Statistical Analysis Plan

A Randomized, Open-Label, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Dosing Regimens of Netarsudil Ophthalmic Solution in Patients with Corneal Edema Due to Fuchs Corneal Dystrophy

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STATISTICAL ANALYSIS PLAN

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Sponsor: Aerie Pharmaceuticals, Inc.

Protocol Number: AR-13324-CS210

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Statistical Analysis Plan Approval

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List of Abbreviations

AD	Analysis Dataset
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	Twice Daily
CCT	Central Corneal Thickness
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FCD	Fuchs Corneal Dystrophy
FCS	Fully Conditional Specification
ICH	International Conference on Harmonisation
ICT	Inferior Corneal Thickness
IOP	Intraocular Pressure
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NCS	Not Clinically Significant
NCT	Nasal Corneal Thickness
ODO	Observed Data Only
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
QD	Once Daily
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Superior Corneal Thickness
SD	Standard Deviation
SDC	Statistics & Data Corporation
SE	Standard Error
SOC	System Organ Class
TCT	Temporal Corneal Thickness
TEAE	Treatment-Emergent Adverse Event
V-FUCHS	Visual Function and Corneal Health Status

WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AR-13324-CS210 (Amendment 1) dated 03FEB2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

The primary objective of the study is:

- To evaluate the reduction in central corneal thickness (CCT) in eyes dosed with either Netarsudil Ophthalmic Solution 0.02% (netarsudil) once-daily (QD) or netarsudil twice-daily (BID) for the treatment of corneal edema due to Fuchs corneal dystrophy (FCD).

The secondary objectives of the study are:

1. To evaluate the proportion of subjects demonstrating improvement in vision following treatment for FCD with netarsudil QD or netarsudil BID; and
2. To evaluate the safety of netarsudil QD and netarsudil BID in subjects with FCD.

2.1 Efficacy

Efficacy endpoints are described below. The primary comparisons in this trial will be within a treatment group on the mean change from baseline. The primary comparisons for proportion of subjects achieving a specified endpoint will be between treatment groups.

2.1.1 Primary Endpoint

- Mean change from baseline in CCT as assessed by ultrasound pachymetry at Week 4

2.1.2 Secondary Endpoints

- Mean change from baseline in CCT as assessed by ultrasound pachymetry at Week 8
- Mean change from baseline in best corrected visual acuity (BCVA) at Weeks 4, and 8
- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Weeks 4, and 8
- Proportion of subjects with complete resolution of corneal edema at Weeks 4, and 8

2.1.3 EXPLORATORY ENDPOINTS

- Proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 2
- Proportion of subjects who gained ≥10 letters (2 lines) in BCVA at Weeks 2, 4, and 8
- Proportion of subjects who gained ≥5 letters (1 line) in BCVA at Weeks 2, 4, and 8
- Mean change from baseline in CCT as assessed by Pentacam® at Week 4 (selected sites only)
- Mean change from baseline in visual function and corneal health status (V-FUCHS) glare and diurnal variation (Glare Factor) score at Week 4
- Proportion of subjects with complete resolution of epithelial edema at Weeks 4, and 8

2.2 Safety

The safety of netarsudil QD and BID will be evaluated by:

- Adverse events (AEs)
- BCVA
- Anterior segment biomicroscopy
- Intraocular pressure (IOP)
- Ophthalmoscopy
- Vital signs (heart rate and blood pressure)

2.3 Statistical Hypotheses

The null and alternative hypotheses, based on the primary variables, are as follows:

H_{01}: The mean change from baseline in CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 = 0.

H_{11}: The mean change from baseline in CCT by ultrasound pachymetry in study eyes treated with netarsudil QD at Week 4 ≠ 0.

H_{02}: The mean change from baseline in CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 = 0.

H_{12}: The mean change from baseline in CCT by ultrasound pachymetry in study eyes treated with netarsudil BID at Week 4 ≠ 0.

3. Study Design and Procedures

3.1 General Study Design and Plan

This is an 8-week, randomized, open-label, multicenter, efficacy and safety study in subjects with FCD. The study will be conducted at approximately 20 sites in the USA. Two different dosing regimens (QD and BID) of netarsudil will be investigated for their efficacy in reducing or resolving corneal edema in subjects with FCD. Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in their study eye every morning, and one drop of netarsudil in their study eye

every evening. Subjects randomized to the netarsudil BID dosing regimen will instill one drop of netarsudil in their study eye every morning and evening.

CCT will be measured by ultrasound pachymetry at approximately the same time of day ± 60 minutes and always before noon (local time), at each of the 5 scheduled visits (Screening, Baseline [Day 1], Week 2, Week 4, and Week 8/Exit). In order to be eligible to participate in the study, subjects will have been diagnosed with visually significant central corneal edema due to FCD, in at least one eye, for no longer than 12 months' duration.

At the Screening visit, the subject's diagnosis of FCD will be confirmed and CCT measured using an ultrasonic pachymeter. IOP and BCVA will also be collected.

At the Baseline visit (Day 1), the eligibility assessments conducted during Screening will be repeated to ensure that the subject meets all criteria for enrollment in the study. The same eye must qualify at both the Screening and Baseline visits. If qualified, the subject will be provided with the V-FUCHS patient reported visual disability questionnaire (Wacker 2018). The subject will be randomized (1:1) into the study and provided with study medication. The subject will also be trained on appropriate techniques for applying eye drops.

At the Week 2 and Week 4 visits, the subject will return to the study site for efficacy and safety assessments.

At the Week 4 visit, any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study. For these subjects, the morning administration of Study Artificial Tear will be terminated.

At the Week 8 visit, a final assessment of efficacy and safety parameters will be conducted, and the subject will exit the study.

Scheduled study visits (Screening, Baseline, Week 2, Week 4, and Week 8/Exit) will be referred to in all tables and listings to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Figure 1 shows the scheduled study visits and visit window (days) for each study visit. There is no Day 0, Day 1 is the day of study eye determination and randomization, on which the subjects get their first study medication dispensation. All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day will be calculated as [Date of Event] – [Date of First Dose] + 1. For event dates before Day 1, study day will be calculated as [Date of Event] – [Date of First Dose]. The first dose of study medication will not be captured on the electronic case report form (eCRF) and therefore will be assumed to be same as the first study medication dispensation date.

