SPIFD-101 PROTOCOL: FUCHS' CORNEAL ENDOTHELIAL DYSTROPHY

A PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED, VEHICLE CONTROLLED, PAIRED-EYE PHASE 1/2 CLINICAL STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF

MTP-131 TOPICAL OPHTHALMIC SOLUTION (OCUVIA) IN SUBJECTS WITH FUCHS' CORNEAL ENDOTHELIAL DYSTROPHY (FCED) PRESENTING WITH MILD TO MODERATE CORNEAL EDEMA

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Study Phase:	Phase 1/2
Product Name:	MTP-131 Ophthalmic Solution (Ocuvia™)
IND Number:	114,234
Formulation:	Topical Ophthalmic
Study No.:	SPIFD-101
Sponsor:	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466
Sponsor Contact:	Greg Gordon, MD
Investigators:	Michael B. Raizman, M.D. Ophthalmic Consultants of Boston – Boston, MA, USA Edward Holland, M.D. Cincinnati Eye Institute – Cincinnati, OH, USA
Protocol Date/Version:	18 August 2015 / Version 1.0

Confidentiality Statement

Table 1: Emergency Contact Information

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Sponsor Medical Monitor	Gregory Gordon, MD	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 +1 (617) 936-7778

1. SYNOPSIS

Investigational Drug Product:	MTP-131 1.0% Ophthalmic Solution (Ocuvia™)
Active Ingredient:	MTP-131

Study Title:	A Prospective, Randomized, Double-Masked, Vehicle Controlled, Paired-Eye Phase 1/2 Clinical Study To Evaluate the Safety, Tolerability and Efficacy of MTP-131 Topical Ophthalmic Solution (Ocuvia) in Subjects with Fuchs' Corneal Endothelial Dystrophy (FCED) Presenting with Mild to Moderate Corneal Edema
Study Number:	SPIFD-101
Study Phase:	Phase 1/2
Study Objective:	To evaluate the safety, tolerability and efficacy of MTP-131 1.0% ophthalmic solution relative to vehicle administered topically two times per day (BID) for 12 weeks in the treatment of FCED presenting with mild to moderate corneal edema.
Study Design:	This will be a prospective, randomized, double-masked, vehicle controlled, paired-eye, up to 2-center study in which approximately 16 FCED subjects presenting with mild to moderate corneal edema are planned to be treated with 1 drop of MTP-131 1.0% ophthalmic solution in the randomly selected study eye BID and 1 drop of vehicle ophthalmic solution BID in the fellow control eye. Written informed consent will be obtained from all subjects or their legal guardian(s) prior to the Screening Visit. Once written consent has been provided, data will be collected from a complete pre-treatment examination, consisting of vital signs, routine blood chemistries, serum pregnancy test for women of child-bearing potential, measurement of best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, manifest refraction, contrast sensitivity, specular microscopy, corneal pachymetry, Pentacam, intraocular pressure (IOP) measurement, and slit lamp examination. This Screening Visit examination will be performed no more than 28 days prior to the Baseline Visit. If applicable, urine pregnancy testing will be performed prior to initiation of treatment. The study eye will be determined via randomization. Patients will be considered enrolled in the study upon randomization. The day of randomization is defined as Study Day 1. Patients will receive one drop of MTP-131 1.0% ophthalmic solution topically BID to the randomly selected study eye and one drop of vehicle BID to the fellow control eye. At the time of randomization, patients will be read a standard script explaining the importance of applying the correct drug product to each eye on a twice per day basis.
Investigational Product, Dose and Mode of Administration:	MTP-131 1.0% ophthalmic solution administered topically BID to the study eye and vehicle administered topically BID to the fellow control eye.
Study Population:	Approximately 16 subjects with FCED and mild to moderate corneal edema in both eyes (OU) documented by subject history and medical records, clinical examination, and ophthalmic testing procedures. Subjects will be enrolled at up to 2 sites in the United States.

Inclusion Criteria:	t must meet the following criteria to be eligible for inclusion in the study: 1. Adults ≥18 years old at the time of Screening Visit 2. Diagnosis of FCED OU based on clinical and ophthalmic test findings 3. Clinical evidence of corneal edema OU diagnosed with FCED, including one or more of the following signs: corneal epithelial microcysts, corneal epithelial bullae, stromal folds, or stromal haze 4. Subjective complaint of progressive visual change OU or subjective complaint of greater visual disturbance in the morning compared to afternoon or evening OU 5. Central corneal thickness of 550 µm to 700 µm (inclusive) in both eyes diagnosed with FCED, as measured by ultrasonic pachymetry at the time of Screening Visit and Baseline Visit 6. Best-corrected distance visual acuity (BCVA) of 20/32 to 20/320 (inclusive) at the time of Screening Visit and Baseline Visit OU 7. Media clarity sufficient for specular microscopy 8. Patient cooperation sufficient for adequate ophthalmic testing and anatomic assessment 9. Able to self-administer eye drops as demonstrated at Screening or having a care provider who can do so 10. Women of childbearing potential must agree to use one of the following methods of birth control from the date they sign the informed consent form (ICF) until after the last study visit (Followup Visit): a.) Abstinence, when it is in line with the preferred and usual lifestyle of the subject; b.) Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis); c.) Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted or injectable) or an intrauterine device or system. Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening). 11. Able to give informed consent and willing to comply with all study visits and examinations

Exclusion Criteria:	A subject who meets any of the following criteria will be excluded from the study: Ocular conditions 1. Corneal findings of any type (including, but not limited to stromal haze or stromal scarring), in either eye, that, based on investigator's assessment, limit the probability of visual improvement after corneal deturgescence 2. Any ocular pathology requiring treatment with topical ophthalmic drops, with the exception of glaucoma or ocular hypertension 3. Concurrent use of any and all topical ophthalmic medications, prescription and non-prescription (with the exception of study medication, or stable use of topical prostaglandin analogs, alphaadrenergic agents, and beta-blockers) 1 week prior to Screening Visit and throughout the duration of the study 4. Use of topical hypertonic saline drops for 3 days prior to Screening and throughout the duration of the study 5. Any active ocular or periocular infection; any history of recurrent or chronic infection or inflammation in either eye 6. History of herpetic infection in either eye 7. History of corneal disease (other than FCED) or corneal surgery in either eye 8. Measurable central corneal edema based on investigator's assessment 9. Current use or likely need for the use of contact lens at any time during the study 10. History of punctual cautery, non-dissolvable punctual plug implants within 1 year of the Screening Visit, or collagen punctual plugs within 6 weeks of the Screening Visit, or anticipated use of any of these treatments in either eye during the study 11. Concurrent disease in either the study eye or fellow eye that could require medical or surgical intervention during the study period 12. History of previous corneal or anterior segment surgery such as LASIK, photorefractive keratectomy, endothelial keratoplasty, penetrating keratoplasty, cataract surgery or glaucoma surgery. Systemic conditions 13. Concurrent use of topical or systemic cyclosporine A for 3 weeks prior to the Screening Visit or during the study 14. Any disease or medical condition that in the opinion of the investigator would prevent the subject from participating in the study or might confound study results General 15. Participation in any other investigational drug or device clinical trials within 30 days prior to enrollment, or planning to participate in any

