A Prospective, Randomized, Double-Masked, Vehicle Controlled, Phase 2 Clinical Study with Open Label Extension to Evaluate the Safety, Tolerability and Efficacy of Elamipretide (MTP-131) Topical Ophthalmic Solution in Subjects with Leber's Hereditary Optic Neuropathy (LHON)

NCT02693119

11 Mar 2019

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Study Phase:	Phase 2
Product Name:	Elamipretide Topical Ophthalmic Solution
IND Number:	114,234
Formulation:	Topical Ophthalmic
Sponsor:	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 +1 (617) 600-6880
Sponsor Chief Clinical Development Officer:	Jim Carr, Pharm.D. Chief Clinical Development Officer 275 Grove Street 3-107, Newton, MA 02466, USA Jim.Carr@StealthBT.com +1 617-762-2503
Sponsor Study No.:	SPILH-201/SPILH-201OLE
Protocol Date:	11 Mar 2019
Protocol Version:	Version 10.0

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sponsor Medical Monitor	Sandrin Bergheanu, MD, PhD	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 +31 (0) 641 476 460

Note: Individual site contacts will be included as part of the study file.

SPONSOR'S PROTOCOL SIGNATURE PAGE

A Prospective, Randomized, Double-Masked, Vehicle Controlled, Phase 2 Clinical Study with Open Label Extension to Evaluate the Safety, Tolerability, and Efficacy of Elamipretide Topical Ophthalmic Solution in Subjects with Leber's Hereditary Optic Neuropathy (LHON)

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275 Grove Street, Suite 3-107

Newton, MA 02466

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Signature: **Date:**

Jim Carr 03/11/2019

Jim Carr, Pharm.D.
Chief Clinical Development Officer
Stealth BioTherapeutics Inc.

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

A Prospective, Randomized, Double-Masked, Vehicle Controlled, Phase 2 Clinical Study with Open Label Extension to Evaluate the Safety, Tolerability and Efficacy of Elamipretide (MTP-131) Topical Ophthalmic Solution in Subjects with Leber's Hereditary Optic Neuropathy (LHON)

Study No.: SPILH-201/SPILH-201OLE

Sponsor: Stealth BioTherapeutics, Inc.
275 Grove Street, Suite 3-107
Newton, MA 02466
+1 (617) 600-6888

Protocol Date/Version: 11 Mar 2019/Version 10.0

I have read all pages of this clinical study protocol for which Stealth BioTherapeutics is the sponsor. I agree to conduct the study 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:	

1. SYNOPSIS

Name of Sponsor/Company: Stealth BioTherapeutics Inc.

Investigational Product: Elamipretide Topical Ophthalmic Solution

Title of Study: A Prospective, Randomized, Double-Masked, Vehicle Controlled, Phase 2 Clinical Study with Open Label Extension To Evaluate the Safety, Tolerability and Efficacy of Elamipretide (MTP-131) Topical Ophthalmic Solution in Subjects with Leber's Hereditary Optic Neuropathy (LHON)

Study Centers: This single center study will be conducted at the Doheny Eye Center, University of California, Los Angeles, California, United States (US).

Study Objective: This study has two parts: a double-masked period and an open-label extension period. The objectives for each part of the study are as follows:

- The objective of the double-masked period is to evaluate the safety, tolerability, and efficacy of elamipretide 1.0% topical ophthalmic solution relative to vehicle administered two times per day (BID) for 52 weeks in the treatment of LHON.
- The objective of the open-label extension is to evaluate the safety and tolerability up to an additional 108 weeks of treatment via in an open label setting for subjects who complete the double-masked period.

Study Design

This is a prospective, randomized, double-masked, vehicle controlled, single-center study plus open label extension (OLE) in approximately 12 subjects with LHON having the genetic mitochondrial DNA mutation m.11778G>A. Each subject will be randomized in a blinded manner into one of three treatment groups in a 1:1:1 ratio: (a) 1 drop of elamipretide 1.0% topical ophthalmic solution BID applied to the left eye (OS) and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, (b) 1 drop of elamipretide 1.0% topical ophthalmic solution BID applied to the right eye (OD) and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, or (c) 1 drop of elamipretide 1.0% topical ophthalmic solution BID to each eye (OU). After completing 52 weeks of masked treatment, all subjects will be invited to continue into an OLE of 1 drop of elamipretide 1.0% topical ophthalmic solution BID instilled into both eyes (Oculus Uterque [OU]) for up to an additional 108 weeks.

There are 4 periods in this study:

- Screening (up to 6 weeks)
- Double-masked treatment period (52 weeks)
- Open-Label Extension period (108 weeks)
- Follow-up Period (4 weeks) after completion of End of Treatment (EOT) visit (for subjects not enrolling in an expanded access program (EAP)).

Screening

Written informed consent will be obtained from all subjects prior to the Screening Visit. Screening procedures may be completed on more than one day, as long as all procedures are

completed during the Screening Period. All other visits may be completed over a 1 or 2 day period, at the discretion of the Investigator, as long as all procedures are completed during the allowable window for that visit.

The Screening examination will be performed no more than 42 days prior to the Baseline visit. For applicable female subjects, urine pregnancy testing will be performed prior to initiation of treatment. The day of randomization is defined as Study Day 1. Subjects will be considered enrolled in the study upon randomization.

Once informed consent has been obtained, confirmation of LHON genetic mutation m.11778G>A by mitochondrial deoxyribonucleic acid (DNA) analysis will be performed, if not previously confirmed by written documentation using reliable test methods. Additional data will be collected from a complete pre-treatment examination, consisting of vital signs, physical exam, serum pregnancy test for women of child-bearing potential, routine blood chemistries and urinalysis, measurement of best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, manifest refraction, intraocular pressure (IOP) measurement, slit lamp examination, dilated fundus examination, fundus photography, Humphrey automated visual field testing (SITA FAST 30-2 stimulus III), mean retinal nerve fiber layer (RNFL) and mean retinal ganglion cell layer (RGCL) thickness as measured by spectral domain optical coherence tomography (SD-OCT; Cirrus), photopic negative response electroretinography (PhNR-ERG), full field ERG and the Visual Functioning Questionnaire-39 (VFQ-39) to assess visual quality-of-life measures.

Subjects will undergo Humphrey automated visual field testing at both Screening (Visit 1) and Baseline (Visit 2) visits (performed at least 1 day apart). In the event that a subject's 2 visual field tests differ by greater than 5 dB, an additional two Humphrey automated visual field tests may be performed at either the Baseline Visit or within 1 week of the Baseline Visit. If the test does not occur on the day of the Baseline Visit, other Baseline procedures, which have already been completed, should not be repeated. In order to be randomized into the study, subjects must have two consecutive visual field tests with results that meet the study criteria and that are within 5 dB of each other. Subjects will be considered enrolled in the study upon randomization.

Double-masked Treatment Period
At the time of randomization, training on the proper administration of topical ophthalmic solution and self-administration (by the subject or regular caregiver) will occur. Subjects will be read a standard script explaining the importance of applying the correct drug product to each eye on a twice daily basis for the 52-week Treatment Period. Efficacy, safety, and tolerability will be measured throughout the Treatment Period. Visits will occur at: Day 5 (±2 days), Week 4 (± 4 days), Week 8 (± 4 days), Week 12 (± 4 days), Week 16 (± 7 days), Week 20 (± 7 days), Week 24 (± 7 days), Week 28 (± 7 days), Week 32 (± 7 days), Week 36 (± 7 days), Week 40 (± 7 days), Week 44 (± 7 days), Week 48 (± 7 days), and Week 52 (± 7 days). After completion of the 52-week Treatment Period or the Week 56 follow up period, subjects will be invited to participate in the OLE for up to 108 weeks. If a subject does not consent to the OLE, he/she will complete the study at the Week 56 (±7 days) visit.

Open-Label Extension

The OLE will begin after the subject completes the Week 52 or Week 56 visit. Following completion of all Week 52 or Week 56 procedures described in the Schedule of Events

(Attachment 1), subjects will receive a supply of 1.0% elamipretide topical ophthalmic drops to instill at home. Subjects (or trained caregivers) should administer elamipretide OU BID every day. Subjects will visit the trial site for the 16-Month Visit (Week 68), the 20-Month Visit (Week 84), the 24-Month Visit (Week 100), the 28-Month Visit (Week 116), the 32-Month Visit (Week 132), the 36-Month Visit (Week 148), and the 39-Month/End of OLE Treatment (EOT) Visit (Week 160) to complete assessments as described in the Schedule of Events. Monthly safety telephone calls will be completed in between site visits. The monthly safety telephone call script is provided in Attachment 4. Subjects will have the opportunity to continue receiving elamipretide through an EAP immediately following the 36 or 39-Month (EOT) Visit. For those subjects who consent to enroll in the EAP at either visit, there will not be a Follow-Up Period. That visit will be considered the End-of-Study visit. For those subjects who wishes not to enroll in an EAP, the Follow-up Period will begin after completion of 39-Month (EOT) visit and will last for 4 weeks. During the Follow-Up Period, subjects will continue to follow all study requirements. At the end of the Follow-Up Period, subjects will return to the trial site for the End-of-Study visit for final study assessments and to return used and unused bottles and all other study instruments/materials to the trial site.