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments along with study design schema is provided below.

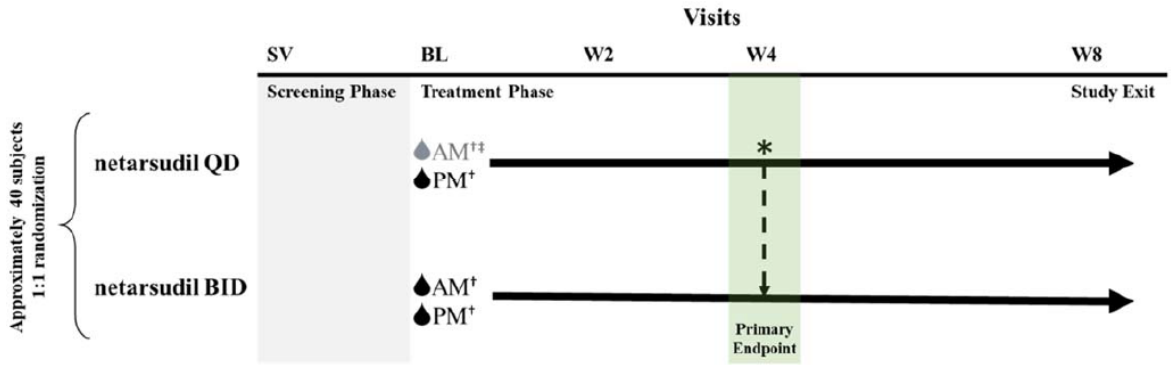
Figure 1. Schedule of Visits and Procedures

Visit[1]	Screening Visit[1]	Baseline Visit[1]	Week 2[1]	Week 4[1]	Week 8/Exit[1]
Visit Window (Days)	**Day -8 to -1**	**Day 1**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 56 ± 3**
Visit Sequence Number	**1**	**2**	**3**	**4**	**5**
Informed Consent	X				
Inclusion/Exclusion	X	X			
V-FUCHS Questionnaire		X		X	X
Demography	X				
Medical/Ophthalmic History	X	X			
Concomitant Medications	X	X	X	X	X
HR/BP	X	X			X
Urine Pregnancy Test[2]		X			X
Ocular Symptoms/AEs	OU	OU	OU	OU	OU
BCVA (ETDRS protocol)	OU	OU	OU	OU	OU
Biomicroscopy	OU	OU	OU	OU	OU
Ultrasound Pachymetry (CCT)[3]	OU	OU	OU	OU	OU
IOP	OU	OU	OU	OU	OU
Dilated Ophthalmoscopy	OU				OU
Undilated Ophthalmoscopy		OU	OU	OU	
Tomography (Pentacam®)[4]	OU	OU	OU	OU	OU
SE Determination[5] and Randomization		X			
Eye Drop Instruction and Demonstration		SE			
Dispense Study Medication		X		X	

Abbreviations: AEs = adverse events; BCVA = best corrected visual acuity; BP = blood pressure; CCT = central corneal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = heart rate; IOP = intraocular pressure; OU = both eyes; SE = Study Eye; V-FUCHS = Visual Function and Corneal Health Status

1 Subjects should be scheduled at approximately the same time of day ± 60 mins in the morning (ideally at or before 10:00 AM local time) for each visit
2 Required only for females of childbearing potential
3 Ultrasound pachymetry should be performed at approximately the same time of day ± 60 mins and always before noon local time
4 Selected sites only, may be completed prior to ophthalmoscopy at the Screening and Week 8/Exit Visit while the subject is dilating
5 Please refer to Section 4.4 for instructions on study eye determination

Figure 2. Study Design Schema



* Any subject randomized to netarsudil QD who, in the opinion of the Investigator, has not responded adequately to treatment, may have their netarsudil dosing frequency increased to BID for the remainder of the study.
† Study eye only. AM dosing should occur between 06:00 and 09:00 hours. PM dosing should occur between 19:00 and 22:00 hours.
‡ Subjects randomized to the netarsudil QD dosing regimen will be instructed to instill one drop of the Study Artificial Tear in their study eye every morning, and one drop of netarsudil in their study eye every evening.

4. Study Treatments

4.1 Treatment Administered

Subjects will be randomized using a 1:1 allocation ratio to one of two treatment groups:

- Netarsudil QD Dosing Regimen

  Study Artificial Tear: one drop in the study eye in the morning

  Netarsudil 0.02% ophthalmic solution: one drop in the study eye in the evening
- Netarsudil BID Dosing Regimen

  Netarsudil 0.02% ophthalmic solution: one drop in the study eye in the morning and in the evening

Doses will be self-administered by the study subjects. If the subject is using any another topical ophthalmic drop (e.g., ocular hypotensive medications) at the same time as netarsudil, the subject should be instructed to instill netarsudil first, and wait at least 15 minutes before instilling any additional drops.

For subjects deemed unable to self-administer the doses, a caregiver will be asked to administer the medication. All subjects will administer study medication for approximately 8 weeks.

4.2 Method of Assigning Patients to Treatment Groups

Subjects will be assigned to treatment groups through the use of an interactive response technology (IRT) system. Subjects will be identified by subject ID (xxx-xxx) with 3 digits for site ID followed by 3 digits for subject number in all datasets and listings for this study.

4.3 Masking and Unmasking

This is an open-label study, therefore masking and unmasking procedures do not apply.

5. Sample Size and Power Considerations

This study is not powered to detect a pre-stated efficacy signal, but rather will be used to inform the design and power for any possible future studies. With a sample size of up-to 20 subjects per treatment group, the precision of the point estimate of mean change from baseline in CCT, as measured by the half-width of the two-sided 90% confidence interval (CI), will be approximately 1/2.7 of the standard deviation (SD) of the change from baseline, yielding 90% confidence that the true mean change from baseline is within $\pm$ SD/2.7 μm of the observed mean change from baseline. That is, if the SD of the change from baseline is 60 μm, then the half-width of the two-sided 90% CI would be 60 μm x 1/2.7 = 22.2 μm, yielding 90% confidence that the true mean change from baseline is within $\pm$ 22.2 μm of the observed mean change from baseline.

