A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

NCT03891875

06 Jan 2022

CLINICAL TRIAL PROTOCOL

A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

Clinical Phase:	Phase 2
Product Name:	Elamipretide delivery system
IND Number:	114,234
Formulation:	Elamipretide (MTP-131) 80 mg/mL sterile solution for subcutaneous injection
Protocol No.:	SPIAM-202
Sponsor:	Stealth BioTherapeutics Inc. 140 Kendrick St., Building C-West Needham, MA 02494
Sponsor Chief Clinical Development Officer:	Jim Carr, PharmD Chief Clinical Development Officer Stealth BioTherapeutics Inc 140 Kendrick St., Building C-West Needham, MA 02494 Jim.Carr@StealthBT.com +1 617-762-2503
Protocol Date/Version:	06 Jan 2022/Version 4.0

Confidentiality Statement

SPONSOR'S PROTOCOL SIGNATURE PAGE

A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

Protocol No.:	SPIAM-202
Sponsor:	Stealth BioTherapeutics Inc 140 Kendrick St., Building C-West Needham, MA 02494
Protocol Date/Version:	06 January 2022/Version 4.0

Printed Name: Jim Carr

Signature: Jim Carr

Date: 01/06/2022

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

Protocol No.:	SPIAM-202
Sponsor:	Stealth BioTherapeutics Inc 140 Kendrick St., Building C-West Needham, MA 02494
Protocol Date/Version:	06 January 2022/Version 4.0

I have read all pages of this clinical trial protocol for which Stealth BioTherapeutics, Inc. is the sponsor. I agree to conduct the trial as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the trial in accordance with all applicable local laws and regulations and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (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. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
Investigator:

Printed Name: _____

Signature: _____

Date: _____

Site Address: _____

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with ICH GCP and applicable United States (US) Code of Federal Regulations (CFR) and must comply with the ICH E6 Good Clinical Practice: Consolidated Guideline, the principles that have their origin in the Declaration of Helsinki, as well as all applicable local regulations and guidelines. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND), Clinical Trial Application (CTA), or Investigational Device Exemption (IDE) sponsor or funding agency and documented approval from the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this trial have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the trial. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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2. SYNOPSIS

Sponsor/Company: Stealth BioTherapeutics Inc.
Investigational Combination Product: Elamipretide delivery system
Active Ingredient: Elamipretide (MTP-131)
Title of Trial: A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)
Protocol Number: SPIAM-202
Clinical Phase: Phase 2
Objectives: **Primary Objective** The primary objective of this trial is to: • Evaluate the safety and tolerability of subcutaneous (SC) injections of elamipretide administered with the elamipretide delivery system in subjects with age-related macular degeneration (AMD) with non-central geographic atrophy (GA) **Secondary Objectives** The secondary objectives of the trial are to: • Evaluate the efficacy of SC injections of elamipretide administered with the elamipretide delivery system in subjects with AMD with non-central GA. • Study the pharmacokinetic profile of elamipretide and its metabolites.

Criteria for Evaluation

Primary Efficacy Endpoints:

- Low-luminance best-corrected visual acuity (LL BCVA).
- GA area as measured by optical coherence tomography (OCT).

Secondary Efficacy Endpoints:

- Low-luminance reading acuity (LL RA).
- Best-corrected visual acuity (BCVA).
- GA area as measured by fundus autofluorescence (FAF).

Exploratory Efficacy Endpoints:

- Volumetric OCT and ellipsoid zone (EZ) mapping as defined as:
    - Macular Percentage of EZ Total Attenuation
    - Macular Percentage of EZ Partial Attenuation
    - Central 1-mm mean EZ-RPE thickness
    - Central 2-mm mean EZ-RPE thickness
- National Eye Institute Visual Function Questionnaire-39 (VFQ-39) score.
- Reading acuity at standard light.
- Visual function by the Low-luminance Questionnaire (LLQ).
- EQ-5D-5L score.
- Conversion to choroidal neovascularization (CNV).
- BCVA and LL BCVA in non-study eyes.
- GA area as measured by OCT in non-study eyes with GA.

For efficacy endpoints, the unit of analysis will be the study eye as defined as the following:

Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria and none of the exclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse LL BCVA at baseline. If the eyes have equal LL BCVA, then the right eye will be the study eye.

Safety Endpoints:

- The incidence and severity of adverse events (AEs)/ adverse device effects (ADEs).
- Vital sign measurements.
- Clinical evaluations (ocular and non-ocular).
- Clinical laboratory evaluations.
- Slit lamp examination.
- Dilated fundus examination.

Pharmacokinetics (PK) Variables:
Characterization of the PK parameters of elamipretide and its metabolites in plasma, including apparent clearance, maximum plasma concentration (C_{max}), and area under the plasma concentration time-curve from 0 to 24 hours (AUC_{0-24}), will be performed via population PK (PopPK) modelling.

Trial Population: Adults ≥ 55 years of age with at least 1 eye with AMD with non-central GA as determined by FAF. GA must be ≥ 0.05 mm^2 and ≤ 10.16 mm^2 in size and reside completely within the FAF 30 or 35 degree image. All GA lesions must be extrafoveal (at least 150 µm from foveal center) with preserved outer retinal structural details, as confirmed by the reading center. Subjects must not have evidence of CNV (by history, OCT, or fluorescein angiography [FA]), have a BCVA score of ≥ 55 letters, an LL BCVA score of ≥ 10 letters, or an LL VA deficit (defined as the difference between BCVA and LL BCVA) of > 5 letters. Subjects (or a caregiver) must also be able to administer the investigational medicinal product (IMP).

Investigational Medicinal Product, Dose and Administration:
Elamipretide injection will be supplied as a sterile 3 mL single-patient-use, multi-dose glass cartridge containing sterile elamipretide solution (elamipretide HCl [80 mg/mL], phosphate buffer, and benzyl alcohol) for use with the elamipretide delivery system (the IMP [elamipretide or placebo], the elamipretide pen injector, and single-use needle). The dose of elamipretide is administered as a once daily fixed dose of 0.5 mL (40 mg) SC injection with the elamipretide delivery system.

Trial site staff will train subjects (and caregivers if needed) and ensure understanding of proper SC injection technique on Day 1 with use of the elamipretide delivery system. An elamipretide delivery system training kit and checklist will be provided to the trial site to assist in training. On Day 1, site staff should witness IMP administration by subject or caregiver. Any new caregiver should complete the training at a trial site visit before administering IMP to a subject. On non-visit days, the subject (or trained caregiver) will administer the IMP via daily SC injections rotating around the four abdominal quadrants. If necessary, SC injection in the thigh may be utilized after Investigator consultation with the Sponsor. The time of the IMP administration should be approximately the same time each day. If a subject is concurrently receiving another SC therapy, unique locations for injections for the IMP, independent from the location of the concomitant therapy injections, should be used (after Investigator consultation with the Sponsor).

Reference therapy, dosage and mode of administration:
The placebo for this trial will be composed of sodium chloride, phosphate buffer, and benzyl alcohol similar to the excipients used to manufacture the active drug but without the active drug substance. The placebo will be handled and administered identically to active drug.

Methodology:

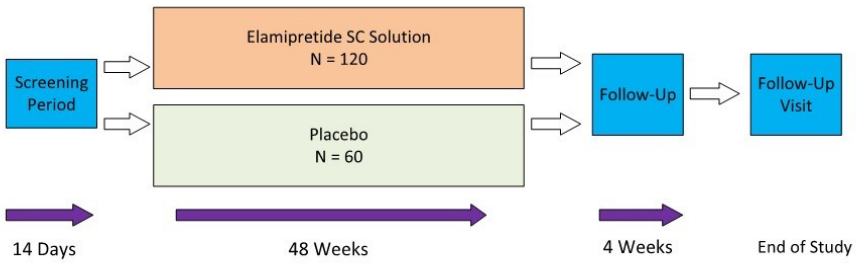
This is a Phase 2, randomized, placebo-controlled, double-masked, multi-center, safety, efficacy, and PK trial to be conducted in the U.S. Approximately 180 subjects who have at least 1 eye with AMD with non-central GA will be included.

A Screening Visit (Visit 1) will be performed no more than 14 days before the Baseline Visit (Visit 2, Day 1). Eligible subjects will return for the Baseline visit, at which time subjects will be randomized in a 2:1 ratio (approximately 120 subjects in the treatment arm and 60 subjects in the placebo arm) to receive either 0.5 mL (40mg) elamipretide or placebo administered with the elamipretide delivery system as a single daily SC injection.

Safety, tolerability, and efficacy will be evaluated throughout the Treatment Period (Visit 2 to Visit 8), while exploratory anatomical and physiologic endpoints will be measured at time points as specified in the Schedule of Events. Plasma samples for PK evaluations will be collected at Visit 3 (Week 4) and Visit 4 (Week 8). Ocular imaging will be read by an independent reading center.

After completion of the 48-week Treatment Period (Visit 2 to Visit 8), subjects will continue to be monitored for safety during the 4-week Follow-Up Period. The Follow-Up Period is an IMP administration-free period. A Follow-Up visit is scheduled at Week 52 (Visit 9).

SPIAM-202 Design Schematic



Visit Schedule:

Subjects will be required to participate in 9 visits at the trial site, including 1 Screening Visit (Visit 1), 7 Treatment Period visits (Visit 2 to Visit 8) over 48 weeks, and 1 Follow-Up Visit (Visit 9) 4 weeks after the last day of treatment. Subjects discontinuing IMP, but willing to continue participation in the trial, will remain in the trial and have all possible trial assessments completed.

SPIAM-202 Visit Schedule

Period	Screening Visit	Baseline Visit and Treatment Period	Follow-Up Visit
Visit Number	1	2 to 8	9
Day/Week	Day -14 to Day -1	Day 1 to Week 48	Week 52

Planned Duration of Trial and Treatment Period:
The trial duration is 54 weeks, which includes 2 weeks of screening, a 48-week Treatment Period, and a Follow-Up Visit scheduled at 4 weeks after the last day of IMP administration.

Inclusion Criteria

Subjects must meet all of the following Inclusion Criteria to be eligible for the study:

1. Adults ≥ 55 years of age with at least 1 eye with AMD with non-central GA. For this study, non-central GA is defined as:
    a. well-demarcated area(s) of GA; presence and area will be determined primarily by FAF.
    b. All GA lesions must be at least 150 µm from foveal center with preserved outer retinal structural details, as confirmed by the reading center.

Ocular conditions–study eye

2. GA in the study eye at the Screening Visit may be multi-focal, but the cumulative GA lesion and size (by FAF, as determined by the reading center) must:
    a. be ≥ 0.05 mm^2 and ≤ 10.16 mm^2 and
    b. reside completely within the FAF 30 or 35 degree image.
3. No evidence of CNV by history, OCT or FA in the study eye.
4. BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) score of ≥ 55 letters (Snellen equivalent ≥ 20/70) in the study eye at the Screening Visit and Baseline Visit.
5. LL BCVA by ETDRS score of ≥ 10 letters in the study eye at the Screening Visit and Baseline Visit.
6. LL VA deficit (defined as the difference between BCVA and LL BCVA) of > 5 letters in the study eye at Screening and Baseline Visits.
7. The fellow eye may have any of the following: no AMD, AMD without GA, AMD with GA, CNV AMD, or central GA. Ongoing treatment with anti-angiogenic therapies in the fellow eye is allowable.
8. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and ability to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment in the study eye.

Systemic and general criteria

9. Able to administer IMP or have an appropriate designee who can administer the IMP (i.e., a capable family member or a caregiver).
10. Able to provide informed consent and willing to comply with all study visits, examinations, IMP administrations, and conditions of the study protocol.

