PROTOCOL 101090401IN

Protocol Title: A Phase IIa, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of STN1010904 Ophthalmic Suspension 0.03% and [redacted] Compared with Vehicle in Subjects with Fuchs Endothelial Corneal Dystrophy (FECD) – PHANTOM Study

Protocol Number: 101090401IN

Compound: STN1010904

Study Phase: Phase IIa

Sponsor Name: SANTEN INCORPORATED

Legal Registered Address: 6401 Hollis Street, Suite 125, Emeryville, CA 94608

Regulatory Agency Identifier Number: IND Number: 146866

Protocol Version/ Date: Amendment 1: 24MAY2022

I have read the 101090401IN protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form (eCRF) indicates that the data there in has been reviewed and accepted by me as the Investigator.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

Address: _____

_____

Phone: _____

This study will be conducted in accordance with applicable Good Clinical Practices (GCP), United States Code of Federal Regulations, International Conference on Harmonization (ICH) guidelines, and the Declaration of Helsinki.



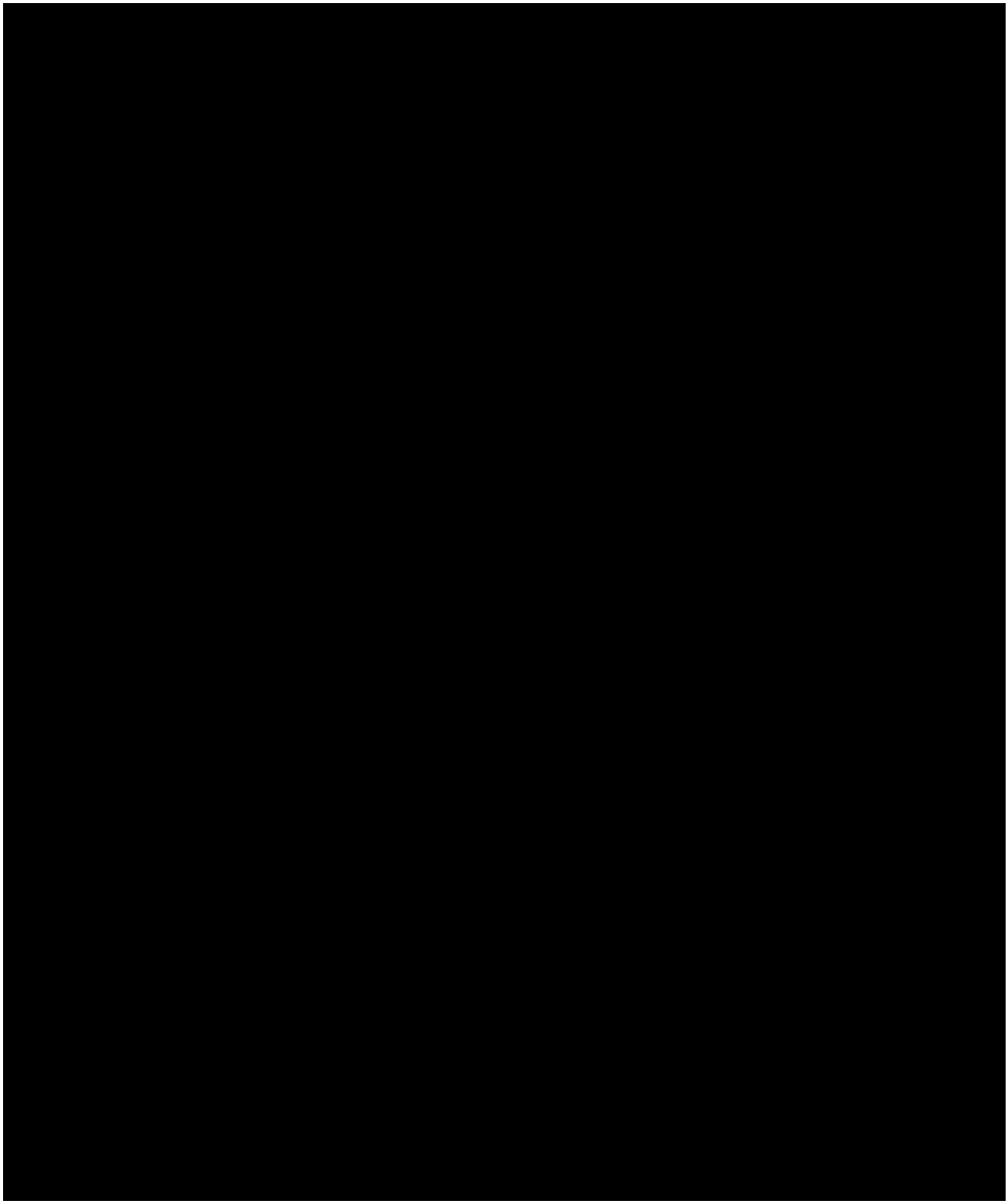




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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:
Santen Inc.
6401 Hollis Street, Suite 125
Emeryville, CA 94608, USA

Name of Investigational Product: STN1010904 Ophthalmic Suspension

Name of Active Ingredient: Sirolimus (INN)

Title of Study: A Phase IIa, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of STN1010904 Ophthalmic Suspension 0.03% and [redacted] Compared with Vehicle in Subjects with Fuchs Endothelial Corneal Dystrophy (FECD)

Protocol Number: 101090401IN

Number of Subjects (planned): Approximately 80 subjects with FECD.

Number of Sites (planned): Approximately 10 sites in the United States, 1 site in France, 2 sites in India

Study Period: Approximately 37 months	**Phase of Development**: Phase IIa

Study objectives and endpoints:

Study Objectives	**Corresponding Study Endpoints**
Primary Efficacy Objective: To assess the efficacy of two concentrations of STN1010904 ophthalmic suspension (0.03%, and [redacted] dosing when compared to Placebo in subjects diagnosed with FECD	**Primary Efficacy Endpoints:** • Change from baseline in best corrected visual acuity (BCVA) with contrast level of 100% at Month 18 • Change from baseline in BCVA with contrast level of 10% at Month 18 • Change from baseline in contrast sensitivity with glare light at Month 18

Secondary Efficacy Objective: To assess the dose response of STN1010904 ophthalmic suspension.	**Secondary Efficacy Endpoints:** • Best corrected visual acuity (BCVA) with contrast level of 100% at all post-baseline visits • BCVA with contrast level of 10% at all post-baseline visits • Contrast sensitivity with glare light at all post-baseline visits • Contrast sensitivity without glare light at all post-baseline visits • Change and percent change from baseline in BCVA with contrast level of 100% at all post-baseline visits • Change and percent change from baseline in BCVA with contrast level of 10% at all post-baseline visits • Change and percent change from baseline in contrast sensitivity with glare light at all post-baseline visits • Change and percent change from baseline in contrast sensitivity without glare light at all post-baseline visits • Change and percent change from baseline in central corneal thickness at all post-baseline visits. • Change and percent change from baseline in endothelial cell density at all post-baseline visits • Change and percent change in Guttae formation (Modified Krachmer scale) at all post-baseline visits
Safety Objective: • To assess the safety of two concentrations of STN1010904 ophthalmic suspension (0.03%, and [redacted] dosing when o in subjects diagnosed with FECD	**Safety Endpoint:** • Safety of DE-109D will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), and laboratory tests (serum chemistry, hematology, and urinalysis).
Exploratory Objective:	**Exploratory Endpoint:** • V-FUCHS questionnaire at all post-baseline visits

Duration of Treatment: 18 months

Methodology:

This is a Phase IIa, randomized, double-masked, placebo-controlled, parallel-group study assessing the efficacy and safety of STN1010904 ophthalmic suspension in subjects with FECD.

Subjects diagnosed with FECD who meet all eligibility criteria at Visit 1 (Screening) will be randomized at Visit 2 (Baseline) to receive treatment for 18 months.

Approximately 80 subjects with FECD who meet all eligibility criteria will be randomized in a 3:3:2 ratio to one of three treatment arms:

- 0.03% STN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min)
- [redacted] STN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min)
- Placebo (vehicle) BID (8:00 & 20:00 ± 60 min)

Study Design: (Refer to Figure 1)

This study will consist of a Screening Period of up to 15 days and an 18-month Double-Masked Treatment Period.

At the Visit 1 (Screening), subjects will be screened against the inclusion and exclusion criteria and if subject meets all eligibility criteria, subjects will proceed to Visit 2 (Baseline).

The study eye will be the eye that qualifies per eligibility criteria at Visit 1. If both eyes meet the eligibility criteria, the right eye will be designated as the study eye.

Both eyes should be treated with the study medication for the duration of the study if they both have signs of FECD, even if only one eye is eligible per inclusion criteria. If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication.

Double-Masked Treatment Period (18 months):

At Visit 2 (Baseline), approximately 80 eligible subjects will be randomized to receive 0.03% STN1010904 ophthalmic suspension BID or [redacted] TN1010904 ophthalmic suspension BID or Placebo (vehicle) BID in a 3:3:2 ratio. Subjects will be treated for 18 months with scheduled visits at Visits 2 (Baseline), Visit 3 (Month 1), Visit 4 (Month 3), Visit 5 (Month 6), Visit 6 (Month 9), Visit 7 (Month 12), Visit 8 (Month 15) and Visit 9 (Month 18).

At Visit 2 (Baseline), subjects will administer their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (± 60 min). The next day, subjects will subsequently dose with their assigned study medication at 8:00 & 20:00 (± 60 min) and continue dosing through Visit 9 (Month 18).

Pharmacogenomics/Genomics:

Subjects who consent to the optional pharmacogenomics/genomics (PGx) laboratory study will provide a blood sample for future testing. This sample will be collected at Visit 2

(Baseline). The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

Santen Steering Committee:

An internal Santen steering committee (SSC) whose members will not be participating in the 101090401IN study conduct will serve as an advisory board to the Santen senior management team. The SSC will review the data when [redacted] of patients have completed [redacted] visit and make recommendations based on interim data; unmasked data will only be reviewed in closed SSC sessions without participation of Santen personnel involved in the clinical study. The organization, responsibilities, and procedures of the SSC will be specified in a governing charter.

Masking:

This is a double-masked study. The subjects, Investigators, Examiners, and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member at the investigator site who is not the Investigator or Examiner will dispense and collect study medication(s) and will query about dosing compliance.

Subjects will be instructed not to show the [redacted] or discuss the eye drops to either the Investigator or the Examiner or other study subjects.

Each eligible subject will receive a numbered study medication kit assigned by Central randomization via Interactive Response Technology at Visits 2 (Baseline), Visit 4 (Month 3), Visit 5 (Month 6), Visit 6 (Month 9), Visit 7 (Month 12), and Visit 8 (Month 15).

Inclusion Criteria:

Subjects are eligible to be included in the study only if all the following criteria are met at Visit 1 (Screening):

1. Male or female, from 30 to 75 years of age, diagnosed with FECD.
2. Provide signed informed consent prior to any study procedures being performed.
3. Best-corrected visual acuity (BCVA) of +0.2 LogMAR or better (equivalent to ≥ 75 ETDRS letters, or at least Snellen 20/32) in the study eye as measured using an ETDRS chart.
4. Grade 3-5 of the Modified Krachmer scale in the study eye.
5. At least two out of three tomographic features are observed by Pentacam™, evaluated by the Investigator in the study eye:

Tomographic Features

Parameter	Definition
Loss of parallel isopachs	Any single isopach not being almost circular/oval or parallel to adjacent isopachs within the central 4 mm of the cornea (relative to the pupil center)

Displacement of the thinnest point of the cornea	Being located outside of the inferotemporal quadrant (centered at the pupil center) or more than 1 mm from the pupil center in any quadrant.
Focal posterior corneal depression	Any isolated area of depression (negative elevation relative to a sphere with best fit zone of 8 mm with float function) within the central 4 mm of the cornea (relative to the pupil center)

6. Endothelial cells are visible >50% of area in at least one image obtained by noncontact specular microscopy in the central or paracentral-peripheral area in the study eye.
7. If a subject is a female of childbearing potential (*i.e.*, not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of surgery]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
    - Abstinence
    - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
    - Placement of a copper-containing IUD
    - Condom with spermicidal foam/gel/film/cream/suppository
8. The male partner of the female subject of childbearing potential should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study informed consent form (ICF) and beginning screening), or other contraception deemed adequate by the investigator during the study.
9. Male subjects, with a female partner of childbearing potential, should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study ICF), or other contraception deemed adequate by the investigator during the study.
10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Exclusion Criteria:

Subjects are excluded from the study if any of the following criteria apply:

Ocular Conditions:

1. Monocular vision, or vision worse than +0.7 LogMAR (equivalent to < 50 ETDRS letters, or worse than Snellen 20/100) in the fellow eye;

2. No guttae in either eye (evaluated by slit-lamp and specular microscope).
3. Clinically evident stromal and/or epithelial edema in the study eye (evaluated by slit-lamp microscope).
4. Descemet folds in the study eye (evaluated by slit-lamp microscope).
5. Central corneal thickness is 660μm or more in the study eye (evaluated by Scheimpflug image).
6. Moderate/severe cataract in the study-eye (mild cataract or pseudophakic eye is eligible for enrolment).
7. Evidence of any other ocular disease other than FECD in the study eye that may confound the outcome of the study (*e.g.*, active diabetic retinopathy, posterior uveitis, age-related macular degeneration or any other maculopathy, severe myopia >10D, pterygium, recurrent corneal erosion syndrome).
8. Any ocular surgery for FECD (*e.g.*, penetrating keratoplasty (PKP), Descemet stripping endothelial keratoplasty (DSEK), Descemet membrane endothelial keratoplasty (DMEK), Descemet stripping automated endothelial keratoplasty (DSAEK), Descemet stripping only (DSO) in the study eye.
9. Cataract surgery or any kind of ocular surgery in the study eye within 6 months prior to Visit 1.
10. Past history of filtering surgery for glaucoma in either eye (patients who underwent Minimally Invasive Glaucoma Surgery (MIGS) more than 6 months prior to Visit 1 are eligible for enrolment).
11. Laser treatment for glaucoma within 6 months prior to Visit 1 in the study eye.
12. Need for ocular surgery or ocular laser treatment in either eye throughout the study.
13. Media opacity that would affect contrast sensitivity in the study eye.
14. Presence of any active inflammation, or infection of the eye and/or eyelids in either eye.
15. History of herpetic infection in either eye or adnexa.
16. History of ophthalmic malignancy.