With a sample size of up-to 20 subjects within a treatment group, the study will have 80% power to reject H_{01} or H_{02} and in favor of H_{11} or H_{12} respectively and demonstrate a statistically significant mean change from baseline, assuming the true effect size (mean change / SD) is 0.577 or larger (e.g. assuming the true mean change from baseline is 34.6 μm and the SD is 60 μm), a one sample t-test and a two-sided alpha = 0.10.

With a sample size of up-to 20 subjects per treatment group, the study will have 95% confidence of ruling out AEs with true incidence rates of 13.9% or higher within each treatment group. That is, with up-to 20 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that adverse event is less than 13.9%.

Similarly, with a sample size of up-to 40 subjects combined over treatment groups, the study will have 95% confidence of ruling out AEs with true incidence rates of 7.2% or higher within each treatment group. That is, with up-to 40 subjects in a treatment group, if an AE of a specific type is not observed, then with 95% confidence, the true incidence rate of that AE is less than 7.2%.

6. Data Preparation

6.1 Input Data

Study data will primarily be recorded on the electronic case report form (eCRF) supplied by Statistics & Data Corporation (SDC) using electronic data capture (EDC) system, iMednet™. The only external data source is the site level protocol deviations that will be collected separately at site and will be transferred to SDC from Aerie. It will be combined with the protocol deviations in EDC by SDC for the final deviation classification by Aerie.

When all prerequisites for database lock have been met, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of all final versions of external vendor data, with written authorization provided by appropriate SDC and Sponsor personnel
- Protocol deviations have been identified and status defined (major/minor deviations)
- Analysis populations have been determined

6.2 Output Data

Data from EDC will be transferred to SDC Biostatistics and will then be mapped to analysis datasets (ADs). Raw data will be used to create the subject listings along with ADs as needed, while all tables will be based on the ADs.

7. Analysis Populations

A total of approximately 40 subjects will be enrolled into the study at approximately 20 investigational sites within the United States. Subjects will be at least 18 years of age with a diagnosis of FCD, each of whom should meet all of the inclusion criteria and none of the exclusion criteria.

7.1 Modified Intent-to-Treat (mITT) Population

The mITT population will include all randomized subjects who have received at least one dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize a subset of efficacy variables and will summarize subjects as randomized.

7.2 Per Protocol (PP) Population

The PP population is a subset of the mITT population, which will include those subjects (and their visits) who do not have major protocol deviations likely to seriously affect the primary outcome of the study. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and mITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

7.3 Safety Population

The safety population will include all randomized subjects who have received at least one dose of investigational product. This population will be used to summarize safety variables and will summarize subjects as treated.

8. General Statistical Considerations

8.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the primary unit of analysis will be the study eye defined based on CCT of at least 600 μm evaluated by ultrasound pachymetry. If both eyes qualify based on CCT and enrollment criteria, the study eye will be the eye with the thinner cornea at the baseline. If both eyes have the same CCT, the study eye will be the right eye. Qualified fellow eyes will also be summarized. A qualified fellow eye for a given subject is a fellow eye that also met all of the inclusion criteria and none of the exclusion criteria at the Screening and Baseline Visits.

8.2 Missing or Inconclusive Data Handling

8.2.1 Assessment Windows

Assessment window mapping will be applied to both efficacy and safety outcomes for table summaries using observed data only (ODO). Unscheduled or early termination visits that are within the protocol specified window of a scheduled visit will be mapped to that visit to replace the missing scheduled visit. Missing data handling for efficacy variables as described in Section 8.2.2 will be applied after assessment window mapping. Both the actual visit and windowed visit will be displayed in the listings.

8.2.2 Missing Data Handling for Efficacy Variables

The primary analysis will be completed with available data per subject from the mITT population. Robustness analyses will also be presented based on the multiple imputation (MI) methodology under different assumptions of missingness and intercurrent events, using last observation carried forward (LOCF), and using the PP population with available data per subject. Imputation using MI or LOCF will

only be performed on study eye missing data at post-baseline scheduled visits. No imputation will be performed for missing fellow eye data and unscheduled post-baseline visits.

Intercurrent events will be primary handled in the following manner:

1. Discontinuation of study medication and non-optimal compliance will be ignored, values measured after discontinuation of study medication or regardless of compliance will be used in the analyses [treatment policy strategy].
2. Withdrawal due to lack of efficacy or AEs: missing data will be singly imputed as the worst within subject observation prior to the intercurrent event [hypothetical strategy]. For efficacy variable CCT, the worst is the maximum within subject observations. In addition, the worst observation should come from post-baseline scheduled and unscheduled visits prior to the intercurrent event.
3. Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AEs: missing data will be imputed employing MI fully conditional specification (FCS) regression method.

For the LOCF imputation, only the observations from post-baseline visits including scheduled, unscheduled, and early termination visits for a given subject will be carried forward.

8.2.3 MISSING DATA HANDLING FOR PARTIAL MISSING DATES

In general, there will be no imputation of missing dates other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.

- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, prior or concomitant medication etc).

8.3 Definition of Baseline

Baseline is defined as the last measurement (including measurement from unscheduled visits) prior to the first dose of study medication. The date of first dose of study medication is assumed to be same as the first study medication dispensation date.

8.4 Data Analysis Conventions

All data analysis will be performed by SDC. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, and listings using landscape orientation. Unless otherwise specified, all study data for randomized subjects will be listed by treatment group, subject number, visit, and parameter as applicable. Only a disposition listing will be created for screen failure subjects. Summaries will be presented by treatment group and visit as applicable.

Continuous study assessments will be summarized by treatment group and visit as applicable using descriptive statistics (n, mean, median, SD, minimum, and maximum). Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Categorical study assessments will be summarized by treatment group and visit as applicable using discrete descriptive statistics (frequency counts and percentages). All percentages will be rounded to one decimal place (ie, XX.X%). Change from baseline will be calculated as follow-up visit – baseline visit.