	other investigational drug or device clinical trials within 30 days of study completion 16. History of allergic reaction to the investigational drug or any of its components 17. Current use of or likely need for any excluded medication, including systemic medications known to be toxic to or affect the cornea (e.g., carbonic anhydrase inhibitors) 18. Women who are pregnant or lactating
Planned Duration of Treatment:	Twelve weeks, with a four week follow-up period for safety.
Visit Schedule:	• Screening (Day -28 to Day 1) • Baseline evaluation and enrollment (Day 1) • Week 1 (± 3 days) • Week 4 (± 3 days) • Week 8 (± 3 days) • Week 12 (± 3 days; End-of-Treatment Visit) • Week 16 (± 3 days; Follow-up Visit)
Primary (Safety) Endpoints:	• The incidence and severity of systemic and ocular adverse events (AEs) • Change from Baseline in slit lamp findings • Change from Baseline in intraocular pressure (IOP)
Secondary (Efficacy) Endpoints:	• Change from Baseline in central corneal thickness • Change from Baseline in best corrected visual acuity (BCVA, ETDRS scale) • Change from Baseline in endothelial cell count • Change from Baseline in endothelial cell morphology including: o Hexagonality o Cell density o Coefficient of variation • Change from Baseline in: o Corneal area affected by microcysts o Number, size, and location of corneal bullae o Severity (as determined by investigator) of corneal stromal folds • Change from Baseline in contrast sensitivity
Sample Size:	For this Phase 1/2 study, no formal hypothesis testing is planned. The sample size of approximately 16 subjects is based on a reasonably sized study for demonstrating clinical safety, tolerability and initial efficacy.

Statistical Methods:	Analysis Populations: All subjects who receive at least one dose of study drug will be included in the Safety Population. Safety Analyses: AEs will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having
	AEs. Severity and relationship to study drug will be listed as appropriate. Any formal statistical testing will be considered exploratory. Efficacy Analyses: Baseline demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, and minimum and maximum). Discrete variables will be summarized by frequencies and percentages. All study data are to be displayed in the data listings. Statistical analysis of this study will be the responsibility of the sponsor or its designee. Subject disposition summaries will include the number of subjects treated (i.e., in the Safety population). The number and percentage of subjects who complete or discontinue from the study will be summarized by reason. Subject's age, sex, weight, height, BMI, and other demographic characteristics will be recorded and summarized. Medical history will be listed.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS

The following abbreviations and specialist terms are used in this study protocol:

Abbreviation	Definition or Explanation
AE	Adverse Event
ATP	Adenosine triphosphate
BCVA	Best Corrected Visual Acuity
BID	Twice daily
CST	Central Subfield Thickness
eCRF	Electronic Case Report Form
EC	Ethics committee
ERB	Ethical Review Board
ETDRS	Early Treatment Diabetic Retinopathy Study
FCED	Fuchs' Corneal Endothelial Dystrophy
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intention-to-Treat
LASIK	Laser in-situ keratomileusis
M1, M2	Major metabolite of MTP-131
MedDRA	Medical Dictionary for Regulatory Activities
PRDXs	Peroxiredoxins
PT	Preferred term
ROS	Reactive Oxygen Species
RPE	Retinal pigmented epithelium
SAE	Serious Adverse Event

SLE	Slit Lamp Examination
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction

4. INTRODUCTION

4.1. Introduction

Mitochondria normally produce a small amount of reactive oxygen species (ROS) including superoxide anions and hydrogen peroxide as physiological byproducts of electron transport and adenosine triphosphate (ATP) production. Under conditions of metabolic or genetic stress, mitochondria can become a major endogenous source of ROS such as superoxide anions, peroxynitrite, and hydroxyl radicals. Increased oxidative damage to the inner membrane of the mitochondria leads to imbalances in the electron transport chain, resulting in further increased superoxide and hydrogen peroxide production, which in turn can initiate a cycle of further damage to membrane and mitochondrial proteins and mitochondrial DNA. Excess ROS can damage mitochondrial proteins and lipids to a point that triggers mitochondria to release cytochrome c and provoke apoptosis (Madsen-Bouterse, 2008). Apoptotic cell death can manifest in the eye as visual abnormalities affecting the retina and cornea.

Fuchs' Corneal Endothelial Dystrophy (FCED) is a vision-threatening condition that is characterized by the loss of corneal endothelial cell function and quantity. FCED typically presents in the fourth and fifth decade of life and progresses to vision loss over another one or two decades (Adamis, 1993). Vision loss can result from several pathologic changes: the development of corneal guttae, which degrade the refractive properties of the cornea; the presence of stromal edema, arising from the increased permeability of Descemet's membrane and endothelium along with pump dysfunction in the endothelium; and the development of epithelial bullae (Waring, 1982). If untreated, the bullae may rupture, causing infection, pain, and eventual vascularization and opacity of the cornea (Yanoff, 1996). FCED is thought to occur in about 4% of the US population over age 40 (Krachmer, 1978). At present, the only treatment is corneal transplantation; no non-surgical therapy is available.