Study procedures, their timing, and additional details are found in the Schedule of Events, Attachment 1.

Investigational Product, Dosage and Mode of Administration:
Double-Masked Period: Elamipretide topical ophthalmic solution 1.0%, 1 drop administered topically BID to treatment eye. Vehicle solution, 1 drop administered topically BID to control eye.
OLE Period: Elamipretide topical ophthalmic solution 1.0%, 1 drop administered topically BID into both eyes

Number of Subjects (planned):
Approximately 12 subjects will be enrolled in this study and open label extension.

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

1. Adults ≥18 and ≤ 50 years old at the time of loss of vision in the second eye. Loss of vision in both eyes of ≥1 year and ≤10 years at the time of the Screening Visit.
2. Able to provide informed consent and willing to comply with all study visits and examinations
3. Diagnosis of LHON based on clinical and ophthalmic functional/anatomic test findings, and satisfactory documentation of the mitochondrial DNA mutation m.11778G>A
4. Loss of vision in both eyes of ≥1 year and ≤10 years at the time of the Screening Visit and current clinically stable visual function (as assessed by the Investigator)
5. Mean Deviation (MD) between -7.5 and -30 dB on Humphrey automated visual field testing (SITA FAST 30-2, stimulus III) on two tests during the Screening Period. In addition, the MD on the two qualifying, exams must be within 5 dB of each other for the subject to qualify for study inclusion
   Note: As described in the Study Design, up to four Humphrey automated visual field tests are allowed during the Screening Period.

6. Adequate mean retinal nerve fiber layer (RNFL) thickness based on the investigator's assessment with consideration of spectral domain optical coherence tomography (SD-OCT) values, such as between 50 and 90 microns (inclusive) OU.
7. Adequate retinal ganglion cell layer (GCL) thickness based on the investigator's assessment with consideration of SD-OCT values of at least 40 microns OU.
8. Media clarity, subject able to undergo pupillary dilation and able to cooperate sufficiently for adequate ophthalmic visual function 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. Documentation of having satisfactorily completed at least two previous Humphrey automated visual field tests prior to screening.
11. If of childbearing potential or in a relationship with a partner of childbearing potential, are able to abstain from sex or use acceptable contraception during the study and for 28 days after dosing.
    a. For men: Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. The subject also agrees to use an acceptable method of contraception should they become sexually active with a partner of child-bearing potential. Subjects must use a condom with spermicide from the date of informed consent until at least 28 days after the last dose of study drug. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

    For women: Abstinence is only acceptable when it is in line with the preferred and usual lifestyle of the subject. The subject agrees to use an acceptable method of contraception should they become sexually active. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days before the Screening visit or confirmed via sperm analysis), 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 are acceptable methods.

    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).

Exclusion Criteria:

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

Ocular conditions

1. Any other ocular pathology requiring treatment with prescription topical ophthalmic drops (e.g., glaucoma, dry eye)
2. Cup to disc ratio of > 0.8 in either eye
3. Any active ocular or periocular infection; any history of recurrent or chronic infection or inflammation in the study eye
4. History of herpetic infection in either eye
5. History of intraocular surgery
6. Active corneal disease
7. Current use or likely need for the use of contact lens at any time during the study
8. Concurrent disease in either the study eye or fellow control eye that could require medical or surgical intervention during the study period
9. Media opacity, suboptimal pupillary dilatation, or severe refractive error that interferes with adequate retinal imaging

Systemic conditions

10. Known to be immunocompromised or receiving systemic immunosuppression
11. Any systemic or non-ocular symptoms that in the opinion of the Investigator may be related to LHON (i.e. "LHON-plus"), per investigator's assessment and decision.
12. Any disease, medical condition or psychological condition that in the opinion of the Investigator would prevent the subject from participating in the study or might confound study results

General

13. 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
14. History of participation in an interventional clinical trial investigating the use of gene therapy as a treatment for LHON
15. History of allergic reaction to the investigational drug or any of its components
16. History of histamine intolerance (e.g., a known deficiency of endogenous histamine degradation)
17. Current use of or likely need for any excluded medication (idebenone and vitamins acceptable)
18. Women who are pregnant or lactating

Planned Study Duration:

Up to 170 weeks, including up to 6 weeks for screening prior to Day 1/Baseline study randomization, a 52 week double-masked treatment period, a 108 week OLE, and a 4 week safety follow-up period (for subjects not enrolling in an EAP).

Criteria for Evaluation:
Safety Endpoint:

- The incidence and severity of systemic and ocular adverse events (AEs)

Efficacy Endpoints:

- Change from Baseline in photopic negative response electroretinography (PhNR-ERG) response pattern
- Change from Baseline in visual field MD as measured by Humphrey automated visual field testing stimulus III
- Change from Baseline in color discrimination / contrast sensitivity
- Change from Baseline in best corrected visual acuity (BCVA)
- Change from Baseline in VFQ-39 score
- Change from Baseline in mean retinal nerve fiber layer thickness by SD-OCT
- Change from Baseline in mean retinal ganglion cell layer thickness by SD-OCT

Optional (per subject secondary use consent):
Exploratory Biomarkers may be evaluated post study completion:

- Serum phosphorylated axonal neurofilament analysis
- Serum mitochondrial DNA copy number

Statistical Methods:
This study has a double-masked treatment component, in which comparisons of the elamipretide treated eye will be compared to the vehicle treated eye. Outcomes for the double-masked period will be analyzed consistent with this design characteristic.

This study also has an open-label treatment component, in which both eyes will receive elamipretide treatment. The key outcomes of interest will be the comparison of the vehicle eye outcomes (per the double-masked treatment period) to the continued outcomes from the elamipretide eye (also from the double-masked treatment period) as both eyes are treated with elamipretide. Open-label data will be presented using the following treatment identifier conventions:

- Vehicle to Elamipretide (eyes originally randomized to vehicle in DB and then treated with elamipretide in OLE)
- Elam to Elam (eyes originally randomized to elamipretide in DB and continuing treatment with elamipretide in OLE)
- Total (pooling both eyes)

Analysis Populations: All subjects who receive at least one dose of study drug will be included in the Safety Population. In general, subjects in the Safety Population are expected to have received active treatment in at least one eye and so will be identified as such.

Safety Analyses: Adverse events will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having treatment-emergent AEs. SAEs and AEs resulting in discontinuation will be presented.

For the Double-masked period, AEs will be presented as follows:
Adverse Events attributed to an individual eye or both eyes will be tabulated by specific treatment received in that eye or eyes.
Systemic AEs will be presented overall (as all patients during the double-masked period receive both elamipretide AND vehicle).

For the OLE, AEs will be presented overall for all patients (and eyes) combined. Severity and relationship to study drug will be listed as appropriate.

OLE analysis will consist of all safety data being presented overall (pooled) for all subjects.

Efficacy Analyses: Baseline, demographic and other non-eye specific characteristics will be presented by single eye vs. both eye (receiving active) treatment groups. 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. 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.

Plots and figures that demonstrate the time-course of changes in efficacy parameters over time, from baseline (prior to the start of double-masked treatment) through the double-masked treatment period and through the open-label treatment period will be presented. A mixed model for repeated measures (MMRM) will be used, with effects for treatment, study visit, and treatment*visit interaction, and a random effect for subject. The model-based adjusted means (LSMeans) and standard errors will be presented in these plots.

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

Additional details regarding analyses of efficacy measures within single eye treated subjects and between subjects (single eye vs. bilateral) will be included in separate statistical analysis plan.

Sample Size:
For this Phase 2 study, the sample size of 12 subjects is based on the rarity of the disease under investigation and is judged as reasonable for exploring clinical safety, tolerability, and efficacy outcomes in this first study in the target population.