11. Women of childbearing potential who are not pregnant or nursing and have a negative serum pregnancy test at screening.
12. 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 1 month after last dose.
    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. Acceptable methods include: 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. Subjects must use a condom with spermicide from the date of informed consent until at least 1 month after the last dose of study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects with pregnant partners must use a condom.
    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 for 1 month after last dose should they become sexually active. Acceptable methods include: 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. Alternatively, 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). Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or post-menopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

Exclusion Criteria:

Subjects with a study eye who meets any of the following criteria will be excluded from the study:

Ocular conditions–study eye

1. The absence of observable hyper-FAF at the margins of the GA in the study eye (only for lesions ≥ 0.25mm^2).
2. Atrophic retinal disease of causality other than AMD including myopia-related maculopathy and monogenetic macular dystrophies including pattern dystrophy and adult-onset Stargardt disease in the study eye.
3. Presence or diagnosis of exudative AMD or CNV in the study eye.
4. Presence of retinal vein occlusion in the study eye.
5. Presence of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion) in either eye.
6. Presence of vitreous hemorrhage in the study eye.
7. History of retinal detachment in the study eye.
8. History of macular hole (stages 2 to 4) in the study eye.
9. Presence of an epiretinal membrane that causes distortion of the retinal contour in the study eye.
10. Presence of vitreomacular traction in the study eye.
11. At the Screening Visit, advanced glaucoma resulting in a cup to disc ratio of > 0.8 in the study eye.
12. History of glaucoma filtration surgery or uncontrolled glaucoma defined as intraocular pressure (IOP) > 22 mmHg at baseline despite anti-glaucoma treatment with or without topical anti-hypertensive eye drops in the study eye OR currently using > 2 medications (note: combination medications count as 2 medications).
13. Presence of visually significant cataract OR presence of significant posterior capsular opacity in the setting of pseudophakia. Significant cataract is defined as > +2 nuclear sclerosis based upon the scale below or any Posterior Subcapsular Cataract in the study eye. The Sponsor, or its designee, will supply the trial sites with a copy of the standard photographs.

Grade	Description
+1	Opacity is absent

+2	Opacity is present, but less than Nuclear Standard Photograph #2

+3	Opacity is present, and as severe as or worse than Nuclear Standard Photograph #2

Source: (Chew et al. 2010)

14. Presence of significant keratopathy or any other media or corneal opacity that would cause scattering of light or alter visual function, especially in LL conditions in the study eye.
15. Ocular incisional or laser surgery (including cataract surgery) in the study eye within 90 days before Day 1.
16. Yag laser capsulotomy in the study eye within 30 days before Day 1.
17. Aphakia in the study eye.
18. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery in the study eye.
19. Prior treatment with Visudyne® (verteporfin) ocular photodynamic therapy, externalbeam radiation therapy (for intraocular conditions), or transpupillary thermotherapy in the study eye.
20. History of subthreshold laser treatment or other forms of photobiomodulation for AMD in the study eye.
21. Intravitreal drug delivery in the past 60 days or 5-half-lives of the injected drug whichever is longer (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye.
22. Current use of medications known to be toxic to the lens, retina, or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides) from the Screening Visit through the completion of the trial.
23. Concurrent disease in the study eye that could require medical or surgical intervention during the study period.

Ocular conditions—<u>either eye</u>

24. History of herpetic infection in either eye.
25. Active uveitis and/or vitritis (grade trace or above) in either eye.
26. History of idiopathic or autoimmune-associated uveitis in either eye.
27. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

Systemic conditions

28. Known to be immunocompromised or receiving systemic immunosuppression for ≥ 4 consecutive weeks prior to screening.

29. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the study or might confound study results.

General

30. Participation in other investigational drug or device clinical studies within 30 days of enrollment and/or planning to participate in any other investigational drug or device clinical studies within 30 days of study completion.
31. History of allergy to fluorescein that is not amenable to treatment.
32. Creatinine clearance of ≤ 30 mL/min at the Screening Visit (using Modification of Diet in Renal Disease Study formula)
33. Inability to comply with study or follow-up procedures.
34. Inability to obtain color fundus photograph, FAF, and FA of sufficient quality to be analyzed and interpreted.
35. Active malignancy or any other cancer from which the subject has been cancer-free for < 2 years.
36. History of allergic reaction to the investigational drug or any of its components.
37. Prior treatment with Elamipretide.

Safety Variables:

AEs, ADEs, clinical laboratory measurements (chemistry, hematology, and urinalysis), vital signs, and physical examinations will be assessed.

Statistical Methods:

Determination of Sample Size

A sample size of 180 subjects provides ≥ 80% power to detect a 5 letter (1 line) change from baseline mean difference in LL BCVA between drug and placebo, assuming a standard deviation of 11 letters, at a two-sided alpha-level of 0.1, and provides approximately 80% power to detect a 30% difference in the change from baseline in square root transformed total GA area by OCT between drug and placebo, assuming a standard deviation of 0.2 mm/year, and an average change of 0.33 mm/year, at a two-sided alpha-level of 0.1.

General Considerations

Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). Discrete variables will be summarized by frequencies and percentages. Tabulated data will be presented for each treatment arm.

All data will be displayed in the data listings, sorted by subject and visit, where appropriate. Each listing will indicate which treatment arm each subject was assigned to.

Analysis Populations:

Statistical analysis will be performed in the following populations:

Safety Population – Includes all trial subjects who receive at least 1 dose of IMP. Subjects will be analyzed according to the actual treatment they received.

Intent-to-Treat (ITT) Population – Includes all randomized subjects. Subjects will be analyzed in the treatment group to which they were randomized.

Modified Intent-to-Treat (mITT) Population – Includes all ITT subjects who receive at least 1 dose of IMP and have at least 1 post-baseline value for LL BCVA or GA area on OCT. Subjects will be analyzed in the treatment group to which they were randomized and generally included in efficacy analyses for which post-baseline data are available.

Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations likely to affect the primary outcome of the trial as judged by a masked evaluation prior to the unmasking of the study treatment. Subjects will be analyzed according to the actual treatment they received.

PK Population – Includes all trial subjects who have at least 1 evaluable PK sample taken during their participation.

Baseline Characteristics and Disposition of Subjects

The subject disposition summary will include the number of subjects in each population. The number and percentage of subjects who complete or discontinue from the trial will be summarized by reason. Each subject's age, sex, weight, and other demographic characteristics will be recorded and summarized. Medical history will be listed.

Safety Analyses

Safety data analysis will be conducted using the Safety population.

All AEs will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be listed, but only treatment-emergent AEs (TEAEs) will be summarized. The incidence of all TEAEs, injection site TEAEs (e.g., pain/tenderness, erythema, induration/swelling, and pruritus), treatmentemergent serious adverse events (TESAEs), drug-related TEAEs, and TEAEs by severity will be summarized by SOC, PT, and treatment arm.

All ADEs will be coded to SOC and PT using the MedDRA. All reported ADEs will be listed, but only treatment-emergent ADEs (TEADEs) will be summarized. The incidence of all TEADEs, injection site TEADEs (e.g., pain/tenderness, erythema, induration/swelling, and pruritus), treatment-emergent serious adverse device effects (TESADEs), device-related TEADEs, and device-related TEADEs by severity will be summarized by SOC, PT, and treatment arm.

Summary tables for laboratory parameters (i.e., clinical hematology, chemistry laboratory parameters, and urinalysis) will include descriptive statistics for change from 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. Vital signs will be summarized by changes from baseline values for each treatment arm using descriptive statistics.

Efficacy Analyses

For efficacy endpoints, the unit of analysis will be the study eye as defined by the following: Eyes are eligible for analysis if they meet all of the inclusion criteria and none of the exclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse LL BCVA as determined at baseline. If the eyes have equal LL BCVA, then the right eye will be the study eye.

Changes from baseline in efficacy endpoints will be presented by time point for each treatment arm. For continuous data, a mixed model for repeated measures (MMRM) will be used for each eye separately (study eye and fellow eye), with fixed effects for treatment arm, study visit, the treatment arm-by-visit interaction, baseline as a covariate, a baseline-by-visit interaction and a random effect for subject using an unstructured covariance structure. The primary time point for analysis is planned to be Week 48 (End of Treatment Visit). A decision may be made to conduct an interim analysis prior to completion of the trial.

For efficacy, the primary analysis population will be the mITT on observed data.

A family-wise alpha level of 0.1 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 48 weeks. If both primary endpoints are significantly different from placebo at the 0.1 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise, the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.05 (two-sided) level of significance.

PK Analyses

PopPK analyses will be conducted on the PK Population. The PK model will be generated and validated using data reported from historical, thorough PK studies. Where sufficient data allow, covariates will include age, gender, race, renal function (as described by eGFR), intercurrent conditions, and concomitant medications. Plasma samples will be analyzed for elamipretide using a validated liquid chromatography/tandem mass spectrometry assay. Pharmacokinetics modelling will be performed using NONMEM computer software.

3. LIST OF ABBREVIATIONS

Abbreviation	Definition or Explanation
ADE	Adverse device effect
AE	Adverse event
AMD	Age-related macular degeneration
ATP	Adenosine triphosphate
$AUC_{0\text{-}24h}$	Area under the plasma concentration time-curve from 0 to 24 hours

BCVA	Best-corrected visual acuity
C_{max}	Maximum plasma concentration
CNV	Choroidal neovascularization
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ETC	Electron transport chain
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FDA	Food and Drug Administration
GA	Geographic atrophy
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMM	Inner mitochondrial membrane
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
IRB	Institutional Review Board
ISR	Injection Site Reaction
LL	Low-luminance
LLQ	Low-Luminance Questionnaire
M1, M2	Major metabolite of elamipretide (MTP-131)
MMRM	Mixed Model for Repeated Measures
MedDRA	Medical Dictionary for Regulatory Activities
mtDNA	Mitochondrial DNA
MTP-131	Elamipretide, SS-31, SBT-031,

Abbreviation	**Definition or Explanation**
NOAEL	No-observed-adverse-effect-level
OCT	Optical coherence tomography
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
PT	Preferred term

RA	Reading acuity
RBC	Red blood cells
ROS	Reactive oxygen species
RPE	Retinal pigment epithelium
SADE	Serious adverse device effect
SAE	Serious adverse event
SC	Subcutaneous
SD-OCT	Spectral domain-optical coherence tomography
SMP	Safety Management Plan
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TEADE	Treatment-emergent adverse device effect
TESADE	Treatment-emergent serious adverse devise effect
UADE	Unanticipated Adverse Device Effect
VFQ-39	Visual Function Questionnaire-39
WBC	White blood cells

4. INTRODUCTION

This trial will be conducted in strict accordance with the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline, and all applicable laws and regulations. For detailed information on the elamipretide delivery system and the pre-clinical and clinical studies conducted to date, refer to the Investigator's Brochure.

Stealth BT is developing elamipretide injection with the elamipretide delivery system for the treatment of retinal diseases involving mitochondrial dysfunction such as Leber's hereditary optic neuropathy, Diabetic Macular Edema, and age-related macular degeneration (AMD). Elamipretide (also known as MTP-131) is a first-in-class mitochondrial protective tetrapeptide that has been extensively studied in multiple pre-clinical and clinical studies for the normalization of mitochondrial dysfunction.

4.1. Rationale for Mitochondrial-Targeted Therapies in Dry Age-Related Macular Degeneration

The eye is the highest consumer of mitochondrial adenosine triphosphate (ATP) in the brain, due to the intensive bioenergetics required to support visual function. Mitochondrial-mediated oxidative stress is considered a likely contributing factor to the underlying pathologic processes of AMD, with reactive oxygen species (ROS) causing injury to the photoreceptors, the retinal pigment epithelium (RPE), and the choriocapillaris. Pre-clinical studies suggest that diseases of

the RPE, such as dry AMD, may be exacerbated by light-induced mitochondrial dysfunction, and that mitochondrial DNA (mtDNA) mutations appear to accumulate over time in diseased RPE as a consequence of chronic and ongoing oxidative stress. Mitochondrial dysmorphology observed in RPE cells from human dry AMD donor eyes is consistent with severe dysfunction, and mtDNA from these human eyes demonstrate increased oxidative damage with increases commensurate with disease severity. Cigarette smoking and high fat diets, both of which contribute to mitochondrially deleterious oxidative stress, are known to be environmental risk factors for dry AMD onset and progression. These findings suggest a key role for mitochondrial dysfunction in the pathology of the disease.

Although mitochondria have been suggested as a source of reactive oxidants in AMD, mitochondrial dysfunction is not oxidant overproduction alone; it also includes loss of ATP, calcium flux dysregulation, and other changes, which have been overlooked as pathogenic mechanisms in AMD (Feher et al. 2006, Decanini et al. 2007, Ethen et al. 2007, Owsley et al. 2007, Nordgaard et al. 2008). Pre-clinical studies suggest that many AMD triggers induce mitochondrial dysfunction, leading to activation of specific signaling molecules, followed by activation of mediators of deposit formation, all of which will precede and contribute to sub-RPE deposits. It is hypothesized that prevention or reversal of mitochondrial dysfunction by specific mitochondria-targeting molecules may prevent and perhaps reverse pre-existing deposit biochemistry at the RPE, restoring physiologic function of the RPE and promoting clearance of drusen deposits in dry AMD. In turn, mitochondria-targeted therapies may facilitate improved visual function in affected eyes and may prevent progression to vision-threatening AMD disease, neovascular AMD, and geographic atrophy (GA).