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided with a significant level of 0.10 ($\alpha = 0.1$). Where applicable, 2-sided 90% and 95% confidence intervals (CIs) will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as ”<0.0001” and p-values greater than 0.9999 presented as ”>0.9999”. All odds ratios less than 0.01 will be presented as “<0.01” and all odds ratio greater than 999.99 will be presented as “>999.99”. Difference between netarsudil QD and netarsudil BID will be calculated as netarsudil QD – netarsudil BID.

8.5 Adjustments for Multiplicity

Adjustments for multiplicity will not be made in this early phase trial.

9. Disposition of Subjects

Disposition will be presented in terms of numbers and percentage of subjects by treatment group and for all subjects. Percentages will be calculated using treated subjects as the denominator unless otherwise specified.

The numbers and percentages of subjects who were screened, enrolled, screen failed, and treated will be presented. The reasons for screen failure will be displayed with the percentages calculated using total number of screen failures as the denominator. The screen failure reason will include eligibility criteria not met, lost to follow up, investigator decision, enrollment complete, withdrawal of consent, and other. The number of subjects with COVID-19 related screen failure will be identified.

The number and percentages of subjects in each analysis population (mITT, PP, and Safety) will be presented.

The number and percentage of subjects who completed the study or prematurely discontinued from the study will be presented. The reasons for study discontinuation will include AE, withdrawal of consent, non-compliant, lost to follow up, lack of efficacy, disallowed concurrent medication, investigator decision, protocol deviation, and other. Percentages will be calculated using the number of discontinued subjects as the denominator. The number of subjects with COVID-19 related study discontinuation will be identified.

The number and percentage of subjects with any deviation, major deviation, and minor deviation will be presented. The protocol deviations that will be reviewed include informed consent, inclusion/exclusion, test article/study drug instillation and assignment at site, improper protocol procedures at site, site's failure to report serious adverse event (SAE)/AE, visit out of window, subjects' use of prohibited concomitant medication, subjects' failure to follow instructions and other. The number of subjects with COVID-19 related protocol deviations will be identified.

In addition, subject listings for randomization schedule, disposition (for all randomized subjects and for screen failed subjects), protocol deviations, COVID-19 related protocol deviations, and analysis populations will be provided.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables including age, sex, race, and ethnicity will be summarized for mITT population.

Age (years) will be summarized by treatment group and for all subjects, using continuous descriptive statistics. In addition, age will be categorized into four age groups, <18, 18–65, 66–75, >75, and summarized using counts and percentages.

Sex, race, and ethnicity will be summarized by treatment group and for all subjects using discrete descriptive statistics. Subjects who record more than one race will be grouped into a single category denoted as multi-racial.

Subject listings will be provided for demographic variables, childbearing potential for female subjects, and pregnancy tests for female subjects with childbearing potential.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical and ophthalmic history will be obtained at the Screening and Baseline visit and coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

Medical history will be summarized using discrete descriptive statistics and presented by treatment group and for all subjects at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the mITT population. Ocular and non-ocular medical history will be summarized separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. If a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs are listed in alphabetical order; PTs within a SOC are listed in order of descending frequency across all subjects.

Subject listings will be provided for ocular medical history, ocular surgery and laser procedure, and non-ocular medical history.

11.2 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global (B3, March 2020) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next highest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study medication administration and continuing for any period of time following the first administration of study medication or (2) at any time following the first administration of study medication.

Prior and concomitant medications will be summarized using the mITT population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes are listed in alphabetical order and preferred names within an ATC class are listed in order of descending frequency across all subjects.

A subject listing of prior and concomitant medications will be provided.

12. Efficacy Analyses

Efficacy assessments include CCT by ultrasound pachymetry, BCVA using Early Treatment of Diabetic Retinopathy Study (ETDRS) method, tomography (Pentacam®) and V-FUCHS questionnaire that are described in Section 12.1. All collected efficacy measurements will be presented in subject listings. Efficacy analyses for primary, secondary, and exploratory endpoints will be produced in summary tables as specified in Sections 12.2, 12.3, and 12.4.

12.1 Efficacy Assessments

12.1.1 Central Corneal Thickness by Ultrasound Pachymetry

CCT will be measured at all scheduled visits for both eyes at approximately the same time of day ± 60 minutes, always before noon (local time) and always performed before IOP measurements. Every effort should be made to ensure that the same individual performs the measurement and uses the same device for a given subject at each visit. Five consecutive measurements of CCT will be measured for each subject, for each eye at each visit. The mean CCT and SD of the five readings will be recorded, and the mean will be analyzed for efficacy.

12.1.2 Best Corrected Visual Acuity by ETDRS Method

The BCVA assessment using the ETDRS method will be performed at all scheduled visits for both eyes following manifest refraction, and prior to the slit lamp examination. BCVA will be analyzed for efficacy and presented as letter score and logarithm of the minimum angle of resolution (logMAR), calculated as: (85 – letter core)/50.

12.1.3 Biomicroscopy

An external magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated. Examinations of the conjunctiva (hyperemia and edema), cornea (staining, stromal edema, and epithelial edema), anterior chamber (cells and flare), eyelid (erythema and edema), iris/pupil, and lens (lens status and lens opacity for phakic only) will be performed at all scheduled visits for both eyes. The result scoring values are None (0), Mild (+1), Moderate (+2), Severe (+3), and Hypopyon (+4 for anterior chamber cells only). Positive findings will be graded as being clinically significant (CS) and being non-clinically significant (NCS). A “No positive findings” result as collected on the CRF is considered a score value of 0 and NCS. Resolution of corneal edema (a grade of 0 for both stromal edema and epithelial edema) and resolution of epithelial edema (a grade of 0 for epithelial edema) will be identified and analyzed for efficacy.

12.1.4 Tomography (Pentacam®; Selected Sites Only)

Tomography assessments using a Pentacam® will be performed at selected sites only for both eyes at all scheduled visits. Measurements of CCT, superior corneal thickness (SCT), temporal corneal thickness (TCT), nasal corneal thickness (NCT), and inferior corneal thickness (ICT) will be collected and analyzed for efficacy.