Concomitant Medications:

17. Use of Rho-Associated kinase (ROCK) inhibitor eye drop in the study eye within 4 weeks prior to Visit 1 and during the course of the study.
18. Use of CYP3A strong inhibitors during the course of the study.
19. Use of topical Cyclosporin within 3 months prior to Visit 1 and during the course of the study.
20. Use of Xiidra within 1 month prior to Visit 1 and during the course of the study

Non-Ocular Conditions:

21. Allergy or hypersensitivity to study medication product, fluorescein dye, or other study related procedures/medications.
22. Current or planned participation in any other clinical study involving an investigational product or device within 4 weeks prior to Visit 1 or at any time during this study.
23. History of any disease or condition that in the opinion of the study investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (*e.g.*, uncontrolled cardiovascular disease etc.).
24. Immunosuppressive therapy (*e.g.*, methotrexate, cyclosporine, cyclophosphamide, chlorambucil, mycophenolate mofetil, tacrolimus or azathioprine) other than prednisone or other corticosteroids within 4 weeks prior to Visit 1 or at any time during this study.
25. Any recent systemic infection within 4 weeks prior to Visit 1.
26. Known to be immunocompromised.
27. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
28. Malignancy in remission for less than 5 years prior to study participation (except basal cell or squamous cell skin cancer, or treated melanoma of the skin less than 24 months since last treatment).
29. Females who are pregnant or lactating and females of child-bearing potential who are not willing to use one of the acceptable contraceptive methods listed in inclusion #7 during the study and for 4 weeks following the last dose.
30. Any decision by the Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

Investigational product, dosage, and mode of administration:

Subjects will be randomly assigned 3:3:2 ratio to one of three treatment arms to receive either: 0.03% STN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min), STN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min), or placebo (vehicle) BID (8:00 & 20:00 ± 60 min) as described below:

Investigational Product:

0.03% STN1010904 ophthalmic suspension contains 0.03% STN1010904. Other ingredients include [redacted]

TN1010904 ophthalmic suspension contains [redacted] STN1010904. Other ingredients [redacted]

Vehicle:

The vehicle is identical to the investigational product but does not contain the active ingredient STN1010904.

Route of Administration of Investigational Product: Topical ocular

Duration of the Study: The study duration consists of an 18-month Double-Masked Treatment Period.

Statistical Methods:

The sample size of this study is not based on any statistical power calculation due to the exploratory nature of the study and limited knowledge of the treatment effect of study medications.

An analysis using a linear mixed-effect model for repeated measures (MMRM) will be used for each primary endpoint. From this model, least square means, standard errors, treatment differences in least square means, and 95% confidence intervals will be reported. For inferential analysis of each endpoint, a MMRM model-based t-test will be performed for the treatment difference at Month 18 visit and the corresponding p-value will be reported. To control the overall Type I error rate associated with the primary endpoints' hypothesis testing, the Hochberg procedure will be used, and the statistical significance will be evaluated with the adjusted p-values.

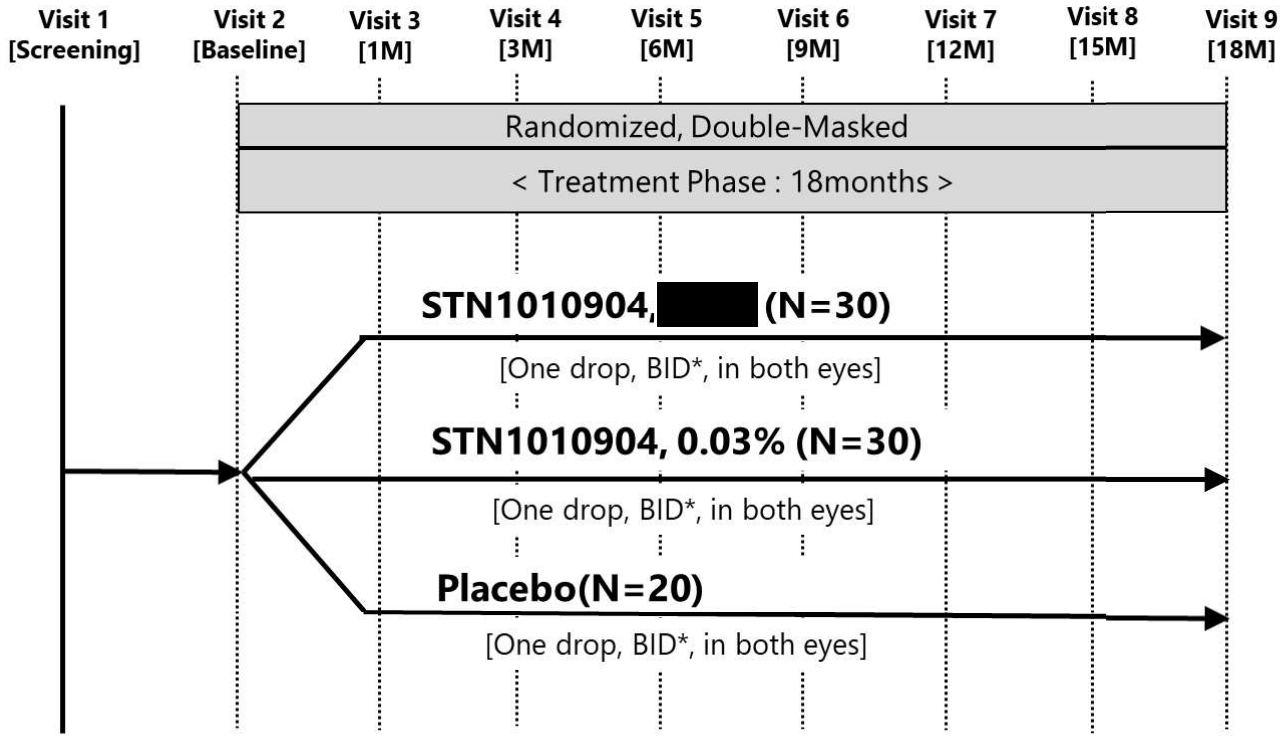
The superiority of DE-109D over placebo based on a specific primary endpoint is established if the difference between treatment and placebo group is statistically significant. The efficacy of DE-109D is established if at least one of the three primary endpoint shows its superiority of DE-109D over the placebo.

A mixed-effect model for repeated measures (MMRM) will be carried on observed cases up to Month 18 for each of the secondary endpoints. At each visit, least square mean of each treatment arm and 95% confidence interval for the difference in least square means between DE-109D arm and placebo arm will be estimated. Due to the exploratory nature of the study, no formal hypothesis testing will be performed on secondary endpoints. Two-sided 95% confidence intervals and nominal p-values may be reported for them.

An interim analysis is planned when the first [redacted] subjects (*i.e.* [redacted] of randomized subjects) complete their [redacted] visit. Two goals for the interim analysis are to assess for futility and to access for efficacy. The alpha splitting scheme to control the overall Type I error for both interim and final analysis will be specified in the SAP.

1.2. Schema

Figure 1: Schema



* Both eyes should be treated with the study medication for the duration of the study if they both have signs of FECD, even if only one eye is eligible per inclusion criteria. If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication

1.3. Schedule of Activities (SoA)

Please follow the Table 2 "Schedule of Activities" below for subjects who have both eyes with signs of FECD and are receiving study medication in both eyes.

For cases where subjects have only one eye with signs of FECD (because the fellow eye underwent corneal graft surgery), and will receive study medication only in that eye, please refer to the bottom of Table 2 for direction on assessments that will not need to be performed for the non-treated eye.

Table 2: Schedule of Activities (SoA)

Procedure	Visit 1 Screening (up to 15 days before Day 1)	Double-Masked Treatment Period							
		Visit 2 Baseline[a] (Day 1)	Visit 3[a] (M1)	Visit 4[a] (M3)	Visit 5[a] (M6)	Visit 6[a] (M9)	Visit 7[a] (M12)	Visit 8[a] (M15)	Visit 9[a] (M18) Exit or E/T
Study day		D 1	D30	D90	D180	D270	D360	D450	D540
Visit window in days	NA	NA	±3	±7	±10	±10	±10	±10	±10
Informed consent[b]	X								
Inclusion and exclusion criteria	X	X							
Demographics and medical/surgical history	X								
Concomitant medications/ therapies	X	X	X	X	X	X	X	X	X
Dosing compliance			X	X	X	X	X	X	X
Pregnancy test[c]	X	X							
V-FUCHS questionnaire[d]	X[e]		X	X	X	X	X	X	X
BCVA with contrast level of 100%	X[e]	X	X	X	X	X	X	X	X
BCVA with contrast level of 10%[i]	X[e]	X	X	X	X	X	X	X	X
Contrast sensitivity test (with and without glare light)[i]	X[e]		X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X[e]	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy photography	X[e]				X		X		X
Slit-lamp retroillumination photography (guttae)[i]	X[e]				X		X		X
Non-contact specular microscopy[i]	X[e]		X	X	X	X	X	X	X
Pentacam™ evaluation (Three tomographic features)[i]	X[e]		X	X	X	X	X	X	X

Table 2: Schedule of Activities (SoA) (Continued)

Procedure	Visit 1 Screening (up to 15 days before Day 1)	Double-Masked Treatment Period							
		Visit 2 Baseline[a] (Day 1)	Visit 3[a] (M1)	Visit 4[a] (M3)	Visit 5[a] (M6)	Visit 6[a] (M9)	Visit 7[a] (M12)	Visit 8[a] (M15)	Visit 9[a] (M18) Exit or E/T
Central Corneal Thickness[f, i]	X[e]		X	X	X	X	X	X	X
Intraocular pressure	X[e]	X	X	X	X	X	X	X	X
Dilated Ophthalmoscopy[i]	X[e]				X		X		X
Undilated Ophthalmoscopy		X	X	X		X		X	
Urinalysis, hematology, chemistry serum sample[g]	X								X
Blood sampling for pharmacogenomics/genomics		X							
Adverse events[h]	X[e]	X	X	X	X	X	X	X	X
Dispense study medication		X		X	X	X	X	X	
Collect study medication			X	X	X	X	X	X	X
Post-Study Clinical Trial Experience Survey									X
If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye will NOT need to undergo the following assessments:									
BCVA with contrast level of 10%[i]	X[e]	X	X	X	X	X	X	X	X
Contrast sensitivity test (with and without glare light)[i]	X[e]		X	X	X	X	X	X	X
Slit-lamp biomicroscopy photography [i]	X[e]				X		X		X

Table 2: Schedule of Activities (SoA) (Continued)