4.2. Elamipretide–Mechanism of Action

Elamipretide is a small peptide that targets the mitochondria and normalizes and protects dysfunctional mitochondria, without affecting healthy mitochondria and cells, via a novel mechanism that ameliorates electron transport chain (ETC) deficiencies in disease. Extensive investigation has shown that elamipretide effectively maintains mitochondrial bioenergetics, including membrane potential and respiration, under pathological conditions. Elamipretide has been shown to improve cellular ATP levels in dysfunctional mitochondria, prevent pathological ROS formation and opening of the mitochondrial permeability transition pore, and, as a consequence, reduce the extent of both apoptosis and necrosis. Elamipretide has minimal or no effect in normal mitochondria, cells, or organs (Min et al. 2011, Siegel et al. 2013).

Elamipretide binds reversibly to cardiolipin, which plays a key role in multiple mitochondrial functions, including establishing the structure of the inner mitochondrial membrane (IMM) and keeping the complexes of the ETC in optimal close proximity to one another, optimizing their function (Houtkooper and Vaz 2008, Wallace et al. 2010, Claypool and Koehler 2012). Cardiolipin is particularly susceptible to peroxidation by ROS, leading to dysfunctional ETC structure, impaired oxidative phosphorylation, and electron leakage.

Stealth BT has demonstrated that treatment of cells or isolated organs undergoing oxidative stress with elamipretide can maintain the normal morphology of the IMM and the association of the ETC complexes within the IMM, protecting them from degradation in the presence of increased ROS (Figure 1). Numerous studies have shown an improvement in various downstream consequences of mitochondrial dysfunction following treatment with elamipretide, including reduced fibrosis, inflammation, and cell death.

Elamipretide has been extensively studied in multiple pre-clinical studies and in clinical trials for diseases involving mitochondrial dysfunction. Multiple peer-reviewed publications from more than 20 independent laboratories demonstrate elamipretide consistently improves mitochondrial, cellular, and organ function in both in vitro and in vivo disease models for which mitochondrial dysfunction is understood to be an important component, including cardiovascular, renal, metabolic, skeletal muscle, neurodegenerative, and genetic mitochondrial disease (Manczak et al. 2010, Birk et al. 2013, Dai et al. 2013, Eirin et al. 2013, Siegel et al. 2013). Conversely, elamipretide is expected to have minimal or no effect in disease models in which mitochondrial dysfunction is not critical to pathogenesis or disease etiology.

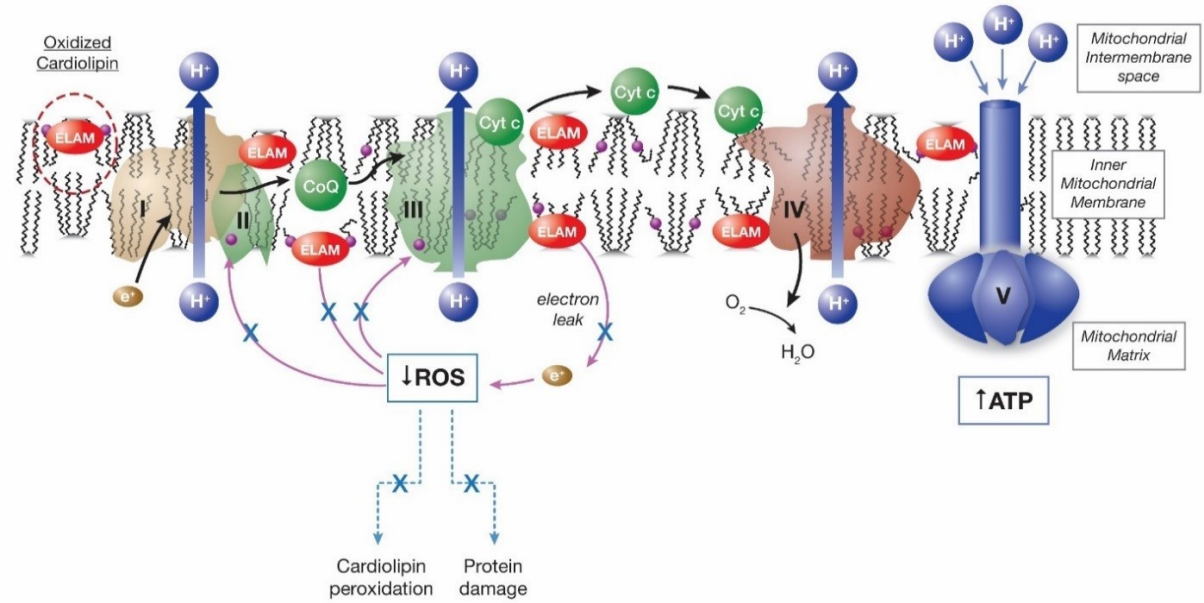


Figure 1 Beneficial Effects of Elamipretide on Mitochondrial Function

Elamipretide Mechanism of Action: ATP=adenosine triphosphate; CoQ=coenzyme Q10; Cyt C=cytochrome C; ELAM=elamipretide; ROS=reactive oxygen species Source:
(Brown et al. 2013)

As in models of stress induced ROS, Elamipretide stabilizes ETC structure and function in disease states, ultimately reducing cellular apoptosis and necrosis and improving function in highly energy dependent organ systems including the eye.

Notably, elamipretide is efficacious in pre-clinical models of eye disease. For example, in cultured cells, elamipretide has been shown to reduce glucose- and peroxide-induced oxidative stress and apoptosis and to improve cell survival in human retinal endothelial cells, human

trabecular meshwork cells, and human retinal pigmented epithelial cells (Liang et al. 2010, Chen et al. 2011, Li et al. 2011, Dai et al. 2013). Also, when given subcutaneously to diabetic rats, elamipretide reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye (Huang et al. 2013). Finally, elamipretide given to diabetic mice not only prevented but also corrected visual functional loss (Alam et al. 2012).

4.3. Elamipretide Risk/Benefit Assessment

For additional information regarding elamipretide safety and efficacy, and risk/benefit assessment, please refer to the elamipretide Investigator's Brochure.

4.3.1. Pre-clinical Studies

Several pre-clinical studies have demonstrated the potential effect of elamipretide treatment for AMD. In RPE cells cultured from dry AMD donor eyes, elamipretide treatment improved mitochondrial function at baseline, particularly on maximal respiration and spare respiratory capacity, both important indicators of mitochondrial health. Elamipretide also improved cell viability for AMD donor cells at baseline, protected cells from low level oxidative stress (150 μM), and reduced reactive oxygen species (Kapphahn et al. 2017).

In pre-clinical models of dry AMD, researchers at Duke Eye Center observed that elamipretide prevented disease progression and reversed symptoms of disease in mice. Elamipretide protected mice against dry AMD-like symptoms induced by hydroquinone, a toxic chemical in tobacco tar, as evidenced by a reduction of the drusen-like deposit formation, maintenance of normal membrane thickness, mitochondrial morphology, and ultrastructure of the retinal pigment endothelium cells in treated mice (Cousins 2015).

Elamipretide was also tested in a murine model of AMD (Cousins 2017). Treatment with elamipretide improved photoreceptor function and improved apparent visual acuity. After treatment with elamipretide, it was also observed that the sub-retinal pigment endothelium layer deposits in the diseased retinas were reduced or eliminated, and the mitochondrial morphology within and the ultrastructure of the retinal pigment endothelium cells was improved.

4.3.2. Clinical Studies

Thus far, in human clinical trials, systemic elamipretide has been studied for the treatment of acute coronary syndrome, chronic heart failure, ischemic kidney disease, and mitochondrial myopathy, and has been found to have an acceptable safety profile; sufficient data has been accumulated to support subcutaneous (SC) administration of up to 40 mg dosage of elamipretide.

For AMD subjects, the safety and efficacy of topically and parenterally administered elamipretide was evaluated in 2 studies: SPIOC-101 and SPIAM-101. This study will use the elamipretide delivery system for SC administration of the IMP. See the current Investigator's Brochure for more information.

4.4. Rationale for Dose Selection

During clinical development, multiple clinical pharmacology studies have been conducted to assess the safety, tolerability, and pharmacokinetics (PK) of elamipretide and its metabolites.

The dose and route of administration (40 mg by SC injection) for the current trial has previously been tested in clinical studies involving healthy and dry-AMD subjects. The 0.5 mL (40 mg) dose for the current trial with the elamipretide delivery system was chosen based on the systemic exposure profile, as well as the safety observed in previous clinical studies.
The exposure to elamipretide and its major metabolites (M1, and M2) at the systemic noobserved-adverse-effect-level (NOAELs) reported in the chronic rat and dog studies are comparable to those reported at steady-state in the clinical pharmacology studies. Safety margins for a clinical dose of 40 mg/day SC elamipretide are demonstrated to be > 5-fold for elamipretide. A 24-weeks safety and efficacy study in AMD subjects (SPIAM-101) demonstrated that a dosing at 40 mg/day SC was associated with a favorable benefit-risk profile. Thus the 0.5 mL/day (40 mg) SC dose with the elamipretide delivery system is proposed for testing in this population.

5. OBJECTIVES

5.1. Primary Objective

The primary objective of the trial is to:

- Evaluate the safety and tolerability of SC injections of elamipretide administered with the elamipretide delivery system in subjects with AMD with non-central GA.

5.2. Secondary Objectives

The secondary objectives of the trial are to:

- Evaluate the efficacy of SC injections of elamipretide administered with the elamipretide delivery system in subjects with AMD with non-central GA.
- Study the PK profile of elamipretide and its metabolites.

6. METHODOLOGY AND PROCEDURES

6.1. Summary of Methodology

This is a Phase 2, randomized, placebo-controlled, double-masked, multi-center, safety, efficacy, and PK trial to be conducted in the U.S. Approximately 180 subjects who have at least 1 eye with AMD with non-central GA will be included.

A Screening Visit (Visit 1) will be performed no more than 14 days before the Baseline Visit (Visit 2, Day 1). Eligible subjects will return for the Baseline Visit, at which time subjects will be randomized in a 2:1 ratio (approximately 120 subjects in the treatment arm and 60 subjects in the placebo arm) to receive either 0.5 mL (40 mg) elamipretide or placebo administered with the elamipretide delivery system as a single daily SC injection.

Investigational medicinal product (IMP) will be administered with the elamipretide delivery system at approximately the same time each day by SC injection (rotating clockwise around the 4 abdominal quadrants). If necessary, SC injection in the thigh may be utilized after Investigator consultation with the Sponsor. At the Baseline Visit (Visit 2), site staff should witness subject or caregiver administering the IMP with the elamipretide delivery system. At the time of initial IMP administration, the subject, regular caregiver, or subject's appropriate designee (as applicable) will receive training on the proper SC administration of the IMP with the elamipretide delivery system.

Safety, tolerability, and efficacy will be evaluated throughout the Treatment Period (Visit 2 to Visit 8), while exploratory anatomical and physiologic endpoints will be measured at time points as specified in the Appendix 1. Schedule of Events. Plasma samples for PK evaluations will be collected at Visit 3 (Week 4) and Visit 4 (Week 8). Ocular imaging will be read by an independent reading center.

After completion of the 48-week Treatment Period (Visit 2 to Visit 8), subjects will continue to be monitored for safety during the 4-week Follow-Up Period. The Follow-Up Period is an IMP administration-free period. A Follow-Up Visit is scheduled at Week 52 (Visit 9).