There is growing evidence that oxidative stress plays a role in the pathogenesis of FCED (Jurkunas, 2010). As early as 1986, decreased numbers of mitochondria and a reduced activity of cytochrome oxidase in mitochondria was detected in FCED corneas (Tuberville, 1986). Antibodies against lipid peroxidation and other ROS byproducts have shown oxidative damage in FCED corneas (Buddi, 2002). A marker of oxidative damage, 8-hydroxy-2'-deoxyguanosine, was shown in FCED endothelial cells to co-localize to mitochondria, strongly suggesting that in FCED the mitochondrial genome is the target of oxidative stress (Jurkunas, 2010). In addition, endothelial cells and Descemet's membrane from human corneas of patients with FCED demonstrate marked overexpression of clusterin, a protein that is overexpressed in many tissues undergoing stress (Jurkunas 2008a). Serial analysis of gene expression (SAGE) to compare the endothelial of normal patients and those with FCED has shown alteration in the expression of genes regulating cellular energy metabolism, pump functions, and apoptotic and antioxidant cell defense. Mitochondrial transcripts accounted for the majority of the downregulated genes (Elhalis, 2010). Peroxiredoxins (PRDXs) are a novel class of antioxidants that remove cellular

hydrogen peroxide and inhibit apoptosis from reactive oxygen species. PRDXs are decreased in FCED (Jurkunas, 2008b).

MTP-131 reduces mitochondrial oxidative stress by enhancing mitochondrial function via selective binding and protection of cardiolipin from peroxidation (Birk, 2013). In cell cultures, MTP-131 has been shown to reduce glucose- and peroxide- induced oxidative stress and apoptosis and to improve survival of human retinal endothelial cells (Li, 2011), human trabecular meshwork cells (Chen, 2011), and human retinal pigment epithelial cells (Liang, 2010). Intraperitoneal administration of MTP-131 in mice reduced laser-induced choroidal neovascularization more than 50% (Liang, 2010), and when given subcutaneously to streptozotocin-induced diabetic rats, reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye (Huang, 2013). MTP-131 given subcutaneously (Alam, 2012) or topically (Prusky, 2013) to high fat and/or streptozotocininduced diabetic mice prevented and corrected visual functional loss. As noted above, the pathophysiology of FCED in humans is characterized by corneal endothelial abnormalities that share features with the oxidative stress observed in human retinal endothelial cells. Thus, it is theorized that treatment with MTP-131 of subjects suffering from FCED associated with mitochondrial dysfunction may have an effect on mitochondrial oxidative stress levels and corneal disease activity.

5. STUDY OBJECTIVES

5.1. Primary Objectives

To evaluate the safety, tolerability and efficacy of MTP-131 1.0% ophthalmic solution relative to vehicle administered topically two times per day (BID) for 12 weeks in the treatment of FCED presenting with mild to moderate corneal edema.

6. INVESTIGATIONAL PLAN

6.1. Summary of Design

This will be a prospective, randomized, double-masked, vehicle controlled, paired-eye, up to 2center study in which approximately 16 FCED subjects presenting with mild to moderate corneal edema are planned to be treated with 1 drop of MTP-131 1.0% ophthalmic solution in the randomly selected study eye BID and 1 drop of vehicle ophthalmic solution BID in the fellow control eye.

Written informed consent will be obtained from all subjects or their legal guardian(s) prior to the Screening Visit. Once written consent has been provided, data will be collected from a complete pre-treatment examination, consisting of vital signs, routine blood chemistries, serum pregnancy test for women of child-bearing potential, measurement of best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, manifest refraction, contrast sensitivity, specular microscopy, corneal pachymetry, Pentacam, intraocular pressure (IOP) measurement, and slit lamp examination.

This Screening Visit examination will be performed no more than 28 days prior to the Baseline Visit. If applicable, urine pregnancy testing will be performed prior to initiation of treatment.

The study eye will be determined via randomization. Patients will be considered enrolled in the study upon randomization. The day of randomization is defined as Study Day 1.

Patients will receive one drop of MTP-131 1.0% ophthalmic solution topically BID to the randomly selected study eye and one drop of vehicle BID to the fellow control eye. At the time of randomization, patients will be read a standard script explaining the importance of applying the correct drug product to each eye twice a day on a daily basis.

6.2. Discussion of Design and Control

In this study, MTP-131 1.0% ophthalmic solution will be administered twice per day for 84 days to evaluate the safety, tolerability, and efficacy for the treatment of FCED. Approximately 16 subjects are planned to be enrolled into the study. Randomization will be used to minimize bias in the assignment of subjects' eyes to treatment or vehicle, and to increase the likelihood that known and unknown ocular attributes are evenly balanced across groups. Masked treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

6.2.1. Dose Justification

The dose selected for this clinical study is based on data from nonclinical pharmacology studies in metabolically stressed mice, where both 1% and 3% MTP-131 applied topically once daily has been associated with restoration of visual function in a dose dependent manner (Prusky, 2004). Additionally, MTP-131 given subcutaneously to high fat and/or streptozotocin-induced diabetic mice prevented and corrected visual functional loss (Alam, 2012) and subcutaneously to streptozotocin-induced diabetic rats reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye (Huang, 2013).

In the recently completed SPIOC-101 clinical trial, twice daily dosing with MTP-131 ophthalmic solution administered topically BID at concentrations of 0.3% and 1.0% for 28 days to subjects with DME and age-related macular degeneration was well tolerated at both doses and in subjects with both ocular conditions. There were no significant safety or tolerability findings in that study. This is consistent with the 90-day toxicology studies, completed in rabbits and dogs, in which no treatment-related systemic toxicity or ocular pathology affecting the major visioncritical structures of the eye was observed. Mononuclear cell infiltrates in the palpebral and bulbar conjunctivae and nictitating membranes were observed in the more sensitive species (dog), which regressed during a recovery phase. Although the aforementioned preclinical toxicological findings were reversible upon cessation of treatment, in any patient complaining of persistent, local ocular irritation such as stinging or burning upon instillation of drops, the MTP131 treatment regimen should be stopped.

6.3. Schedule of Events

Study assessments and procedures are presented by study visit in Table 2.

Table 2. Schedule of Events

	Screening Period	Treatment Period					Follow-up Period	Early Discontinuation Visit
Days/Weeks	**Screening (Day -28 to Day 1)** [a]	**Day 1/ Baseline**	**Week 1 (± 3 days)**	**Week 4 (± 3 days)**	**Week 8 (± 3 days)**	**Week 12 (± 3 days) End-of Treatment Visit**	**Week 16 (± 3 days) Follow-up Visit**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Informed consent	X							
Eligibility	X	X						
Demographics	X							
Medical/Ocular history	X							
Vital signs[b]	X	X	X	X	X	X	X	X
Blood and urine for safety[c]	X	X	X				X	X
Pregnancy test[d]	X	X				X	X	X
ETDRS BCVA / manifest refraction[e]	X	X	X	X	X	X	X	X
Contrast sensitivity	X	X	X	X	X	X	X	X
Specular microscopy		X	X	X	X	X	X	X
Corneal pachymetry (ultrasound)	X	X	X	X	X	X	X	X
Pentacam	X	X	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X	X	X
Slit lamp exam	X	X	X	X	X	X	X	X
Randomization [f]		X						

Adverse events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X

Note: All ophthalmic testing must be conducted on both eyes at each time point.