Table of Contents

2. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition or Explanation
AE	adverse event
BCVA	best corrected visual acuity
BID	two times per day
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
dB	Decibel
DFE	dilated fundus examination
DNA	deoxyribonucleic acid
EAP	Expanded Access Program
EC	Ethical Committee
eCRF	electronic case report form
ECG	Electrocardiogram
EDC	electronic data capture
ERB	Ethical Review Board
ETC	electron transport chain
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
GCL	ganglion cell layer
ICF	informed consent form
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IOP	intraocular pressure
IWRS	Interactive Web Randomization System
ISCEV	International Society for Clinical Electrophysiology of Vision
LHON	Leber's hereditary optic neuropathy
MD	mean deviation
MedDRA	Medical Dictionary for Regulatory Activities
mtDNA	mitochondrial DNA
OD	right eye
OLE	Open Label Extension
OS	left eye
OU	each eye
PhNR-ERG	photopic negative response electroretinography
PT	preferred term
RGC	retinal ganglion cells
RGCL	retinal ganglion cell layer

Abbreviation	Definition or Explanation
RNFL	Retinal nerve fiber layer
SAE	serious adverse event
SD-OCT	spectral domain optical coherence tomography
SLE	slit lamp examination
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
US	United States
VEGF	vascular endothelial growth factor
VFQ-39	Visual Functioning Questionnaire-39

3. INTRODUCTION

Stealth BioTherapeutics Inc. (Stealth) is a biotechnology company with a focus on treating mitochondrial dysfunction. Stealth's lead candidate is elamipretide, a novel tetrapeptide, for the treatment of diseases in which mitochondrial dysfunction is an integral component. Stealth has conducted preclinical and Phase 1 and 2 clinical studies to assess elamipretide in diseases with unmet treatment needs including inherited mitochondrial diseases.

Optic neuropathies are common to more than 20 inherited mitochondrial diseases (Yu-Wai-Man et al. 2011). Leber's hereditary optic neuropathy (LHON) is the most common mitochondrial DNA (mtDNA) disorder. It results from a single point mutation occurring in mtDNA. Over 95% of cases are due to one of three point mutations in the mitochondria genome: m.3460G>A, m.11778G>A and m.14484T>C (Schrier and Falk 2011). The disease is maternally transmitted and primarily affects young adults between 20 and 30 years of age. Importantly, all three primary LHON mitochondrial DNA mutations result in amino acid substitutions in protein subunits that compose Complex I of the electron transport chain (ETC). LHON differs from most other mitochondrial diseases in that it shows high tissue specificity. Subjects with most other mitochondrial diseases have defects in multiple organs, including brain, muscle, heart and other vital organs, whereas the clinical features of LHON are usually localized to the eye's retinal ganglion cells. These cells are essential for transmission of visual information from the photoreceptors of the retina to the brain, which processes this information into visual images.

Clinically, LHON is characterized by bilateral sub-acute loss of central vision as a result of degeneration of the retinal ganglion layer, initially within the papillomacular bundle. At onset, patients describe a loss of color vision in one eye followed by a painless subacute decrease in central vision accompanied by an enlarging centrocaecal scotoma (a horizontal oval defect in the field of vision situated between and embracing both the point of fixation and the blind spot).

The presence of mtDNA point mutations is required for the development of LHON, although there are other factors that contribute to disease manifestation. Additional genetic and environmental factors such as tobacco smoke and drinking alcohol can interact with the primary mtDNA defect and determine whether a carrier of one of the genetic mutations ultimately develops optic nerve dysfunction leading to blindness.

A characteristic pathologic finding of LHON is the selective deterioration of retinal ganglion cells (RGC) whose axons form the optic nerve. The mechanism(s) that directly links mitochondrial dysfunction to the selective vulnerability of the RGC's is not fully understood. In the chronic phase of LHON, patients typically have a bilateral visual deficit that is symmetrical and permanent. Most remain legally blind, unable to drive, or find employment.

Leber's hereditary optic neuropathy shows incomplete penetrance with only 50% of male and 10% of female carriers developing the optic neuropathy in their lifetime. Secondary (non-environmental) factors modulating the mitochondrial DNA LHON mutations still remain largely

undefined, although the gender bias has been linked to the synergistic influence of visual-loss susceptibility loci on the X-chromosome. Genetic factors, however, cannot provide a complete explanation for the reduced penetrance.

In summary, LHON is genetic multifactorial disease, with environmental triggers operating at the individual level contributing to the observed intra- and inter-familial variability in penetrance.

MTP-131 reduces mitochondrial oxidative stress by enhancing mitochondrial function via selective interaction with cardiolipin. It has been found effective in multiple preclinical models of eye disease. In cultured cells, MTP-131 has been shown to reduce glucose- and peroxide-induced oxidative stress, apoptosis and to improve cell survival in human retinal endothelial cells (Li et al. 2011), human trabecular meshwork cells (Chen et al. 2011), and human retinal pigmented epithelial cells (Liang et al. 2010). Pre-treatment with MTP-131 has been shown to protect cultured retinal pigmented epithelium from mitochondrial dysfunction caused by repetitive hydroquinone exposure (Cousins, 2015). When given subcutaneously to streptozocin-diabetic rats, MTP-131 reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye (Huang et al. 2013). MTP-131 given subcutaneously to high fat and/or streptozotocin diabetic mice prevented and corrected visual functional loss (Alam et al. 2012). In a recent open-label, dose-escalation study, two of fifteen patients with diabetic macular edema treated for 28 days with topical MTP-131 solution showed a greater than twenty percent decrease in central subfield thickness (unpublished data, Stealth BioTherapeutics Protocol SPIOC-101). In this study, twenty subjects with either DME or AMD were enrolled into one of two dosing cohorts; 0.3% ophthalmic solution to one eye twice daily for 28 days or 1.0% ophthalmic solution to one eye twice daily for 28 days. A total of four AEs were reported in the study; none were considered related to MTP-131 by the investigator. There were no local tolerability issues reported, and there were no significant findings on physical examinations, ophthalmic examinations, vital signs or laboratory measurements. It is theorized that treatment with MTP-131 of subjects suffering from retinal diseases associated with mitochondrial dysfunction may have an effect on mitochondrial oxidative stress levels and retinal disease activity.

SPIFD-101: A Phase 1/2 Clinical Study to Evaluate the Safety, Tolerability and Efficacy of elamipretide Topical Ophthalmic Solution in Subjects with Fuchs' Corneal Endothelial Dystrophy (FCED) Presenting with Mild to Moderate Corneal Edema has completed treatment of 16 subjects. This was a Randomized, Double-Masked, Vehicle Controlled Dosing regimen which included MTP-131 1.0% topical ophthalmic solution relative to vehicle administered two times per day (BID) for 12 weeks, and 4 weeks of follow up evaluation. Two SAEs occurred in one subject that were unrelated to study drug; small bowel blockage and dehydration. Both SAEs resolved with no sequelae. The subject withdrew from the study during the SAE. No serious adverse reactions (SARs), or suspected unexpected SARs (SUSARs) have been reported.

SPIFD-101 is extending to a Part B portion and is expected to enroll an additional 11 subjects to be treated with 3.0% elamipretide topical ophthalmic solution or vehicle BID for 12 weeks.

4. STUDY OBJECTIVE

This study has two parts: a double-masked period and an open-label extension period. The objectives for each part of the study are as follows:

- The objective of the double-masked period is to evaluate the safety, tolerability, and efficacy of elamipretide 1.0% topical ophthalmic solution relative to vehicle administered two times per day (BID) for 52 weeks in the treatment of LHON.
- The objective of the open-label extension is to evaluate the safety and tolerability over an additional 108 weeks of treatment in an open label setting for subjects who complete the double-masked period.

5. INVESTIGATIONAL PLAN

5.1. Summary of Design

This is a prospective, randomized, double-masked, vehicle-controlled, single-center study plus OLE in which approximately 12 subjects with LHON having the genetic mitochondrial DNA mutation m.11778G>A are planned to be randomized in a blinded manner into one of three groups in a 1:1:1 ratio: (a) 1 drop of elamipretide 1.0% topical ophthalmic solution BID OS and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, (b) 1 drop of elamipretide 1.0% topical ophthalmic solution BID OD and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, or (c) 1 drop of elamipretide 1.0% topical ophthalmic solution BID OU. After completion of the 52-week Treatment Period or the Week 56 follow up period, subjects will be invited to participate in the OLE for up to 108 weeks. If a subject does not consent to the OLE, he/she will complete the study at the Week 56 (±7 days) visit. There are 4 periods in this study:

- Screening (up to 6 weeks)
- Double-Masked treatment period (52 weeks)
- Open-Label Extension period (108 weeks)
- Follow-up Period (4 weeks) after completion of End of Treatment (EOT) visit (for subjects not enrolling in an EAP).

Screening

Written informed consent will be obtained from all subjects prior to the Screening Visit. Screening procedures may be completed on more than one day, as long as all procedures are completed during the Screening Period. All other visits may be completed over a 1 or 2 day period, at the discretion of the Investigator, as long as all procedures are completed during the allowable window for that visit.

The Screening examination will be performed no more than 42 days prior to the Baseline visit. For applicable female subjects, urine pregnancy testing will be performed prior to initiation of treatment. The day of randomization is defined as Study Day 1.

