be based on the number of patients randomized. The total number of significant protocol deviations and the number of significant protocol deviations under each protocol deviation category will also be presented

6. Demographics and Baseline Characteristics

6.1 Demographics

Demographic information and baseline characteristics collected at Screening will be summarized for the FAS and SFS. Continuous variables, including age (years), baseline weight (kg), baseline height (cm), and baseline body mass index (BMI) (kg/m2) will be summarized using descriptive statistics for each treatment group and overall. Continuous variables will be tested with ANOVA. The following categorical variables will be summarized by reporting the number and percentage of patients in each category for each treatment group and overall. Fisher's exact test will be used for the following categorical variables to test whether there is a difference between each treatment group.

- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race* (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple and Other)
- Iris color of study eye (Blue, Brown, Hazel, Green, Grey, Other)

- Family History of FECD † (Yes, No)
    - If Yes, Father, Mother, or Both

*The statistical comparison between the Race categories will not be presented because the Race categories are not mutually exclusive. i.e. One subject could be marked in multiple race categories.

†The statistical comparison on Family History of FECD will be between the categories of 'Yes' and 'No'.

Percentages will be based on the total number of patients in the SFS, FAS and PPS. All demographic and baseline characteristics will be listed for all randomized patients.

6.2 Baseline Ocular Characteristics

Descriptive statistics will be provided for patient ocular baseline characteristics on study eye and non-study eye by treatment group and overall for ophthalmological assessments including Corneal ECD Measurement by specular microscopy (including Corneal Morphology Parameters), Corneal ECD Measurement by Heidelberg Retina Tomography (HRT) (including Corneal Morphology Parameters), BCVA score, Corneal Thickness, presence/absence of Corneal Oedema categories of epithelial, stromal, or endothelial, Contrast Sensitivity, [redacted] domain and total scores, IOP, longest and shortest diameter of descemetorhexis. Tests for baseline disease characteristics of study eye will be performed in a pairwise manner with each dosing regimen (QID and BID) of K-321 0.4% compared to placebo. Numerical results will be tested with ANOVA; Categorical results will be tested with Fisher's Exact Test. Summary and tests will be based on the FAS and SFS on study eye, non-study eye and the [redacted] Score where applicable.

6.3 Medical History

6.3.1 General Medical History

Ocular and non-ocular medical histories are captured separately on the eCRF. For non-ocular medical history, the investigator will record the body system, verbatim term, start date, and stop date or indication of ongoing. For ocular medical history, the investigator will record the eye (right, left, both), verbatim term, start date, and stop date or indication of ongoing. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1or above. The number and percentage of patients with any medical history (ocular and non-ocular), any ocular medical history in the study eye, any ocular medical history in the non-study eye, an any non-ocular medical history will be summarized by treatment

group. Additionally, non-ocular medical history will be summarized by the number and percentage of patients with any non-ocular medical history by reported body system and treatment group on SFS.

Percentages will be calculated based on number of patients in the SFS. Also, by-patient listings of ocular and non-ocular medical histories will be presented.

6.4 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented for randomized patients in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Therapies: Medications and Surgical Procedures

At screening, the following prior therapies will be recorded in the eCRF:

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

At screening, all patients' prior medications used and surgical procedures undergone within the previous 30 days will be recorded in the eCRF.

Any medicinal product prescribed or over-the-counter (OTC), including herbal products, vitamins, and minerals is considered a prior or concomitant medication. All patients' surgical procedures undergone concomitantly during the study must be reported and recorded in the eCRF. Prior medication is defined as any medication with the stop date prior to the date of the first dose of study drug. Concomitant medication is defined as any medication with a stop date after the date of the first dose of study drug. Any medications used during the study will be coded with the World Health Organization Drug (WHODrug) Dictionary dated March 2019., which will be updated whenever available throughout the life of the study. All surgical procedures will be coded as "All other therapeutic products".

All concomitant medications and surgical procedures will be presented in data listings with an indicator to identify whether their use is prior and /or concomitant. Concomitant medications and surgical procedures will be summarized and listed for the SFS.