[a] Screening visit should begin at 10:00AM ± 2 hours. Screening procedures may be completed on more than one day, so long as all procedures are completed during the Screening Period. Screening and Baseline assessments may be combined and completed at a single visit. All other visits should begin at the same time of day as the Screening visit ± 1 hour, and may be

completed over a one or two day period at the discretion of the investigator, so long as all procedures are completed during the allowable window for that visit. At each visit, the measurements of corneal thickness and BCVA should occur within ± 1.5 hour of the time in which these measurements were completed at the Baseline visit.

[b] Vital signs include temperature, respiratory rate, sitting blood pressure and pulse.

[c] Blood for safety will consist of hematology panel and clinical chemistry. Urinalysis will be performed at Baseline Visit only.

[d] Women of childbearing potential only; serum pregnancy test to be done at screening and urine pregnancy test to be done at all other time points.

[e] Manifest refraction required at Screening and Week 16 visits only.

[f] The day of randomization is defined as Study Day 1.

7. STUDY POPULATION

7.1. Number of Subjects Planned

Approximately 16 subjects with FCED presenting with mild to moderate corneal edema are planned to be enrolled at up to 2 sites in the United States.

7.2. Study Population

Subjects who have FCED presenting with mild to moderate corneal edema.

7.2.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Adults ≥18 years old at the time of Screening Visit
2. Diagnosis of FCED OU based on clinical and ophthalmic test findings
3. Clinical evidence of corneal edema OU diagnosed with FCED, including one or more of the following signs: corneal epithelial microcysts, corneal epithelial bullae, stromal folds, or stromal haze
4. Subjective complaint of progressive visual change OU or subjective complaint of greater visual disturbance in the morning compared to afternoon or evening OU
5. Central corneal thickness of 550 µm to 700 µm (inclusive) in at least one eye diagnosed with FCED, as measured by ultrasonic pachymetry at the time of Screening Visit and Baseline Visit
6. Best-corrected distance visual acuity (BCVA) of 20/32 to 20/320 (inclusive) at the time of Screening Visit and Baseline Visit OU
7. Media clarity sufficient for specular microscopy
8. Patient cooperation sufficient for adequate ophthalmic testing and anatomic assessment
9. Able to self-administer eye drops as demonstrated at Screening or having a care provider who can do so
10. Women of childbearing potential must agree to use one of the following methods of birth control from the date they sign the informed consent form (ICF) until after the last study visit (Follow-up Visit):
    a.) Abstinence, when it is in line with the preferred and usual lifestyle of the subject;
    b.) Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis);

c.) Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted or injectable) or an intrauterine device or system. Note: Non-childbearing potential is defined as surgical sterilization (i.e., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as not having a period for at least 12 consecutive months prior to Screening).

11. Able to give informed consent and willing to comply with all study visits and examinations

7.2.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study: Ocular conditions

1. Corneal findings of any type (including, but not limited to, stromal haze or stromal scarring), in either eye, that, based on investigator's assessment, limit the probability of visual improvement after corneal deturgescence
2. Any ocular pathology requiring treatment with topical ophthalmic drops, with the exception of glaucoma or ocular hypertension
3. Concurrent use of any and all topical ophthalmic medications, prescription and nonprescription (with the exception of study medication, or stable use of topical prostaglandin analogs, alpha-adrenergic agents, and beta-blockers) 1 week (prior to Screening Visit and throughout the duration of the study
4. Use of topical hypertonic saline drops for 3 days prior to Screening and throughout the duration of the study
5. Any active ocular or periocular infection; any history of recurrent or chronic infection or inflammation in either eye
6. History of herpetic infection in either eye
7. History of corneal disease (other than FCED) or corneal surgery in either eye
8. Central corneal edema based on investigator's assessment
9. Current use or likely need for the use of contact lens at any time during the study
10. History of punctual cautery, non-dissolvable punctual plug implants within 1 year of the Screening Visit, or collagen punctual plugs within 6 weeks of the Screening Visit, or anticipated use of any of these treatments in either eye during the study
11. Concurrent disease in either the study eye or fellow eye that could require medical or surgical intervention during the study period
12. History of previous corneal or anterior segment surgery such as LASIK, photorefractive keratectomy, endothelial keratoplasty, penetrating keratoplasty cataract surgery or glaucoma surgery.

Systemic conditions

13. Concurrent use of topical or systemic cyclosporine A for 3 weeks prior to the Screening Visit or during the study
14. Any disease or medical condition that in the opinion of the investigator would prevent the subject from participating in the study or might confound study results

General

15. Participation in other investigational drug or device clinical trials within 30 days prior to enrollment, or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion
16. History of allergic reaction to the investigational drug or any of its components
17. Current use of or likely need for any excluded medication, including systemic medications known to be toxic to or affect the cornea (e.g., carbonic anhydrase inhibitors)
18. Women who are pregnant or lactating

7.3. Discontinuation

7.3.1. Discontinuation of Subjects

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to withdraw a subject from the study in the event of an intercurrent illness, AE, treatment failure, pregnancy, protocol violation, cure, non-compliance with study visits, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Should a subject (or a subject's legally authorized guardian or representative) decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Early termination procedures should be followed.

8. TREATMENTS

8.1. Treatments Administered

MTP-131 1.0% ophthalmic solution administered topically BID to the study eye and vehicle administered topically BID to the fellow control eye

8.2. Discontinuation of Treatment

8.2.1. Dose Modification

Dose modification for an individual subject is not allowed.

8.2.2. Subject Discontinuation

All efforts should be made to schedule an early termination visit for subjects who prematurely discontinue from study drug.

Reasons for discontinuation may include, but are not limited to, the following:

- Investigator determination that it is not in the best interest of the subject to continue participation
- Investigator determination that the subject has met the rescue criteria
- Pregnancy
- SAE
- Any other safety concerns

8.3. Treatments

8.3.1. Study Drug Identification

All study drug is intended for ophthalmic administration. MTP-131 ophthalmic solution or vehicle solution is packaged in white, 10 ml polypropylene bottles with dropper. Each bottle contains nominally 3 mL of solution as either MTP-131 1.0% ophthalmic solution or vehicle. Each bottle also contains sodium chloride appropriate for isotonicity and acetic acid and/or sodium hydroxide as needed for pH adjustment.