Procedure	Visit 1 Screening (up to 15 days before Day 1)	Double-Masked Treatment Period							
		Visit 2 Baseline[a] (Day 1)	Visit 3[a] (M1)	Visit 4[a] (M3)	Visit 5[a] (M6)	Visit 6[a] (M9)	Visit 7[a] (M12)	Visit 8[a] (M15)	Visit 9[a] (M18) Exit or E/T
Slit-lamp retroillumination photography (guttae)[i]	X[e]				X		X		X
Non-contact specular microscopy[i]	X[e]		X	X	X	X	X	X	X
Pentacam™ evaluation (Three tomographic features)[i]	X[e]		X	X	X	X	X	X	X
Central Corneal Thickness[f, i]	X[e]		X	X	X	X	X	X	X
Dilated Ophthalmoscopy[i]	X[e]				X		X		X
For these subjects where only one eye is being treated, the non-treated eye will undergo undilated ophthalmoscopy at every visit:									
Undilated Ophthalmoscopy[j]	X	X	X	X	X	X	X	X	X

[a] Visit should be performed ≥ 4 hours after subject awakes in the morning
[b] Informed Consent Form must be signed and dated before study procedures are performed. Informed consent for the optional PGx laboratory research study must be obtained prior to collecting the PGx blood sample.
[c] A urine pregnancy test will be conducted for all female subjects of childbearing potential.
[d] V-FUCHS questionnaire will be administered by subject
[e] Evaluations should be completed ≥ 4 hours after subject awakes in the morning
[f] Central Corneal Thickness will be performed with the Pentacam™
[g] Subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests. At Visit 1 (Screening) instruct subject to fast and return to clinic at appointed date and time for clinical lab collection. Results of clinical lab must be received and reviewed prior to Visit 2 (Baseline).
[h] AE's will be recorded starting after the signing of the informed consent form until subject completes the study
[i] If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye will not need to undergo the following assessments: BCVA with contrast level of 10%, Contrast sensitivity test (with and without glare light), slit-lamp biomicroscopy photography, slit-lamp retroillumination photography (guttae), non-contact specular microscopy, Pentacam evaluation (three tomographic features), Central corneal thickness, dilated ophthalmoscopy.
[j] If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye will only need to undergo an undilated ophthalmoscopy and not undergo the dilated ophthalmoscopy.

2. INTRODUCTION

2.1. Background: Fuchs Endothelial Corneal Dystrophy (FECD)

Fuchs endothelial corneal dystrophy (FECD) is the most common form of corneal dystrophy and is characterized by a progressive loss of corneal endothelial cells associated with a clinically phenotypical hallmark of guttae, which are excrescences of Descemet membrane formed by abnormal deposition of extracellular matrix (ECM). The corneal endothelium maintains corneal transparency by regulating the degree of hydration in the corneal stroma, thus severe corneal endothelial cell loss caused by FECD, induces corneal haziness resulting in eventual vision loss (Eghrari et al., 2010, Eghrari et al., 2015, Matthaei et al., 2019, Moshirfar et al., 2020, Sarnicola et al., 2019).

Though the estimated incidence and prevalence of guttae varies greatly, it may occur in up to 4% of patients older than 40 years old in the U.S., for example. These malformations less commonly co-occur with corneal edema, and therefore, many patients with guttae do not receive the diagnosis of FECD (Moshirfar et al., 2020, Sarnicola et al., 2019). The development and progression of this disease is influenced by age, and FECD shows a gender dichotomy. Initial clinical findings, corneal guttae, manifests in the fourth decade of life, and FECD patients typically will not require intervention until much later, generally in their 60s or 70s (Moshirfar et al., 2020, Sarnicola et al., 2019).

In the early phase of FECD, patients experience visual disturbance due to light scattering induced by guttae (Wacker et al., 2015, Watanabe et al., 2015). The integrity of the endothelial physical barrier, and the molecular pumps and transporters located within the membrane, are essential for maintaining corneal transparency. Therefore, in the advanced stages of FECD, patients have corneal edema and significant visual disturbance characterized by the loss of image resolution and glare (Moshirfar et al., 2020).

2.2. Study Rationale

Currently the only therapy for treating FECD is corneal transplantation using donor corneas. Penetrating keratoplasty, in which a full-thickness patient cornea is replaced with full-thickness donor cornea, has been performed since 1906. New surgical procedures, such as Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK), selectively replaces the diseased corneal endothelial layer with a lamellar donor graft which includes the corneal endothelium. Lamellar surgeries have advantages over penetrating keratoplasty procedures, but can incur associated problems, such as donor cornea shortage, surgical difficulty and invasiveness, infection, inflammation, and transplant rejection (Patel, 2012, Tan et al., 2012).

Therefore, the development of pharmaceuticals to suppress the progression of FECD is an unmet medical need, which would allow patients with FECD to avoid or postpone invasive treatments like corneal transplantation (Okumura et al., 2018).

Nowadays, a cell-based screening system for FECD was established, and sirolimus (rapamycin) was discovered as a potential drug for the treatment of FECD (Nakagawa et al., 2019, Oshima et al., 2018).

Sirolimus is an orally administered drug for the prevention of allograft rejection, due to its potent immunosuppressive effects by inhibiting actions of mTOR (Martel et al., 1977). The pharmacological and therapeutic effects, along with its pharmacokinetics and safety profile as an oral drug, have been extensively studied in both humans and animals (Napoli et al., 2001); (Sehgal, 2003).

Santen is currently developing a formulation of Sirolimus ophthalmic suspension, STN1010904 (DE-109D). Santen has conducted nonclinical and clinical studies, including a Phase I study in healthy Japanese adults and has confirmed the safety and tolerability of STN1010904. Santen plans to conduct a Phase IIa clinical trial in the U.S., France and India in order to explore the efficacy of STN1010904 for FECD patients. Santen expects that STN1010904 ophthalmic suspension would be the first pharmacologic treatment of FECD, allowing for the prevention of low vision and corneal transplantation in FECD patients.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of STN1010904 ophthalmic suspension may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective: • To assess the efficacy of two concentrations of STN1010904 ophthalmic [redacted] and [redacted] osing [redacted] lacebo in subjects diagnosed with FECD	**Primary Efficacy Endpoints:** • Change from baseline in Best corrected visual acuity (BCVA) with contrast level of 100% at Month 18 • Change from baseline in BCVA with contrast level of 10% at Month 18 • Change from baseline in contrast sensitivity with glare light at Month 18
Secondary Efficacy Objective: • To assess the dose response of STN1010904 ophthalmic suspension.	**Secondary Efficacy Endpoints:** • Best corrected visual acuity (BCVA) with contrast level of 100% at all post-baseline visits • BCVA with contrast level of 10% at all post-baseline visits • Contrast sensitivity with glare light at all post-baseline visits • Contrast sensitivity without glare light at all post-baseline visits • Change and percent change from baseline in BCVA with contrast level of 100% at all post-baseline visits • Change and percent change from baseline in BCVA with contrast level of 10% at all post-baseline visits • Change and percent change from baseline in contrast sensitivity with glare light at all post-baseline visits • Change and percent change from baseline in contrast sensitivity without glare light at all post-baseline visits • Change and percent change from baseline in central corneal thickness at all post-baseline visits. • Change and percent change from baseline in endothelial cell density at all post-baseline visits • Change and percent change in Guttae formation (Modified Krachmer scale) at all post-baseline visits

Table 3: Objectives and Endpoints (Continued)

Objectives	Endpoints
Safety Objective: • To assess the safety of two concentrations of STN1010904 ophthalmic [redacted] and [redacted]dosing [redacted]lacebo in subjects diagnosed with FECD	**Safety Endpoint:** • Safety of DE-109D will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), and laboratory tests (serum chemistry, hematology, and urinalysis).
Exploratory Objective:	**Exploratory Endpoint:** • V-FUCHS questionnaire at all post-baseline visits

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, randomized, double-masked, placebo-controlled, parallel-group study assessing the efficacy and safety of STN1010904 ophthalmic suspension in subjects with FECD.

Subjects diagnosed with FECD who meet all eligibility criteria at Visit 1 (Screening) will be randomized at Visit 2 (Baseline) to receive treatment for 18 months.

Approximately 80 subjects with FECD who meet all eligibility criteria will be randomized in a 3:3:2 ratio to one of three treatment arms:

- 0.03% STN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min)
- [redacted] TN1010904 ophthalmic suspension BID (8:00 & 20:00 ± 60 min)
- Placebo (vehicle) BID (8:00 & 20:00 ± 60 min)

See study design diagram in Figure 1. This study will consist of a Screening Period of up to 15 days and an 18-month Double-Masked Treatment Period.

Visit 1 (Screening):

At the Visit 1 (Screening), subjects will be screened against the inclusion and exclusion criteria and if subject meets all eligibility criteria, subjects will proceed to Visit 2 (Baseline).

The study eye will be the eye that qualifies per eligibility criteria at Visit 1. If both eyes meet the eligibility criteria, the right eye will be designated as the study eye.

Both eyes should be treated with the study medication for the duration of the study if they both have signs of FECD, even if only one eye is eligible per inclusion criteria. If only one eye has

signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication.

Double-Masked Treatment Period (18 months):

At Visit 2 (Baseline), approximately 80 eligible subjects will be randomized to receive 0.03% STN1010904 ophthalmic suspension BID or [redacted] STN1010904 ophthalmic suspension BID or Placebo (vehicle) BID in a 3:3:2 ratio. Subjects will be treated for 18 months with scheduled visits at Visits 2 (Baseline), Visit 3 (Month 1), Visit 4 (Month 3), Visit 5 (Month 6), Visit 6 (Month 9), Visit 7 (Month 12), Visit 8 (Month 15) and Visit 9 (Month 18).

At Visit 2 (Baseline), subjects will administer their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (± 60 min). The next day, subjects will subsequently dose with their assigned study medication at 8:00 & 20:00 (± 60 min) and continue dosing through Visit 9 (Month 18).

Pharmacogenomics/Genomics:

Subjects who consent to the optional pharmacogenomics/genomics (PGx) laboratory study will provide a blood sample for future testing. This sample will be collected at Visit 2 (Baseline). The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

Santen Steering Committee:

An internal Santen steering committee (SSC) whose members will not be participating in the 101090401IN study conduct will serve as an advisory board to the Santen senior management team. The SSC will review the data when [redacted] of patients have completed [redacted] visit and make recommendations based on interim data; unmasked data will only be reviewed in closed SSC sessions without participation of Santen personnel involved in the clinical study. The organization, responsibilities, and procedures of the SSC will be specified in a governing charter.

4.2. Scientific Rationale for Study Design

The study is designed to assess the efficacy and safety of 0.03% and [redacted] STN1010904, administered [redacted] to subjects with FECD for 18 months. FECD has a relatively slow progression; this is why the primary endpoint has been set after 18 months of treatment. Santen plans to conduct a double masked study to avoid bias. Several parameters will be assessed (as described in the Section 8) in order to evaluate the effect of sirolimus.

4.3. Justification for Dose

Based on nonclinical data, the concentrations of sirolimus in the ocular tissues increased dose-dependently following a single ocular administration of either [redacted] or [redacted] sirolimus ophthalmic suspension to male pigment rabbits, but comparable rates of increase were much lower than the initial dose ratios. In the 26-week repeated dose toxicity study in pigment rabbit, no ocular changes were observed following ocular administration of up to [redacted] sirolimus ophthalmic suspension [redacted] Sufficient concentrations of sirolimus for predicting efficacy in the corneal endothelium, the target tissue for FECD, has been observed following administration of [redacted] sirolimus ophthalmic suspension.

Based on the results of Phase I clinical study (CSR 0109C01LT) in Japan, the safety and tolerability of STN1010904 (up to [redacted] dosing was confirmed.

The systemic exposure of sirolimus in human subjects increased with dose escalation and dose frequency. After twice-daily administration o[redacted] STN1010904 for [redacted] there were no subjects in which the C_{max} exceeded 5 ng/mL, the target trough concentration for systemic effect of Rapamune®, sirolimus oral tablets (RAPAMUNE-PI, 2019).

Therefore, 0.03 and[redacted] STN1010904,[redacted] are considered to be the appropriate concentration values to test in the study.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including Visit 9 (Month 18).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria are met at Visit 1 (Screening):

1. Male or female, from 30 to 75 years of age, diagnosed with FECD.
2. Provide signed informed consent prior to any study procedures being performed.
3. Best-corrected visual acuity (BCVA) of +0.2 LogMAR or better (equivalent to ≥ 75 ETDRS letters, or at least Snellen 20/32) in the study eye as measured using an ETDRS chart.
4. Grade 3-5 of the Modified Krachmer scale in the study eye.
5. At least two out of three tomographic features are observed by Pentacam™, evaluated by the Investigator in the study eye:

Table 4: Tomographic Features

Parameter	Definition
Loss of parallel isopachs	Any single isopach not being almost circular/oval or parallel to adjacent isopachs within the central 4 mm of the cornea (relative to the pupil center)
Displacement of the thinnest point of the cornea	Being located outside of the inferotemporal quadrant (centered at the pupil center) or more than 1 mm from the pupil center in any quadrant.