Descemetorhexis of the Study Eye will be listed in a separated data listing. Partial dates on prior and concomitant medications and surgical procedures start date will be handled as follows:

- Partial start dates of prior and concomitant medications and surgical procedures will be assumed to be the earliest possible date consistent with the partial date.
- If the year is present and the month is missing, then the month is set to January.
- If the month and year are present and the day is missing, then the day is set to the 1st day of month.
- If the year is missing, then the year will be assumed to be the year part of the patient's informed consent date.

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

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

7.2 Study Treatments

7.2.1 Extent of Exposure

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

7.2.2 Treatment Compliance and Modifications

Percent compliance will be calculated as the total number of study drug instillations/planned number of instillations × 100.

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

- For all study visits during the treatment period, the planed number of instillations will be adjusted based on the time all planned study visit assessments are completed on the respective study visit days, as activities on these days may reduce the number of doses that can be given. Thus, on the study visit days, the number of planned instillations will be based on the time of the first dose. (E.g. if the first dose of the day is taken in the morning then the planned instillation will be considered to be 4 doses; if the first dose of the day is taken at noon then the planned instillation will be considered to be 3 doses).
- 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.
- Patients will be considered compliant with study treatment if the calculated percent compliance is between 80% and 125%, inclusive.

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

8. Efficacy Analysis

The FAS will be the primary analysis set for efficacy analyses. Selected efficacy analyses will be repeated for the PPS. Unless otherwise specified, efficacy will be analysed and summarized for the study eye only.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the central corneal ECD at Week 12 as assessed by the [redacted]

8.1.1. Primary Analysis

The primary analysis of central corneal ECD will be performed on the study eye within the FAS via a Wilcoxon rank sum test and will be based on assessments performed by specular microscopy. Testing will be performed in a pairwise manner with each dosing regimen (QID and BID) of K-321 0.4% compared to placebo. The ranks are based on the observations of the two groups that are compared. P values from the Wilcoxon rank sum test will be presented.

A closed 2-step ordered testing procedure will be used to control overall type I error for the primary efficacy endpoint, central corneal ECD at Week 12. In step 1, the K-321 0.4% QID group will be statistically compared with the placebo group. If the step 1 comparison is significant, step 2 will be performed to statistically compare K-321 0.4% BID group with the placebo group. If the statistical

comparison made during step 1 is not significant, testing will still be performed to compare the BID group to placebo; however, all p values will be considered nominal/descriptive only.

For each dosing regimen, 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 between the active and placebo groups being compared: ie,

$X_i = e_i$ for i = 1 to n for the placebo patients

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

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. [redacted]

Week 12 assessments that are unable to be performed by investigators due to corneal oedema will be [redacted] based on the information recorded in eCRF. Week 12 specular microscope images that are unable to be analysed and categorized as [redacted] and [redacted] by [redacted] will be imputed as [redacted] and [redacted], respectively. Week 12 assessments that are [redacted] due to other reasons will be [redacted] Patients who receive a rescue keratoplasty performed prior to Week 12 will be [redacted] or [redacted] by [redacted]).

Wilcoxon rank sum test will be conducted after all the [redacted] and [redacted] values are [redacted].

8.1.2. Sensitivity Analysis

Several sensitivity analyses will be performed for the primary endpoint in FAS and PPS.

In the first, the primary analysis will be repeated for PPS.

- In the rare event that unmasking is needed because of a medical emergency, the investigator may unmask an individual patient through the IWRS. Patients who are unmasked will be [redacted] or [redacted]). Otherwise, the [redacted] data handling methods for Week 12 assessments will be the same as stated under primary analysis.

In the second, the primary analysis methods will be repeated for the FAS using the [redacted] visit data. The [redacted] data handling methods will be the same as primary analysis for ungradable Week 12 assessments, or the Week 12 assessments that could not be performed due to oedema. Week 12 assessments that are [redacted] due to other reasons will be [redacted] Patients who receive a rescue keratoplasty performed prior to Week 12 will be [redacted].