8.3.2. Packaging, Labeling, and Storage

Study drug will be supplied as bottles containing 3 mL of MTP-131 1.0% ophthalmic solution paired with an equal quantity of vehicle bottles designated for use in the left or right eye. Study drug bottles are to be stored in a secure area refrigerated (2-8°C) while at the investigative site, and are to be stored in a refrigerator by the subject.

8.3.3. Treatment Logistics and Accountability

All drug accountability records must be kept current, and the investigator must be able to account for all used and unused bottles of study drug. These records should contain the dates, quantity, and study medication:

- Received at site
- Dispensed to each subject
- Returned from each subject (if applicable), and
- Disposed of at the site or returned to the sponsor or designee.

Subjects will be instructed in the proper administration of each study bottle and will be asked to return study medication bottles at the Week 8, Week 12, and Week 16 visits. The clinical monitor responsible for the study site will provide written approval for the destruction or return of unused study medication bottles following reconciliation of all clinical supplies.

8.4. Masking

This is a double-masked, vehicle controlled, paired-eye study.

8.5. Concomitant Medications

Subjects may not use any medication known to be toxic to the cornea.

Subjects may not receive any medications (approved or investigational) for any other ocular condition in the study eye other than the study medication from thirty days prior to Baseline until the End-of-Study Visit (with the exception of study medication, or stable use of topical prostaglandin analogs, alpha-adrenergic agents, and beta-blockers).

All other medications must be used at a stable dose from the time of signing informed consent until the End-of-Study Visit.

8.6. Study Visit Descriptions

8.6.1. Screening (Day -28 to Day 1)

Screening and Baseline assessments may be combined and completed at a single visit. All ophthalmic testing must be conducted on both eyes at each time point. Screening visit should begin at 10:00AM ± 2 hours. Screening procedures may be completed on more than one day, so long as all procedures are completed during the Screening Period. All other visits should begin at the same time of day as the Screening visit ± 1 hour, and may be completed over a one or two day period, at the discretion of the investigator, so long as all procedures are completed during the allowable window for that visit. At each visit, the measurements of corneal thickness and BCVA should occur within ± 1.5 hour of the time in which these measurements were completed at the Baseline visit. Written ICF will be obtained from all subjects prior to conducting any screening procedures. After the subject has provided the ICF, the following assessments will be collected:

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- Inclusion/Exclusion criteria
- Demographics will include ethnicity, race, eye color, history of smoking, and drug/alcohol abuse
- Medical and ocular history and concurrent illnesses
  Concomitant medications
- Record AEs: AEs that occur between the time the subject signs the ICF and the time the subject is dosed with study drug will be summarized in the medical history eCRF and not as an AE unless the event meets the definition of an SAE. This applies to screen failures as well. For subjects who fail screening, AEs and updates (if applicable) must be recorded in the medical history eCRF until the date the subject was determined to have failed screening.
- Vital signs will include temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS scale) and manifest refraction
- Slit lamp examination (SLE)
- Intraocular pressure (Goldman applanation tonometry)
- Blood draw for clinical chemistry
- Blood draw for clinical hematology
- Urine Pregnancy Test (UPT)
- Contrast Sensitivity using VectorVision's CSV-1000 instrument
- Corneal Pachymetry by ultrasound
- Pentacam

8.6.2. Baseline Visit (Day 1)

- Inclusion/Exclusion criteria
- Vital signs will include temperature, respiratory rate, blood pressure after sitting for 15 minutes and pulse
- BCVA (ETDRS scale)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Slit lamp examination (SLE)

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- IOP (Goldman applanation tonometry)
- Specular Microscopy using Konan KSS 409SP
- Blood draw for clinical chemistry and hematology
- Urinalysis
- Urine pregnancy test (only for women of childbearing potential)
- Randomization and training on the proper administration of MTP-131 ophthalmic solution
- Dispense study medication
- Self-administration of 1 drop of MTP-131 ophthalmic solution to the study eye
- Concomitant medications
  Record AEs

8.6.3. Week 1 (+/-3 days)

- Subjects will be examined by the investigator to determine ocular safety and tolerability.
- Subjects that have no signs of ocular toxicity will continue to apply MTP-131 ophthalmic solution BID for the full 12 week treatment period with treatment follow-up visits at Weeks 4, 8, and 12.
- The following assessments will be conducted:
- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes and pulse
- BCVA (ETDRS scale) and manifest refraction
- SLE
- IOP (Goldman applanation tonometry)
- Specular Microscopy
- Corneal pachymetry by ultrasound
- Pentacam
- Record AEs
- Concomitant medications
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Blood draw for clinical chemistry and hematology
- Dispense study medication/ drug accountability

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8.6.4. Week 4 (+/-3 days)

Subjects will continue treatment as described for Day 7 and the following assessments will be conducted:

- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS scale)
- SLE
- IOP (Goldman applanation tonometry)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Specular microscopy
- Record AEs
- Concomitant medications
- Dispense study medication/ drug accountability

8.6.5. Week 8 (+/-3 days)

Subjects will continue treatment as described for Day 7 and the following procedures and assessments will be conducted:

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- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS)
- SLE
- IOP (Goldman applanation tonometry)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Specular microscopy
- Record AEs
- Concomitant medications
- Dispense study medication/ drug accountability

8.6.6. End of Treatment Week 12 (+/-3 days)

The following assessments will be conducted:

- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS)
- SLE
- IOP (Goldman applanation tonometry)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Specular microscopy
- Record AEs
- Concomitant medications
- Urine pregnancy test (only for women of childbearing potential)

8.6.7. Follow-up Week 16 (+/-3 days)

The following assessments will be conducted:

- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS scale)
- SLE

- IOP (Goldman applanation tonometry)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Specular microscopy
- Record AEs
- Concomitant medications
- Blood draw for clinical chemistry and hematology
- Urine pregnancy test (only for women of childbearing potential)

8.6.8. Early Discontinuation Visit/Unscheduled Visits

The following assessments will be conducted:

- Vital signs including temperature, respiratory rate, blood pressure after sitting for 15 minutes, and pulse
- BCVA (ETDRS scale)
- SLE
- IOP (Goldman applanation tonometry)
- Contrast sensitivity using VectorVision's CSV-1000 instrument
- Corneal pachymetry by ultrasound
- Pentacam
- Specular microscopy
- Record AEs
- Concomitant medications
- Blood draw for clinical chemistry and hematology
- Urine pregnancy test (only for women of childbearing potential)

9. EFFICACY, SAFETY EVALUATIONS, SAMPLE COLLECTION AND TESTING, AND APPROPRIATENESS OF MEASURES

9.1. Efficacy Measures

- Change from Baseline in central corneal thickness
- Change from Baseline in best corrected visual acuity (BCVA, ETDRS scale)

- Change from Baseline in endothelial cell count
- Change from Baseline in endothelial cell morphology including:
  1. Hexagonality
  2. Cell density
  3. Coefficient of variation
- Change from Baseline in:
  1. Corneal area affected by microcysts
  2. Number, size, and location of corneal bullae
  3. Severity (as determined by investigator) of corneal stromal folds
- Change from Baseline in contrast sensitivity

9.2. Safety Evaluations

The investigator is responsible for monitoring the safety of subjects who have entered this study and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for the appropriate medical care of subjects during the study. The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study.

The safety profile of MTP-131 ophthalmic solution will be assessed through the recording, reporting, and analyzing of adverse events, clinical evaluations, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by study subjects will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the investigator or reported by the subject. The reporting period for AEs is described in Section 9.6.

9.2.1. Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerge or worsen relative to Baseline during administration of an Investigational Medicinal Product (IMP), regardless of causal relationship.

Adverse Events may include the following:

- Suspected adverse drug reactions: side effects known, or suspected, to be caused by the IMP
- Other medical experiences, regardless of their relationship with the IMP, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing, or physical examination findings
- Events occurring as a result of protocol interventions (pre- or post-IMP administration)

- Reactions from IMP overdose, abuse, withdrawal, sensitivity, or toxicity.

9.3. Pre-Treatment Events

Untoward events and/or incidental diagnoses that occur prior to IMP administration are by definition, unrelated to the study drug. Pre-treatment events or incidental diagnoses will be recorded on the past medical history eCRF. However, if a pre-treatment event is assessed by the investigator as related to a study procedure and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF and processed and followed accordingly.

9.4. Baseline Medical Conditions

Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the IMP, are NOT considered as AEs and should not be recorded as such in the eCRF. These are handled in the efficacy assessments and should be documented on the medical history page of the eCRF.

Baseline medical conditions, not in the therapeutic area of interest/investigation, that worsen in severity or frequency during the study should be recorded and reported as AEs.

9.4.1. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs. However, abnormal laboratory findings or other objective measurements that

- meet the criteria for a SAE,
- result in discontinuation of the Investigational Medicinal Product,
- require medical intervention or
- are judged by the investigator to be clinically significant changes from Baseline should be reported on the AE pages of the eCRF.

When reporting an abnormal laboratory finding on the AE pages of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available (for example, “anemia” rather than “decreased red blood cell count” or “hemoglobin = 10.5 g/dl”).

9.4.2. Serious Adverse Events

A SAE is any AE that:

- Results in death. In case of a death, the cause of death is used as the AE term, and the fatality is considered as the OUTCOME.
- Is life-threatening. The term “life-threatening” refers to a SAE in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise medically important: Important medical events may be considered as SAEs when, based upon medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE and all such cases should be reported in an expedited manner as described in Section 9.7.

9.4.3. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to simplify study treatment or study procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations (not documented prior to ICF signing) or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

9.4.4. Recording of Adverse Events

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period will be recorded on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs must be additionally documented and reported using the study specific SAE eCRF as described in Section 9.4.2.

It is important that each AE report include a description of the event along with the duration (onset and resolution dates), severity, relationship to IMP, potential causal/confounding factors, treatment given or other action taken (including dose modification or discontinuation of the IMP), and the outcome.

As the quality and precision of acquired AE data are critical, investigators should use the AE definitions provided and should observe the following guidelines when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than lay terms (for example, ‘influenza’ rather than ‘flu’), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if available, rather than a list of signs or symptoms (for example, ‘congestive heart failure’ rather than ‘dyspnea, rales, and cyanosis’). However, signs and symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.
- Provisional diagnoses (e.g., “suspected myocardial infarction”) are acceptable, but should be followed up with a definitive diagnosis if later available. Similarly, a fatal event with an unknown cause should be recorded as “death of unknown cause.”
- In cases of surgical or diagnostic procedures, the condition or illness leading to the procedure is considered the AE rather than the procedure itself.

Adverse events occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the eCRF.

9.5. Investigator Assessments

9.5.1. Severity/Intensity

Investigators must assess the severity/intensity of AEs according to the following qualitative toxicity scale:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

9.5.2. Relationship to the Investigational Medicinal Product

Investigators must systematically assess the causal relationship of AEs to the IMP using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the IMP):

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the IMP, and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the IMP.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be excluded and another documented cause of the AE is most plausible.

9.6. Adverse Event Reporting Period

The AE reporting period begins when the subject signs the informed consent and continues through the clinical study's post-treatment follow-up period defined as 30 days after last administration of study drug (Day 58). Within a study, all subjects who took at least 1 dose of IMP - whether they completed the treatment period or not - should enter the 30-day safety follow-up period as defined above.

New protocol-related AEs (caused by any intervention required by the protocol) and updates on all AEs ongoing or with an unknown outcome must be recorded until the last subject visit required by the protocol. A last batch of queries will be sent after the last study visit if remaining ongoing/unknown outcomes of reported AEs are pending. However, SAEs and medically

relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization by the sponsor's Pharmacovigilance department.

Beyond the defined reporting period, any new unsolicited SAE spontaneously reported to the sponsor by the investigator will be collected and processed. This and any additional information on SAEs obtained after database lock will reside solely in the Pharmacovigilance study file.

If a subject is documented as lost-to follow-up, ongoing/unknown outcome AEs will not be followed-up.

For subjects who fail screening, AEs and updates must be recorded in the medical history eCRF until the date the subject was determined to have failed screening. Beyond that date, only SAEs and medically relevant AEs will be followed-up by the sponsor's Pharmacovigilance group and all data will be housed within the Pharmacovigilance study file.