12.1.5 V-FUCHS QUESTIONNAIRE

Patient-reported V-FUCHS questionnaire will be administered at the Baseline, Week 4, and Week 8 visits (Wacker 2018). Raw questionnaire data will be processed and be converted to Rasch-based scores including visual acuity factor mean score and SD and glare and diurnal variation (Glare Factor) mean score and SD. Rasch-based factor mean score will be analyzed for efficacy.

12.2 Primary Efficacy Analysis

The primary comparisons in this trial will be within a treatment group on the mean change from baseline CCT by ultrasound pachymetry at Week 4/Day 28 (visit 4) for each of netarsudil QD and BID. The summary will be provided for the study eye. The primary efficacy endpoint change from baseline in CCT will be summarized using continuous descriptive statistics and analyzed primarily using one-sample t-tests by treatment group; comparisons between treatment groups (QD – BID) will be completed using two-sample t-tests. Sensitivity analyses will be completed using Wilcoxon signed-rank tests within a treatment group, Wilcoxon rank sum tests between treatment groups and an analysis of covariance (ANCOVA) model with terms for baseline CCT value and treatment.

The mean change from baseline in CCT for each treatment group along with 2-sided p-values and 90% and 95% CIs around the change from baseline within each treatment group for the mean from one-sample t-test will be presented. The mean difference in change from baseline between treatment groups along with 2-sided p-values and 90% and 95% CIs for the mean differences between treatment groups from two-sample t-test will be presented. P-values from Wilcoxon signed-rank test within each treatment group, and Wilcoxon rank-sum test between treatment groups will be presented. The least squares (LS) mean for each treatment group along with 2-sided p-values and 2-sided 90% and 95% CIs around the change from baseline within each treatment group will be presented from the ANCOVA model. Comparisons between treatment groups on the change from baseline in CCT will also be made including the LS mean difference and the corresponding 2-sided p-values and 90% and 95% CIs.

Example SAS® code for the primary efficacy analysis on change from baseline (CHG_CCT):

One-sample t-test within a treatment:

```
proc ttest data = indata;
  var CHG_CCT;
  by treatment;
run;
```

Wilcoxon signed-rank test within a treatment:

```
proc univariate data = indata;
   var CHG_CCT;
   by treatment;
run;
```

Two-sample t-test for comparison between treatments:

```
proc ttest data = indata;
  class treatment;
  var CHG_CCT;
```

```
run;
```

Wilcoxon rank sum test for comparison between treatments:

```
proc npar1way data = indata wilcoxon;
  class treatment;
  var CHG_CCT;
run;
```

ANCOVA model for modeling the treatment effect:

```
proc mixed data = indata;
  class treatment;
  model CHG_CCT = treatment baseline_CCT;
  lsmeans treatment / cl pdiff;
run;
```

The primary analysis will use the mITT population with available data per subject at eye level (ie, ODO). Robustness analyses (details provided in in Section 8.2.1) will also be presented based on the MI methodology under different assumptions of missingness and intercurrent events (where missing data or withdrawal due to lack of efficacy or AEs will be imputed using FCS regression method and missing data for all other reasons will be imputed using worst within subject observation prior to the intercurrent event).

Missing data handling using MI under different assumptions of missingness and intercurrent events are described in steps along with example SAS® code for the primary analyses one-sample t-test and two-sample t-test.

Step 1: Imputation step

The following SAS® code will be employed to produce twenty "complete" (imputed) datasets using MI FCS methodology:

```
proc mi data = indata (where (seye = eye)) seed = 999 out = outdata1
nimpute = 20;
  class treatment;
  var treatment baseline_CCT aval2 aval4 aval8;
  fcs;
run;
```

where

- `indata` is the name of the input dataset
- `outdata1` is the name of the output dataset;
- `treatment` is the treatment group variable;
- `baseline_CCT` is the baseline mean CCT value; and
- `aval2`, `aval4`, and `aval8` are the mean CCT values at Week 2, Week 4, and Week 8, respectively.

Step 2. Finalization of imputed datasets from MI under different assumptions of missingness and intercurrent events

After obtaining twenty "complete" datasets, for subjects with withdrawal due to lack of efficacy or AEs, the imputed missing values in each dataset will be replaced by the worst within subject observation from post-baseline visits (including both scheduled and unscheduled visits) prior to the intercurrent event. After replacement, change from baseline mean CCT (CHG_CCT) will be calculated all post-baseline visits in each dataset.

Step 3. Analysis step

For each of the "complete" datasets from step 2, the following SAS® code will be employed to run the primary analyses.

One-sample t-test

```
proc sort data = outdata1;
  by visit treatment _imputation_;
run;
ods output statistics = outdata2;
proc ttest data = outdata1 alpha = 0.05;
  by visit treatment _imputation_;
  var chg_cct;
run;
```

Two-sample t-test

```
<data outdata1;
  set outdata1;
  if treatment = "Netarsudil QD" then treatment1 = "1";
  else treatment1 = "2";
  treatment = treatment1;
  drop treatment1;
run;>
proc sort data = outdata1;
  by visit _imputation_;
run;
ods output statistics = outdata2;
proc ttest data = outdata1 alpha = 0.05;
  by visit _imputation_;
  class treatment;
  var chg_cct;
run;
```

Step 4. Pooling step

SAS® procedure MIANALYZE will then be used to combine results from step 3 across imputations to obtain final estimates for inference.

One-sample t-test

```
ods output ParameterEstimates = outdata3;
proc mianalyze data = outdata2;
  by visit treatment;
  modeleffects mean;
  stderr stderr;
run;
```

Two-sample t-test

```
proc sort data = outdata2;
  by visit class;
run;
ods output ParameterEstimates = outdata3;
proc mianalyze data = outdata2;
  by visit class;
  modeleffects mean;
  stderr stderr;
run;
```

Additional example SAS® code to be employed in MI step 3 and 4 for other sensitivity analyses for the primary efficacy endpoints.