In the third, permutation test will be performed for the FAS. The p value from the permutation test based on the two-sample rank-sum statistics will be presented.

In the fourth, the primary analysis analyses methods will be repeated for the FAS but using the assessments results performed by HRT for the subset of patients for which the assessments are available.

8.1.3 Exploratory Analysis

As exploratory analysis, the primary endpoint will be analyzed by the van Elteren test, an extension of the Wilcoxon rank sum test in a stratified experiment. The p values from the van Elteren test will be presented. The baseline [redacted] corneal ECD will be stratified in different scenarios. For baseline [redacted] corneal ECD, we will use the average of [redacted] assessment results. If the [redacted] result is [redacted], the [redacted] result will be used, vice versa. The analysis will be done separately in the below stratification scenarios.

- The first stratification scenario includes four strata:
- The second stratification scenario will only include the subjects with . There will be three strata which will be classified according to the first stratification scenario's 2nd to 4th strata.
- The third stratification scenario will include three strata:
- The fourth stratification scenario will be similar to the first stratification scenario, except that the
- In the fifth stratification scenario, the patients with he p values under all possible combinations will be compared and the largest one will be adopted.

8.2 Secondary Efficacy Endpoint

Secondary endpoints will be summarised for the FAS. The [redacted] data handling methods will be the same as primary analysis for ungradable Central ECD assessments, or the Central ECD assessments that could not be performed due to oedema. Assessments of central ECD, central corneal thickness, and corneal oedema after rescue keratoplasty will be [redacted]. Otherwise, secondary efficacy analyses will be [redacted].

The following secondary endpoints based on continuous measures will be analysed by pairwise Wilcoxon rank sum tests comparing each active K-321 0.4% treatment. The Hodges-Lehmann estimate and Moses 95% CI for the shift in location will also be presented regimen to placebo:

- Central corneal ECD at each visit
- Central corneal thickness change from baseline to each subsequent visit.
- Percent change of central corneal thickness from baseline to each subsequent visit

The Central corneal ECD at each visit by Specular Microscopy, the central corneal ECD at each visit by HRT, the Central corneal thickness at each visit will also be presented in spaghetti plot and box plot, respectively.

The following secondary endpoints based on the number and percentage of patients achieving the endpoint will be analysed by Pearson chi-square test comparing each active K-321 0.4% treatment regimen to placebo. The 95% CI for the difference in percentage of patients achieving the endpoint will also be presented. Should the number of responders be less than 5 in either group, Fisher's exact test will be used instead. If Fisher's exact test is used, the unconditional CI for the difference in response rates will be provided

- Number and percentage of patients who achieve central corneal ECD of 700 cells/mm2 or more at each visit
- Number and percentage of patients who achieve cornea clearance at each visit where corneal clearance is defined as patients achieving a cornea thickness less than or equal to baseline cornea thickness and who have no corneal oedema
    - Number and percentage of patients who achieve cornea thickness less than or equal to baseline cornea thickness
    - Number and percentage of patients who achieve no corneal oedema

The following secondary endpoints based on time-to-event endpoints will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo. Kaplan-Meier estimates and plots will also be presented.

Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be [redacted] Patients who receive rescue keratoplasty will be [redacted]:

- Time to achieve central corneal ECD 700 cells/mm2 or more
- Time to cornea clearance
  - Time to return of cornea thickness to less than or equal to baseline cornea thickness
  - Time to no corneal oedema

8.3 Exploratory Efficacy Endpoints

Exploratory endpoints will be summarised for the FAS. The [redacted] data handling methods will be the same as primary analysis for ungradable [redacted] ECD assessments, or the [redacted] ECD assessments that could not be performed due to oedema. Assessments after rescue keratoplasty will be [redacted]. Endpoints will be analysed in a similar manner to the secondary efficacy endpoints.