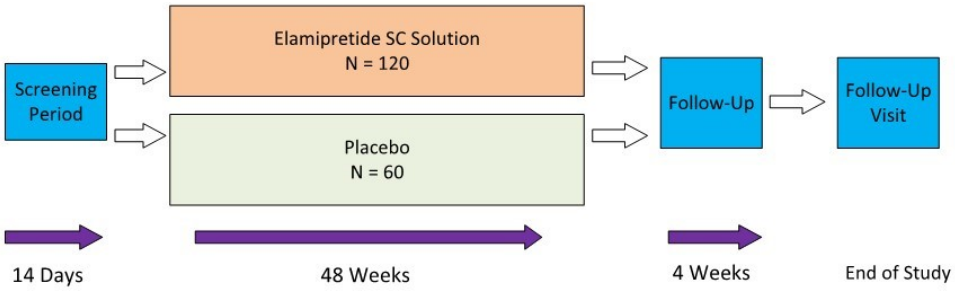


Figure 2 SPIAM-202 Design Schematic

6.2. Visit Schedule

Subjects will be required to participate in 9 visits at the trial site, including 1 Screening Visit (Visit 1), 7 Treatment Period visits (Visit 2 to Visit 8) over 48 weeks, and 1 Follow-Up Visit (Visit 9) 4 weeks after the last day of study treatment. Subjects discontinuing IMP, but willing to continue participation in the trial, will remain in the trial and have all possible trial assessments completed per the schedule of assessments (with the exception of PK sampling), according to the visit schedule as described below and in Appendix 1. Schedule of Events. The trial assessments are outlined in Section 6.4 as well as in the Study Procedure Manual.

The assessments to be performed at each visit are detailed below and ordered based on recommended priority.

Table 1 SPIAM-202 Visit Schedule

Period	Screening Visit	Baseline Visit and Treatment Period	Follow-Up Visit
Visit Number	1	2 to 8	9
Day/Week	Day -14 to Day -1	Day 1 to Week 48	Week 52

6.2.1. Screening Visit (Visit 1, Day -14 to Day -1)

A signed and dated informed consent form (ICF) will be obtained from the subject before any screening procedures are conducted. A signed copy of the ICF will be given to the subject.

A complete medical history will be obtained during the Screening Visit (Visit 1) within 14 days before the first dosing of IMP with the elamipretide delivery system at the Baseline Visit (Visit 2). The subject's medical history will be recorded on the Medical History section of the electronic case report form (eCRF). Any pre-treatment events reported from the time of consent until first dose of the IMP will be recorded as medical history or an adverse event (AE) (as described in Section 10.3).

The subject's ocular history should also be recorded in the eCRF, including date of diagnosis, involvement in 1 or both eyes, and associated symptoms.

Subjects will undergo the following screening procedures ordered based on recommended priority, which may be completed on more than 1 day, as long as all procedures are completed during the Screening Period.

- Informed consent
- Demographics
- Medical/ocular history
- Concomitant medications
- Vital signs

- Physical examination
- Blood for safety, consisting of hematology panel and clinical chemistry
- Urinalysis
- Exploratory plasma and urine samples, withdrawn and stored for future analysis; analysis may include genetic and/or metabolomic testing (optional)
- Pregnancy testing (serum)
- Refraction
- Best-corrected visual acuity (BCVA)
- Low-luminance BCVA (LL BCVA)
- Reading acuity (RA) at standard and low-luminance (LL RA)
- Slit lamp examination
- Intraocular pressure (IOP)
- Dilated fundus examination
- Spectral-domain optical coherence tomography (SD-OCT)
- Optical coherence tomography (OCT) angiography (optional); recommended for trial sites that have OCT angiography
- Fundus photography examination for safety assessment of the RPE, choroid, neuroretinal structure, retinal vessels, optic nerve, and vitreous
- Fundus autofluorescence (FAF)
- Fluorescein angiography (FA) (FA completed for reasons of standard of care and within 30 days prior to first dose can be used for screening purposes if official documentation is provided)
- Eligibility
- AEs/adverse device effects (ADEs), as described in Section 10.1)

Re-screening of subjects may be allowed, depending on the reason for screen-failure, after consultation with the Sponsor.

6.2.2. Baseline Visit (Visit 2, Day 1)

- Medical/ocular history and
- Concomitant medications
- Low Luminance Questionnaire (LLQ)
- Visual Function Questionnaire-39 (VFQ-39)
- EQ-5D-5L Questionnaire
- Vital signs
- Physical examination
- Blood for safety, consisting of hematology panel and clinical chemistry
- Urinalysis
- Pregnancy testing (urine)
- Refraction
- BCVA

- LL BCVA
- RA and LL RA
- Slit lamp examination
- IOP
- Dilated fundus examination
- SD-OCT
- OCT angiography (optional; recommended for trial sites that have OCT angiography)
- Fundus photography examination
- FAF
- Eligibility
- Randomization
- Dispense IMP and subject diary
- IMP training and subject administration during visit
- AEs/ADEs

6.2.3. Trial Treatment Period

6.2.3.1. Week 4 (± 3 days), 8 (± 3 days), 12 (± 3 days), 24 (± 3 days), and 36 (± 3 days) Visits (Visits 3-7)

- Concomitant medications
- LLQ (Weeks 12, 24, and 36 only)
- VFQ-39 (Weeks 12, 24, and 36 only)
- Vital signs
- Physical examination (Week 24 only)
- Blood for safety
- Urinalysis
- Exploratory plasma and urine samples (optional, Week 24 only)
- Pregnancy testing (urine)
- Refraction
- BCVA
- LL BCVA
- RA and LL RA (Weeks 4, 12, and 36 only)
- Slit lamp exam
- IOP (Weeks 24 and 36 only)
- Dilated fundus exam
- SD-OCT and OCT angiography (optional) (Weeks 12, 24, and 36 only)
- Fundus photography (Weeks 12, 24, and 36 only)
- FAF (weeks 12, 24, and 36 only)
- Dispense IMP and subject diary
- IMP accountability

- PK sampling (Weeks 4 and 8); see Section 6.4.7 for sampling time points
- AEs/ADEs

6.2.3.2. Week 48 (± 3 days) Visit (End of Treatment) / Early Termination Visit

- Concomitant medications
- LLQ
- VFQ-39
- EQ-5D-5L
- Vital signs
- Physical examination
- Blood for safety
- Urinalysis
- Exploratory plasma and urine samples (optional) (End of Treatment Visit only)
- Pregnancy testing (urine) (Week 48 only)
- Pregnancy testing (serum) (Early Termination Visit only)
- Refraction
- BCVA
- LL BCVA
- RA and LL RA
- Slit lamp exam
- IOP
- Dilated fundus exam
- SD-OCT
- OCT angiography (optional)
- Fundus photography
- FAF
- IMP accountability
- Random PK sample (Early Termination Visit only); see Section 6.4.7 for sampling time points
- AEs/ADEs

6.2.4. Follow-up Period

A Follow-Up Visit will occur 4 weeks after the last dose of IMP administration. Assessments will be collected according to Appendix 1. Schedule of Events. Subjects withdrawing from the trial will be asked to complete the Early Termination Visit assessments.

6.2.4.1. Week 52 (± 3 days) Follow-up Visit (End of Trial)

- Concomitant medications
- Physical examination

- Pregnancy testing (serum)
- AEs/ADEs

6.3. Schedule of Events

Trial procedures and their recommended order of priority are summarized in the Schedule of Events (Appendix 1. Schedule of Events). A list of all clinical laboratory tests to be performed is found in Section 6.4.

6.4. Trial Assessments

6.4.1. Medical/Surgical History and Concomitant Medications/Procedures

Medical history and any concomitant medications will be recorded during the Screening Visit. At the Baseline Visit, a review of any additional medical history and/or new concomitant medication/procedures that occurred during the Screening Period will be completed. Concomitant medications/procedures should be updated and recorded at each trial site visit.

6.4.2. Vital Sign Measurements

Vital sign measurements (temperature, respiratory rate, sitting blood pressure after resting for 5 minutes, and pulse) and weight will be collected. All vital sign measurements are to be obtained with the subject in a position that is consistent throughout the trial. The equipment should be properly calibrated/ certified. If possible, the same equipment and evaluator should be used throughout the trial period.

6.4.3. Physical Examination

The physical examination will include assessment of head, eyes, ears, nose, and throat, general appearance, skin, chest, heart, abdomen, extremities, and the nervous system. Height will be measured at the Screening Visit only. Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed, and bladder empty.

6.4.4. Clinical Laboratory Testing

All standard blood and urine tests will be analyzed by a central laboratory designated by the Sponsor. All laboratory results must be reviewed by the Investigator to note for clinically significant events. Any clinically significant event must be followed and reported (see Section 10.6 for AEs and abnormal laboratory values). Exploratory plasma and urine samples may be withdrawn and stored for future analysis (analysis may include genetic and/or metabolomic testing, this assessment is optional). Detailed instructions for blood sample collection will be provided to sites in the Laboratory Manual.

Clinical laboratory assessments performed:

Chemistry	Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, creatine phosphokinase, glucose (non-fasting), lactate dehydrogenase, sodium, potassium, albumin, total protein, calcium, chloride, and bicarbonate
Hematology	Hemoglobin, hematocrit, erythrocyte (red blood cell [RBC]) count, leukocytes (white blood cells [WBC]) count, and differential (neutrophils, segmented; lymphocytes; monocytes; eosinophils; basophils), platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, and leukocyte esterase; if the dipstick is abnormal for protein, blood, nitrite, or leukocyte esterase, include RBCs, WBCs, bacteria, and casts

6.4.5. Pregnancy Testing

For female subjects of child bearing potential, pregnancy testing by assessment of serum betahuman chorionic gonadotrophin will be performed at the time of the Screening Visit and at trial conclusion. Female subjects of child bearing potential will have a urine pregnancy test at the Baseline Visit and all visits during the Treatment Period, and the results of the Baseline Visit pre-dose pregnancy test must be evaluated before randomization to ensure eligibility. Female subjects who are considered not to be of child bearing potential must have a history of being post-menopausal (no menses for 12 months without an alternative medical cause), tubal ligation, or other surgical sterilization such as hysterectomy or bilateral oophorectomy that is clearly documented in the subject's source documents.

6.4.6. Subject Diary

Subjects will be asked to complete paper diaries documenting IMP compliance. Trial site personnel will review the subject diary at each visit and retrain the subject on administration of IMP if necessary.

6.4.7. Pharmacokinetics Sampling

To characterize the PK of elamipretide and its metabolites, PK sampling will be conducted at the defined time points below:

- Week 4 Visit ○ Pre-dose (-30 minutes) ○ 0.5 hours post-dose (± 5 minutes) ○ 1 hour post-dose (± 15 minutes) ○ 2 hours post-dose (± 15 minutes)

- Week 8 Visit ○ 4 hours post-dose (± 1 hour) ○ 8 hours post-dose (± 2 hours)
- Early Termination Visit ○ Random PK sample (one sample at any time during visit)

For the Week 4 Visit, the subject will administer IMP at the trial site within 30 minutes after the pre-dose PK sample is collected. For the Week 8 Visit, the subject will administer IMP at home, approximately 4 hours before arriving at the trial site. Samples should be collected as close to nominal as possible.

6.4.8. Other Trial Assessments

Subjects will undergo a number of examinations to establish the subject's baseline disease and change in disease over time. The following assessments will be performed during Screening and/or at Baseline, and at various times throughout the trial.

- LLQ is a vision-related quality of life scale assessing mainly mesopic and scotopic functioning. Subjects will be asked 36 questions about problems that involve his/her vision under different lighting conditions. This assessment will be administered by the site staff.
- VFQ-39 is designed to assess the health-related quality of life of subjects with visual impairment and includes: general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, color vision, and peripheral vision. This assessment will be administered by the site staff.
- EQ-5D-5L is a general quality of life Questionnaire assessing mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall assessment of health. This assessment will be completed by the subjects.
- BCVA, LL BCVA, RA, and refraction will be assessed as detailed in their respective study procedure manuals. Sites and site staff will be trained and certified on these procedures.
- IOP will be measured by Goldmann tonometry or Tonopen. The same method for each individual subject should be used throughout the study, if possible. IOP measurement must be performed prior to dilation. If IOP is > 35 mmHg as measured with a tonopen, IOP should be measured again by Goldmann tonometry.
- The anterior segment of the eye will be analyzed by slit lamp biomicroscopy. Magnification, slit beam, and examination procedure will be consistent with Investigator's standard practice. Findings which are deemed clinically significant by the Investigator will be documented on each subject's source document and corresponding eCRF.