ANCOVA model

```
<data outdata11;
  set outdata1;
  if treatment = "Netarsudil QD" then treatment1 = "1";
  else treatment1 = "2";
  treatment = treatment1;
  drop treatment1;
run;>
proc sort data = outdata11;
  by visit _imputation_;
run;
ods output lsmeans = lsm diffs = diff;
proc mixed data = outdata11;
  by visit _imputation_;
  class treatment;
  model CHG_CCT = treatment baseline_CCT / solution ;
  lsmeans treatment / pdiff cl alpha = 0.05;
  lsmeans treatment / pdiff cl alpha = 0.1;
run;

proc sort data = lsm;
  by visit treatment alpha;
run;
ods output ParameterEstimates = outdata2;
proc mianalyze data = lsm;
  by visit treatment alpha;
  modeleffects estimate;
  stderr stderr;
run;

proc sort data = diff;
  by visit treatment alpha;
run;
ods output ParameterEstimates = outdata3;
proc mianalyze data = diff;
  by visit treatment alpha;
  modeleffects estimate;
  stderr stderr;
run;
```

Wilcoxon signed-rank test

```
**Read the imputed dataset for study eye;
data eff2;
  set outdata1;
```

```
  chg=aval-baseline;
  achg=abs(chg);
run;

**ignore zero values;
proc rank data=eff2 (where=(chg ne 0))  ties=mean out=rank;
  by _imputation_ visit treatment;
  var achg;
  ranks rchg;
run;

proc sort data=rank;
  by _imputation_ visit treatment chg;
run;
** distinguish negative and positive values;
data sign;
  set rank;
  by _imputation_ visit treatment chg;
  if chg <0 then type="Neg";
  else if chg >0 then type="Pos";
run;

proc sort data=sign;
  by _imputation_ visit treatment type rchg;
run;
** calculate sum of positive and negative ranks separately;
data sign2;
  set sign;
  by  _imputation_ visit treatment type rchg;
  if first.type then cum_sum=rchg;
  else cum_sum+rchg;
  if last.type;
  keep _imputation_ visit treatment type cum_sum;
run;

**Calculate Wilcoxon location parameter;
proc transpose data=sign2 out=sign3;
  by  _imputation_ visit treatment;
  var cum_sum;
  id type;
run;

** Calculate number of observations for each treatment;
data sign4;
  set sign3;
  pos1=pos;
  neg1=neg;
  if pos= . then pos1 = 0;
  if neg= . then neg1 = 0;
  pos = pos1;
  neg = neg1;
  stat=abs(neg-pos)/2;
  keep _imputation_ visit treatment stat;
  drop neg1 pos1;
run;

proc sort data=sign4;
```

```
  by _imputation_;
run;
** Calculate number of observations for each treatment;
Proc freq data=rank;
  tables visit*treatment*achg/out=counts;
  tables visit*treatment/out=freq (rename=(count=n));
  by _imputation_;
run;

data cfactor;
  set counts (where=(count>1));
  ci=count*(count-1)*(count+1);
run;
** calculate correction factor;
data cfactor2;
  set cfactor;
  by _imputation_ visit treatment;
  if first._imputation_ then cum_c=ci;
  else cum_c+ci;
  if last.treatment;
run;

** Perform Wilcoxon test;
data final;
  merge freq (keep=_imputation_ visit treatment n)
  cfactor2(keep=_imputation_  visit treatment cum_c) sign4;
  by _imputation_ visit treatment;
  v=(n*(n+1)*(2*n+1)-cum_c/2)/24;
  tderr=sqrt((n*v-stat**2)/(n-1));
  est=stat/stderr;
  p=2*(1-probt(test,n-1));
run;

**verify location parameter calculated manually is same as the one from
  SAS procedure;
ods output  TestsForLocation=location(where=(test="Signed Rank"));
proc univariate data = eff2;
  var CHG;
  by _imputation_ visit treatment;
run;
proc sort data=final;
  by visit treatment;
run;

**combine all results;
ods output ParameterEstimates = outdata3;
proc mianalyze data = final;
  by visit treatment;
  modeleffects stat;
  stderr stderr;
run;
```

Wilcoxon rank sum test

```
<data outdata1;
  set outdata1;
  if treatment = “Netarsudil QD” then treatment1 = “1”;
```

```
    else treatment1 = "2";
    treatment = treatment1;
    drop treatment1;
run;>
proc sort data = outdata1;
    by visit _imputation_;
run;
ods output WilcoxonScores = outdata2 (where=(class="1"));
proc npar1way data = outdata1 wilcoxon;
    by visit _imputation_;
    class treatment;
    var chg_cct;
run;

data outdata2;
    set outdata2;
    by visit _imputation_;
    mean = (sumofscores - expectedsum);
    if mean > 0 then mean1 = mean - 0.5;
    else mean1 = mean + 0.5;
    mean = mean1;
    stderr = stddevofsum;
    drop mean1;
run;
ods output ParameterEstimates = outdata3;
proc mianalyze data = outdata2;
    by visit;
    modeleffects mean;
    stderr stderr;
run;
```

Robustness analysis will also be performed on mITT population using LOCF imputation as well as using PP population ODO (see Section 8.2.1 for additional imputation details).

12.3 Secondary Efficacy Analyses

The secondary efficacy analyses will be conducted on the mITT population ODO. Descriptive statistics will be presented by treatment group for both study eye and qualified fellow eye. Summarization and analysis of the mean change from baseline in BCVA at Weeks 4 and 8 and mean change from baseline in mean CCT by ultrasound pachymetry at Week 8 will be completed using a similar strategy as for the primary endpoints described in Section 12.2.

Testing of the proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Weeks 4 and 8 (separately) and testing of the proportion of subjects with complete resolution of corneal edema at Weeks 4 and 8 (separately), will be completed using logistic regression with fixed effects of treatment and corresponding baseline measure. The adjusted odds ratios, marginal proportion of each treatment group, and difference in marginal proportions along with corresponding two-sided 95% CIs and p-values will be presented. When none of the subjects in both treatment groups achieve a gain of 3 lines in BCVA, no inferential statistics for the testing of the proportions will be produced. Treatment comparisons will also be made using Pearson's chi-squared test or Fisher's exact test if any of the cell counts are less than five as a sensitivity analysis.