The following exploratory endpoints based on continuous measures will be analysed by pairwise Wilcoxon rank sum tests comparing each active K-321 0.4% treatment regimen to placebo with the Hodges-Lehmann estimate for the different in medians and Moses 95% CI for the difference in medians also presented:

- BCVA (letters) by ETDRS change from [redacted] to [redacted]
- [redacted] corneal ECD at [redacted]
- [redacted] corneal ECD change from [redacted] at [redacted]
- Percent change of [redacted] corneal ECD from [redacted] at [redacted]
- [redacted] at [redacted]
- [redacted] at [redacted]
- Changes in [redacted] from [redacted] by [redacted]
- Percent changes in [redacted] from [redacted] by [redacted]
- Contrast sensitivity change (log values) from [redacted]
- [redacted] domain and total scores change from [redacted]

* The [redacted] total score algorithm and sub-scale are based on the [redacted] Scoring algorithm manual (version 2000).

The [redacted] ECD by specular Microscopy will also be presented in spaghetti plot and box plot, respectively.

The following secondary endpoints based on the number and percentage of patients achieving the endpoint will be analysed by Pearson chi-square test comparing each active K-321 0.4% treatment regimen to placebo. The 95% CI for the difference in percentage of patients achieving the endpoint will also be presented. Should the number of responders be less than 5 in either group, Fisher's exact test will be used instead. If Fisher's exact test is used, the unconditional confidence interval for the difference in response rates will be provided.

- Number and percentage of patients who achieve [redacted] or more improvement (BCVA by ETDRS)

The following exploratory endpoint based on time-to-event endpoints will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo with Kaplan-Meier estimates and plots also presented. Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be [redacted]. Patients who receive rescue keratoplasty will be [redacted].

- Time to achieve BCVA by ETDRS letter score [redacted]

8.4 Efficacy Endpoints for the Non-study Eye

Central and [redacted] corneal ECD by [redacted] central and [redacted] by [redacted], change from [redacted] in [redacted] corneal ECD by [redacted], change from [redacted] in BCVA (letters) by ETDRS by [redacted], and percentage change from [redacted] in [redacted] corneal ECD and [redacted] by [redacted] will be summarized with the mean, the SD, median, minimum value, and maximum value. Patient listings will also be provided.

9 Safety Analysis

Safety parameters include monitoring of AEs, TEAEs, TESAEs, vital sign measurements, laboratory examinations, slit-lamp biomicroscopy, IOP, and ophthalmoscopy.

Safety data will be summarised and listed with no statistical hypothesis testing performed. Continuous variables will be summarised using the mean, the SD,

median, Q1, Q3, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages.

9.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) which will be updated whenever available throughout the life of the study.

In general, all AEs will be listed and all TEAEs and TESAEs will be summarized. AE will be deemed treatment-emergent if the onset date is on or after the date of first treatment.

An overall summary of TEAEs and TESAEs will be provided, with number (percentage) of patients and number of events for all TEAEs/TESAEs by the following categories: any TEAEs, any TESAEs, Study Drug-Related TEAEs/TESAEs, TEAEs/TESAEs by Severity, TEAEs/TESAEs leading to treatment discontinuation, TEAEs/TESAEs leading to study discontinuation, TEAEs leading to death).

TEAEs and TESAEs will be summarized separately by ocular (study eye and fellow eye) and non-ocular TEAEs/TESAEs. TEAEs and TESAEs will also be summarized for the treatment period, the tapering phase and the 9-month follow-up period:

- TEAEs/TESAEs during Treatment Period is defined as TEAEs/TESAEs with onsite date on or after the first treatment date (Day 1) until the Week 12 Visit. For patients who miss Week 12 Visit and/or do not complete treatment period, the end date for this definition will be the last dose of study treatment.
- TEAEs/TESAEs during Tapering Phase of Follow up Period is defined as TEAEs with the onsite date after the Week 12 Visit date until taper dosing is ended, which is defined as the Week 12 Visit date +14 days. For patients who do not take any Tapering Phase treatment but are followed-up for safety, TEAEs/TESAEs during Tapering Phase should be null.
- TEAEs/TESAEs during 9-month Follow-up Period is defined as TEAEs/TESAEs other than two categories defined above.