Parameter	Definition
Focal posterior corneal depression	Any isolated area of depression (negative elevation relative to a sphere with best fit zone of 8 mm with float function) within the central 4 mm of the cornea (relative to the pupil center)

6. Endothelial cells are visible >50% of area in at least one image obtained by noncontact specular microscopy in the central or paracentral-peripheral area in the study eye.
7. If a subject is a female of childbearing potential (*i.e.*, not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of surgery]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
   - Abstinence
   - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
   - Placement of a copper-containing IUD
   - Condom with spermicidal foam/gel/film/cream/suppository
8. The male partner of the female subject of childbearing potential should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study informed consent form (ICF) and beginning screening), or other contraception deemed adequate by the investigator during the study.
9. Male subjects, with a female partner of childbearing potential, should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study ICF), or other contraception deemed adequate by the investigator during the study.
10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Ocular Conditions:

1. Monocular vision, or vision worse than +0.7 LogMAR (equivalent to < 50 ETDRS letters, or worse than Snellen 20/100) in the fellow eye;
2. No guttae in either eye (evaluated by slit-lamp and specular microscope).
3. Clinically evident stromal and/or epithelial edema in the study eye (evaluated by slit-lamp microscope).
4. Descemet folds in the study eye (evaluated by slit-lamp microscope).

5. Central corneal thickness is 660μm or more in the study eye (evaluated by Scheimpflug image).
6. Moderate/severe cataract in the study eye (mild cataract or pseudophakic eye is eligible for enrolment).
7. Evidence of any other ocular disease other than FECD in the study eye that may confound the outcome of the study (*e.g.*, active diabetic retinopathy, posterior uveitis, age-related macular degeneration or any other maculopathy, severe myopia >10D, pterygium, recurrent corneal erosion syndrome).
8. Any ocular surgery for FECD (*e.g.,* penetrating keratoplasty (PKP), Descemet stripping endothelial keratoplasty (DSEK), Descemet membrane endothelial keratoplasty (DMEK), Descemet stripping automated endothelial keratoplasty (DSAEK), Descemet stripping only (DSO) in the study eye.
9. Cataract surgery or any kind of ocular surgery in the study eye within 6 months prior to Visit 1.
10. Past history of filtering surgery for glaucoma in either eye (patients who underwent Minimally Invasive Glaucoma Surgery (MIGS) more than 6 months prior to Visit 1 are eligible for enrolment).
11. Laser treatment for glaucoma within 6 months prior to Visit 1 in the study eye.
12. Need for ocular surgery or ocular laser treatment in either eye throughout the study.
13. Media opacity that would affect contrast sensitivity in the study eye.
14. Presence of any active inflammation, or infection of the eye and/or eyelids in either eye.
15. History of herpetic infection in either eye or adnexa.
16. History of ophthalmic malignancy.

Concomitant Medications:

17. Use of Rho-Associated kinase (ROCK) inhibitor eye drop in the study eye within 4 weeks prior to Visit 1 and during the course of the study.
18. Use of CYP3A strong inhibitors during the course of the study.
19. Use of topical Cyclosporin within 3 months prior to Visit 1 and during the course of the study.
20. Use of Xiidra within 1 month prior to Visit 1 and during the course of the study.

Non-Ocular Conditions:

21. Allergy or hypersensitivity to study medication product, fluorescein dye, or other study related procedures/medications.
22. Current or planned participation in any other clinical study involving an investigational product or device within 4 weeks prior to Visit 1 or at any time during this study.
23. History of any disease or condition that in the opinion of the study investigator may put the subject at significant risk, may confound study results, or may interfere significantly

with the subject's participation in the study (*e.g.*, uncontrolled cardiovascular disease etc.).

24. Immunosuppressive therapy (*e.g.*, methotrexate, cyclosporine, cyclophosphamide, chlorambucil, mycophenolate mofetil, tacrolimus or azathioprine) other than prednisone or other corticosteroids within 4 weeks prior to Visit 1 or at any time during this study.
25. Any recent systemic infection within 4 weeks prior to Visit 1.
26. Known to be immunocompromised.
27. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
28. Malignancy in remission for less than 5 years prior to study participation (except basal cell or squamous cell skin cancer, or treated melanoma of the skin less than 24 months since last treatment).
29. Females who are pregnant or lactating and females of child-bearing potential who are not willing to use one of the acceptable contraceptive methods listed in inclusion #7 during the study and for 4 weeks following the last dose.
30. Any decision by the Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

5.3. Lifestyle Considerations

5.3.1. Contraception Requirements

There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 4 weeks for female subjects of childbearing potential and 12 weeks for male subjects capable of fathering children after the completion of the study. Females of childbearing potential and male subjects able to father children abstain from intercourse or agree to practice acceptable methods of contraception throughout the course of the study (*i.e.,* intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the investigator).

5.3.2. Fasting Prior to Blood Draws for Hematology and Chemistry Laboratory Tests

Requirements for fasting 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at visits is specified in the SoA (Table 2).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to a study medication/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography,

screen failure details, eligibility criteria, and any adverse events (AE) or serious adverse event (SAE).

In this study, a subject who fails screening may be considered for rescreening in consultation with the Sponsor or its designee and providing that the subject undergoes re-consent. In no case will a subject be allowed to be rescreened more than once. If a subject is to be rescreened after failing screening, a new screening period will begin, and all study eligibility criteria will need to be re-assessed and confirmed prior to randomization into the study. Rescreened subjects will be assigned a new subject number.

6. STUDY INTERVENTION

6.1. Study Medications Administered

Table 5: Descriptions of Study Medications

ARM Name	**STN1010904[redacted]**	**STN1010904, 0.03%**	**Placebo**
Intervention Name	STN1010904	STN1010904	Placebo
Type	Drug	Drug	Other
Dose Formulation	Ophthalmic suspension	Ophthalmic suspension	Ophthalmic solution
Unit Dose Strength(s)	[redacted]	0.03%	Not Applicable
Dosage Level(s)	One drop, BID, in the eye with signs of FECD, or in both eyes if both eyes have signs of FECD, throughout the Treatment Period from Visit 2 (Baseline) to Visit 9 (Month 18)	One drop, BID, in the eye with signs of FECD, or in both eyes if both eyes have signs of FECD, throughout the Treatment Period from Visit 2 (Baseline) to Visit 9 (Month 18)	One drop, BID, in the eye with signs of FECD, or in both eyes if both eyes have signs of FECD, throughout the Treatment Period from Visit 2 (Baseline) to Visit 9 (Month 18)
Route of Administration	Topical ocular	Topical ocular	Topical ocular
Use	Experimental	Experimental	Placebo- comparator
IMP and NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee

ARM Name	STN1010904	STN1010904, 0.03%	Placebo
Packaging and Labeling	Study Medication will be provided i and packed in a kit carton. Each kit carton will be labeled with protocol number, unique kit number, storage conditions, as required per country requirement	Study Medication will be provided i and packed in a kit carton. Each kit carton will be labeled with protocol number, unique kit number, storage conditions, as required per country requirement	Study Medication will be provided and packed in a kit carton. Each kit carton will be labeled with protocol number, unique kit number, storage conditions, as required per country requirement

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Medication Storage

All study medication will be provided by Santen and will be stored in an appropriate secure area at the investigational site.

Study medications should be stored under and stored During the storage, temperature will be recorded daily and the Investigator (or his/her designee) will verify and record in a temperature log at least once every seven days that the temperature was maintained at at the investigational site until the last subject has exited the study at the site. In the event of a temperature excursion or any study medications damaged during storage, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee).

Subjects will be reminded to store all study medication unde and kept in as much as possible and carton in an Study medications should not be

6.2.2. Study Medication Preparation

6.2.3. Study Medication Administration

During the Double-Masked Treatment Period, subjects will instill one drop of study medication in the eye with signs of FECD, or in both eyes if both eyes have signs of FECD, at approximately 8:00 & 20:00 ± 60 min daily for 18 months.

6.2.4. Study Medication Accountability

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The temperature chart recorder from the shipment will be deactivated, and the Investigator (or his/her designee) will verify that the temperature was maintained at

[redacted] uring transit. In the event of a temperature excursion or any study medications damaged during transit, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee). The receipt of clinical supplies form should be completed, signed, dated, and returned as directed. A copy must be maintained at the site for the Investigator's records.

The Investigator (or his/her designee) will keep a current record of the inventory, storage conditions and dispensing of all study medications. This record will be made available to Santen (or designee) for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigational site must be accounted for and in no case will study medications be used in any unauthorized situation. It is the responsibility of the Investigator to ensure that any used and unused supplies are available to Santen (or designee) for accountability purposes throughout the study.

6.2.5. Study Medication Handling and Disposal

The used study medication kits will be stored a[redacted] nd the unused study medication kits will be [redacted] until final study medication accountability has been completed by Santen (Following final study medication accountability and reconciliation by Santen (or designee), all used and unused study medication will be returned to the assigned central drug depot, or destroyed at the site at the direction of Santen.

6.3. Measures to Minimize Bias: Randomization and Masking

A stratified permuted-block randomization will be employed to randomize eligible subjects in a 3:3:2 ratio to either 0.03% STN1010904 ophthalmic suspension or[redacted] STN1010904 ophthalmic suspension or Placebo (vehicle). The randomization will be centralized and stratified by country.

The randomization schedule will be generated and implemented using central randomization via Interactive Response Technology (IRT). Each randomized subject will receive numbered study medication kits as assigned by IRT.

This is a double-masked study. The kit carton and [redacted]will be identical; however, the study medication appearance will be different depending on drug concentration. The subjects, Investigators, Examiners, and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member at the investigative site who is not the Investigator or Examiner will dispense and collect study medication(s) and will query about dosing compliance.

Subjects will be instructed not to show the [redacted] or discuss the eye drop with either the Investigator or the Examiner or other study subjects.

In case of a medical emergency, the Principal Investigator may reveal the treatment information by unmasking through IRT to know which treatment the subject has received.

The Principal Investigator (or his/her designee) should contact Santen, or Santen's designee, before taking this measure, if there is sufficient time. Santen, or Santen's designee, must be informed of all instances where the code is broken and of the reasons for such instances.

Additionally, the AE or SAE for which study treatment was unmasked should be reported to Santen Pharmacovigilance.

6.4. Study Medication Compliance

To obtain reliable efficacy and safety data, the following precautions will be taken to ensure compliance with the study medication during the study:

- Subjects will receive verbal and written instructions for proper instillation of the study medication, the dosing regimen, and the conditions of the study medication storage.
- Subjects will be reminded at study visits to consistently dose at the same time of the day
  - [redacted] at 8:00 and 20:00 (± 60 min) from Visit 2 (Baseline) to Visit 9 (Month 18).
- Subjects will be queried regarding compliance with study medication at each visit from Visit 3 (Month 1) through Visit 9 (Month 18)/ Early Termination. Compliance will be assessed by direct questioning during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.
- Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%.
- A subject's dosing compliance for a specific period is determined by the total number of days that subject followed the proper dosing procedures and dosing schedule. Stoppage of study medication use, overdosing of study medication, incorrect time of study medication administration, will be noted as non-compliance. The subject's dosing compliance will be recorded in the subject's source documents at Visit 3 (Month 1) through Visit 9 (Month 18)/ Early Termination.
- Subjects may be discontinued from the study at the discretion of the Investigator if the subject cannot be brought into compliance.

A record of the number of kit cartons dispensed to and taken by each subject must be maintained and reconciled with study medication and compliance records. Medication start and stop dates, including dates for medication delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

Medication or therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. Subjects may continue participation in the study if the instituted medication or therapy will not interfere with the evaluation of the study medication. Whenever possible, medications should be administered in dosages that remain constant throughout the study. Any treatment other than the study medication during the study duration will be considered as a concomitant treatment. The information of concomitant treatment must be recorded in the subject's source documents and on the eCRF.

- Concomitant medication: name of medication, route of administration, treated eye(s) (if applicable), dose, frequency, indication, start date, and stop date.
- Concomitant therapy: name of therapy, treated eye(s) (if applicable), indication, start date, and stop date.

6.5.1. Collection of Prior and Concomitant Medication Information

At Screening, information on prior and concomitant medications taken within the previous 90 days will be collected. At each study visit, subjects should be questioned concerning any new medications or changes in their current medications since their previous study visit and the information should be recorded in the eCRF. For all medications, the generic name, indication, route of administration, frequency, dose, start date, and stop date (if applicable) will be collected; for combination products, the brand name will also be documented.