Example SAS® code for analyzing categorical outcomes ("Y" when desired criterion is met, "N" if not)

Logistic regression for modeling the treatments effect on outcome:

```
proc logistic data = indata descending alpha = 0.05;
  class treatment (ref = 'BID') / param=glm;
  model  outcome = treatment baseline_BCVA;
  lsmeans treatment / diff oddsratio cl exp;
  ods output ParameterEstimates = pe;
run;
```

In the logistic model for the probability of outcome = Y, the following call to "Margins" (a SAS macro) estimates the treatment predictive margins and their difference (the margin effect) and reverses the direction of the difference (QD – BID rather than default BID – QD):

```
%Margins(data = indata,
         class = treatment,
         response = outcome,
         roptions = event='Y',
         model = treatment baseline_BCVA,
         dist = binomial,
         margins = treatment,
         options = cl diff reverse)
```

Chi-Squared test / Fisher's Exact test for comparison between treatments:

```
proc freq data=indata;
  tables outcome*treatment / chisq fisher;
  weight count/zeros;
run;
```

Robustness analysis for secondary efficacy endpoints will be performed using PP population ODO. In the summaries using PP population ODO, subjects whose dosing regimen was increased from QD to BID starting from Week 4 will be reported separately from the subjects who did not change regimens throughout the study duration under a group called "Netarsudil QD to BID" for the Week 8 visit. The baseline value for these subjects will remain the same. At Week 8 visit, comparisons for efficacy endpoints between subjects treated under QD and subjects who switched from QD to BID will be performed as appropriate. However, a high degree of caution should be exerted when interpreting the results as sample sizes might be smaller.

12.4 Exploratory Efficacy Analyses

The exploratory efficacy analyses will be conducted in the mITT population with available data per subject. Descriptive statistics will be presented by treatment group and for study eye and qualified fellow eye. Testing of the proportion of subjects who gained ≥15 letters (3 lines) in BCVA at Week 2, testing of the proportion of subjects who gained ≥10 letters (2 lines) and ≥5 letters (1 line) in BCVA at all scheduled visits (ie, Weeks 2, 4, and 8), and testing of the proportion of subjects with complete resolution of epithelial edema (a grade 0 for epithelial edema assessed by biomicroscopy) at all scheduled visits (ie, Weeks 2, 4, and 8) for those who have epithelial edema at Baseline visit (a grade > 1 for epithelial edema assessed by biomicroscopy) will be completed in a similar manner as the secondary endpoints. If there

are less than 5 subjects who have epithelial edema at Baseline visit within each treatment group, no inferential statistics will be produced. Summarization and analysis of the mean change from baseline in corneal thickness including CCT, SCT, TCT, NCT, and ICT as assessed by Pentacam® at all scheduled visits (ie, Weeks 2, 4, and 8), and mean change from baseline in V-FUCHS factor score including glare and diurnal variation (Glare Factor) mean score and visual acuity factor mean score at all scheduled visits (ie, Weeks 2, 4, and 8) will be completed using a similar strategy as for the continuous secondary endpoints.

Robust analysis will be performed on the exploratory efficacy endpoints, the proportion of subjects who gained ≥15 letters [3 lines], ≥10 letters [2 lines], or ≥5 letters [1 line] in BCVA using PP population ODO in similar manner as secondary endpoints. No imputation will be performed on other exploratory efficacy endpoints.

12.5 Ad-hoc Efficacy Analyses

If PP population is not exactly the same as mITT population, ad-hoc efficacy tables using mITT population ODO reported as treated may be produced in the same format as efficacy tables using PP population ODO. In the ad-hoc tables, subjects whose dosing regimen was increased from QD to BID starting from Week 4 will be reported under the group “Netarsudil QD to BID” at Week 8 visit. ” If PP population is exactly the same as mITT population, no additional analyses will be performed.

13. Safety Analyses

All safety analyses will be conducted using the safety population. For visit-based safety summaries (BCVA, biomicroscopy, IOP, and vital signs), subjects who switched dose group from QD to BID starting from Week 4 will be reported under treatment group BID at Week 8 visit. The baseline value for these subjects will remain the same.

13.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period starts from the time the subject signs the informed consent until the subject’s last study visit. All AEs will be coded using MedDRA Version 23.0.

A treatment-emergent adverse event (TEAE) is defined as any event that occurs or worsens on or after the first dose of study medication. Adverse events recorded on the eCRF which began prior to treatment and remained unchanged or improved will not be included in the summary tables but will be included in the AE data listings. For all AE summary tables, a third group other than QD and BID dose group will be presented to capture the AEs for those subjects who switched the treatment dose from QD to BID starting from Week

4. The AE that began on or after the switch will be considered treatment emergent to the BID treatment; The AE that began before the switch and continued after the switch will be considered treatment emergent to the QD treatment only; if the AE worsened on or after the switch, the new AE (one with higher severity) would become a TEAE for the BID dose and the original AE would be treatment emergent to the QD dose.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one TEAE, by treatment group. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye and fellow eye separately with TEAEs occurred on both eyes counted towards study eye once and fellow eye once) or non-ocular, TEAEs by maximum severity, TEAEs by maximum relationship to study medication, TEAE by expectedness, serious TEAEs, TEAEs leading to study medication discontinuation, TEAEs leading to death.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE by treatment group. Non-ocular TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject level by SOC and PT. Ocular TEAEs will be summarized similarly at the subject level for study eyes and fellow eyes, separately. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOCs and PTs within each SOC will be listed in ascending alphabetical order.

Separate summaries will be provided for the following categories of AEs:

- Ocular TEAEs in the study eye and fellow eye
- Non-ocular TEAEs
- Ocular TEAEs related or possibly related to study medication
- Non-Ocular TEAEs related or possibly related to study medication
- Serious TEAEs
- Serious TEAEs related or possibly related to study medication

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

- Mild: Present and noticeable, but not distressing, and no disruption of normal daily activities.
- Moderate: Bothersome, discomfort sufficient to possibly reduce or affect normal daily activity.
- Severe: Incapacitating, with inability to work or perform normal daily activity.