TEAEs/TESAEs will be presented in descending order from the system organ class (SOC) code with the highest incidence to the SOC with the lowest incidence from K-321 QID group. Within the SOC level, TEAEs/TESAEs will be presented in descending order from the MedDRA preferred term (PT) with the highest incidence to the PT with the lowest incidence from K-321 QID group. If the incidence for any

two or more PTs within the SOC from K-321 QID group is equal, the PTs will be presented descending order of incidence from K-321 QID group. If the incidence for any two or more PTs within the SOC from K-321 QID and K-321 BID groups are both equal, the PTs will be presented descending order of incidence from Placebo group. If the PTs from all three treatment groups within an SOC are equal, the PTs will be presented in alphabetical order. Patients who experienced multiple TEAEs/TESAEs for a SOC will be counted once, similarly for patients with multiple TEAEs/TESAEs per PT will be counted once. Patients who experienced multiple TEAEs/TESAEs for a PT will be counted once.

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

- If the onset date is completely missing, onset date is set to the date of first dose.
- If the year is present and the month is missing, then the month is set to January. If the year is same as the year of the date of first dose and the AE end date is not prior to the date of first dose, then onset date is set to the date of first dose.
- If the month and year are present and the day is missing, then the day is set to the 1st day of month. If the month and year are same as the month and year of the date of first dose and the AE end date is not prior to the date of first dose, then onset date is set to the date of first dose.
- If the AE end date is present, then the imputed start date will be no later than the end date.

9.1.3 Incidence of Adverse Events

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

9.1.4 Relationship of Adverse Events to Study Drug

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

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

9.1.5 Severity of Adverse Event

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

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

9.1.6 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation

TEAEs leading to treatment discontinuation will be identified as TEAEs on the AE eCRF page, where the action taken with study drug is "Drug Withdrawn". The TEAEs leading to treatment discontinuation will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. All TEAEs leading to treatment discontinuation will be listed in a data listing.

9.1.5 Treatment-Emergent Adverse Events Leading to Study Discontinuation

TEAEs leading to study discontinuation will be identified as TEAEs on the AE eCRF page, where the "Caused Study Discontinuation?" is "Yes". The TEAEs leading to study discontinuation will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. All TEAEs leading to study discontinuation will be listed in a data listing.

9.1.6 Serious Adverse Events

The TESAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. The TESAE leading to treatment discontinuation and study discontinuation will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.4 and 9.1.5. For All TESAE summaries, the number of events under each SOC and PT will also be presented. All SAE data will be listed in a data listing.

9.1.7 Death

Deaths will be identified as AEs on the AE eCRF page. Patient deaths will be identified as AEs where the outcome is "Death". Deaths will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. All deaths will be listed in a data listing.

9.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory and no conversion will be performed. Lab test names listed in the statistical analysis plan are the same as indicated in the protocol; however, the tables and listings will report results using the test names based on Clinical Data Interchange Standards Consortium (CDISC)-controlled terminologies.

9.2.1 Hematology

Routine laboratory testing will be performed at Screening and EOT (Week 12 or ET) visits. All hematology parameters will be summarized using descriptive statistics for each treatment group at Screening and EOT (Week 12 or ET). Additionally, shift tables providing the number of patients with indicated shifts (low, normal, high) in their results from Screening and EOT (Week 12 or ET) will also be presented for all hematology parameters.

All summaries will be done for the SFS and all hematology data will be listed.

9.2.2 Chemistry

Routine laboratory testing will be performed at Screening and EOT (Week 12 or ET) visits. All chemistry parameters will be summarized using descriptive statistics for each treatment group at Screening and EOT (Week 12 or ET). Additionally, shift tables providing the number of patients with indicated shifts (low, normal, high) in their results from Screening and EOT (Week 12 or ET) will also be presented for all chemistry parameters.

All summaries will be done for the SFS and all chemistry data will be listed.