- Dilated indirect ophthalmoscopy will be performed to examine the vitreous, retina, macula, choroid, optic nerve, and blood vessels. Findings that are deemed clinically significant by the Investigator will be documented on each subject's source document and corresponding eCRF.
- Fundus photography of the posterior segment, SD-OCT of the macula, FAF imaging of the RPE and neurosensory retina, and FA to examine the circulation of the retina and choroid and to rule out choroidal neovascularization (CNV) will be performed as outlined in the imaging manual. FA completed for standard of care within 30 days prior to first dose can be used as the screening assessment if the official medical record is provided.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects meeting the following criteria will be eligible to participate in the trial. The Investigator will review all inclusion/exclusion criteria and make a recommendation to the Reading Center for subject eligibility. The Reading Center will review all retinal imaging for inclusion/exclusion criteria as well as the Investigator's recommendation and make the final determination for subject eligibility and selection of study eye.

7.1. Inclusion Criteria

1. Adults ≥ 55 years of age with at least 1 eye with AMD with non-central GA. For this study, non-central GA is defined as:

    a. well-demarcated area(s) of GA; presence and area will be determined primarily by FAF.

    b. All GA lesions must be at least 150 µm from foveal center with preserved outer retinal structural details, as confirmed by the reading center.

Ocular conditions–study eye

2. GA in the study eye at the Screening Visit may be multi-focal, but the cumulative GA lesion and size (by FAF, as determined by the reading center) must:
    a. be ≥ 0.05 mm^2 and ≤ 10.16 mm^2 and
    b. reside completely within the FAF 30 or 35 degree image.
3. No evidence of CNV by history, OCT or FA in the study eye.
4. BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) score of ≥ 55 letters (Snellen equivalent ≥ 20/70) in the study eye at the Screening Visit and Baseline Visit.
5. LL BCVA by ETDRS score of ≥ 10 letters in the study eye at the Screening Visit and Baseline Visit.
6. LL VA deficit (defined as the difference between BCVA and LL BCVA) of > 5 letters in the study eye at Screening and Baseline Visits.

7. The fellow eye may have any of the following: no AMD, AMD without GA, AMD with GA, CNV AMD, or central GA. Ongoing treatment with anti-angiogenic therapies in the fellow eye is allowable.
8. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and ability to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment in the study eye.

Systemic and general criteria

9. Able to administer IMP or have an appropriate designee who can administer the IMP (i.e., a capable family member or a caregiver).
10. Able to provide informed consent and willing to comply with all study visits, examinations, IMP administrations, and conditions of the study protocol.
11. Women of childbearing potential who are not pregnant or nursing and have a negative serum pregnancy test at screening.
12. 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 1 month after last dose.
    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. Acceptable methods include: 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. Subjects must use a condom with spermicide from the date of informed consent until at least 1 month after the last dose of study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects with pregnant partners must use a condom.
    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 for 1 month after last dose should they become sexually active. Acceptable methods include: 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. Alternatively, 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). Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or post-menopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

7.2. Exclusion Criteria

Subjects with a study eye who meets any of the following criteria will be excluded from the study:

Ocular conditions–study eye

1. The absence of observable hyper-FAF at the margins of the GA in the study eye (only for lesions ≥ 0.25mm^2).
2. Atrophic retinal disease of causality other than AMD including myopia-related maculopathy and monogenetic macular dystrophies including pattern dystrophy and adult-onset Stargardt disease in the study eye.
3. Presence or diagnosis of exudative AMD or CNV in the study eye.
4. Presence of retinal vein occlusion in the study eye.
5. Presence of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion) in either eye.
6. Presence of vitreous hemorrhage in the study eye.
7. History of retinal detachment in the study eye.
8. History of macular hole (stages 2 to 4) in the study eye.
9. Presence of an epiretinal membrane that causes distortion of the retinal contour in the study eye.
10. Presence of vitreomacular traction in the study eye.
11. At the Screening Visit, advanced glaucoma resulting in a cup to disc ratio of > 0.8 in the study eye.
12. History of glaucoma filtration surgery or uncontrolled glaucoma defined as IOP > 22 mmHg at baseline despite anti-glaucoma treatment with or without topical antihypertensive eye drops in the study eye OR currently using > 2 medications (note: combination medications count as 2 medications).
13. Presence of visually significant cataract OR presence of significant posterior capsular opacity in the setting of pseudophakia. Significant cataract is defined as > +2 nuclear sclerosis based upon the scale below or any Posterior Subcapsular Cataract in the study eye. The Sponsor, or its designee, will supply the trial sites with a copy of the standard photographs.

Grade	Description
+1	Opacity is absent
+2	Opacity is present, but less than Nuclear Standard Photograph #2

+3	Opacity is present, and as severe as or worse than Nuclear Standard Photograph #2

Source: (Chew et al. 2010)

14. Presence of significant keratopathy or any other media or corneal opacity that would cause scattering of light or alter visual function, especially in LL conditions in the study eye.
15. Ocular incisional or laser surgery (including cataract surgery) in the study eye within 90 days before Day 1.
16. Yag laser capsulotomy in the study eye within 30 days before Day 1.
17. Aphakia in the study eye.
18. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery in the study eye.
19. Prior treatment with Visudyne® (verteporfin) ocular photodynamic therapy, externalbeam radiation therapy (for intraocular conditions), or transpupillary thermotherapy in the study eye.
20. History of subthreshold laser treatment or other forms of photobiomodulation for AMD in the study eye.
21. Intravitreal drug delivery in the past 60 days or 5-half-lives of the injected drug whichever is longer (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye.
22. Current use of medications known to be toxic to the lens, retina, or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides) from the Screening Visit through the completion of the trial.
23. Concurrent disease in the study eye that could require medical or surgical intervention during the study period.

Ocular conditions—<u>either eye</u>

24. History of herpetic infection in either eye.
25. Active uveitis and/or vitritis (grade trace or above) in either eye.
26. History of idiopathic or autoimmune-associated uveitis in either eye.
27. Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

Systemic conditions

28. Known to be immunocompromised or receiving systemic immunosuppression for ≥ 4 consecutive weeks prior to screening.

29. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the study or might confound study results.

General

30. Participation in other investigational drug or device clinical studies within 30 days of enrollment and/or planning to participate in any other investigational drug or device clinical studies within 30 days of study completion.
31. History of allergy to fluorescein that is not amenable to treatment.
32. Creatinine clearance of ≤ 30 mL/min at the Screening Visit (using Modification of Diet in Renal Disease Study formula)
33. Inability to comply with study or follow-up procedures.
34. Inability to obtain color fundus photograph, FAF, and FA of sufficient quality to be analyzed and interpreted.
35. Active malignancy or any other cancer from which the subject has been cancer-free for < 2 years.
36. History of allergic reaction to the investigational drug or any of its components.
37. Prior treatment with Elamipretide.

7.3. Discontinuation of Subjects

Subjects may be discontinued for the following reasons:

- Investigator decision
- Subject decision
- Sponsor decision
- AE/ ADE

Any subject withdrawing from the trial will be asked to complete the Early Termination Visit assessments (see Section 6.2.3.2).

7.4. Replacement of Subjects

Replacement of subjects will not occur in this study.

7.5. Discontinuation of Trial Sites

Trial site participation may be discontinued if the Sponsor or its designee, the Investigator, or the Institutional Review Board (IRB) of the trial site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.6. Discontinuation of the Trial

The trial will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.7. Discontinuation of Investigational Medicinal Product

Subjects who discontinue from IMP may be asked if they wish to continue participation in the study. In these cases, after agreement between the Investigator and Sponsor, subjects will return to the clinic for all remaining study visits and assessments (except for PK sampling) per the visit schedule outlined in Section 6.2. If subjects discontinue from IMP and do not remain in the study, they should complete assessments for an Early Termination Visit, as outlined in Section 6.2.

8. TREATMENT AND RESTRICTIONS

8.1. Investigational Medicinal Product

8.1.1. Elamipretide Injection or Placebo

Elamipretide injection and placebo will be supplied separately from the elamipretide pen injector and single-use needle as labeled sterile 3 mL single-patient-use, multi-dose glass cartridges for use with the assembled elamipretide delivery system. Each cartridge contains elamipretide solution for up to five 0.5 mL doses. Elamipretide solution for injection is an aqueous sterile solution of 80 mg/mL elamipretide HCl formulated in sodium phosphate buffer and benzyl alcohol. The placebo solution is composed of sodium chloride, sodium phosphate buffer, and benzyl alcohol.

Elamipretide injection and the placebo single-patient-use, multi-dose glass cartridges are to be stored at 2 to 8°C (36 to 46°F) in a secure area and dispensed according to the Pharmacy Manual. Temperature records must be maintained, and temperature excursions must be reported as soon as they are discovered. The sponsor should be notified in the case of an excursion.

8.1.2. Elamipretide Pen Injector

The labeled elamipretide pen injector and Instructions for Use (IFU), developed by Stealth BT exclusively for use with the elamipretide injection or placebo 3 mL cartridges, will be supplied separately from the pen injector and needle.

The elamipretide pen injector must be stored at room temperature and not refrigerated. The ancillary supplies (e.g., single-use needle) are to be stored at room temperature as well.

8.1.3. Elamipretide Delivery System

The elamipretide pen injector along with IMP cartridge and the single-use needle constitutes the elamipretide delivery system for use in this trial. The elamipretide delivery system is for personal use (single subject) for SC administration of a fixed dose (0.5 mL) of elamipretide injection or placebo. The needle provided must be used. The elamipretide delivery system is operated mechanically and contains no electronics. The elamipretide delivery system is depicted in Figure 3. The user will assemble and use the elamipretide delivery system per the IFU that will be provided to each subject. Once assembled with the single-patient-use, multi-dose cartridge, the elamipretide delivery system is to be stored at room temperature for up to 5 doses and must not be refrigerated.

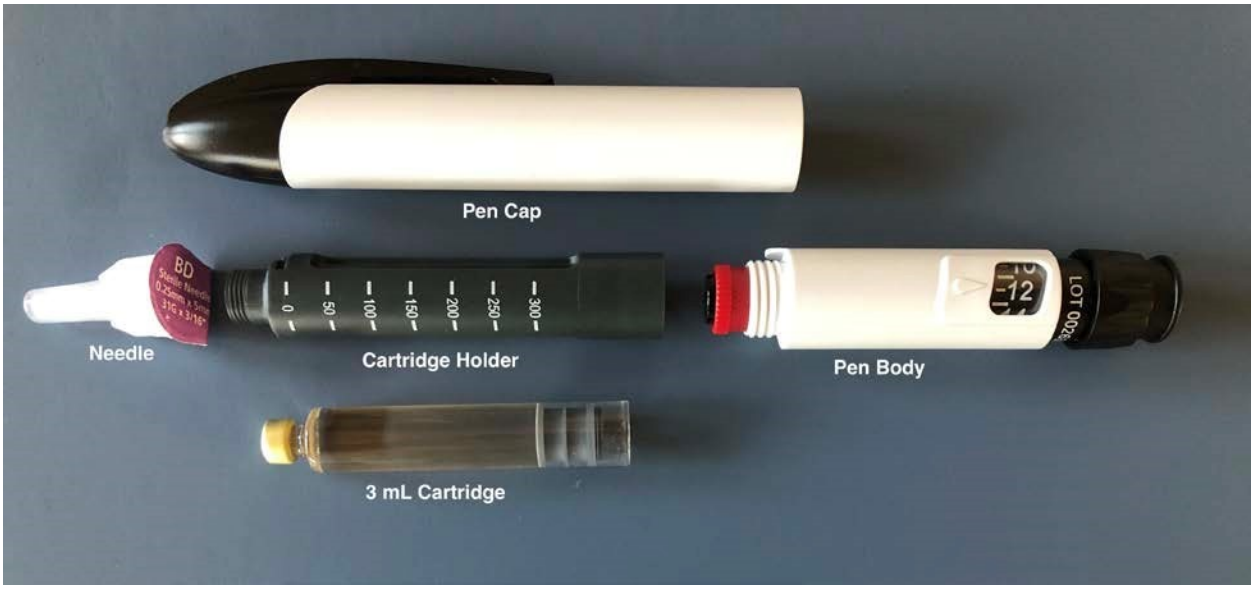


Figure 3: Elamipretide Delivery System

Each subject or caregiver will be trained in the use of the elamipretide delivery system per the IFU prior to administration of the first dose. An elamipretide delivery system training kit and checklist will be provided to the trial site to assist in training. Any new caregiver should complete training at a trial site visit before administering IMP to a subject.