9.7. Serious Adverse Event Expedited Reporting

In the event of an SAE occurring during the reporting period, the investigator must immediately (i.e., within a maximum of 24 hours after becoming aware of the event) inform the sponsor as detailed in the Clinical Study Pharmacovigilance Procedural Manual.

For any SAE, the following minimum information is required as initial notification:

- Investigator/Reporter with full contact information
- Subject identification details (study number, site number, subject number)
- Investigational medicinal product administration details (dose and dates)
- Event verbatim, a brief description of signs/symptoms/or diagnosis and the date of onset
- Seriousness criteria(ion) met
- Relationship of the event to the IMP (e.g., the causality according to the investigator) Reporting procedures and timelines are the same for any new information (follow-up) on a previously reported SAE.

All SAE reports must be completed as described in the eCRF completion guidelines and submitted to the Drug Safety through the Electronic Data Capture (EDC) system of the clinical database. Other relevant information from the clinical database (including demographic data, medical history, concomitant medication, and study drug dosing information) will automatically be sent to the sponsor's safety department via the EDC system when the SAE form is submitted.

For names, addresses, and telephone and fax numbers for SAE back-up reporting, refer to the information included in the Clinical Study Pharmacovigilance Procedural Manual.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the sponsor may have on the SAE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor and (as applicable) to allow the sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

9.8. Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the investigator as related to study treatment (e.g., resulting from an interaction between study drug and a contraceptive medication) are considered adverse events unto themselves. However, all pregnancies with an estimated conception date during the AE reporting period, as defined in Section 9.6 must be recorded in the AE section of the eCRF. This applies to both pregnancies in female subjects and in female partners of male subjects.

The investigator must notify the sponsor in an expedited manner of any pregnancy using the Pregnancy Form and the back-up reporting procedure as described Clinical Study Pharmacovigilance Procedural Manual. Investigators must actively follow up, document, and report on the outcome of all pregnancies, even if subjects are withdrawn from the study.

The investigator must notify the sponsor of these outcomes using Section II of the Pregnancy Form and submit the information using the back-up reporting procedure. Any abnormal outcome must be reported in an expedited manner as described in Section 9.7, while normal outcomes must be reported within 45 days from delivery.

In the case of an abnormal outcome, whereby the mother sustains an event, the SAE Report Form is required and will be submitted as described above.

9.9. Responsibilities to Regulatory Authorities, Investigators, Ethics Committees, and Ethical/Institutional Review Boards

The sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her subjects to the Ethics Committee and/or Ethical/Institutional Review Board (EC/ERB/IRB) that approved the study

In accordance with ICH GCP guidelines, the sponsor will inform the investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study, or alter the EC's/IRB's approval/favorable opinion to continue the study. In particular, and in line with respective regulations, the sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions or SUSARs). The investigator should place copies of these safety reports in the investigator site file. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the sponsor will provide appropriate safety reports directly to the IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any safety reports provided by the sponsor and of filing copies of all related correspondence in the investigator site file.

For studies covered by the European Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that directive and with the related detailed guidance's.

9.10. Sample Collection and Testing

Table 2 lists the schedule for sample collections in this study.

Attachment 1 lists the laboratory tests that will be performed for this study.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.11. Appropriateness of Measures

The measures used to assess safety in this study are consistent with those widely used and generally recognized as reliable, accurate, and relevant.

10. SAMPLE SIZE AND STATISTICAL METHODS

10.1. Determination of Sample Size

For this Phase 1/2, a sample size of approximately 16 patients is considered sufficient. The sample size of the study is based on precedent set by prior Phase 1/2 studies of similar nature and design. It is considered sufficient to provide for preliminary assessment of safety and tolerability at each dose.

10.2. Statistical and Analytical Plans

10.2.1. General Considerations

In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation, median, minimum, and maximum values.

All study data are to be displayed in the data listings.

Statistical analysis of this study will be the responsibility of the sponsor or its designee. Subject disposition summaries will include the number of subjects entered and the numbers treated (included in the Safety population) by treatment regimen and disease group for all subjects. The number and percentage of subjects who complete or discontinue from the study will be summarized by reason for discontinuation for each treatment regimen/disease group.

Subject's age, sex, weight, height, BMI, and other demographic characteristics will be recorded and summarized by treatment group. Medical history will be listed.

All study data are to be displayed in the data listings.

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Additional details regarding analyses will be included in separate statistical analysis plan.

10.2.2. Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.3. Subject Characteristics

Baseline characteristics will include standard demography (e.g., ethnicity, race, eye color, history of smoking, and drug/alcohol abuse), disease characteristics including medical history, and medication history for each subject.

10.2.4. Concomitant Therapy

Current use of or likely need for systemic medications known to be toxic to the cornea are prohibited from the Screening Visit until completion of the study (completion of the Follow-Up Visit).

All other medications, including any over-the-counter treatments, vitamins, or supplements, must have been unchanged and constant for at least one month prior to the Baseline Visit and must remain stable through the completion of the study (completion of the Follow-up Visit).

10.2.5. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

10.2.6. Endpoints and Methodology

10.2.6.1. Analysis Populations

All subjects who receive at least one dose of study drug will be included in the Safety Population according to the treatment received.

10.2.6.2. Primary (Safety) Endpoints The

primary endpoints for this study include:

- The incidence and severity of systemic and ocular AEs
- Change from Baseline in slit lamp findings
- Change from Baseline in intraocular pressure

10.2.7. Secondary (Efficacy) Endpoints

The efficacy endpoints are listed in Section 9.1.

10.2.8. Safety Analyses

AEs will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having AEs and dose level. Severity and relationship to study drug will be listed as appropriate.

10.2.8.1. Adverse Events

All AEs will be coded to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (version to be specified in the clinical study report).

All reported AEs will be listed.

In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will

be included in related tables (i.e., considered related). Summary tables will be sorted by SOC, then PT.

10.2.8.2. Deaths and Other Serious Adverse Events Listings

will be provided for the following:

- Deaths
- SAEs
- AEs leading to discontinuation of study drug

10.2.8.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics by post-dosing shifts relative to Baseline where appropriate, and data listings of clinically significant abnormalities

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Shift tables (i.e., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment, will be produced.

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each treatment group.

10.2.8.4. Vital Signs

Vital signs will be summarized by changes from Baseline values at each dose level using descriptive statistics.

10.2.8.5. Other Safety Parameters

Any other safety data captured on the eCRF will be listed.

10.2.8.6. Interim Analyses

No interim analyses are planned for this study.