6.5.2. Prohibited Medications or Therapies

- Any ocular surgery for FECD (*e.g.*, PKP, DSEK, DMEK, DSAEK, DSO) in the study eye.
- Cataract surgery or any kind of ocular surgery in the study eye within 6 months prior to Visit 1.
- Past history of filtering surgery for glaucoma in either eye (Patients with Minimally Invasive Glaucoma Surgery (MIGS) performed more than 6 months prior to Visit 1 are eligible for enrolment).
- Laser treatment for glaucoma within 6 months prior to Visit 1 in the study eye.
- Use of Rho-Associated kinase (ROCK) inhibitor eye drop in the study eye within 4 weeks prior to Visit 1 and during the course of the study.
- Use of CYP3A strong inhibitors during the course of the study.
- Use of topical Cyclosporin within 3 months prior to Visit 1 and during the course of the study.
- Use of Xiidra within 1 month prior to Visit 1 and during the course of the study.
- Need for ocular surgery or ocular laser treatment in either eye throughout the study
- Current or planned participation in any other clinical study involving an investigational product or device within 4 weeks prior to Visit 1 or at any time during this study.

6.6. Dose Modification

Dose modification is not allowed for this study.

6.7. Intervention after the End of the Study

No subsequent intervention is planned for subjects after completing 18 months of treatment.

7. DISCONTINUATION OF STUDY MEDICATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Medication

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study medication. If study medication is definitively discontinued and the subject has an AE related to study medication, he/she will remain in the study to be evaluated until the resolution of the AE. If the subject does not have any AE's related to study medication, the subject does not need to remain on the study after discontinuation of study medication. See the SoA (Table 2) for data to be collected at the time of discontinuation of study medication and follow-up and for any further evaluations that need to be completed.

7.2. Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 2). See SoA (Table 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The subject will be permanently discontinued both from the study medication and from the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Visit Details

- Study procedures and their timing are summarized in the SoA (Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study medication.
- Adherence to the study design requirements, including those specified in the SoA (Table 2), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.1. Visit 1 (Screening)

- Explain the purpose and conduct of the study to the subject and obtain written individual informed consent. Informed consent for the optional PGx consent must be obtained prior to blood sample collection at Visit 2 (Baseline). Ensure the subject understands that if he/she does not wish to provide a blood sample for the PGx laboratory research study that their decision will have no influence on their participation in the main study.
- Prepare the list of screening/registration of subjects.
- Obtain demographics.
- Obtain medications, procedures/therapies, and medical and surgical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 10 years, diagnosis, ocular surgical history, current ocular, and systemic conditions.
- Obtain urine and perform a urine pregnancy test, if the subject is a female of child-bearing potential.

Evaluations below should be completed ≥ 4 hours after subject awakes in the morning:

- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform slit-lamp biomicroscopy photography*
- Perform slit-lamp retroillumination photography (guttae)*
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
  - Ensure at least two out of three tomographic features are observed as per Table 4.
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform dilated ophthalmoscopy*
- Assess for adverse events (occurring after the signing of the informed consent)
- Assess eligibility of subject by reviewing the inclusion and exclusion criteria. A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- Enter the subject information into the EDC system for Visit 1 (Screening) to obtain the subject ID
- Instruct subject to fast and return to clinic at appointed date and time for clinical lab collection (urinalysis, hematology, and chemistry analysis). Results of clinical lab must be received and reviewed prior to Visit 2 (Baseline).

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Slit-lamp biomicroscopy photography
- Slit-lamp retroillumination photography (guttae)
- Non-contact specular microscopy
- Pentacam™ evaluation

- Central corneal thickness
- Dilated ophthalmoscopy
  - Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.

8.1.2. Visit 2 (Baseline)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Obtain urine and perform a urine pregnancy test, if the subject is a female of child-bearing potential
- Update concomitant medications and procedures/therapies
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10% *
- Perform slit-lamp Biomicroscopy
- Measure intraocular pressure
- Perform undilated ophthalmoscopy
- Collect blood sampling for pharmacogenomics/genomics, if subject signed consent for the optional pharmacogenomics consent.
- Assess for adverse events
- Perform final review of eligibility criteria. If all eligibility criteria, the subject will then be randomized, via IRT.
- After the subject has been randomized to a treatment arm, and assigned a treatment kit by IRT, an authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Dispense the assigned kit to the subject which will contain the following:
    - [redacted] packaged in kit carton.
  - Instruct the subject on how to properly instill the study medication daily in the eye with signs of FECD, or in both eyes if both eyes have signs of FECD, starting from this evening at 20:00 (± 60 min); explain the dosing regimen and study medication storage.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%

8.1.3. Double Masked Treatment Period, Visit 3 (Month 1)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform undilated ophthalmoscopy
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used [redacted] of study medication.
  - Remind the subject on how to properly instill study medication, the dosing regimen, and study medication storage.
  - Remind the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness

8.1.4. Double Masked Treatment Period, Visit 4 (Month 3)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform undilated ophthalmoscopy
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
  - Dispense the assigned kit to the subject which will contain the following:
    - [redacted] and packaged in kit
  - Instruct the subject on how to properly instill the study medication, the dosing regimen, and study medication storage.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness

8.1.5. Double Masked Treatment Period, Visit 5 (Month 6)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform slit-lamp biomicroscopy photography*
- Perform slit-lamp retroillumination photography (guttae)*
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform dilated ophthalmoscopy*
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
  - Dispense the assigned kit to the subject which will contain the following:

  - [redacted] packaged in kit carton.
- Instruct the subject on how to properly instill the study medication, the dosing regimen, and study medication storage.
- Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Slit-lamp biomicroscopy photography
- Slit-lamp retroillumination photography (guttae)
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness
- Dilated ophthalmoscopy
  - Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.

8.1.6. Double Masked Treatment Period, Visit 6 (Month 9)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*

- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform undilated ophthalmoscopy
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
  - Dispense the assigned kit to the subject which will contain the following:
    - [redacted] packaged in kit carton.
  - Instruct the subject on how to properly instill the study medication, the dosing regimen, and study medication storage.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness

8.1.7. Double Masked Treatment Period, Visit 7 (Month 12)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*

- Perform slit-lamp Biomicroscopy
- Perform slit-lamp biomicroscopy photography*
- Perform slit-lamp retroillumination photography (guttae)*
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform dilated ophthalmoscopy*
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
  - Dispense the assigned kit to the subject which will contain the following:
    - [redacted] packaged in kit carton.
  - Instruct the subject on how to properly instill the study medication, the dosing regimen, and study medication storage.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Slit-lamp biomicroscopy photography
- Slit-lamp retroillumination photography (guttae)
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness
- Dilated ophthalmoscopy
  - Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.

8.1.8. Double Masked Treatment Period, Visit 8 (Month 15)

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform undilated ophthalmoscopy
- Assess for adverse events
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
  - Dispense the assigned kit to the subject which will contain the following:
    - [redacted] nd packaged in kit
  - Instruct the subject on how to properly instill the study medication, the dosing regimen, and study medication storage.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%
- Contrast sensitivity test with and without glare light
- Non-contact specular microscopy

- Pentacam™ evaluation
- Central corneal thickness

8.1.9. Visit 9 (Month 18), Exit/ Early Termination

Visit should be performed ≥ 4 hours after subject awakes in the morning.

- Update concomitant medications and procedures/therapies
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Obtain V-FUCHS questionnaire
- Perform BCVA with contrast level of 100%
- Perform BCVA with contrast level of 10%*
- Perform contrast sensitivity test with and without glare light*
- Perform slit-lamp Biomicroscopy
- Perform slit-lamp biomicroscopy photography*
- Perform slit-lamp retroillumination photography (guttae)*
- Perform non-contact specular microscopy*
- Perform Pentacam™ evaluation*
- Obtain measurement for central corneal thickness*
- Measure intraocular pressure
- Perform dilated ophthalmoscopy*
- Collect serum sample for urinalysis, hematology, chemistry analysis
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused [redacted] of study medication.
- Assess for adverse events
- Administer the post-study Clinical Trial Experience survey
- Exit the subject from the study.

*** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:**

- BCVA with contrast level of 10%

- Contrast sensitivity test with and without glare light
- Slit-lamp biomicroscopy photography
- Slit-lamp retroillumination photography (guttae)
- Non-contact specular microscopy
- Pentacam™ evaluation
- Central corneal thickness
- Dilated ophthalmoscopy
  - Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.

NOTE:

If the study medication administration is discontinued prior to Visit 9 (Month 18), then to the extent possible, all procedures for Study Exit/Early Termination as per SoA (Table 2) will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.

8.1.10. Unscheduled Visits

If subject requires an unscheduled visit, procedures and assessments will be performed as needed.

8.2. Efficacy Assessments

The BCVA and contrast sensitivity measured in the study eye (identified at the baseline visit) are the efficacy measures for this study. BCVA will be measured with contrast level of 10% and 100%. The contrast sensitivity will be measured with and without glare light. Besides the observed BCVA and contrast sensitivity measurements, change and percent change from baseline in BCVA with contrast level of 10% and 100%, change and percent change from baseline in contrast sensitivity with and without glare light will also be calculated and evaluated.

As this is a proof of concept study, the following parameters will also be assessed for efficacy:

- Change and percent change from baseline in central corneal thickness at all post-baseline visits.
- Change and percent change from baseline in endothelial cell density at all post-baseline visits
- Change and percent change in Guttae formation (Modified Krachmer scale) at all post-baseline visits
- V-FUCHS questionnaire at all post-baseline visits

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2).

Safety of DE-109D will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), and laboratory tests (serum chemistry, hematology, and urinalysis).

8.4. Adverse Events and Serious Adverse Events

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the subject to discontinue the study medication (Section 10.3).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time informed consent is obtained at the time points specified in the SoA (Table 2) from the signing of the Informed Consent Form (ICF) until the subject withdrawal or the scheduled exit visit. (Note: Although AEs will be monitored for and collected prior to Investigational Product (IP) administration, the statistical data analysis will determine and summarize treatment-emergent AEs, *i.e.*, those AEs that began or worsened in severity after the first IP administration.)

Medical occurrences that begin before the start of study medication but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

8.4.3.1. SAEs

Independent of whether a subject has already had their scheduled study exit visit or not, any ongoing following types of event should be followed by the investigator until the event is determined to be resolved, irreversible, stable, the subject withdraws consent, or no further information is available.

- Ongoing SAEs
- Early termination and withdrawal from the study due to study medication related AEs

If the information requested by Santen is not part of the eCRF, or when database lock has already been completed, the site's response to follow-up requests should be emailed, faxed or reported in writing to the appropriate Email/fax numbers or personnel identified in the Attachment Contact Information in Table 1.

8.4.3.2. Related AEs

The other types of related AEs should be also followed by the same manner as SAEs in principle, and this follow up should be continued, as needed, up until the time database lock.

Generally, the status/resolution of the AE should be confirmed via an on-site visit, frequency as per investigator's judgement. However, in cases where the investigator considers an on-site visit is not necessary, such as with an AE based on subjective symptoms, the Investigator may confirm the outcome of the AE by telephone, email etc.

8.4.3.3. Unrelated AEs

The other types of unrelated AE should be followed until resolution or the scheduled exit visit.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to Santen of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- Santen has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Santen will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Santen will prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Santen policy and forward them to investigators as necessary. An investigator who receives an investigator safety report describing a SAE or other specific safety information (*e.g.*, summary or listing of SAEs) from the sponsor will review and then file it along

with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy Testing, Monitoring, and Reporting

8.4.5.1. Pregnancy Testing

If the subject is a woman of child-bearing potential, a urine sample will be obtained during Visit 1 (Screening) and Visit 2 (Baseline) for a urine pregnancy test. Urine samples will be analyzed at the site.

8.4.5.2. Pregnancy Monitoring and Reporting Procedures

Pregnancy in female subjects and female partners of male subjects will be monitored starting from screening through the End of study duration/Exit/Early Termination visit.

Although not considered an AE or SAE, pregnancy is an Event of Special Interest (ESI) and requires careful monitoring and follow up. If a pregnancy is reported by a study subject (or in the partner of a study subject), the investigator must:

- Inform Santen within 24 hours of learning of the pregnancy.
- If the pregnancy has occurred in a study subject, discontinue further IP administration and/or withdraw the subject from the study.
- Report pregnancy information on the eCRF following instructions.
- Follow the pregnancy until outcome is known. Santen will request specific follow-up on a case-by-case basis.