Once informed consent has been obtained, confirmation of LHON genetic mutation m.11778G>A mitochondrial DNA by mitochondrial DNA analysis will be performed, if not previously confirmed by written documentation using reliable test methods. Additional data will be collected from a complete pre-treatment examination, consisting of vital signs, physical exam,

routine blood chemistries and urinalysis, measurement of best corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, manifest refraction, intraocular pressure (IOP) measurement, slit lamp examination, dilated fundus examination, fundus photography, Humphrey automated visual field testing (SITA FAST 30-2 stimulus III), mean retinal nerve fiber layer and mean retinal ganglion cell layer thickness as measured by spectral domain optical coherence tomography (SD-OCT; Cirrus), photopic negative response electroretinography (PhNR-ERG), full field ERG and the Visual Functioning Questionnaire-39 (VFQ-39) to assess visual quality-of-life measures.

Subjects will undergo Humphrey automated visual field testing at both the Screening (Visit 1) and Baseline (Visit 2) visits (performed at least one day apart). In the event that a subject's two visual field tests differ by greater than 5 dB, additional Humphrey automated visual field tests may be repeated until a qualifying exam is produced or the investigator suspends repeat examination. If the test does not occur on the day of the Baseline Visit, other Baseline procedures, which have already been completed, should not be repeated. In order to be randomized into the study, subjects must have two visual field tests with results that meet the study criteria and that are within 5 dB of each other.

Double-Masked Treatment Period

At the time of randomization, training on the proper administration topical ophthalmic solution and self-administration (by the subject or regular caregiver) will occur. Subjects will be read a standard script explaining the importance of applying the correct drug product to each eye on a twice daily basis for the 52-week Treatment Period. Safety, tolerability and efficacy will be measured throughout the Treatment Period. After completion of the 52-week treatment period or the Week 56 follow up period, subjects will be invited to participate in the OLE for up to 108weeks. If a subject does not consent to the OLE, depending on when the OLE was offered, he/she will either complete the study or continue to be monitored for safety and efficacy during a 4-week Follow-Up Period and will complete a Week 56 (±7 days) visit.

Open Label Extension Period

The OLE will begin after the subject completes the Week 52 or Week 56 visit. Following completion of all Week 52 or Week 56 procedures described in the Schedule of Events (Attachment 1), subjects will receive a supply of 1.0% elamipretide topical ophthalmic drops for self-instillation at home. Subjects (or trained caregivers) should administer elamipretide OU BID every day. Subjects will return to the site for assessments at the 16-Month Visit (Week 68), the 20-Month Visit (Week 84), the 24-Month Visit (Week 100), the 28-Month Visit (Week 116), the 32-Month Visit (Week 132), the 36-Month Visit (Week 148), and the 39-Month Visit /End of Treatment (EOT) Visit (Week 160) as described in the Schedule of Events. Monthly safety telephone calls will be conducted between site visits. The script is provided in Sample Monthly Telephone Script Attachment 4. The OLE 4 week follow-up period will begin after completion of self-dosing and the OLE EOT visit. During the follow-up period, subjects will continue to follow all study requirements. At the end of the follow-up period, subjects will return to the trial site for the End-of-Study/Early Termination/Discontinuation visit for final safety and efficacy assessments and to return all used and unused bottles and any other study instruments/materials to the trial site. Subjects will have the opportunity to continue receiving elamipretide through an EAP immediately following the 36-Month Visit (Week 148) or the EOT visit (Week 160). For those subjects who consent to the EAP at either visit, there will not be a Follow-Up Period. That visit will be considered the End-of-Study visit for these subjects.

Note: The end of study may occur following Regulatory approval and commercial availability or at the termination of the clinical development of 1% topical elamipretide solution in subjects with LHON.

5.2. Discussion of Design and Control

This prospective, randomized, double-masked, vehicle-controlled, Phase 2 clinical study is designed to evaluate the safety, tolerability, and efficacy of elamipretide topical ophthalmic solution administered at a concentration of 1.0% BID for 52 weeks. The OLE is designed to investigate long term safety and efficacy of treatment with elamipretide 1.0% topical ophthalmic solution during an additional 108 weeks of treatment.

5.3. Schedule of Events

Study procedures, their timing, and additional details are found in the Schedule of Events, Attachment 1.

6. STUDY POPULATION

6.1. Number of Subjects Planned

Approximately 12 subjects will be enrolled in this study.

6.2. Study Population

6.2.1. Inclusion Criteria

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

1. Adults ≥18 and ≤ 50 years old at the time of loss of vision in the second eye. Loss of vision in both eyes of ≥1 year and ≤10 years at the time of the Screening Visit.
2. Able to provide informed consent and willing to comply with all study visits and examinations
3. Diagnosis of LHON based on clinical and ophthalmic functional/anatomic test findings, and satisfactory documentation of the mitochondrial DNA mutation m.11778G>A
4. Loss of vision in both eyes of ≥1 year and ≤10 years at the time of the Screening Visit and current clinically stable visual function (as assessed by the Investigator)
5. Mean Deviation (MD) between -7.5 and -30 dB on Humphrey automated visual field testing (SITA FAST 30-2, stimulus III) on two consecutive tests during the Screening Period. In addition, the MD on the two qualifying, consecutive exams must be within 5 dB of each other for the subject to qualify for study inclusion.
   Note: As described in the Study Design, up to four Humphrey automated visual field tests are allowed during the Screening Period.
6. Adequate mean retinal nerve fiber layer (RNFL) thickness based on the investigator's assessment with consideration of spectral domain optical coherence tomography (SD-OCT) values, such as between 50 and 90 microns (inclusive) OU.
7. Adequate retinal ganglion cell layer (GCL) thickness based on the investigator's assessment with consideration of SD-OCT values of at least 40 microns OU.

8. Media clarity, subject able to undergo pupillary dilation and able to cooperate sufficiently for adequate ophthalmic visual function 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. Documentation of having satisfactorily completed at least two previous Humphrey automated visual field tests prior to screening
11. If of childbearing potential or in a relationship with a partner of childbearing potential, are able to abstain from sex or use acceptable contraception during the study and for 28 days after dosing.
    a. For men: Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. The subject also agrees to use an acceptable method of contraception should they become sexually active with a partner of child-bearing potential. Subjects must use a condom with spermicide from the date of informed consent until at least 28 days after the last dose of study drug. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
    b. For women: Abstinence is only acceptable when it is in line with the preferred and usual lifestyle of the subject. The subject agrees to use an acceptable method of contraception should they become sexually active. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days before the Screening visit or confirmed via sperm analysis), 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 are acceptable methods.

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).

6.2.2. Exclusion Criteria

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

Ocular conditions

1. Any other ocular pathology requiring treatment with prescription topical ophthalmic drops (e.g., glaucoma, dry eye)
2. Cup to disc ratio of > 0.8 in either eye
3. Any active ocular or peri-ocular infection; any history of recurrent or chronic infection or inflammation in the study eye
4. History of herpetic infection in either eye
5. History of intra-ocular surgery
6. Active corneal disease
7. Current use or likely need for the use of contact lens at any time during the study
8. Concurrent disease in either the study eye or fellow control eye that could require medical or surgical intervention during the study period
9. Media opacity, suboptimal pupillary dilatation, or severe refractive error that interferes with

adequate retinal imaging

Systemic conditions

10. Known to be immunocompromised or receiving systemic immunosuppression
11. Any systemic or non-ocular symptoms that in the opinion of the Investigator may be related to LHON (i.e. "LHON-plus"), per investigator's assessment and decision.
12. Any disease, medical condition or psychological condition that in the opinion of the Investigator would prevent the subject from participating in the study or might confound study results

General

13. 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
14. History of participation in an interventional clinical trial investigating the use of gene therapy as a treatment for LHON
15. History of allergic reaction to the investigational drug or any of its components
16. History of histamine intolerance (e.g., a known deficiency of endogenous histamine degradation)
17. Current use of or likely need for any excluded medication (idebenone and vitamins acceptable)
18. Women who are pregnant or lactating

6.3. Discontinuation

A subject has the right to withdraw from the study at any time, for any reason.

The Investigator and Sponsor have the right to withdraw a subject from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, pregnancy, protocol violation, non-compliance with study visits, and for any other reason. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Should a subject decide to withdraw, all efforts will be made to complete and report observations as thoroughly as possible. Appropriate early termination/study discontinuation procedures should be followed.

6.4. Replacement of Subjects

In the event that a subject is randomized into the study but is discontinued prior to receiving any study drug, then an additional subject may be enrolled. Any other subjects who prematurely discontinue from the study will not be replaced and no other additional subjects will be enrolled.

7. STUDY TREATMENTS

7.1. Dose Modification and Discontinuation of Subject Dosing

7.1.1. Dose Modification

Dose modification for individual subjects is permitted as below, if the Primary Investigator and Sponsor agree it is in the best interest of the subject. A subject who experiences an AE related to local tolerability of (e.g., ocular burning/stinging, discharge, or conjunctival erythema) may be withdrawn, or instructed to skip a number of days of treatment and/or the subject may be instructed to decrease the frequency of dose administration per day for either a number of days or until the end of the treatment phase of the study.