8.2. Investigational Medicinal Product Administration

8.2.1. Investigational Medicinal Product Treatment Regimen

A fixed dose (0.5 mL) of elamipretide injection is administered with the elamipretide delivery system by SC administration. Subjects will receive IMP administered as a single daily SC injection of elamipretide injection or placebo. The first IMP injection with the elamipretide delivery system will occur at the trial site on Day 1 by the subject (or designated caregiver) and witnessed by site staff. Each subject (or caregiver) will be trained on the use of the elamipretide delivery system on Day 1. A diary will be used to document administration. Any new caregiver should complete training at a trial site visit before administering IMP to a subject.

Administration should occur at approximately the same time each day (e.g., early morning, noon, or early afternoon) by subject or caregiver. If necessary, SC injection in the thigh may be utilized after Investigator consultation with the Sponsor. If a subject is concurrently receiving another SC therapy, unique locations for injections for the IMP, independent from the location of the concomitant therapy injections, should be used (after Investigator consultation with the Sponsor).

The Week 8 Visit requires subjects to administer the IMP with the elamipretide delivery system 4 hours prior to a PK blood draw (± 1 hour).

8.2.2. Dose Interruption of Individual Subjects

Elamipretide administration for an individual subject may be stopped for safety reasons by the Investigator or following the Sponsor's recommendation. The determination of the length of the discontinuation, temporary or permanent, depends on the clinical situation. With the exception of emergency situations, the Investigator is responsible for contacting the Sponsor or designee prior to interrupting the subject's daily study drug dosing regimen.

8.3. Investigational Medicinal Product and Accountability

All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused elamipretide delivery system supplies (with the exception of needles). The clinical monitor responsible for the trial site will provide written approval for the destruction or return of used and unused IMP following reconciliation of all clinical supplies.

The elamipretide delivery system supplies are to be available to the principal Investigator, his/her named sub-Investigator(s), or the study staff and are to only be used in accordance with this protocol. The elamipretide delivery system supplies must only be distributed to subjects properly qualified under this protocol to receive them.

8.4. Investigational Medicinal Product Compliance

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

8.5. Randomization/Method of Assigning Investigational Medicinal Product

Each subject who signs an ICF will be assigned a screening number. Screening numbers will be assigned in sequential order at each site beginning with 001 and will follow the two-digit site number (for example, Subject 077 at Site 99 will have Screening Number 99077). Inclusion and exclusion criteria will be reviewed, and qualifying subjects will be enrolled into the study. Each subject who qualifies for entry will be assigned a subject number and corresponding treatment according to the randomization code. Study drug will be randomly assigned using a 2:1 assignment ratio, via an interactive response system.

8.6. Masking and Unmasking Procedures

Trial personnel, subjects, and the Sponsor study team will be masked to treatment until the database is locked. The Investigator will contact the Sponsor prior to unmasking any subject's treatment unless in the instance of a medical emergency.

In case of an immediate medical emergency or if directed by the Sponsor, and only if the information is required by the Investigator to manage a subject's AE, is a subject's treatment assignment to be unmasked prematurely. In cases of medical emergency, the Investigator may unmask a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor must be notified as soon as possible regarding the reason for unmasking.

Whenever the treatment assignment of an individual subject is unmasked, the individual who performed the unmasking, the date, time, and reason for the unmasking must be logged in the computerized unmasking system and also included in source documentation. The name of the individual who broke the masking must be included in the clinic's source documentation.

The Sponsor designated contract research organization (CRO) will control and document, according to the appropriate Standard Operating Procedures, the disclosure of treatment assignments, and treatment identity. These procedures ensure that no masked staff (CRO, trial site staff, Sponsor) will have premature access to the subjects' treatment assignments.

8.7. Concomitant Medications

Current use of or likely need for systemic medications known to be toxic to the lens, retina, or optic nerve (e.g., deferoxamine, chloroquine/hydroxychloroquine [Plaquenil®], tamoxifen, phenothiazines, ethambutol, digoxin, and aminoglycosides) are prohibited from the Screening Visit until completion of the trial (completion of the Follow-Up Visit).

All chronic medications, including over-the-counter treatments, vitamins, or supplements, must be unchanged and constant for at least 1 month before the Baseline Visit (Day 1) or for what is equivalent to 5 half-lives, whichever is longer. All concomitant medications will be recorded in the source data and the eCRF. Changes in dosages of current therapeutic agents during the conduct of the trial will be discouraged, unless medically necessary or required to treat an AE/ADE.

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

Subjects will be instructed to maintain their normal diet, daily caffeine, and regular fiber intake throughout the Treatment Period.

No diagnostic drops used for trial assessments will be collected as concomitant medications.

8.8. Prohibited Medications and Therapies

The use of any other investigational drug except elamipretide is prohibited from the Screening Visit until completion of the trial (completion of the Follow-Up Visit). Prohibited medications include:

- Medications known to be toxic to the lens, retina, or optic nerve, or have a potential to interact with the investigational product. Examples include deferoxamine, chloroquine, hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines, ethambutol, sacubitril – valsartan (Entresto®), digoxin, and aminoglycosides.
- Any periocular and ocular intravitreal injected/implanted medications used in the study eye.

Any ophthalmic topical medications used in the study eye will be reviewed and deemed safe and approved by the investigator. Topical drops for treatment of elevated IOP are allowed, including for ongoing/intermittent application of artificial tears/ lubricating ointments for the treatment of mild ocular surface disease/dry eye.

Chronic systemic medications (prescription or non-prescription) for the treatment of ocular conditions may be used if deemed safe and appropriate by the Investigator and must have been unchanged and constant for at least 1 month before the Baseline Visit (Day 1) or for what is equivalent to 5 half-lives, whichever is longer.

8.9. Subject Management

There are no specific restrictions for the subject.

8.10. Continued Access to Investigational Medicinal Product

The elamipretide delivery system will not be made available to subjects at the conclusion of their participation in the trial.

9. EFFICACY, PHARMODYNAMICS, AND PHARMOKINETICS ASSESSMENTS

9.1. Efficacy Measures

For efficacy endpoints, the unit of analysis will be the study eye as defined by the following:

- Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria and none of the exclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse LL BCVA at baseline. If the eyes have equal LL BCVA, then the right eye will be the study eye.

9.1.1. Primary Efficacy Endpoints:

- LL BCVA
- GA area as measured by OCT

9.1.2. Secondary Efficacy Endpoints

- LL RA
- BCVA
- GA area as measured by FAF

9.1.3. Exploratory Efficacy Endpoints

- Volumetric OCT and ellipsoid zone (EZ) mapping as defined as:
  - Macular Percentage of EZ Total Attenuation
  - Macular Percentage of EZ Partial Attenuation
  - Central 1-mm mean EZ-RPE thickness
  - Central 2-mm mean EZ-RPE thickness
- National Eye Institute VFQ-39 score
- RA at standard light
- Visual function by the LLQ
- EQ-5D-5L score
- Conversion to CNV
- BCVA and LL BCVA in non-study eyes
- GA area as measured by OCT in non-study eyes with GA.

9.2. Pharmacokinetics Measures

Characterization of the PK parameters of elamipretide and its metabolites in plasma, including apparent clearance, maximum plasma concentration (C_{max}), and area under the plasma concentration time-curve from 0 to 24 hours (AUC_{0-24}), will be performed via population PK (PopPK) modelling.

10. SAFETY ASSESSMENTS

For safety assessments, the unit of analysis will be the study eye for ophthalmological assessments and the subject for systemic assessments. The primary safety and tolerability endpoints for the trial are:

- The incidence and severity of AEs/ADEs.
- Vital sign measurements.
- Clinical evaluations (ocular and non-ocular).
- Clinical laboratory evaluations.
- Slit lamp examination
- Dilated fundus examination

10.1. Adverse Events/Adverse Device Effects

An AE is any untoward medical occurrence or clinical investigation in a subject administered a pharmaceutical product and it does not necessarily have to have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered related to the IMP.

An ADE is an AE related to the use of an investigational medical device. This includes any event resulting from insufficient or inadequate instructions for use, deployment, installation, or operation; any malfunction of the investigational medical device; or any event resulting from user error or from intentional misuse of the investigational medical device.

10.2. Safety Evaluations

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every trial visit and the evaluation must be documented. Subjects should be asked about the status of any previously reported events or effects. Trial site personnel will report any AEs/ADEs, whether observed by the Investigator (or designee) or reported by the subject.

Should the IMP be discontinued due to an AE/ADE (per Section 10.10.2), reinitiating (rechallenge) of the IMP may be possible, after consultation with the Sponsor (per Section 8.2.2).

The Investigator is responsible for promptly documenting and reporting all AEs/ADEs observed during the trial in the subject's eCRF and applicable forms. Investigators are responsible for monitoring the safety of subjects who have entered this trial 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 facilitating the appropriate medical care of subjects during the trial and for an AE/ADE, should one occur.
The Investigator remains responsible for following, through an appropriate health care option, AEs/ADEs that are serious, considered related to the elamipretide delivery system or the trial, or

that caused the subject to discontinue before completing the trial. The subject should be followed until the event is resolved or explained.

The Sponsor will periodically review trial safety data as outlined in the Medical Monitoring Plan.

10.3. Pre-Treatment Events

Untoward events that occur prior to the first IMP administration (pre-treatment event) and assessed by the Investigator as related to a trial procedure and/or meeting seriousness criteria will be recorded as an AE/SAE on the subject's eCRF and applicable forms, processed, and followed accordingly. AEs/SAEs that occur prior to IMP administration are by definition, unrelated to the IMP and will be reported as such in the data listings.

10.4. Baseline Medical History Conditions

Pre-treatment events or diagnoses not related to a trial procedure and/or meeting seriousness criteria will be recorded as medical history on the subject's eCRF. Medical history conditions related or not related to the therapeutic area of interest/investigation that worsen in severity or frequency during the trial in a way that is not consistent with natural disease progression, in the opinion of the Investigator, should be recorded and reported as AEs/ADEs.

10.5. Medical and Surgical Procedures

Medical or surgical procedures (including hospitalizations) scheduled prior to signing the informed consent but occurring during the trial should not be captured as AEs. The condition leading to the procedure should be listed in the medical history and the procedure should be captured on the concurrent procedures page. Medical or surgical procedures not scheduled prior to signing the informed consent should not be recorded as AEs; the condition that led to the need to perform the medical or surgical procedure will be the AE or SAE, and the procedure should be captured on the concurrent procedures page.

10.6. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings or other objective measurements deemed clinically significant by the Investigator should be reported as an AE/ADE.

When reporting an abnormal laboratory finding as an AE/ADE or SAE/SADE, the description of the abnormality, rather than the abnormal value itself, should be recorded. A clinical diagnosis should be reported if the Investigator believes the finding is consistent with a disease process.

10.7. Symptomatic Overdose

In the event of an overdose of trial medication, the Investigator should use clinical judgment in evaluating the presence of and treating the signs and symptoms of the overdose. The signs and symptoms should be reported as AEs/ADEs. Overdoses must be reported immediately to the trial Medical Monitor (or designee).

10.8. Serious Adverse Events/Serious Adverse Device Effects

A serious adverse event (SAE) or SADE is any AE/ADE that:

- Leads to death. (In the case of a death, the cause of death is used as the AE term, and the fatality is considered as the outcome)
- Leads to serious deterioration in the health of the subject, that either results in ○ A life-threatening illness or injury (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), or
    - A permanent impairment of a body structure or a body function (which may manifest as a persistent or significant disability or incapacity), or
    - Inpatient or prolonged hospitalization, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Lead to fetal distress, fetal death, or a congenital abnormality or birth defect
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered medically important

A SADE is an SAE that is related to the use of the elamipretide delivery system including the pen injector and needle.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any non-serious AE/ADE that worsens and meets the criteria for a SAE/SADE should be reported as a SAE/SADE. The start date of the SAE/SADE should be the date the AE/ADE worsened to meet the criteria for a SAE/SADE.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE/SADE. Any medications or procedures necessary for treatment of the SAE/SADE must be recorded on the subject's eCRF.
As part of the routine medical monitoring, the Medical Monitor (or designee) will review all SAEs/SADEs reported in this trial, looking for any safety data trends or IMP-related or elamipretide delivery system-related issues.

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

Elective hospitalizations are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered medication) must be documented and reported as SAEs/SADEs.