Additional details regarding collection, reporting, and follow-up of pregnancy is provided below:

Female subjects who become pregnant: The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Santen within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to Santen. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an ESI). Abnormal pregnancy outcomes (*e.g.*, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to Santen. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting. Any female subject who becomes pregnant while participating in the study will discontinue IP.

Male subjects with partners who become pregnant: The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Santen within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Santen. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.4.6. Adverse Events of Special Interest

Pregnancy

There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 4 weeks for female subjects of childbearing potential and 12 weeks for male subjects capable of fathering children after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject will be discontinued from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.

Medication administration errors

Study medication administration errors determined to be **significant** by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: incorrect dose of study medication and administration of study medication from an incorrect kit. An AE does not necessarily need to have occurred to count as a study medication administration error. A medication administration error is an unintended failure in the process of treatment with a medicinal product that leads to, or has the potential to lead to harm of the subject.

8.5. Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Pharmacogenomics/ Genomics

For future exploratory research, blood sample will be collected from the participants who have consented to participate in the collection.

8.8. Biomarkers

Biomarkers will not be evaluated for this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments will not be performed for this study.

8.10. Health Economics/ Medical Resource Utilization and Health Economics

Health Economics/ Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11. Visual Function and Corneal Health Status Questionnaire (V-FUCHS)

The Visual Function and Corneal Health Status Questionnaire (V-FUCHS), version May 2018, will be administered (Patel et al., 2018). The V-FUCHS questionnaire is a self-administered instrument that has been validated for the assessment of visual disability in Fuchs endothelial corneal dystrophy. The V-FUCHS questionnaire is provided in Section 10.5.

9. STATISTICAL CONSIDERATIONS

This section outlines topics related to the statistical methods used in the design and analysis of the study. A more detailed description of all the analyses and methods is provided in the statistical analysis plan (SAP).

9.1. Statistical Hypotheses

The primary endpoints are change from baseline in best-corrected visual acuity (BCVA) with contrast level of 10% and 100%, and change from baseline in contrast sensitivity with glare light at Month 18. For each primary endpoint, the null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \mu_T \leq \mu_C$$

$$H_1: \mu_T > \mu_C$$

where μ_T and μ_C denote the mean values of the corresponding primary endpoint in DE-109D arm and placebo arm, respectively.

9.2. Sample Size Determination

The sample size of this study is not based on any statistical power calculation due to the exploratory nature of the study and limited knowledge of the treatment effect of study medications. Based on the feasibility of conducting the trial, a total of approximately 80 subjects will be randomized into a 3:3:2 ratio to [redacted]STN1010904, 0.03% STN1010906, and placebo arms. That is, an approximately 30 subjects and 20 subjects will be randomized into each of 101090401IN study arms and placebo arm, respectively.

(Meadows et al., 2009). studied the progression of FECD in a cohort if 13 patients over a period of more than 30 months. Based on the data reported in the article, the change in number of guttae over time was extrapolated with mean of 471.7 and standard deviation of 514.1. If the treatment

effect slows down the progression by 50% and the primary endpoints progress similar to number of guttae, the study has 62% power to detect such treatment effect with the current sample size at 10% significant level.

9.3. Populations for Analyses

9.3.1. Safety Population

The Safety Population will include all randomized subjects who received at least one dose of the study medication. The safety analysis will be performed on the Safety Population by actual treatment received.

9.3.2. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who received at least one dose of study medications and provided at least one post-baseline efficacy measurement. The efficacy analysis will be performed on the FAS or a subset of the FAS by planned treatment.

9.3.3. Per-Protocol Set

Then Per-Protocol Set (PPS) is a subject of the FAS, restricted to the subjects who fulfill the protocol in terms of the eligibility, medications, and outcome measurement. It will be the analysis population for some sensitivity analyses. More details will be provided in SAP.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. General Considerations

Unless specified otherwise, efficacy measures will be summarized by planned (*i.e.*, randomized) treatment and based on the FAS, and safety measures will be summarized by actual treatment received and based on the Safety population. All efficacy endpoint analyses will be performed on eyes enrolled in the study (referred to as study eyes). The study eye is defined as the eye which fulfill all inclusion/exclusion criteria, if both eyes are eligible, then the right eye will be used. Safety assessments that pertain to the eye will be analyzed by the study eye and fellow eye separately. Safety assessments that pertain to the subject will be analyzed at the subject level.

Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, medium, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%). Additional considerations will be described in SAP which will be finalized prior to unmasking the data.

9.4.2. Handling of Missing Values

In the analysis of the primary endpoints (change from baseline in BCVA at 10% and 100% contrast level and change from baseline in contrast sensitivity with glare light), the multiple imputation approach will be performed to impute missing values. The multiple imputation model

will be include the treatment arm and baseline characteristics. Sensitivity analyses using other imputation methods and using MMRM models on observed cases will be performed.

The analysis of the secondary continuous endpoints will be performed using the MMRM analysis on observed cases. Therefore, no imputation will be performed.

For medical events including AEs and medical history, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. Similar rules will be followed to impute the completely or partially missing start and end dates of non-study medications.

Unless specified otherwise, descriptive summaries will be based on observed cases.

More details on handling missing data will be provided in the SAP.

9.4.3. Analysis of Primary Endpoint

Three primary efficacy endpoints are (1) change from baseline in BCVA with 100% contrast level, (2) change from baseline in BCVA with 10% contrast level, and (3) change from baseline in contrast sensitivity with glare light at Month 18. An analysis using a linear mixed-effect model for repeated measures (MMRM) will be used for each primary endpoint. From this model, least square means, standard errors, treatment differences in least square means, and 95% confidence intervals will be reported. For inferential analysis of each endpoint, a MMRM model-based t-test will be performed for the treatment difference at Month 18 and the corresponding p-value will be reported. To control the overall Type I error rate associated with the primary endpoints' hypothesis testing, the Hochberg procedure will be used, and the statistical significance will be evaluated with the adjusted p-values. The alpha splitting scheme to control the overall Type I error for both interim and final analysis will be specified in the SAP.

The superiority of DE-109D over placebo based on a specific primary endpoint is established if the difference between treatment and placebo group is statistically significant. The efficacy of DE-109D is established if at least one of the three primary endpoint shows its superiority of

DE-109D over the placebo.

9.4.4. Analysis of Secondary Endpoints

A mixed-effect model for repeated measures (MMRM) will be carried on observed cases up to Month 18 for each of the secondary endpoints. At each visit, least square mean of each treatment arm and 95% confidence interval for the difference in least square means between DE-109D arm and placebo arm will be estimated. Due to the exploratory nature of the study, no formal hypothesis testing will be performed on secondary endpoints. Two-sided 95% confidence intervals and nominal p-values may be reported for them.

9.4.5. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs and evaluation with slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), and laboratory tests (serum chemistry, hematology, and urinalysis).

AEs will be coded using the latest version of MedDRA. Subjects with any AE(s) will be tabulated by system organ class (SOC) and preferred term specified in MedDRA dictionary. Similarly, subjects with any ocular and non-ocular AEs will be tabulated separately. AEs, ocular and non-ocular AEs will be summarized by relationship to treatment and maximum severity. In addition, SAEs and discontinuations due to AEs will be summarized.

Safety parameters listed in Section 8.3 will be summarized using descriptive statistics by actual treatment received. Changes from baseline in these safety parameters will also be summarized by treatment.

9.5. Interim Analyses

An interim analysis is planned when the first [redacted] subjects (*i.e.*, [redacted] of randomized subjects) complete their [redacted] Visit. There are two goals for this interim analysis to assess for futility and to assess for efficacy. The study will continue while the interim analysis is conducted and reviewed. The alpha splitting scheme to control overall Type I error for both interim and final analysis will be specified in the SAP. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the SSC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the SSC charter. The SAP will describe the planned interim analyses in greater detail.

9.6. Santen Steering Committee (SSC)

An internal Santen steering committee (SSC) whose members will not be participating in the 101090401IN study conduct will serve as an advisory board to the Santen senior management team. The SSC will review the data when [redacted] of patients have completed [redacted] visit and make recommendations based on interim data; unmasked data will only be reviewed in closed SSC sessions without participation of Santen personnel involved in the clinical study. The organization, responsibilities, and procedures of the SSC will be specified in a governing charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (*e.g.*, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Obligations of Investigators

In summary, the Principal Investigator has agreed to the following obligations:

- Obtaining informed consent from every subject before the subject's participation in any study-related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the IRB or IEC before involving any subject in any study-related activity; submitting verification of the approval to Santen; submitting periodic progress reports (at least annually) and final report to IRB or IEC.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing Santen of all deviations from the protocol.
- Informing the IRB or IEC of all protocol amendments/modifications; sending Santen a copy of the letter from the IRB or IEC approving the amendment/modification.
- Reporting to Santen any AEs and reporting to the IRB or IEC any reportable AEs that occur in the course of the investigation.
- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB or IEC and of all action by the IRB or IEC regarding the study.
- Making study records available for inspection by Santen and representatives of regulatory agencies and the IRB or IEC; keeping records until notified by Santen that they may be destroyed.

- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to Santen. See I, II, and III as listed below.

I. Before the Beginning of the Study Providing Santen the following:

A signed Form FDA 1572, Statement of Investigator, if applicable.

A signed Financial Disclosure Form.

A current curriculum vitae (CV) if not submitted to Santen previously or if updated.

CVs for all Sub-Investigators.

A letter from the IRB or IEC indicating that the protocol was approved, including the name and address of the IRB or IEC.

A copy of the consent form approved by the IRB or IEC.

A list of current members of the IRB or IEC.

A copy of the source data location list.

A copy of delegation list/log.

A copy of training log.

II. While the Study is in Progress

Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.

eCRFs for each subject enrolled in the study.

Information regarding all deviations from the protocol.

Information regarding all AEs occurring to a subject while enrolled in the study.

Annual progress report (if study is on-going for more than one year). Letter from the IRB or IEC indicating approval of the annual progress report.

III. Once the Study is Completed

Disposition of all used and/or unused test and control articles, as well as documentation of all and drug accountability.

Providing Santen a final study report.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study if there is an updated version of the ICF.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.
- The ICF will contain a separate section that addresses blood samples collected and stored for subsequent pharmacogenomics analysis by Santen. The investigator or authorized designee will explain to each subject the objectives of this exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.5. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Committees Structure

- A SSC charter will be developed to document the structure, frequency of meetings and rules for this committee.

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (*e.g.*, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (*e.g.*, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (*e.g.*, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until notified by Santen that the records may be destroyed. No records may be destroyed during the retention period without the written approval of Santen. No records may be transferred to another location or party without written notification to Santen.

10.1.8. Source Documents

The Principal Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents include subject medical

records, hospital charts, clinic charts, study files, as well as the results of diagnostic tests (*e.g.*, laboratory tests). Source documents are filed at the investigator's site.

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number
- The study protocol number and the name of Santen
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (*e.g.*, medical history, study procedures, and/or evaluations)
- The dates of all study-related subject visits (scheduled and unscheduled)
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study medication accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination
- If unmasking at the site occurred, proper documentation and notifications were made

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study medication development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.10. Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied that is indicated as confidential. Information pertaining to this study will be published on www.clinicaltrials.gov.

The data generated by this clinical study are the property of Santen and should not be disclosed without the prior written permission of Santen. These data may be used by Santen now and in the future for presentation or publication at Santen's discretion or for submission to governmental regulatory agencies. Santen reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the Principal Investigator agrees to the release of the data from this study, and acknowledges the above publication policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing

Table 6: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting,]	Calcium	Alkaline phosphatase	
Urinalysis	Urinary glucose	Urinary proteins	Urobilinogen	

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (*i.e.*, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition. • Medical or surgical procedure (*e.g.*, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (*e.g.*, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical medication to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (*e.g.*, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Santen in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Santen. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Santen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Santen. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Santen.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Santen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Santen within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Santen via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Santen will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Santen Global Pharmacovigilance (Table 1). Contacts for SAE reporting can be found in Table 1.
SAE Reporting to Santen via Paper CRF (If Electronic Data Collection Tool is Unavailable)
• Complete both the paper AE and SAE Forms (located in your site regulatory binder) • Attach a Fax Cover Sheet with your contact information and fax to Santen Global Pharmacovigilance (Table 1). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in Table 1.

10.4. Procedures for Assessments

10.4.1. BCVA with contrast level of 100% and with contrast level of 10%

Please refer to the manual of procedures for further instructions on BCVA testing.

10.4.2. Contrast Sensitivity Test

Please refer to the manual of procedures for further instructions on contrast sensitivity testing with and without glare light.