7.1.2. 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 et al 2004). Additionally, MTP-131 given subcutaneously to high fat and/or streptozotocin diabetic mice prevented and corrected visual functional loss (Alam et al. 2012) and subcutaneously to streptozotocin-diabetic rats reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye (Huang, Li et al. 2013).

In the completed SPIOC-101 clinical trial, twice daily dosing with elamipretide topical ophthalmic solution administered at either 0.3% or 1.0% was well tolerated and no safety issues emerged at either dose during twenty-eight days of daily treatment. Four unrelated, non-ophthalmic adverse events were reported, and there were no reports of local tolerability issues. This is consistent with the 90-day toxicology studies, completed in rabbits and dogs, and in the 39-week toxicity study in dogs, in which no treatment-related systemic toxicity or ocular pathology affecting the major vision critical 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 elamipretide treatment regimen should be reduced or stopped.

7.2. Treatment of Subjects

7.2.1. Randomization

On study Day 1, each subject will be randomized in a blinded manner into one of three groups in a 1:1:1 ratio: (a) 1 drop of elamipretide 1.0% topical ophthalmic solution BID OS and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, (b) 1 drop of elamipretide 1.0% topical ophthalmic solution BID OD and 1 drop of vehicle topical ophthalmic solution BID in the fellow eye, or (c) 1 drop of elamipretide1.0% topical ophthalmic solution BID OU. After completion of the Week 52 or Week 56 visit, all subjects consenting to the OLE will be provided with elamipretide topical ophthalmic 1.0% solution for use OU BID.

7.2.2. Study Drug Identification

All study drug is intended for ophthalmic administration. Elamipretide topical ophthalmic solution and/or vehicle are supplied as a 1.0% solution packaged in one of three configurations:

1. In white, 10 mL high density polyethylene bottles with a dropper top. Each bottle contains nominally 3 mL of solution as either study drug (elamipretide 1.0% topical 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. Each bottle should be opened and used to dose the subject's single eye twice in one day.

2. In Low Density Polyethylene (LDPE) ampoules also known as blow fill seal units. These are single use units that are manufactured in cards of 4 units and enclosed in a foil pouch. The ampoules contain nominally 0.3 mL of the same solutions of study drug or vehicle. Each ampoule should be used once to dose into the patient's single eye. Each pouch of four units contains enough doses for two days per eye.

3. Elamipretide ophthalmic sterile solution consisting of a sterile, aqueous, isotonic, clear elamipretide solution in a multi-use 7.5 mL polypropylene ophthalmic dropper dispensing bottle that dispenses approximately 40 µL in each drop. The elamipretide solution is formulated at 10 mg/ml (1%) mg/mL in isotonic phosphate buffer, sodium chloride, and benzalkonium chloride (preservative). Solution pH is adjusted with sodium hydroxide or hydrochloric acid. Each bottle contains a 30 day supply of BID drops for both eyes.

7.2.3. Packaging, Labeling, and Storage

Clinical study: Study drug will be supplied in kits or cartons as a supply for each eye during the treatment period. Kits designated for use in the right eye will be labeled with a red border and have a kit number starting with the letter "R" and should only be used in the subject's right eye. Kits designated for use in the left eye will have no border and will be labeled with a kit number starting with the letter "L" and should only be used in the subjects left eye.

OLE (single dose bottle-one a day): Study drug, supplied in kits of 8 10mL high density polyethylene bottles with a dropper top containing 3mL of 1.0% elamipretide topical ophthalmic solution, will be supplied as open label stock labeled for use in both eyes.

OLE (multi-dose bottle - monthly): Study, drug, supplied as a one (1) x 7.5 mL polypropylene bottle with a dropper top nozzle and cap containing 6.5 mL of 10mg/ml (1%) elamipretide topical ophthalmic solution, will be supplied as open label stock labelled for use in both eyes for one (1) month.

Study drug supplies 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.

7.2.4. Supply and Disposition of Treatments

Double-masked period: An Interactive Web Randomization System (IWRS) will be used to designate patients to receive one of three treatment regimens from the following for the duration of the study:

- Active in right eye, placebo in left eye
- Active in left eye, placebo in right eye
- Active in both the left eye and right eye

On the first treatment day and periodically thereafter, each subject will receive a kit with the appropriate quantity of doses containing a solution of the active ingredient or a placebo solution and labeled in a masked fashion. The patient will be instructed to administer one drop in each eye twice in a given day for the duration of the study.

Patients will receive the investigational product either directly from the Investigator's staff or a contract organization responsible for shipping supplies to each study subject in accordance with instructions provided by the Sponsor. Each kit of supply is intended to provide therapy for a single eye for a specific number of days. All remaining solution will be reconciled according to the Sponsor's instructions. All supplies are to be stored refrigerated prior to use. Detailed instructions to the patient for use, storage, and shipping will be provided with each supply of the investigational drug product.

OLE period: Open label treatment will be assigned by the site. An initial supply of treatment will be provided to the patient at each site visit. Additional supplies may be dispensed or shipped to the patient via a contract organization responsible for shipping supplies to study patients. The patient will be instructed to administer one drop in each eye twice a day for the duration of the OLE.

7.2.5. 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 study drug. These records should contain the dates, quantity, and study medication:

- Received at site
- Dispensed to each subject,
- Returned from each subject and
- Disposed of at the site or returned to the Sponsor or designee.

Double-masked period: Subjects will be asked to return study drug supplies at the Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, and Week 44, Week 48, and Week 52 visits. The clinical monitor responsible for the study site will provide written approval for the destruction or return of unused study medication following reconciliation of all clinical supplies.

OLE period: Subjects will be asked to return study drug supplies at Week 68, 84, 100, 116, 132, 148, and 160 visits. A contract organization responsible for shipping supplies to study subjects may be utilized to collect and return study drug supplies to the site for accountability. The clinical monitor responsible for the study site will provide written approval for the destruction or return of unused study medication following reconciliation of all clinical supplies.

7.2.6. Treatment Compliance

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

7.3. Masking and Unmasking

Double-masked portion: This is a double-masked study. Treatment assignment will not be known to the subjects, the Sponsor, or the staff who are involved in the clinical evaluation of the subjects and the analysis of data.

Unmasking the subject allocation to treatment for the purposes of treating AEs is performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being (related to one or both eye(s)) requires knowledge of the subject's treatment assignment. As all subjects are exposed to active drug, systemic AEs do not require unmasking. All instances of unmasking will be recorded and reported by the IWRS.

If an Investigator, site personnel performing assessments, or subject is unmasked, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the Investigator must obtain specific approval from the Sponsor for the subject to continue in the study.

In case of an emergency, the Investigator has the sole responsibility for determining if unmasking of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Sponsor prior to unmasking a subject's treatment assignment. If a subject's treatment assignment is unmasked, the Sponsor must be notified immediately.

OLE portion: Subjects will be assigned to open label treatment, with all subjects consenting to participation, receiving 1.0% elamipretide topical ophthalmic solution.

7.4. Study Visit Descriptions

Study procedures, their timing, and additional details are found in the Schedule of Events, Attachment 1. A list of all clinical laboratory tests to be performed is found in Attachment 2.

Screening procedures may be completed on more than one day, as long as all procedures are completed during the Screening Period. All other visits may be completed over a 1 or 2 day period, at the discretion of the Investigator, as long as all procedures are completed during the allowable window for that visit.