10.9. Recording of Adverse Events/Adverse Device Effects

Complete and accurate data on all AEs/ADEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis on the subject's eCRF. All SAEs/SADEs must be reported using the trial specific SAE/SADE Report Form, in addition to the subject's eCRF.

It is important that each AE/ADE entry include a verbatim term along with, onset and resolution dates, severity, seriousness, relationship to the elamipretide delivery system, action taken with respect to the IMP, and its outcome.

Investigators should use the AE/ADE definitions provided in the above sections and should observe the following guidelines when completing the subject's eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs/ADEs rather than colloquialisms (e.g., 'influenza' rather than 'flu'), and abbreviations should be avoided.
- AEs/ ADEs should be described using a specific clinical diagnosis, if this is available, rather than a list of signs or symptoms (e.g., 'congestive heart failure' rather than 'dyspnea, rales, and cyanosis'). However, signs/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/ADEs.
- Provisional diagnosis (e.g., "suspected Myocardial Infarction") is acceptable but should be followed with a definite diagnosis (if available). Similarly, a fatal event with an unknown cause should be recorded as "Unknown"
- In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE/ADE rather than the procedure itself.

10.10. Investigator Assessments

10.10.1. Severity/Intensity

The following assessment scale applies to all AEs/ADEs with the exception of the injection site reaction (ISR) severity assessment.
Severity, which is a description of the intensity of manifestation of the AE, is distinct from the regulatory definition of *seriousness*. The Investigator is required to grade the severity of each AE/ADE according to the following guidelines.

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

- **Mild:** Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of IMP administration; and/or not needing therapeutic intervention.
- **Moderate:** Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of IMP administration; and/or requiring therapeutic intervention.
- **Severe:** Associated with inability of the subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

10.10.2. Relationship to the Investigational Medicinal Product/Elamipretide Delivery System

Investigators must systematically assess the causal relationship of AEs/ADEs to the IMP or elamipretide delivery system according to the following guidelines:

- **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/use of the elamipretide delivery system, the event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, 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/use of the elamipretide delivery system.
- **Unlikely:** A causal relationship is improbable and/or another documented cause of the AE is most plausible.
- **Unrelated:** A causal relationship is clinically/biologically improbable, there is not a plausible time sequence between onset of the AE and administration of the IMP/use of the elamipretide delivery system, the event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, and there is no reasonable response on withdrawal.

10.10.3. Outcome of an Adverse Event/Adverse Device Effect

Investigators must follow all AEs/ADEs and SAEs/SADEs through the clinical trial's post treatment Follow-Up Period until resolution, stabilization, or withdrawal of consent. Resolution is defined as:

- recovered/resolved,
- recovering/resolving,

- not recovered/not resolved,
- recovered/resolved with sequelae,
- fatal, or • unknown.

10.11. Adverse Events of Special Interest

10.11.1. Investigator Injection Site Reaction Assessment

Any ISR following SC administration should be reported as an AE/ADE. To standardize the reporting of ISRs, the following guidance should be followed when reporting an ISR as an AE/ADE:

- The ISR should be assessed for severity using Appendix 2. Table for Grading the Severity of Injection Site Reactions.
- Any ISR that meets any of the criteria of a SAE/SADE (Section 10.8) should be reported within 24 hours of the trial site first becoming aware of the event (as outlined in Section 10.13).
- The ISR should be reported as the characteristic of the ISR, rather than the general term of “Injection Site Reaction”. For instance, erythema associated with an ISR should be reported as “injection site erythema” or “redness at injection site” rather than the broad term “injection site reaction”.
- For ISRs that reoccur following a subsequent SC injection, only 1 event should be recorded on the eCRF, with the overall duration to include the start date of the first reported event and the end date of the last recurrent event. The severity grade should be the most severe of the recurrent event during this period.

The AEs/ADEs reported as a result of an ISR should be recorded on the subject’s ISR AE eCRF. The Investigator is expected to use their clinical judgment regarding treatments for ISRs. Any medications or procedures necessary for treatment of the ISR signs and/or symptoms must be recorded on the subject’s eCRF.

Additionally, trial site staff involved with the assessment of ISRs should not be involved in the administration of visual and reading acuity assessments, where possible.

10.11.2. Unexpected Adverse Events/Unanticipated Adverse Device Effects

The final determination of expectedness of an SAE and anticipatedness of an ADE/SADE is the responsibility of the Sponsor as defined and outlined in the safety management plan (SMP).

10.12. Adverse Event/Adverse Device Effect Reporting Period

The AE/ADE reporting period begins when the subject signs the ICF and continues through the clinical trial’s post IMP Follow-Up Period, defined as 28 (± 7) days after the last administration of IMP.

Note that AEs that occur between the time subject signs the ICF and the time the subject is dosed with IMP will be summarized in the medical history eCRF and not as an AE unless the event meets the definition of an SAE or is related to a trial procedure. All AEs/ADEs that occur following first administration of IMP, either new events or events that were pre-existing but changed in frequency or severity, will be recorded on the AE CRF page until the last subject visit. Updates to all ongoing AEs/ADEs or AE/ADES with an unknown outcome must be recorded until the last subject visit. A last batch of queries will be sent after last subject visit if there are ongoing/unknown outcomes for the reported AEs/ADEs that are pending. After the last batch of queries has been resolved, the CRFs and database will no longer be updated and the data will be considered final. However, SAEs/SADEs and ongoing AEs/ADEs with unknown, recovering/resolving, or not recovered/not resolved outcomes will be followed-up until resolution or stabilization by the Sponsor's Pharmacovigilance department. Beyond this defined reporting period, any new SAE considered causally related to IMP should be immediately reported to the sponsor using the SAE/SADE report form. Additional SAE/SADE information obtained after database lock will reside solely in the safety database.

Within the trial, all subjects who took at least 1 dose of IMP, whether they completed the IMP period or not, should enter the 28-day period as defined above. If a subject is documented as lostto-follow-up, ongoing/unknown outcome AEs/ADEs will not be followed-up.

For screening failure subjects, new AEs and updates must be recorded in the CRFs until the date the subject was determined to be a screen failure. Beyond that date, only SAEs and medically relevant AEs will be followed-up by the Sponsor’s Pharmacovigilance group and all data will be housed within the safety database.

10.13. Serious Adverse Event/Serious Adverse Device Effect Expedited Reporting

If an SAE/SADE occurs during the reporting period, the Investigator must immediately (within 24 hours after becoming aware of the SAE/SADE) inform the Medical Monitor, Sponsor, and Ora by telephone, fax, or e-mail as detailed in the SMP. Reporting responsibilities for SAEs/SADEs are detailed in the SMP.

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

- Investigator/Reporter with full contact information.
- Subject identification details (trial number, center number, subject number).
- IMP administration details (dose, lot number, serial number of device, and dates of doses).
- Event Verbatim, a brief description of signs/symptoms/or diagnosis and the date of onset.
- Seriousness criteria(ion) met.

Within 24 hours, the relationship of the event to the IMP (e.g., the causality according to the

Investigator) and/or to the elamipretide delivery system (serial number) and needle (e.g., the causality according to the Investigator) should be provided. “Unlikely” and “unrelated” events will be considered unrelated to IMP/use of the elamipretide delivery system and “possible” and “probable” events will be considered related to IMP/use of the elamipretide delivery system.

A final determination of expectedness/anticipatedness of the event will be made by the Sponsor.

All SAE/SADE reports must be completed as described in the eCRF completion guidelines and submitted through the electronic data capture (eDC) system of the clinical database. Other relevant information from the clinical database (including demographic data, medical history, concomitant drugs and IMP dosing information) will automatically be sent via the eDC system when the SAE/SADE form is submitted.

The names, addresses, telephone, and fax numbers for SAE/SADE back-up reporting (paper), are included in the SMP.

The Investigator/Reporter must provide follow-up information as it becomes available, respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed), or to any question the Sponsor or Ora may have on the SAE/SADE within the same timelines as described for initial reports.

All SAE/SADE reports should be transmitted according to the SMP.

10.14. Pregnancy and Contraception

Any pregnancies occurring during the trial and within the 28 days after the last dose of IMP must be reported to the Investigator. In addition, women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 1 month after the last dose of IMP:

- Abstinence, when it is in line with the preferred and usual lifestyle of the subject. 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.

Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to from the date of informed consent and for at 1 month after last dose of IMP. Highly effective methods of contraception are defined as the usage by the female

partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the trial) plus usage by one of the partners of an additional spermicide-containing barrier method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. Male subjects with pregnant partners must use a condom from the start of IMP until 1 month after the last dose of IMP. Sperm or egg donation by subjects is not permitted from the start of IMP until 1 month after the IMP was administered.

Any pregnancy in a female subject or female partner of a male subject during the course of the trial and until the last follow-up visit must be reported (within 24 hours after becoming aware of the pregnancy) even if no AE has occurred, as detailed in the SMP. If the Investigator suspects the pregnancy has resulted from an interaction of the trial medication with contraceptives, then the pregnancy is considered as an AE.

Only pregnancies considered by the Investigator as related to IMP (e.g., resulting from an interaction between IMP and a contraceptive drug) are considered AEs unto themselves. However, all pregnancies with an estimated conception date that occurred during the AE reporting period, as defined in Section 10.12, must be recorded in the AE section of the eCRF. For this trial, this applies to pregnancies in female subjects and in female partners of male subjects.

The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the forms and reporting procedures as described in the SMP. Investigators must actively follow up, document, and report on the outcome of every pregnancy, even if the subject is withdrawn from the trial. Any abnormal outcome must be reported in an expedited manner as described in Section 10.13, 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/SADE report form described in the SMP is required and will be submitted as described above. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that of an aborted fetus]) the Investigator should follow the procedures for reporting an SAE. Additional information about pregnancy outcomes that are classified as SAEs follows.

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the in utero exposure to the investigational product should also be reported.
- In the case of a live birth, the “normality” of the newborn can be assessed at time of birth. The “normality” of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

If the pregnancy is to be terminated, the anticipated date of termination should be provided. If the pregnancy ends for any reason before the anticipated date of birth, the Investigator should notify the Sponsor.

10.15. Responsibilities to Regulatory Authorities, Investigators, and Institutional Review Board

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

The Investigator must comply with (and inform the Sponsor of) any applicable center-specific requirements related to the reporting of SAEs/SADEs involving his/her subjects to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IRB's/IEC approval/favorable opinion to continue the trial. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs/ADEs that are both serious and unexpected and are considered to be related to the administered IMP/elamipretide delivery system ("suspected unexpected serious adverse reactions" [SUSARs] or "unanticipated adverse device effects" [UADEs]). 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 concerned lead IEC/central IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or centerspecific 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.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

A sample size of 180 subjects provides ≥ 80% power to detect a 5 letter (1 line) change from baseline mean difference in LL BCVA between drug and placebo, assuming a standard deviation of 11 letters, at a two-sided alpha-level of 0.1, and provides approximately 80% power to detect a 30% difference in the change from baseline in square root transformed total GA area by OCT between drug and placebo, assuming a standard deviation of 0.2 mm/year, and an average change of 0.33 mm/year, at a two-sided alpha-level of 0.1.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). Discrete variables will be summarized by frequencies and percentages. Tabulated data will be presented for each treatment arm.

All data will be displayed in the data listings, sorted by subject and visit, where appropriate. Each listing will indicate which treatment arm each subject was assigned to.

11.2.2. Analysis Populations:

Statistical analysis will be performed in the following populations:

Safety Population – Includes all trial subjects who receive at least 1 dose of IMP. Subjects will be analyzed according to the actual treatment they received.

Intent-to-Treat (ITT) Population – Includes all randomized subjects. Subjects will be analyzed in the treatment group to which they were randomized.

Modified Intent-to-Treat (mITT) Population – Includes all ITT subjects who receive at least 1 dose of IMP and have at least 1 post-baseline value for LL BCVA or GA area on OCT. Subjects will be analyzed in the treatment group to which they were randomized and generally included in efficacy analyses for which post-baseline data are available.

Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations likely to affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. Subjects will be analyzed according to the actual treatment they received.

Pharmacokinetic (PK) Population – Includes all trial subjects who have at least one evaluable PK sample taken during their participation.