11. STUDY MONITORING

11.1. Source Document Requirements

The investigator will prepare and maintain adequate and accurate subject records (source documents). The investigator will keep all source documents on file. Source documents will be available at all times for inspection by authorized representatives of the regulatory authorities.

11.2. Case Report Form Requirements

Clinical data will be recorded in an electronic Case Report Form (eCRF) by the study investigator or authorized designee. The investigator will ensure the accuracy, completeness, and timeliness of the data reported in the eCRFs. Case report forms will be available at all times for inspection by authorized representatives of the regulatory authorities.

11.3. Study Monitoring

Site monitors contracted by the sponsor will contact and visit the investigator, and will be allowed to review and inspect the various records of the study on request (eCRFs and other pertinent data), provided that subject confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the site monitor's responsibility to inspect the eCRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to good clinical practice (GCP) guidelines.

The investigator agrees to cooperate with the site monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

12. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, the sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the sponsor or

its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs with direct access to original source documents.

12.1. Data Capture System

The computerized handling of the data after receipt of the eCRFs may generate additional requests via electronic queries to which the investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be appended to the eCRFs held by the investigator and sponsor.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor, their designee, and the regulatory authorities. Should this occur, the investigator will be responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the regulatory authorities to resolve any problems found during the audit or inspection

Documents subject to audit or inspection include, but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In all instances, the confidentiality of the data will be respected.

14. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

14.1. Informed Consent

The principles of ICF are described in ICH Guidelines for GCP.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written ICF from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF will be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.

Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that ICF was given.

The original ICF will be retained by the investigator as part of the subject's study record, and a copy of the signed ICF will be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated appropriately. All study subjects will be informed of the new information and provide their written consent if they wish to continue in the study.

14.2. Subject Confidentiality and Data Protection

The investigator will take all appropriate measures to ensure that the anonymity of each study subject will be maintained.

The subject's and investigators' personal data will be treated in compliance with all applicable laws and regulations.

14.3. Ethical Review

An appropriately constituted IRB, as described in ICH Guidelines for GCP, will review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (e.g., advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB will be informed as soon as possible

In addition, the IRB will be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) will be kept on file by the investigator.

14.4. Regulatory Considerations

This study will be conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The ICH GCP Guideline [E6]
3. Applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable IRB(s). Some of the obligations of the sponsor may be assigned to a third party organization.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data.

14.4.1. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, the investigator will sign the protocol signature page and send a copy of the signed page to a sponsor representative.

14.4.2. Final Report Signature

The investigator will sign the final clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14.4.3. Study Monitoring

The investigators and institution(s) will permit trial-related monitoring of the eCRF data by Stealth BioTherapeutics Inc., or their assignee by providing direct access to source data and/or documents. The study monitor will verify the eCRFs 100 % against the source documentation. Deviations from the protocol with regard to subject enrollment or study conduct will also be noted in the source documentation, in the eCRF and a complementary database. A sponsor representative will visit the site to initiate the study, prior to the first treatment of the first subject, and at agreed times throughout the study, including at the end of the study. Medication dispensing and clinical drug supply records will be 100% verified at the study site by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the sponsor.

14.4.4. Retention of Records

All study related material including source documents, eCRFs and EC correspondence and analyses and any other documentation required by applicable laws and regulations will be maintained for fifteen (15) years after completion of the study or notification from the sponsor that the data can be destroyed, whichever comes first.

14.4.5. Disclosure of Information

Information concerning the investigational medication and patent application processes, scientific data or other pertinent information is confidential and remains the property of Stealth BioTherapeutics Inc. The investigator may use this information for the purposes of the study only. It is understood by the investigator that Stealth BioTherapeutics Inc., will use information developed in this clinical study in connection with the development of the investigational medication and, therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the sponsor.

The investigator may not submit for publication or presentation the results of this study without first receiving written authorization from Stealth BioTherapeutics Inc. Stealth BioTherapeutics Inc., agrees that, before it publishes any results of the study, it shall provide the investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript to the publisher.

15. REFERENCES

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SPONSOR'S PROTOCOL SIGNATURE PAGE

A PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED, VEHICLE CONTROLLED, PAIRED-EYE PHASE 1/2 CLINICAL STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF MTP-131 TOPICAL OPHTHALMIC SOLUTION (OCUVIA™) IN SUBJECTS WITH FUCHS' CORNEAL ENDOTHELIAL DYSTROPHY (FCED) PRESENTING WITH MILD TO MODERATE CORNEAL EDEMA Study No.: SPIFD-101

Sponsor: Stealth BioTherapeutics Inc.
275 Grove Street, Suite 3-107
Newton, MA 02466

Protocol Date/Version: 18 August 2015 / Version 1.0

Printed name:	Gregory Gordon, MD Senior Director, Clinical Research
Signature:	
Date:	08/18/2015

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

A PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED, VEHICLE CONTROLLED, PAIRED-EYE PHASE 1/2 CLINICAL STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF MTP-131 TOPICAL OPHTHALMIC SOLUTION

(OCUVIA™) IN SUBJECTS WITH FUCHS' CORNEAL ENDOTHELIAL DYSTROPHY (FCED) PRESENTING WITH MILD TO MODERATE CORNEAL EDEMA

Study No.: SPIFD-101

Sponsor: Stealth BioTherapeutics Inc.
275 Grove Street, Suite 3-107
Newton, MA 02466

Protocol Date/Version: 18 August 2015 / Version 1.0

I have read all pages of this clinical study protocol for which Stealth BioTherapeutics Inc. is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Investigator:

Printed name:	
Signature:	
Date:	
Site address:	

Attachment 1. SPIFD-101 Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Calcium
	Glucose (non-fasting)
	Albumin
Urinalysis:	Chloride
Specific gravity	Bicarbonate
pH	Total protein
Protein	
Glucose	**Pregnancy Test**
Ketones	Serum & urine
Blood	(Women of childbearing potential only)

Signature Certificate

Document Reference: PVB57NJPAK9R2Z67ZKIH2A

RightSignature
Easy Online Document Signing

Gregory Gordon
Party ID: 7WRGJHJ4D3HU3W8EYNK2ZU
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Digital Fingerprint Checksum **45a0c8f9e17bfca54335d96adaefc3ac7170eb30**

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2015-08-18 12:32:37 -0700	All parties have signed document. Signed copies sent to: Gregory Gordon and Kandarp Prajapati.
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