7.4.1. Clinical Study

7.4.1.1. Screening (Day -42 to Day -2) Visit 1

Written ICF will be obtained from all subjects prior to conducting any screening procedures. After the subject has provided the signed ICF, the following assessments and procedures will be conducted:

Assess inclusion and exclusion criteria

Mitochondrial DNA analysis to confirm genetic mutation m11778G>A status (if not previously confirmed by written documentation using reliable test methods)

Demographics including ethnicity, race, eye color, history of smoking, and alcohol use

Medical/ocular history and concurrent illnesses

Concomitant medications

Adverse events. (Note: An AE that occurs 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 electronic case report form [eCRF] and not recorded as an AE unless the event meets the definition of a serious adverse event (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 including temperature, sitting blood pressure after sitting for 5 minutes, and pulse

Physical examination (physical examination will include general appearance, skin, chest, heart, abdomen, extremities, and nervous system)

Electrocardiogram (ECG) (all scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position)

Blood draw for hematology and chemistry

Serum pregnancy test (women of child bearing potential only)

Manifest refraction and BCVA testing per ETDRS protocol

Intraocular pressure (IOP)

Color discrimination and contrast sensitivity

Ophthalmic examination including slit lamp examination (SLE) and dilated fundus examination (DFE)

Spectral domain optical coherence tomography (SD-OCT; Cirrus) for RNFL and RGCL thickness

Fundus photography

Humphrey automated visual field examination

Photopic negative response electroretinography (PhNR-ERG)

Full Field ERG

7.4.1.2. Baseline (Day 1) Visit 2

The following procedures and assessments will be conducted:

Inclusion and exclusion criteria

Concomitant medications

AEs (prior to study drug administration, AEs are captured as medical history, unless they qualify as SAEs)

Vital signs including temperature, sitting blood pressure, and pulse

ECG

Blood draw for hematology and chemistry

Urinalysis

BCVA testing per ETDRS protocol

IOP

Ophthalmic examination including SLE and DFE

SD-OCT for RNFL and RGCL thickness

Humphrey automated visual field examination

PhNR-ERG

Visual Functioning Questionnaire-39 (VFQ-39)

Color discrimination and contrast sensitivity

Serum for phosphorylated axonal neurofilament analysis (Optional: per subject secondary use consent)

Serum for mitochondrial DNA copy number (Optional: per subject secondary use consent)

Urine pregnancy test (for women of child-bearing potential only)

In order to be deemed eligible for the study, the results of both the Screening and Baseline Humphrey automated visual field exams must meet study criteria and be within 5 dB of one another. If the Screening and Baseline exams are not within 5 dB of one another, the Humphrey automated visual field exam may be repeated, as discussed in Summary of Design (Section 5.1).

Subjects deemed eligible for the study based on the above assessments will then undergo the following:

- Randomization to the study; the day of randomization is defined as Study Day 1
- Training on the proper administration of topical ophthalmic solution
- Medication dispensed

7.4.1.3. Day 5 (± 2 days), Week 4 (± 4 days), Week 8 (± 4 days), Week 12 (± 4 days), Week 16 (± 7 days), Week 20 (± 7 days), Week 24 (± 7 days), Week 28 (±7days), Week 32 (± 7 days), Week 36 (± 7 days), Week 40 (± 7 days), Week 44 (± 7 days), Week 48 (± 7 days) Visits

The following information will be collected:

Concomitant medications

AEs

The following procedures and assessments will be conducted:

Vital signs including temperature, sitting blood pressure, and pulse

BCVA testing per ETDRS protocol

IOP

SLE and DFE

Color discrimination and contrast sensitivity

Humphrey automated visual field examination

PhNR-ERG (not on Day 5)

Blood for safety

Medication dispensed

Medication returned

7.4.1.4. Week 52 (± 7 days)/End of Treatment Visit

The following information will be collected:

Vital Signs

Physical Exam

Blood for Safety

Urine pregnancy test (for women of child-bearing potential)

ECG

ETDRS BCVA

IOP

Color discrimination and contrast sensitivity

Slit lamp & fundus exam

SD-OCT for RNFL and GCL thickness

Fundus Photography

Humphrey automated visual field examination (SITA FAST 30-2, stimulus III)

PhNR-ERG

Full field ERG

Quality of Life Questionnaire (VFQ-39)

Serum for phosphorylated axonal neurofilament analysis (Optional per subject secondary use consent)

Serum mitochondrial DNA copy number (Optional per subject secondary use consent)

Medication Returned

Adverse Events

Concomitant medications

Invite subjects to participate in the OLE; obtain informed consent from willing subjects

7.4.1.5. Week 56 (± 7 days)/End-of-Study Visit (Follow-up Period)

All of the assessments listed in Section 7.4.1.4 will be conducted, as well as the following:

Urine pregnancy test (for women of child-bearing potential only)

Manifest refraction

Serum for phosphorylated axonal neurofilament analysis (Optional: per subject secondary use consent)

Serum mitochondrial DNA copy number (Optional: per subject secondary use consent)

VFQ-39

PhNR-ERG

Invite subjects who were not offered participation in the OLE at the prior visit (Week 52) to consider participation; obtain informed consent from willing subjects

7.4.1.6. Early Discontinuation Visit

All of the assessments listed in Section 7.4.1.4 will be conducted, as well as the following:

ECG

Fundus photography

SD-OCT for RNFL and GCL thickness

PhNR-ERG

Full-field ERG

VFQ-39

Physical examination

Blood for safety

Serum for phosphorylated axonal neurofilament analysis (Optional: per subject secondary use consent)

Serum for mitochondrial DNA copy number (Optional: per subject secondary use consent)

Urine pregnancy test (for women of child-bearing potential only)

Medication returned

7.4.2. Open Label Extension

7.4.2.1. Week 52 or Week 56 Visit

When the subject agrees to participate in the OLE (whether Week 52 or Week 56), the following assessments/procedures will be performed.

Written ICF will be obtained from all subjects prior to conducting any OLE procedures.

Train the patient on the proper administration of the OLE topical ophthalmic solution

Dispense OLE supplies

Instruct the patient to self-dose with OLE medication in the evening of the beginning of the OLE.

Schedule return visit; remind patient to expect a telephone contact in approximately one month.

7.4.2.2. Week 68, 84, and 100 (± 14 days) Visit and Week 116, 132, 148 and 160 (± 7

days) Visit

The following information will be collected:

Vital signs

Blood chemistry and hematology

EDTRS BCVA

Manifest Refraction

IOP

Color discrimination and contrast sensitivity

Slit lamp and dilated fundus exam

Humphry Automated Visual Field exam

PhNR-ERG

Full Field ERG (Week 100 and Week 148 only)

SD-OCT for RNFL and GCL (Week 148 only)

Fundus Photography (Week 148 only)

Quality of Life questionnaire (Week 148 only)

AE collection

Concomitant Medication collection

Medication dispensed (excluding Week 160, and week 148 if enrolling in an EAP)

Medication returned. A contract organization responsible for shipping supplies to study subjects may be dispatched to collect and return study drug supplies to the site for accountability.

Schedule next site visit

For subjects continuing into an EAP after the Week 148 or EOT visit (Week 160), in addition to the assessments above, the following will also be collected:

Physical Exam

Urine pregnancy test (for women of child-bearing potential)

Collect all used and unused open-label supplies. A contract organization responsible for shipping supplies to study subjects may be dispatched to collect and return study drug supplies to the site for accountability

7.4.2.3 Monthly Safety Telephone Calls (approximately every 4 weeks between site visits)

Monthly safety telephone calls should follow the monthly telephone script provided in Attachment 4.

Document concomitant medication (including supplements and vitamins) since the last site visit or monthly safety telephone call

Document AEs

Assess and document general compliance with open label self-dosing; document any reported missed doses

7.4.2.4 Week 164 End of OLE/Early Termination/Discontinuation (± 7 days) Visit

Document concomitant medication (including supplements and vitamins) since the last site visit or monthly safety telephone call

Document AEs

Physical Exam

Vital signs

Blood chemistry and hematology

Urine pregnancy test (for women of child-bearing potential)

EDTRS BCVA

Manifest Refraction

IOP

Color discrimination and contrast sensitivity

Slit lamp and dilated fundus exam

SD-OCT for RNFL and GCL

Fundus Photography

Humphry Automated Visual Field exam

PhNR-ERG

Quality of Life questionnaire

Collect all used and unused open-label supplies. A contract organization responsible for shipping supplies to study subjects may be dispatched to collect and return study drug supplies to the site for accountability

7.4.2.5 Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

7.5. Concomitant and Prohibited Medications

From 30 days prior to Baseline until the Follow-up Visit, subjects may not use any of the following medications:

- Medications known to be toxic to the lens, retina or optic nerve. Examples include

deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines, ethambutol, and aminoglycosides

- Systemic immunosuppressive drugs
- Any topical medications (approved or investigational) for any ocular condition in either eye other than the study medication. Systemic medications (prescription or non-prescription) for the treatment of ocular conditions may be used if deemed safe and appropriate by both the Primary Investigator and the Sponsor

All other medications must be used at a stable dose from the time of signing the ICF until the follow-up visit.

8. EFFICACY, SAFETY EVALUATIONS, SAMPLE COLLECTION AND TESTING, AND APPROPRIATENESS OF MEASUREMENTS

8.1. Efficacy Measures

The efficacy measures for this study are:

- Change from Baseline in PhNR-ERG response pattern
- Change from Baseline in visual field MD as measured by Humphrey automated visual field testing stimulus III
- Change from Baseline in color discrimination / contrast sensitivity
- Change from Baseline in BCVA
- Change from Baseline in VFQ-39 score
- Change from Baseline in mean retinal nerve fiber layer thickness by SD-OCT
- Change from Baseline in mean retinal ganglion cell layer thickness by SD-OCT

8.1.1. Appropriateness of Measures

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

8.1.1.1. Photopic Negative Response Electroretinography

Photopic negative response electroretinography (PhNR –ERG) is an electrophysiological technique for assessing ganglion cell function (Preiser, 2013); it is a component of the flash ERG, which follows after the "b wave." Data from patients suffering from glaucoma suggests that a decrease in the amplitude of this component of the ERG is associated with pathologic RGC activity (Viswanathan, 2001). It is hypothesized that patients suffering from LHON may have a decrease in the amplitude of the PhNR-ERG (i.e., become less negative), which may increase (i.e., become more negative) with interventions designed to improve retinal ganglion cell function.