9.2.3 Urinalysis

Routine laboratory testing will be performed at Screening and EOT (Week 12 or ET) visits. All urinalysis parameters will be summarized using descriptive statistics for each treatment group at Screening and EOT (Week 12 or ET).

All summaries will be done for the SFS and all urinalysis data will be listed.

9.3 Vital Sign Measurements

The vital sign variables including blood pressure (systolic and diastolic), pulse rate, body temperature, height, and body weight. Notable abnormal values will be flagged in the data listings. The conversion between conventional unit to SI unit for temperature and weight and definitions for notable abnormal values are listed in the appendix (Table 3 and Table 4). Observed values for vital sign measurements at Baseline and EOT (Week 12 or ET)† — as well as changes from Baseline to postbaseline values in vital sign measurements — will be summarized descriptively by treatment group.

All summaries will be done for the SFS and all vital sign data will be listed.

† Week 12 vital sign measurements will only be done in EU (European Union) countries according to protocol version 2.0.

9.4 Physical Examination

A limited physical examination will be performed at Screening and EOT (Week 12 or ET) †. The limited physical examination includes a review of the patient's medical history, medication history, and evaluation of relevant body systems complaints. In case of relevant findings, full evaluation of the condition needs to be conducted. Physical examination findings will be listed.

† Week 12 vital sign measurements will only be done in EU countries according to protocol version 2.0.

9.5 Ophthalmological assessments

Ophthalmological assessments will be performed at the indicated visits in the SOA (Table 5).

9.5.1 Intraocular Pressure

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

Observed values at Baseline and each subsequent study visit, as well as changes from Baseline in IOP for each subsequent study visit, will be summarized descriptively by treatment group for the study eye and non-study eye. All IOP data will be listed.

9.5.2 Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed at every visit using slit-lamp examination without pupil dilation to evaluate the condition of the lids, conjunctiva, anterior chamber, cornea, and lens.

Ocular findings will be evaluated by the following criteria:

- Normal
- Abnormal with not clinical significance (NCS)
- Abnormal with clinical significance (CS)

The number and percentage of patients with at least 1 treatment-emergent CS abnormality by ocular assessment will be summarised for each treatment group for the study eye and non-study eye. An abnormality will be deemed treatment-emergent if the onset date is on or after the date of first treatment. A patient will be counted once even if the patient experiences more than 1 treatment-emergent CS abnormality.

All slit-lamp biomicroscopy and ophthalmoscopy assessments will be listed.

9.5.3 Ophthalmoscopy

Ocular examination will be performed with pupil dilation using an indirect ophthalmoscope according to the current standard of practice to evaluate the condition of the vitreous, macula, retina, optic nerve, choroid, and retinal periphery.

Ocular findings will be evaluated by the following criteria:

- Normal
- Abnormal (NCS)
- Abnormal with clinical significance (CS)

The number and percentage of patients with at least 1 treatment-emergent CS abnormality by ocular assessment will be summarised for each treatment group for the study eye and non-study eye. An abnormality will be deemed treatment-emergent if the onset date is on or after the date of first treatment. A patient will be counted once even if the patient experiences more than 1 treatment-emergent CS abnormality.

All ophthalmoscopy assessments will be listed.

10 Interim Analysis

No interim analyses will be performed. The analysis for primary, secondary, exploratory, and safety will be conducted at the Week 12 database lock ie, after all patients have completed dose tapering at the Week 16 visit or have been discontinued from the study and/or treatment before this visit. Analysis of the complete study data (through Week 52) will be performed after all patients have completed the Week 52 visits or have been discontinued from the study before the Week 52 visit. As the primary efficacy endpoint is at the Week 12 visit, no alpha adjustments will be required. No changes to study conduct (eg, change to sample size or early stopping) are planned.