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from moderate to severe. In both cases, the start and stop dates should be recorded.

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- **Not Related:** The event is clearly related to other factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.
- **Unlikely Related:** The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.
- **Possibly Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.
- **Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

Summaries of TEAEs by maximum severity will be presented for ocular TEAEs and non-ocular TEAEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximum severity.

Individual subject listing will be provided for all AEs, SAEs, AEs leading to study medication discontinuation, AEs leading to death, AEs related to COVID-19 , and SAEs related to COVID-19.

13.2 Best Corrected Visual Acuity

BCVA testing using ETDRS will be performed at all scheduled visits for both eyes. BCVA will be presented as letter score and logMAR. The observed and change from baseline values will be summarized for each eye (study eye and fellow eye) using continuous summary statistics by visit for each treatment group. A subject listing of visual acuity will also be provided.

13.3 Biomicroscopy

An external magnification and biomicroscopy will be performed using a slit-lamp at all scheduled visits for both eyes as described in Section 12.1.3.

A shift table of score values will also be provided comparing each follow-up visit to the baseline. Additionally, discrete summaries will be provided by region, finding, visit, and eye (study eye and fellow eye) for the number of subjects with at least one severity grade increase from baseline and for the number of subjects judged to be clinically significant by the Investigator. A subject listing of biomicroscopy will also be provided.

13.4 Intraocular Pressure

IOP will be collected at all scheduled visits for both eyes using an Applanation Tonometer. Two or three results (when IOP difference between test 1 and test 2 is more than 2 mmHg in one or both eyes) will be collected for both eyes. Mean IOP (mean when two results are collected or median IOP when three results are collected) will be calculated and summarized. The mean IOP and change from baseline mean IOP will be summarized for each eye (study eye and fellow eye) using continuous summary statistics by visit for each treatment group. A subject listing of IOP will also be provided.

13.5 Ophthalmoscopy

A dilated ophthalmoscopy at Screening visit and Week 8 and an undilated ophthalmoscopy at Baseline visit and Weeks 2 and 4 of the retina, macula, choroid, optic nerve, and vitreous humour will be performed. The results will be graded as normal, abnormal CS, or abnormal NCS.

A shift table will also be provided comparing each follow-up visit to baseline. A subject listing of ophthalmoscopy will also be provided.

13.6 Vital Signs

Vital signs (heart rate, systolic sitting blood pressure, diastolic sitting blood pressure) will be collected at Screening, Baseline and Week 8. The results will be summarized by visit for each treatment group, using continuous summary statistics, including change from baseline. A subject listing of the vital signs results will also be provided.

14. Interim Analyses

No interim analysis is planned.

15. Changes from Protocol-Stated Analyses

1. Assessment window mapping will be applied for missing values at scheduled visits in the table summaries using ODO.
2. Multiple imputations by FCS regression method instead of protocol-stated monotone regression will be employed to handle missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events. FCS is a valid statistical method that has greater flexibility than monotone regression method.
3. Additional exploratory efficacy endpoints are added to look at proportion of subjects with complete resolution of epithelial edema at week 4 and 8 among subjects who have epithelial edema at baseline.

16. References

Wacker K, Baratz KH, Bourne WM, Patel SV. Patient-Reported Visual Disability in Fuchs' Endothelial Corneal Dystrophy Measured by the Visual Function and Corneal Health Status Instrument. Ophthalmology. 2018;125(12):1854-1861.

17. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

18. Tables

Tables that will be included in the topline delivery are shown in boldface font.

Table Number	Title	Population
Table 14.1.1	**Subject Disposition**	
Table 14.1.2	**Demographics**	**Modified Intent-to-Treat Population**
Table 14.1.3.1	Ocular Medical History	Modified Intent-to-Treat Population
Table 14.1.3.2	Non-Ocular Medical History	Modified Intent-to-Treat Population
Table 14.1.4.1	Ocular Prior and Concomitant Medications	Modified Intent-to-Treat Population
Table 14.1.4.2	Non-Ocular Prior and Concomitant Medications	Modified Intent-to-Treat Population
Table 14.2.1.1	**Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry at Week 4 (Study Eye)**	**Modified Intent-to-Treat Population (Observed Data Only)**
Table 14.2.1.2	Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry at Week 4 (Study Eye)	Modified Intent-to-Treat Population (Multiple Imputation)
Table 14.2.1.3	Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry at Week 4 (Study Eye)	Modified Intent-to-Treat Population (LOCF)
Table 14.2.1.4	Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry at Week 4 (Study Eye)	Per Protocol Population (Observed Data Only)
Table 14.2.1.5	**Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry by Visit**	**Modified Intent-to-Treat Population (Observed Data Only)**
Table 14.2.1.6	Change from Baseline in Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry by Visit	Per Protocol Population (Observed Data Only)
Table 14.2.1.7	**Central Corneal Thickness (µm) as Assessed by Ultrasound Pachymetry by Visit**	**Modified Intent-to-Treat Population (Observed Data Only)**

Table 14.2.2.1	**Change from Baseline in Best Corrected Visual Acuity using ETDRS Method by Visit**	**Modified Intent-to-Treat Population (Observed Data Only)**
Table 14.2.2.2	Change from Baseline in Best Corrected Visual Acuity using ETDRS Method by Visit	Per Protocol Population (Observed Data Only)
Table 14.2.2.3	**Best Corrected Visual Acuity using ETDRS Method by Visit**	**Modified Intent-to-Treat Population (Observed Data Only)**
Table 14.2.3.1.1	**Proportion of Subjects Who Gained 15 Letters or More in BCVA using ETDRS Method by Visit**	**Modified Intent-to-Treat Population (Observed Data Only)**
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19. Listings

Listing Number	Title	Population
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20. Figures

Figure Number	Title	Population
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Figure 14.2.2	Line Plot of Mean Change from Baseline in BCVA Assessed by ETDRS (Study Eye)	Modified Intent-to-Treat Population