10.4.3. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the at all visits. Magnification will be consistent with standard clinical practice. The patient will be seated while being examined. Grading will be done using the following scales:

The lid, conjunctiva, cornea, lens, and iris will be observed and graded on a 4-point scale (0-3 scale).

Lid Hyperemia

None	(0) =	Normal
Mild	(1) =	Redness of most or all the lid(s) margin OR skin
Moderate	(2) =	Redness of most or all the lid(s) margin AND skin
Severe	(3) =	Marked diffuse redness of both lid(s) margin AND skin

Lid Edema

None	(0) =	Normal
Mild	(1) =	Localized to a small region of the lid(s)
Moderate	(2) =	Diffuse, most or all the lid(s) but not prominent/protruding
Severe	(3) =	Diffuse, most or all the lid(s) AND prominent/protruding

Conjunctival (Palpebral and Bulbar) Hyperemia

None	(0) =	Normal
Mild	(1) =	Slight localized injection
Moderate	(2) =	Pink color, confined to palpebral OR bulbar conjunctiva
Severe	(3) =	Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Chemosis

None	(0) =	Normal
Mild	(1) =	Slight localized swelling
Moderate	(2) =	Mild/medium localized swelling or mild diffuse swelling
Severe	(3) =	Moderate diffuse swelling

Corneal Edema

None (0) = Normal

Mild (1) = Mild, diffuse stromal haze

Moderate (2) = Dense, diffuse stromal haze or bullae

Severe (3) = Dense, diffuse bullae or stromal haze AND stromal edema

Corneal Staining (with fluorescein)

None (0) = Normal

Mild (1) = Localized, occasional punctate staining

Moderate (2) = Localized, dense OR diffuse occasional punctate staining

Severe (3) = Diffuse, dense punctate staining which may be confluent staining

Keratic Precipitate

None (0) = Normal

Mild (1) = Slight pigmentation or keratic precipitate

Moderate (2) = Moderate pigmentation or keratic precipitate

Severe (3) = Dense pigmentation or keratic precipitate

Anterior Synechiae of Iris

None (0) = No anterior synechiae of iris is found

Mild (1) = <25% anterior synechiae of iris is found

Moderate (2) = 25% to 50% anterior synechiae of iris is found

Severe (3) = >50% anterior synechiae of iris is found

Posterior Synechiae of Iris

None (0) = No posterior synechiae of iris is found

Mild (1) = <25% posterior synechiae of iris is found

Moderate (2) = 25% to 50% posterior synechiae of iris is found

Severe (3) = >50% posterior synechiae of iris is found

Anterior chamber cells and flare will be observed and graded using the SUN scale.

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) = None

(1) = Faint

(2) = Moderate (iris/lens details clear)

(3) = Marked (iris/lens details hazy)

(4) = Intense (fibrin/plastic aqueous)

Lens

The lens will be noted as phakic, aphakic, or pseudophakic. Phakic lens will be graded as described below:

None	(0) = No lens discoloration nor opacification
Mild	(1) = Yellow lens discoloration or small lens opacity (axial or peripheral)
Moderate	(2) = Amber lens discoloration or medium lens opacity (axial or peripheral)
Severe	(3) = Brunescent lens discoloration or complete lens opacification (no red reflex)

10.4.4. Slit-lamp biomicroscopy photography

Please refer to the manual of procedures to perform this procedure.

10.4.5. Slit-lamp retroillumination photography (guttae)

Retroillumination photographs with slit-lamp flash photography after pupillary dilation will be taken of the cornea. Please refer to the manual of procedures to perform this procedure.

10.4.6. Non-contact specular microscopy

Please refer to the manual of procedures to perform non-contact specular microscopy.

10.4.7. Pentacam™ Evaluation

Please refer to the manual of procedures to perform Pentacam™ evaluation.

10.4.8. Central Corneal Thickness

The central corneal thickness (µm) measurement of each eye will be performed during the Pentacam™ evaluation.

10.4.9. Intraocular Pressure

IOP will be performed at each visit. IOP will be measured using calibrated manual Goldmann applanation contact tonometer with the subject in a sitting position. The same Goldmann contact tonometer employing the investigator's standard technique will be used throughout the study. Measurement will be performed preferably by the same authorized study staff throughout the study. The right eye is always tested first.

10.4.10. Ophthalmoscopy

Case where both eyes have signs of FECD: The ophthalmoscopy (fundus) examination with pupil dilation will be performed for each eye at Visit 1 (Screening), Visit 5 (Month 6), and Visit 7 (Month 12), and Visit 9 (Month 18, Exit/Early Termination). Pupil dilation and ophthalmoscopy examination will be performed after all other ocular procedures have been completed.

The ophthalmoscopy examination will be performed without pupil dilated at Visit 2 (Baseline) and Visit 3 (Month 1), Visit 4 (Month 3), Visit 6 (Month 9), and Visit 8 (Month 15).

Health of the optic nerve with cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will also be evaluated across all visits.

Case where only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery): For these subjects where only one eye is being treated, the non-treated eye will undergo undilated ophthalmoscopy at every visit.

10.4.11. Blood Sample for Pharmacogenomics/genomics Study

All subjects participating in the study will have the option to participate in blood sampling for PGx and this will be consented to collect this optional test. Subjects who do not wish to participate in the PGx sampling may still participate in the study. For PGx, one whole blood sample (approximately 10 mL) will be collected on Visit 2 (Baseline), as shown in Schedule of Activities (Table 2). The blood samples will be coded to protect the subject's private information. DNA will be extracted from the blood sample and stored in the DNA repository for potential future PGx research. The samples will be coded to protect the participant's private information. Sample handling, storage, and shipment will be defined in a separate procedure manual.

If conducted, PGx research will be performed by appropriate assay platforms such as Polymerase Chain Reaction (PCR), hybridization, and sequencing. Individual subjects' results from the research testing of their sample will not be communicated to investigator or to participants.

Samples collected and stored, and relevant documents (the list of screening/registration of subjects only for documents to be retained by the medical institution) will be retained for the period agreed in the ICF. Upon completion of analyses or the retention period, they will be anonymized and discarded. If the subject withdraws the consent, samples will be immediately disposed, and the applicable subject will be informed in writing.

10.4.12. Post-Study Clinical Trial Experience Survey

At Visit 9 (Month 18), Study Exit, subjects will be given the Post-Study Clinical Trial Experience Survey to complete. Survey will consist of questions evaluating the subject's experience in participating in a clinical trial. The purpose of this survey is for Santen to better understand patient needs and better define and implement a more 'patient-centric' clinical trial experience. Please refer to the manual of procedures for further instructions.

10.5. Visual Function and Corneal Health Status (V-FUCHS) Questionnaire

The Visual Function and Corneal Health Status Questionnaire (V-FUCHS) is provided below.

MAYO CLINIC

Visual Function and Corneal Health Status (V-FUCHS)

Santen 101090401IN Phantom Study	
Subject ID:	
Visit Name:	Visit Date *(mm-dd-yyyy)*:

Your Vision in Everyday Life

You are being asked to answer the following questions because we want to understand how your eyesight limits your everyday life. It takes about five minutes to complete the questions.

When you answer the following questions we ask you to think only of the difficulties that your sight may be causing you. Please only consider the impact of your sight, and not other problems, in your ability to perform the following tasks.

If you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing your best glasses or contact lenses if necessary.

How often do you have each of the following difficulties? For each question, please select the response that corresponds best to your situation (while wearing your best glasses or contact lenses if necessary).	**Never**	**Rarely**	**Sometimes**	**Most of the time**	**All of the time**
During the past month, my eyesight changed over the course of the day.	☐	☐	☐	☐	☐
During the past month, I have had blurred vision that is worst in the morning.	☐	☐	☐	☐	☐
During the past month, I have had trouble with focusing that is worst in the morning.	☐	☐	☐	☐	☐
At night, bright lights look like a starburst.	☐	☐	☐	☐	☐
At night, a bright circle (halo) appears to surround lights, such as street lights.	☐	☐	☐	☐	☐
Overall, fine details are becoming harder to see, for example, leaves on trees.	☐	☐	☐	☐	☐
During the past month, my vision interfered with my daily activities.	☐	☐	☐	☐	☐

Because of your eyesight, how much difficulty do you have? For each question, please select the response that corresponds best to your situation (while wearing your best glasses or contact lenses if necessary).	**No difficulty**	**A little**	**Moderate**	**A lot**	**Extreme difficulty**
Reading ordinary print on paper?	☐	☐	☐	☐	☐
Reading text on a screen?	☐	☐	☐	☐	☐
Doing work or hobbies that require you to see well up close?	☐	☐	☐	☐	☐
Reading text on medicine bottles and package inserts?	☐	☐	☐	☐	☐
Seeing the prices of items when shopping?	☐	☐	☐	☐	☐
Seeing what is ahead of you when you enter from daylight into a shady area, such as entering into a parking ramp?	☐	☐	☐	☐	☐
Seeing what is ahead of you when an oncoming car has headlights on at night?	☐	☐	☐	☐	☐
Seeing what is ahead of you when the sun is low during sunrise or sunset?	☐	☐	☐	☐	☐

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.

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10.6. Appendix 4: Abbreviations

Abbreviation or Specialist Term	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCVA	Best-Corrected Visual Acuity
BID	Twice a Day
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CV	Curriculum Vitae
CRF	Case Report Form
DMEK	Descemet membrane endothelial keratoplasty
DSAEK	Descemet stripping automated endothelial keratoplasty
DSEK	Descemet stripping endothelial keratoplasty
DSO	Descemet stripping only
EC	Ethics Committee
ECM	Extracellular matrix
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESI	Events of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FECD	Fuchs Endothelial Corneal Dystrophy
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure

Abbreviation or Specialist Term	Definition
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine devices
MIGS	Minimally Invasive Glaucoma Surgery
MMRM	Mixed-effects model for repeated measures
PCR	Polymerase Chain Reaction
PGx	Pharmacogenomics/genomics
PKP	Penetrating keratoplasty
PPS	Per-Protocol Set
RBC	Red blood cell
ROCK	Rho-Associated kinase
SAP	Statistical analysis plan
SoA	Schedule of Activities
SAE	Serious adverse event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOC	System organ class
SSC	Santen Steering Committee
SUSAR	Suspected unexpected serious adverse reactions
V-FUCHS	Visual Function and Corneal Health Status

11. PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	24MAY2022
Original Protocol	24NOV2021

Amendment 1: 24May2022

Overall Rationale for the Amendment:

The current protocol requires study medication to be instilled in both eyes. However, some FECD patients may have signs of FECD in one eye only, because of a corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. The protocol has been amended to reflect that only eye with signs of FECD will be treated with study medication. Please see below for additional description of protocol changes and the brief rationale. New text is identified in ***bold and italicized*** and deleted text with ~~**bold/strikethrough**~~.

Section # and Name	**Description of Change**	**Brief Rationale**
Synopsis Study Design, 4.1 Overall Design	Original Language: Both eyes should be treated with the study medication for the duration of the study, even if only one eye is eligible per inclusion criteria. Revised Language: Both eyes should be treated with the study medication for the duration of the study ***if they both have signs of FECD***, even if only one eye is eligible per inclusion criteria. ***If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication.***	Some FECD patients may have signs of FECD in one eye only, because they had corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. Protocol language will be updated to reflect that only eyes with signs of FECD will be treated with study medication.

Section # and Name	Description of Change	Brief Rationale
Synopsis Exclusion Criteria # 21 5.2 Exclusion Criteria #21 8.4.3.1 SAEs	Global change from "study drug" to "study medication"	To maintain consistency with the wording referring to study medication.
1.2 Schema Figure 1: Schema	Addition of "*" behind "BID" Addition of the footnote text: **** Both eyes should be treated with the study medication for the duration of the study if they both have signs of FECD, even if only one eye is eligible per inclusion criteria. If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication***	Some FECD patients may have signs of FECD in one eye only, because they had corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. Protocol language will be updated to reflect that only eyes with signs of FECD will be treated with study medication.
6.1 Study Medications Administered	Original Language: One drop, BID, both eyes throughout the Treatment Period from Visit 2 (Baseline) to Visit 9 (Month 18) Revised language: One drop, BID, in ***the eye with signs of FECD, or in*** both eyes ***if both eyes have signs of FECD*****,** throughout the Treatment Period from Visit 2 (Baseline) to Visit 9 (Month 18)	Some FECD patients may have signs of FECD in one eye only, because they had corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. Protocol language will be updated to reflect that only eyes with signs of FECD will be treated with study medication.