11.2.3. Baseline Characteristics and Disposition of Subjects

The subject disposition summary will include the number of subjects in each population. The number and percentage of subjects who complete or discontinue from the trial will be summarized by reason. Each subject's age, sex, weight, and other demographic characteristics will be recorded and summarized. Medical history will be listed.

11.2.4. Efficacy Analyses

Changes from baseline in efficacy endpoints will be presented by time point for each treatment arm. For continuous data, a mixed model for repeated measures (MMRM) will be used for each eye separately (study eye and fellow eye), with fixed effects for treatment arm, study visit, the

treatment arm-by-visit interaction, baseline as a covariate, a baseline-by-visit interaction and a random effect for subject and using an unstructured covariance structure. The primary time point for analysis is planned to be Week 48 (End of Treatment Visit).

For efficacy, the primary analysis population will be the mITT on observed data.

A family-wise alpha level of 0.1 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 48 weeks. If both primary endpoints are significantly different from placebo at the 0.1 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise, the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.05 (two-sided) level of significance. Additional details of all statistical analyses will be presented in a separate SAP.

11.2.5. Interim Analysis

A decision may be made to conduct an interim analysis prior to completion of the trial. If so, the SAP, as well as details regarding the methodology for control of alpha and plans for dissemination of results will be finalized prior to unmasking data.

11.2.6. Safety Analyses

Safety data analysis will be conducted using the Safety population.

11.2.6.1. Adverse Events

All AEs will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be listed, but only treatment-emergent AEs (TEAEs) will be summarized. The number and percentage of subjects experiencing 1 or more AEs/ADEs will be summarized by SOC, PT, and treatment arm for each of the following categories: the incidence of all TEAEs, injection site TEAEs (e.g., pain/tenderness, erythema, induration/swelling, and pruritus), treatment-emergent serious adverse events (TESAEs), drug-related TEAEs, and TEAEs by severity.

All ADEs will be coded to SOC and PT using the MedDRA. All reported ADEs will be listed, but only treatment-emergent ADEs (TEADEs) will be summarized. The number and percentage of subjects experiencing 1 or more ADEs will be summarized by SOC, PT, and treatment arm for each of the following categories: the incidence of all TEADEs, injection site TEADEs (e.g., pain/tenderness, erythema, induration/swelling, and pruritus), treatment-emergent serious adverse device effects (TESADEs), device-related TEADEs, and device-related TEADEs by severity.

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/ADE 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 severe (for severity). If drug relationship is missing, subjects will be included in related tables (i.e., considered related).

All AEs/ADEs collected will be listed. In addition, separate listings will be provided for the following:

- Deaths
- SAEs/SADEs
- AEs/ADEs leading to discontinuation of IMP.

11.2.6.2. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics for change from 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 for each treatment arm. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of trial.

11.2.6.3. Vital Signs

Vital signs data will be summarized by changes from baseline values for each treatment arm using descriptive statistics.

11.2.6.4. Other Safety Parameters

The additional safety variables of slit lamp examination and dilated fundus examination will be summarized descriptively using quantitative and qualitative summary statistics as appropriate.

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

11.2.7. Pharmacokinetic Analyses

PopPK analyses will be conducted on the PK Population. The PK model will be generated and validated using data reported from historical, thorough PK studies. Where sufficient data allow, covariates will include age, gender, race, renal function (as described by estimated Glomerular Filtration Rate), intercurrent conditions, and concomitant medications. Plasma samples will be analyzed for elamipretide using a validated liquid chromatography/tandem mass spectrometry

assay. PK modelling will be performed using NONMEM computer software. All model assumptions, validation, and data analysis will be detailed in a separate PK Analysis Plan.

12. TRIAL MONITORING

12.1. Source Document Requirements

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

12.2. Case Report Form Requirements

Clinical data will be recorded in an eCRF by the 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.

The eCRFs should be completed by the Investigator or a qualified designee from the site as soon as the data is available. The Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto the eCRFs. Prior to submission, each completed eCRF must be reviewed for accuracy by the Investigator or designee, corrected as necessary, and approved.

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

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.

Deviations from the protocol with regard to subject enrollment or trial conduct will also be noted in the source documentation, and in the eCRF database. A Sponsor representative will visit the trial site to initiate the trial prior to the first administration of IMP for the first subject and at agreed times throughout the trial, including at the end of the trial. Drug dispensing and clinical drug supply records will be 100% verified at the trial site by the trial monitor. It is understood that all subject-specific information is confidential and no documentation that can link trial information to the specific subject will be collected or retained by the Sponsor.

13. DATA QUALITY ASSURANCE

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

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

In addition, the Sponsor or its representatives will periodically check subject data recorded against source documents at the trial site. The trial 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 trial, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and medical records in the subject files as original source documents for the trial. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

13.1. 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.

An eDC will be used in this trial. The trial site will maintain a separate source for the data entered by the trial site into the Sponsor-provided eDC system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, or any data for which electronic documentation is provided by the subject, will be stored electronically in the central vendor’s database system.

Any data for which paper documentation provided by the subject will serve as a source document will be identified and documented by each trial site in that center’s trial file. Paper documentation provided by the subject may include, for example, a paper diary to collect subject reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

14. INFORMED CONSENT, INSTITUTIONAL REVIEW BOARD, AND REGULATORY CONSIDERATIONS

14.1. Changes in Protocol

Once the protocol has been formally approved by the Sponsor and by the IRB/IEC, any change that might subsequently affect the approval of the IRB/IEC must be documented in the form of an amendment. Protocol amendments, if any, will be reviewed and implemented following IRB/IEC approval. The Sponsor or designee is responsible for submitting protocol amendments to the regulatory authorities, such as the Food and Drug Administration (FDA).

Approval or acceptance is unnecessary for corrections of typographical errors, revisions simply to improve clarity, notifications of changes in monitoring personnel, or for other changes that do not materially affect the conduct of the trial. However, these minor changes will be documented.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to subjects, an amendment may be implemented by the Sponsor without prior approval by the IRB (or equivalent). In this circumstance, however, the Investigator must then notify the IRB in writing within 5 working days after implementation.

All protocol deviations and the reasons for such deviations are to be documented in the source documents and reported to the Sponsor or its designee.

14.2. Informed Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the trial, including answering any questions the subject may have throughout the trial and sharing in a timely manner any new information that may be relevant to the subject willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of trial participation to the subject in simple terms before the subject is entered into the trial, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the trial and desires to participate in the trial.

The Investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

As used in this protocol, the term “informed consent” includes all consent and assent given by subject or their legal representatives.

14.3. Ethics Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP. Documentation of IRB/IEC approval of the protocol and the ICF must be provided to the Sponsor before the trial may begin at the investigative site.

14.4. Regulatory Considerations

This trial will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Council for International Organizations of Medical Sciences International Ethical Guidelines
- The ICH GCP Guideline [E6]
- Applicable local laws and regulations

The Investigator, Sponsor, or designee will promptly submit the protocol to applicable IRB(s)/IEC(s), and regulatory authorities as required. Some of the obligations of the Sponsor may be assigned to a third-party organization. Trial sites will not commence enrollment until Regulatory Authority submission/approval and site IRB/IEC favorable opinion/approval are granted.

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 trial-related data.

14.4.1. Retention of Records

All trial-related material including source documents, eCRFs, Central Authority and IRB/IEC correspondence, analyses, and any other documentation required by applicable laws and regulations will be maintained for 2 years after completion of the trial or notification from the Sponsor that the data can be destroyed, whichever comes first.

The Investigator must obtain the Sponsor's written permission before disposing of any records. If the Investigator retires, relocates, or for any reason withdraws from the trial, then the trial records may be transferred to an acceptable person or institution with the written approval of the Sponsor.

14.4.2. Disclosure of Information

Information concerning the IMP/pen injector and delivery system 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 trial only. It is understood by the Investigator that Stealth BioTherapeutics, Inc. will use information developed in this clinical trial in connection with the development of the IMP 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 trial, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to the Sponsor.

The Investigator may not submit for publication or presentation the results of this trial without first receiving written authorization from Stealth BioTherapeutics, Inc. Authorship and manuscript composition will reflect joint cooperation among all parties involved in the study. Authorship will be established prior to the writing of the manuscript.

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16. APPENDICES

Appendix 1. Schedule of Events

Trial procedures and their recommended order of priority are summarized below.

Days/Weeks	Screening Period[a]	Treatment Period							Follow Up	Early Termination
	Screening (Day -14 to Day -1)	Day 1[b] BL	Wk 4 ±3d	Wk 8 ±3d	Wk 12 ±3d	Wk 24 ±3d	Wk 36 ±3d	Wk 48 ±3d EOT	Week 52 (±3d) Follow Up EOS	Early Termination Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Informed consent	X									
Demographics	X									
Medical/ ocular history	X	X								
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Low-Luminance Questionnaire		X			X	X	X	X		X
Visual Function Questionnaire-39		X			X	X	X	X		X
EQ-5D-5L Questionnaire		X						X		X
Vital signs[c]	X	X	X	X	X	X	X	X		X
Physical examination[d]	X	X				X		X	X	X
Blood for safety[e]	X	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X	X		X
Exploratory plasma and urine samples[f]	X					X		X		

Pregnancy testing (serum)	X								X	X
Pregnancy testing (urine)		X	X	X	X	X	X	X		
Refraction	X	X	X	X	X	X	X	X		X
BCVA	X	X	X	X	X	X	X	X		X
Low-luminance BCVA	X	X	X	X	X	X	X	X		X
Days/Weeks	**Screening Period[a]**	**Treatment Period**							**Follow Up**	**Early Termination**
	Screening (Day -14 to Day -1)	**Day 1[b] BL**	**Wk 4 ±3d**	**Wk 8 ±3d**	**Wk 12 ±3d**	**Wk 24 ±3d**	**Wk 36 ±3d**	**Wk 48 ±3d EOT**	**Week 52 (±3d) Follow Up EOS**	**Early Termination Visit**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Reading acuity at standard and low luminance	X	X	X		X		X	X		X
Slit lamp exam	X	X	X	X	X	X	X	X		X
IOP	X	X				X	X	X		X
Dilated fundus exam	X	X	X	X	X	X	X	X		X
SD-OCT	X	X			X	X	X	X		X
OCT angiography[g] (optional)	X	X			X	X	X	X		X
Fundus photography[h]	X	X			X	X	X	X		X
Fundus autofluorescence	X	X			X	X	X	X		X
Fluorescein angiography[i]	X									
Eligibility	X	X								

Randomization		X								
Dispense IMP and subject diary		X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X		X
IMP training[j]		X								
PK sampling[k]			X	X						X
AEs/ ADEs	X	X	X	X	X	X	X	X	X	X

Abbreviations: BCVA = best-corrected visual acuity; BL = baseline; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; OCT = optical coherence tomography; PK = pharmacokinetics; RPE = Retinal pigment epithelium; SD-OCT = Spectral domain-optical coherence tomography; VA = visual acuity.

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. Re-screening of subjects may be allowed, depending on the reason for screen-failure, after consultation with the Sponsor. b. The first day of treatment is defined as study Day 1.

c. Vital sign measurements include temperature, respiratory rate, sitting blood pressure after resting for 5 minutes, pulse and weight.

d. Physical examination will include assessment of head, eyes, ears, nose, and throat, general appearance, skin, chest, heart, abdomen, extremities, and nervous system. Height will only be recorded at the Screening Visit.

e. Blood for safety will consist of hematology panel and clinical chemistry.

f. Exploratory plasma and urine samples will be withdrawn and stored for future analysis. Analysis may include genetic and/or metabolomic testing (optional).

g. OCT angiography is optional. It is recommended for trial sites that has the OCT angiography capabilities.

h. Fundus examination will be utilized for safety assessment of the RPE, choroid, neuro-retina structure, retinal vessels, optic nerve, and vitreous

i. FA completed for reasons of standard of care and within 30 days prior to first dose can be used for screening purposes if official documentation is provided.

j. The IMP training checklist will be completed for the subject or caregiver at Day 1, prior to the first dose of IMP. Any new caregiver should complete IMP training at any trial site visit before administering IMP to a subject.

k. For the Week 8 visit, the subject will administer IMP at home, approximately 4 hours ± 1 hour before arriving at the trial site. Random PK sample to be taken at Early Termination Visit (one sample at any time during visit).

Stealth BioTherapeutics Inc.
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Appendix 2. Table for Grading the Severity of Injection Site Reactions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area ~~OR~~ Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm of thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm of thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*

Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Adapted from Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.