8.1.1.2. Contrast Sensitivity

Contrast sensitivity will be measured using the Pelli-Robson Contrast Sensitivity Chart.

8.1.1.3. Color Discrimination

Color discrimination will be measured using the Ishihara Color TestBest Corrected Visual Acuity Best corrected visual acuity will be measured using the ETDRS scale.

8.1.1.4. Visual Field Testing

Visual Field Mean Deviation will be measured using Humphrey automated visual field testing stimulus III.

8.1.1.5. Full field ERG

Full field ERG will be performed in compliance with the ISCEV standard.

8.2. 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 procedures, or that caused the subject to discontinue before completing the study.

The safety profile of elamipretide 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 8.6.

8.2.1. 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.

8.3. Pretreatment Events

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

8.4. 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 conditions 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.

8.4.1. 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”).

8.4.2. 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 8.7.

8.4.3. 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.

8.4.4. 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 8.7.

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. Ocular AEs must include which eye(s) are involved.

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 (eg, "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 (eg, 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.

8.5. Investigator Assessments

8.5.1. 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.

8.5.2. 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.

8.6. Adverse Event Reporting Period

The AE reporting period begins when the subject signs the informed consent and continues through the post-treatment Follow-Up Period defined as 30 days after last administration of study drug. For patients continuing treatment with elamipretide through an EAP at the week 148 or EOT visit, the AE reporting period will end at the that visit. 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, unless enrolling in an EAP.

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 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.

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 by the Sponsor's Pharmacovigilance group and all data will be housed within the Pharmacovigilance study file.

8.7. Serious Adverse Event Expedited Reporting

In the event of an SAE occurring during the reporting period, the Investigator must immediately (e.g., 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 (eg, 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.

8.8. 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 8.6 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. Female partners of male subjects will be consented to collection of their personal health information.

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, 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.

8.9. 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 International Conference on Harmonisation (ICH) Good Clinical Practice (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 [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.

8.10. Sample Collection and Testing

Attachment 1 lists the study procedures, their timing, and additional details for the double masked portion of the study

Attachment 2 lists the study procedures, their timing, and additional details for the OLE portion of the study.

Attachment 3 lists the laboratory tests that may be performed for this study.

9. STUDY VARIABLES AND STATISTICAL ANALYSIS

9.1. Determination of Sample Size

For this Phase 2 study plus OLE, the sample size of 12 subjects is based on the rarity of the disease under investigation and is reasonably sized for demonstrating clinical safety, tolerability, and a preliminary signal regarding efficacy.

9.2. Statistical and Analytical Plans

9.2.1. General Considerations

This study has a double-masked treatment component, in which comparisons of the elamipretide treated eye will be compared to the vehicle treated eye. Outcomes for the double-masked period will be analyzed consistent with this design characteristic.

This study also has an open-label treatment component, in which both eyes will receive elamipretide treatment. The key outcomes of interest will be the comparison of the vehicle eye outcomes (per the double-masked treatment period) to the continued outcomes from the elamipretide eye (also from the double-masked treatment period) as both eyes are treated with elamipretide. Open-label data will be presented using the following treatment identifier conventions:

- Vehicle to Elamipretide (eyes originally randomized to vehicle in DB and then treated with elamipretide in OLE)
- Elam to Elam (eyes originally randomized to elamipretide in DB and continuing treatment with elamipretide in OLE)
- Total (pooling both eyes)

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.

Subject disposition summaries will include the number of subjects entered and the numbers treated (included in the Safety population) for all subjects. The number and percentage of subjects who complete or discontinue from the study will be summarized by reason for discontinuation.

Subject's age, sex, weight, BMI and other demographic characteristics will be recorded and summarized. 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 of efficacy measures within single eye treated subjects and between subjects (single eye vs. bilateral) will be included in separate statistical analysis plan.

9.2.2. 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.

9.2.3. Subject Characteristics

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

9.2.4. Treatment Compliance

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

9.2.5. Endpoints and Methodology

9.2.5.1. 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. In general, subjects in the Safety Population are expected to have received treatment in at least one eye and will be identified as having been assigned active treatment to either one or both eyes.

9.2.5.2. Safety Endpoint

The safety endpoint for this study is:

- The incidence and severity of systemic and ocular AEs

9.2.6. Efficacy Endpoints

For the double-masked period analysis, efficacy data (associated with a specific eye) will be summarized by treatment received.

Plots and figures that demonstrate the time-course of changes in efficacy parameters over time, from baseline (prior to the start of double-masked treatment) through the double-masked treatment period. At the time of the analysis of the open-label period data, data will be added to include through the open-label treatment period. A mixed model for repeated measures (MMRM) will be used, with effects for treatment, study visit, and treatment-visit interaction, and a random effect for subject. The model-based adjusted means (LSMeans) and standard errors will be presented in these plots. The efficacy endpoints for this study are:

- Change from Baseline in PhNR-ERG response pattern
- Change from Baseline in visual field MD as measured by Humphrey automated visual field testing stimulus III
- Change from Baseline in color discrimination
- Change from Baseline in contrast sensitivity
- Change from Baseline in BCVA

- Change from Baseline in VFQ-39 score
- Change from Baseline in retinal nerve fiber layer thickness by SD-OCT
- Change from Baseline in mean retinal ganglion cell layer thickness by SD-OCT

9.2.7. Exploratory Biomarkers (Optional: per secondary use consent)

A retrospective, secondary use exploratory analysis of the following may occur post study completion:

- Serum phosphorylated axonal neurofilament analysis
- Serum mitochondrial DNA copy number

9.2.8. Safety Analyses

9.2.8.1. 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).

Adverse events will be summarized by system organ class (SOC) and preferred term (PT), presenting the number and percentage of subjects having treatment-emergent AEs. SAEs and AEs resulting in discontinuation will be presented.

For the Double-masked period, AEs will be presented as follows:

- Adverse Events attributed to an individual eye or both eyes will be tabulated by specific treatment received in that eye or eyes.

- Systemic AEs will be presented overall (as all patients during the double-masked period receive both elamipretide AND vehicle).

For the OLE, AEs will be presented overall for all patients (and eyes) combined. Severity and relationship to study drug will be listed as appropriate. 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 (e.g., considered related). Summary tables will be sorted by SOC, and then by PT.

9.2.8.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

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

9.2.8.3. 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 (e.g., 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. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at Baseline and normal/abnormal at appropriate visits.

9.2.8.4. Vital Signs

Vital signs will be summarized by changes from Baseline values using descriptive statistics.

9.2.8.5. Other Safety Parameters

Change from Baseline in IOP, slit lamp examination findings and fundus examination findings will be analyzed. Other ocular and/or systemic safety data captured on the eCRF will be listed.

10. STUDY MONITORING

10.1. Source Document Requirements

The Investigator will 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.

10.2. Case Report Form Requirements

Clinical data will be recorded in an 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.

10.3. 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 trial 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 trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to 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.

11. 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 case report forms (CRFs), 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 CRF 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 subject 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.

11.1. 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.

12. 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, CRFs, 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.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of the Investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

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

It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed consent 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 and/or changes to the protocol impact subject’s participation, resulting in a protocol amendment, 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.

13.3. 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 Investigator's personal data will be treated in compliance with all applicable laws and regulations.

13.4. Institutional Review Board

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 (eg, 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.

13.5. 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.

13.5.1. 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 a separate protocol acknowledgement document confirmed that he/she has read and agrees to abide by the protocol.

13.5.2. Final Report Signature

The Sponsor's responsible medical officer 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.

13.5.3. 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. Any change from 100% source document verification will be documented in the associated monitoring report. 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.

13.5.4. Retention of Records

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

13.5.5. 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.