Section # and Name	Description of Change	Brief Rationale
6.2.3. Study Medication Administration	Original Language: During the Double-Masked Treatment Period, subjects will instill one drop of study medication in each eye at approximately 8:00 & 20:00 ± 60 min daily for 18 months. Revised language: During the Double-Masked Treatment Period, subjects will instill one drop of study medication in ~~**each eye**~~ ***the eye with signs of FECD, or in both eyes if both eyes have signs of FECD,*** at approximately 8:00 & 20:00 ± 60 min daily for 18 months.	Some FECD patients may have signs of FECD in one eye only, because they had corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. Protocol language will be updated to reflect that only eyes with signs of FECD will be treated with study medication.
8.1.2. Visit 2 (Baseline)	Original language: Instruct the subject on how to properly instill the study medication daily in both eyes, starting from this evening at 20:00 (± 60 min); explain the dosing regimen and study medication storage. Revised language: Instruct the subject on how to properly instill the study medication daily in ~~**both eyes**~~ ***the eye with signs of FECD, or in both eyes if both eyes have signs of FECD***, starting from this evening at 20:00 (± 60 min); explain the dosing regimen and study medication storage.	Some FECD patients may have signs of FECD in one eye only, because they had corneal graft surgery in the fellow eye, and FECD signs are no longer present. In this case only the eye with signs of FECD should be treated with study medication, as the non-FECD eye would not be expected to benefit from study medication treatment. Protocol language will be updated to reflect that only eyes with signs of FECD will be treated with study medication.
1.3 Schedule of Activities (SoA) and Table 2: Schedule of Activities (SoA)	Updated language prior to Table 2: ***Please follow the Table 2 "Schedule of Activities" below for subjects who have both eyes with signs of FECD and are receiving study medication in both eyes.*** ***For cases where subjects have only one eye with signs of FECD (because the fellow eye underwent corneal graft surgery), and will receive study medication only in that eye, please refer to the bottom of Table 2 for***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	direction on assessments that will not need to be performed for the non-treated eye. Addition of rows in the table designating which assessments the non-treated eye will not need to undergo. Addition of footer "I" and "j": ***[i] If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye will not need to undergo the following assessments: BCVA with contrast level of 10%, Contrast sensitivity test (with and without glare light), slit-lamp biomicroscopy photography, slit-lamp retroillumination photography (guttae), non-contact specular microscopy, Pentacam evaluation (three tomographic features), Central corneal thickness, dilated ophthalmoscopy.*** ***[j] If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye will only need to undergo an undilated ophthalmoscopy and not undergo the dilated ophthalmoscopy.***	
8.1.1. Visit 1 (Screening)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	exceptions below that will NOT need to be performed: • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Slit-lamp biomicroscopy photography*** • ***Slit-lamp retroillumination photography (guttae)*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** • ***Dilated ophthalmoscopy*** – ***Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.*** Addition of "*****" to the following assessments: • Perform BCVA with contrast level of 10%***** • Perform contrast sensitivity test with and without glare light***** • Perform slit-lamp biomicroscopy photography***** • Perform slit-lamp retroillumination photography (guttae) *****	

Section # and Name	Description of Change	Brief Rationale
	• Perform non-contact specular microscopy***** • Perform Pentacam™ evaluation***** • Obtain measurement for central corneal thickness***** • Perform dilated ophthalmoscopy*****	
8.1.2. Visit 2 (Baseline)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%*** Addition of "*****" to: Perform BCVA with contrast level of 10% *****	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.
8.1.3. Double Masked Treatment Period, Visit 3 (Month 1)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	• ***Contrast sensitivity test with and without glare light*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness*	
8.1.4. Double Masked Treatment Period, Visit 4 (Month 3)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Non-contact specular microscopy***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	• ***Pentacam™ evaluation*** • ***Central corneal thickness*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness*	
8.1.5. Double Masked Treatment Period, Visit 5 (Month 6)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Slit-lamp biomicroscopy photography*** • ***Slit-lamp retroillumination photography (guttae)*** • ***Non-contact specular microscopy***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	• ***Pentacam™ evaluation*** • ***Central corneal thickness*** • ***Dilated ophthalmoscopy*** – ***Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform slit-lamp biomicroscopy photography* • Perform slit-lamp retroillumination photography (guttae)* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness* • Perform dilated ophthalmoscopy*	
8.1.6. Double Masked Treatment Period, Visit 6 (Month 9)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	exceptions below that will NOT need to be performed: • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness*	
8.1.7. Double Masked Treatment Period, Visit 7 (Month 12)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%***	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	• ***Contrast sensitivity test with and without glare light*** • ***Slit-lamp biomicroscopy photography*** • ***Slit-lamp retroillumination photography (guttae)*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** • ***Dilated ophthalmoscopy*** – ***Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform slit-lamp biomicroscopy photography* • Perform slit-lamp retroillumination photography (guttae)* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation*	

Section # and Name	Description of Change	Brief Rationale
	• Obtain measurement for central corneal thickness* • Perform dilated ophthalmoscopy*	
8.1.8. Double Masked Treatment Period, Visit 8 (Month 15)	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness*	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
8.1.9. Visit 9 (Month 18), Exit/ Early Termination	Addition of the following language: **** If only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery), then only the FECD eye will be treated with study medication. The non-treated eye, will need to undergo the assessments listed above with the following exceptions below that will NOT need to be performed:*** • ***BCVA with contrast level of 10%*** • ***Contrast sensitivity test with and without glare light*** • ***Slit-lamp biomicroscopy photography*** • ***Slit-lamp retroillumination photography (guttae)*** • ***Non-contact specular microscopy*** • ***Pentacam™ evaluation*** • ***Central corneal thickness*** • ***Dilated ophthalmoscopy*** – ***Instead of dilated ophthalmoscopy an undilated ophthalmoscopy will be performed for the non-treated eye.*** Addition of "*" to: • Perform BCVA with contrast level of 10%* • Perform contrast sensitivity test with and without glare light*	Since the non-treated eye will not receive any study medication, certain assessments will not need to be performed as the eye will not be monitored for any changes. This will also decrease Site burden in performing these assessments.

Section # and Name	Description of Change	Brief Rationale
	• Perform slit-lamp biomicroscopy photography* • Perform slit-lamp retroillumination photography (guttae)* • Perform non-contact specular microscopy* • Perform Pentacam™ evaluation* • Obtain measurement for central corneal thickness* • Perform dilated ophthalmoscopy*	
Synopsis Exclusion Criteria 5.2 Exclusion Criteria	Original language: 5. Central cornea thickness is 630µm or more in the study eye (evaluated by Scheimpflug image). Revised language: 5. Central corne***a l*** thickness is ~~**630**~~ ***660***µm or more in the study eye (evaluated by Scheimpflug image).	Extending the upper limit of Central corneal thickness to 660µm will potentially increase the size of the target patient pool, without adversely impacting patient safety. Correction of a typo: "l" is added to "cornea" for a correct spelling of the word "corneal".
Synopsis Exclusion Criteria 5.2 Exclusion Criteria	Original language: 7. Evidence of any other ocular disease other than FECD in the study eye that may confound the outcome of the study (*e.g.*, active diabetic retinopathy, posterior uveitis, age-related macular degeneration or any other maculopathy, severe myopia >10D, pterygium). 22. History of any disease or condition that in the opinion of the	"Recurrent corneal erosion syndrome" was an example disease under Non-Ocular Conditions: Exclusion 22. However, because this is an ocular condition, this example is moved under Ocular Conditions: Exclusion 7.

Section # and Name	Description of Change	Brief Rationale
	study investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (*e.g.*, recurrent corneal erosion syndrome, uncontrolled cardiovascular disease etc.). Revised language: 7. Evidence of any other ocular disease other than FECD in the study eye that may confound the outcome of the study (*e.g.*, active diabetic retinopathy, posterior uveitis, age-related macular degeneration or any other maculopathy, severe myopia >10D, pterygium, **recurrent corneal erosion syndrome**). ~~22~~ **23**. History of any disease or condition that in the opinion of the study investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (*e.g.*, ~~recurrent corneal erosion syndrome~~, uncontrolled cardiovascular disease etc.).	
Synopsis Exclusion Criteria 5.2 Exclusion Criteria	Original Language: 27. History of ophthalmic malignancy Revised Language: ~~27.~~ **16.** History of ophthalmic malignancy	Previously Exclusion Criteria #27 was listed under "Non-Ocular Conditions." However as this is an ocular condition, this is now correctly listed under "Ocular Conditions, " and updated to be Exclusion Criteria # 16.

Section # and Name	Description of Change	Brief Rationale
10.4.10 Ophthalmoscopy	Original Language: The ophthalmoscopy (fundus) examination with pupil dilation will be performed for each eye at Visit 1 (Screening), Visit 5 (Month 6), and Visit 7 (Month 12), and Visit 9 (Month 18, Exit/Early Termination) and graded as described below. Pupil dilation and ophthalmoscopy examination will be performed after all other ocular procedures have been completed. Revised language: ***Case where both eyes have signs of FECD:*** The ophthalmoscopy (fundus) examination with pupil dilation will be performed for each eye at Visit 1 (Screening), Visit 5 (Month 6), and Visit 7 (Month 12), and Visit 9 (Month 18, Exit/Early Termination) ~~**and graded as described below**~~. Pupil dilation and ophthalmoscopy examination will be performed after all other ocular procedures have been completed. Added language: ***Case where only one eye has signs of FECD (because the fellow eye underwent corneal graft surgery): For these subjects where only one eye is being treated, the non-treated eye will undergo undilated ophthalmoscopy at every visit***.	Since the non-treated eye will not receive any study medication, only an undilated ophthalmoscopy will need to be performed as a safety assessment. "and graded as described below" was removed as this was incorrect because no grading was provided.
10.5. Visual Function and Corneal Health Status (V-FUCHS) Questionnaire	Original Language: The Visual Function and Corneal Health Status Questionnaire (V-FUCHS), version May 2018, is provided below. Revised Language: The Visual Function and Corneal Health Status Questionnaire	A new format of the V-FUCHS questionnaire has been provided by Mayo Clinic. All the questions remain the same but only differ in format.

Section # and Name	Description of Change	Brief Rationale
	(V-FUCHS)~~**, version May 2018,**~~ is provided below. Updated version of the V-FUCHS questionnaire added	
1.3 Schedule of Activities 8.1.1. Visit 1 (Screening) 8.1.5. Double Masked Treatment Period, Visit 5 (Month 6) 8.1.7. Double Masked Treatment Period, Visit 7 (Month 12) 8.1.9. Visit 9 (Month 18), Exit/ Early Termination	Addition of assessment: slit-lamp biomicroscopy photography at Visit 1 (Screening), Visit 5 (Month 6), Visit 7 (Month 12), and Visit 9 (Month 18) Exit or Early Termination	Since retroillumination photographs to assess the guttae might occasionally not be of good quality and because the number and distribution of guttae is an important parameter to assess in Fuchs corneal dystrophy, Santen proposes to add a second photographic procedure during slit-lamp examination. This additional procedure will not increase site burden as it is easily performed during slit lamp examination and at the same visit as the retroillumination photographs (*i.e.* Visit 1 Screening, Visit 5 (M6), Visit 7 (M12) and Visit 9 (M18) visits)
10.4.4. Slit-lamp biomicroscopy photography	Addition of Slit-lamp biomicroscopy photography: ***10.4.4. Slit-lamp biomicroscopy photography*** ***Please refer to the manual of procedures to perform this procedure.***	Since retroillumination photographs to assess the guttae might occasionally not be of good quality and because the number and distribution of guttae is an important parameter to assess in Fuchs corneal dystrophy, Santen proposes to add a second photographic procedure during slit-lamp examination. This additional procedure will not increase site burden as it is easily performed during slit lamp examination and at the same visit as the retroillumination photographs (*i.e.* Visit 1 Screening, Visit 5 (M6), Visit 7 (M12) and Visit 9 (M18) visits)

Section # and Name	Description of Change	Brief Rationale
Table 2 Schedule of Activities 8.1.1. Visit 1 (Screening) 8.1.5. Double Masked Treatment Period, Visit 5 (Month 6) 8.1.7. Double Masked Treatment Period, Visit 7 (Month 12) 8.1.9. Visit 9 (Month 18), Exit/ Early Termination 10.4.5. Slit-lamp retroillumination photography (guttae)	Original language: Slit-lamp photography (guttae) Revised language: Slit-lamp ***retroillumination*** photography (guttae)	As the new assessment "slit-lamp biomicroscopy photography" has been added, this change was made to differentiate between the two photography assessments.
Table 1 Emergency Contact Information	Addition of [redacted] as Back-up medical monitor	Addition of new back-up medical monitor

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