11 References

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12 Appendices

12.1 Unit Conversion

Table 3 Unit Conversion

Quantity	From SI to Conventional Unit	From Conventional Unit to SI
Height	0.394 x [cm] = [in]	2.540 [in]. = [cm]
Weight	2.205 x [kg] = [lb]	0.454 x [lb] = [kg]
Temperature	([°C] x 9/5) + 32 = [°F]	([°F] – 32) 5/9 = [°C]

12.2 Notable Abnormal Vital Signs

Table 4 Notable Abnormal Vital Signs

Parameter	Abnormality	Change from Baseline
Pulse	<40 bpm >120 bpm	>=15 bpm increase from baseline >=15 bpm decrease from baseline
Systolic blood pressure	<80 mmHg >180 mmHg	>=20 mmHg increase from baseline >=20 mmHg decrease from baseline
Diastolic blood pressure	<50 mmHg >105 mmHg	>=15 mmHg increase from baseline >=15 mmHg decrease from baseline
Temperature	NA	>= 1 C increase from baseline >=1 C decrease from baseline

12.3 Schedule of Study Procedures

Table 5 Schedule of Study Site Activities

Activity	Screening	Treatment Period									Follow-Up Period				
Time Point	**Day -28**	**Day –1**	**Day 1**	**Week 1**	**Week2**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 38**	**Week 52**
Visit Window (Day)	**-28 to -7**	**-**	**-**	**5-9**	**12-16**	**18-24**	**32-38**	**46-52**	**60-66**	**81-87**	**105-119**	**133-147**	**161-175**	**259-273**	**357-371**
Visit No	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Optional Visit**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**
Informed consent	X														
Demographics	X														
Medical history and concomitant disease	X	X [a]													
Physical examination and vital sign measurements	X									X [h]					
Urine drug screen	X														
Urine pregnancy test (if applicable)		X [a]									X				
Laboratory sampling	X									X					
Eligibility evaluation	X	X [b]													
Descemetorhexis with photo or video documentation		X													
Randomisation		X													
Dispense study drug			X	X		X	X	X	X	X					
[redacted] study drug [c]				X	X	X	X	X	X	X	X				
Study drug administration		←	X	X	X	X	X	X	X	X	→				
Slit-lamp evaluation	X	X [a]	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X

Activity	**Screening**	**Treatment Period**									**Follow-Up Period**				
Time Point	**Day -28**	**Day –1**	**Day 1**	**Week 1**	**Week2**	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 38**	**Week 52**
Visit Window (Day)	**-28 to -7**	**-**	**-**	**5-9**	**12-16**	**18-24**	**32-38**	**46-52**	**60-66**	**81-87**	**105-119**	**133-147**	**161-175**	**259-273**	**357-371**
Visit No	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Optional Visit**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**
Corneal ECD measurement [e] (specular microscopy, non-contact type)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal ECD measurement by HRT [f]	(X)			(X)	(X) [d]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
BCVA (ETDRS scale)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal thickness (ultrasound pachymeters)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal Oedema (slit-lamp evaluation)	X	X[a]	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal morphology (Pentacam or Orbscan)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity [f] (CSV-1000 chart)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Ocular examination with pupil dilation using an indirect ophthalmoscope [i]	X									X					X
Intra-ocular pressure (contact or non-contact type tonometer)	X		(X) [g]	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
[redacted]	X						X			X			X		X
Photo documentation of ocular findings	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Adverse event documentation		X ◄	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X ►

Abbreviation: HRT, Heidelberg retina tomography; [redacted]

[a] Pre-operative.

[b] Post-operative.

[c] Both [redacted] study drug [redacted] will [redacted] and [redacted] will be recorded in the eCRF. Morning/night and mid-day/evening drug will [redacted] separately.

[d] Week 2 is an optional visit (at the discretion of the investigator), but if this visit is applied, all marked assessment items must be conducted.

[e] The study eye must be measured at all indicated visits, whereas the non-study eye must be measured only at Visit 1 and Visit 14.

[f] Only at sites where equipment is available.

[g] If investigator judges it necessary.

[h] Assessment only performed in EU countries

[i] This will be done according to current standard of care to evaluate the condition of the vitreous, macula, retina, optic nerve, choroid, and retinal periphery.