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Attachment 1. SPILH-201 Schedule of Events

	Screening Period	Treatment Period					Follow-up Period	
Days/Weeks	**Screening[a] (Day -42 to Day -2)**	**Day 1/ Baseline**	**Day 5 (± 2 days)**	**Weeks 4, 8, 12 (± 4 days)**	**Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)**	**Week 52 (± 7 days) End-of Treatment Visit**	**Week 56 (± 7 days) Follow-up Visit**	**Early Termination/ Discontinuation Visit**
Visit	**1**	**2**	**3**	**4, 5, 6**	**7, 8, 9, 10, 11, 12, 13, 14, 15**	**16**	**17**	
Informed consent	X							
Eligibility	X	X						
mtDNA testing to confirm m11778A>G status[b]	X							
Randomization[c]		X						
Demographics	X							
Medical/Ocular history	X							
Vital signs[d]	X	X	X	X	X	X	X	X
Physical exam[e]	X					X		X
Blood for safety[f]	X	X[d]		X	X	X		X
Pregnancy test[g]	X	X				X	X	X
ECG[h]	X	X				X		X
ETDRS BCVA	X	X	X	X	X	X	X	X
Manifest refraction	X						X	
IOP	X	X	X	X	X	X	X	X
Color discrimination and contrast sensitivity	X	X	X	X	X	X	X	X

	Screening Period	Treatment Period					Follow-up Period	
Days/Weeks	**Screening[a] (Day -42 to Day -2)**	**Day 1/ Baseline**	**Day 5 (± 2 days)**	**Weeks 4, 8, 12 (± 4 days)**	**Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48 (± 7 days)**	**Week 52 (± 7 days) End-of Treatment Visit**	**Week 56 (± 7 days) Follow-up Visit**	**Early Termination/ Discontinuation Visit**
Visit	**1**	**2**	**3**	**4, 5, 6**	**7, 8, 9, 10, 11, 12, 13, 14, 15**	**16**	**17**	
Slit lamp & fundus exam	X	X	X	X	X	X	X	X
SD-OCT for RNFL and GCL thickness	X	X				X		X
Fundus Photography	X					X		X
Humphrey automated visual field examination (SITA FAST 30-2, stimulus III)[i]	X	X		X	X	X	X	X
PhNR-ERG	X	X[j]		X	X	X	X	X
Full Field ERG	X					X		X
Quality of Life Questionnaire (VFQ-39)		X				X	X	X
(Optional) Serum for phosphorylated axonal neurofilament analysis[k]		X				X	X	X
(Optional) Serum mitochondrial DNA copy number[l]		X				X	X	X
Medication dispensed		X	X	X	X			
Medication returned				X	X	X		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 is conducted on both eyes at each time point.

[a] Screening procedures may be completed on more than one day, as long as all procedures are completed during the Screening Period. All other visits may be completed over a 1 or 2 day period, at the discretion of the Investigator, as long as all procedures are completed during the allowable window for that visit.

[b] If testing previously confirmed by written documentation using reliable test methods received, repeat testing not required

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

[d] Vital signs include temperature, sitting blood pressure after sitting for 5 minutes, and pulse.

[e] Physical examination will include general appearance, skin, chest, heart, abdomen, extremities, and nervous system

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

[g] 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.

[h] All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.

[i] In the event that a subject's Screening and Baseline Visit SITA FAST 30-2 stimulus III exams are not within 5 dB of each other, this test may be repeated two additional times either on the day of the Baseline Visit or within 1 week of the Baseline Visit prior to randomization. If the test does not occur on the day of the Baseline Visit, other Baseline procedures, which have already been completed, should not be repeated.

[j] If Screening Visit and Baseline Visit are less than 72 hours apart, this does not need to be repeated.

[k] According to Protocol version 5.0, collection of serum for phosphorylated axonal neurofilament analysis is optional and subject's consent will be obtained prior to sample collection and analysis. For subjects who have previously consented to sample collection and analysis

under protocol versions 1.0, 2.0, 3.0 or 4.0, investigator will obtain subject's consent for potential secondary use exploratory biomarker analysis.

l. According to Protocol version 5.0, collection of serum mitochondrial DNA copy number is optional and subject's consent will be obtained prior to sample collection and analysis. For subjects who have previously consented to sample collection and analysis under protocol versions 1.0, 2.0, 3.0 or 4.0, investigator will obtain subject's consent for potential secondary use exploratory biomarker analysis.

Attachment 2. SPILH-201OLE Schedule of Events

		Treatment Period		Follow-Up Period[i]
Assessment	**OLE start[e]**	**Monthly Safety Telephone Call (approximately every 4 weeks between site visits)**	**16-Month Visit (Week 68 ±14 days); 20-Month Visits (Week 84 ±14 days); 24-Month Visit (Week 100 ±14 days); 28-Month Visit (Week 116 ±7 days); 32-Month Visit (Week 132 ±7 days); 36-Month Visit (Week 148 ±7 days) 39-Month Visit (Week 160 ±7 days) End of Treatment Visit**	**End-of-Study Visit/ Early Discontinuation Visit (Week 164 ±7 days)**
Visit Number	**1**		**2, 3, 4, 5, 6, 7, 8**	**9**
Informed Consent[a]	X			
Concomitant Medication		X	X	X
Review AEs		X	X	X
Physical Exam[b]			X[h]	X
Vital Signs			X	X
12-Lead ECG[d]				
Pregnancy Test			X[h]	X
Blood Chemistry & Hematology			X	X
Urinalysis				
EDTRS BCVA			X	X
Manifest Reaction			X	X
Intraocular Pressure (IOP)			X	X
Color discrimination and contrast sensitivity			X	X
Slit lamp & dilated fundus exam			X	X
SD-OCT for RNFL and GCL			X[h]	X
Fundus Photography			X[h]	X
Humphrey Automated Visual Field exam			X	X
PhNR-ERG			X	X
Full Field ERG			X[f]	
Quality of Life Questionnaire			X[h]	X
Medication Dispensed	X		X[g]	
Medication Returned			X	X

a. The ICF must be signed prior to any OLE trial related procedures or dosing are performed.
b. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system.
c. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.

d. All scheduled ECGs must be performed after the subject has rested quietly for at least 10 min in the supine position
e. OLE begins at week 52 or week 56 visit (**(± 7 days)** (after all week 52 or week 56 assessments for the double masked treatment period are completed) and the subject consents to the OLE
f. At Week 100 and Week 148 only.
g. Excluding Week 160, and excluding Week 148 if subject enrolling in an EAP.
h. Collected at week 148 only.
i. For subjects enrolling in an EAP at the Week 148 visit or Week 160 (EOT) visit, there is no Follow-Up Period. All Follow-Up Assessments will be performed at the visit where subject enrolls in an EAP.

Attachment 3. 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)
Urinalysis:	Albumin
Specific gravity	Chloride
pH	
Protein	**Optional Secondary Use Exploratory Biomarkers**
Glucose	Serum for mitochondrial DNA copy number
Ketones	Serum for phosphorylated axonal neurofilament analysis
Blood	
Pregnancy Test (Women of childbearing potential only)	

Attachment 4. Sample Monthly Telephone Script

This page provides a sample script for the phone call that should occur approximately every 4 weeks after the patient consents to participate in the OLE portion to ensure the safe and compliant use of the OLE study drug and to appropriately collect the safety events with use of the study drug.

The sample script below is provided to assist clinical sites with conducting monthly safety telephone calls. Additional questions are permitted to ensure completeness of answers.

During each monthly safety telephone call, the following script should be followed:

Script

Hello, my name is_____, and I'm calling from (name of facility and/or Investigator's name office). I am calling since it has been a month since we last spoke about your experience using elamipretide, the study drug in the SPILH-201 OLE trial in which you are participating in. May I ask you a few questions about your experience?

Have you or a trained caregiver been administering the study drug twice a day?

Have you missed administering the study drops? If so, how many times?

Do you have any questions/concerns regarding administering the study drops?

Have you experienced any worsening of your health or any new problems/conditions while on the study drops since (our last telephone call or your last site visit)?

Have you started taking any new medications or changed, increased, or decreased any existing medications since (our last telephone call or your last site visit)?

Could we schedule the next (telephone call or site visit)? (schedule telephone call or site visit)

Do you have any additional questions?

Thank you for speaking with me today. If you have any additional questions, please call me at (phone number)

Signature Certificate

Document Reference: LR2TELJ6TKC6RM78KIP2LS

RightSignature
Easy Online Document Signing

Jim Carr
Party ID: 4AP8S4IKTKNPLL5YW7X6GC
IP Address: 50.203.117.38
VERIFIED EMAIL: jim.carr@stealthbt.com

Electronic Signature:

Jim Carr

Multi-Factor
Digital Fingerprint Checksum

435be9f84d24ad6542251b9894c18af30354c0e8

Timestamp	Audit
2019-03-11 13:31:24 -0700	All parties have signed document. Signed copies sent to: Anthony Abbruscato, Jim Carr, and Quality Systems.
2019-03-11 13:31:23 -0700	Document signed by Jim Carr (jim.carr@stealthbt.com) with drawn signature. - 50.203.117.38
2019-03-11 13:30:56 -0700	Document viewed by Jim Carr (jim.carr@stealthbt.com). - 50.203.117.38
2019-03-11 13:25:51 -0700	Document created by Quality Systems (qualitysystems@stealthbt.com). - 96.230.125.25

This signature page provides a record of the online activity executing this contract.