ReNEW: A Phase 3, Randomized, Double-Masked, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects who have Dry Age-Related Macular Degeneration (Dry AMD)

Trial Phase:	Phase 3
Trial Number:	SPIAM-301
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Confidentiality Statement

PROTOCOL APPROVAL

Protocol Title: ReNEW: A Phase 3, Randomized, Double-Masked, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects who have Dry Age-Related Macular Degeneration (Dry AMD)

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Anthony Abbruscato

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Vice President, Clinical Development
Stealth BioTherapeutics Inc.

03/09/2024

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure (IB) for elamipretide. 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 Council for 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

1. SYNOPSIS

Sponsor/Company: Stealth BioTherapeutics Inc.

Investigational Medicinal Product: Elamipretide hydrochloride

Active Ingredient: Elamipretide

Title of Trial: ReNEW: A Phase 3, Randomized, Double-Masked, Placebo-Controlled Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects who have Dry Age-Related Macular Degeneration (Dry AMD)

Protocol Number: SPIAM-301

Clinical Phase: Phase 3

Trial Sites: Global multi-site

Numbers of Subjects to be Enrolled/Randomized:

Approximately 360 subjects will be randomized (2:1 treatment randomization)

Objectives

Primary Objective

- Evaluate the efficacy of once daily subcutaneous (SC) injections of elamipretide in subjects who have dry age-related macular degeneration (AMD)

Secondary Objectives

- Evaluate the safety and tolerability of once daily SC injections of elamipretide
- Evaluate the Pharmacokinetic (PK) profile of elamipretide and its metabolites

Endpoints (comparing elamipretide to placebo)

Criteria for Evaluation Primary Efficacy Endpoint:

- Rate of change in the macular area of photoreceptor loss (defined as an Ellipsoid Zone – Retinal Pigment Epithelium (EZ-RPE) thickness of 0µm) assessed by spectral domain-optical coherence tomography (SD-OCT) and Ellipsoid Zone (EZ) mapping at Week 48

Secondary Efficacy Endpoints:

- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 72
- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 96
- Proportion of subjects gaining ≥ 10 letters (2 lines) in Low Luminance Best-Corrected Visual Acuity (LL BCVA) from baseline at Week 48
- Proportion of subjects gaining ≥ 15 letters (3 lines) in LL BCVA from baseline at Week 48

Exploratory Efficacy Endpoints:

- Proportion of subjects gaining ≥ 10 letters (2 lines) in LL BCVA from baseline at Weeks 72 and 96
- Proportion of subjects gaining ≥ 15 letters (3 lines) in LL BCVA from baseline at Weeks 72 and 96
- Rate of change in photoreceptor loss to geographic atrophy (GA) area ratio assessed by SD-OCT and EZ mapping at Weeks 48, 72, and 96
- Change in LL BCVA letter score assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart from baseline at Weeks 48, 72, and 96
- Rate of change in the macular area of partial photoreceptor loss (defined as an EZ-RPE thickness of ≤20µm) assessed by SD-OCT and EZ mapping at Weeks 48, 72, and 96
- Change in Best-Corrected Visual Acuity (BCVA) letter score assessed by the ETDRS chart from baseline at Weeks 48, 72, and 96
- Change in LL BCVA Deficit (LLD, defined as the difference between BCVA and LL BCVA) assessed by the ETDRS chart from baseline at Weeks 48, 72, and 96
- Proportion of subjects losing < 10 letters (2 lines) in LL BCVA from baseline at Weeks 48, 72, and 96
- Proportion of subjects losing < 15 letter (3 lines) in LL BCVA from baseline at Weeks 48, 72, and 96
- Rate of change in square root-transformed GA area as assessed by SD-OCT at Weeks 48, 72, and 96
- Change in Low Luminance Reading Acuity (LL RA) from baseline at Weeks 48, 72, and 96
- Change in Reading Acuity at standard light from baseline at Weeks 48, 72, and 96
- Change in the Vision Impairment in Low Luminance (VILL-33) Questionnaire from baseline at Weeks 48, 72, and 96
- Change in the EQ-5D-5L score from baseline at Weeks 48, 72, and 96
- Change in mtDNA copy number from baseline at Weeks 24 and 48
- Change in mtDNA deletion mutation frequency from baseline at Weeks 24 and 48
- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping, in fellow eyes with GA at Weeks 48, 72, and 96

For efficacy endpoints, unless otherwise specified, the unit of analysis will be the study eye 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 the worse LL BCVA at the Baseline Visit (Day 1). If both eyes have equal LL BCVA at Baseline, then the right eye will be the study eye.

Pharmacokinetic Endpoints:

- 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) modeling.

Safety Endpoints:

- The incidence and severity of adverse events (AEs)
- Vital sign measurements
- Physical examination
- Clinical evaluations (ocular and non-ocular)
- Clinical laboratory evaluations

Trial Population:

Adults ≥ 55 years of age with at least 1 eye with dry AMD with photoreceptor loss as determined by existence of extrafoveal GA by fundus autofluorescence (FAF). GA must be ≥ 0.50 mm^2 and ≤ 10.16 mm^2 in size and reside completely within the FAF 30- or 35-degree image, as confirmed by the Reading Center. All GA lesions must be at least 150 µm from foveal center, as confirmed by the Reading Center. Subjects must have a BCVA score of ≥ 55 letters, an LL BCVA score of ≥ 10 letters, and an LLD of > 5 letters. Subjects (or a caregiver) must also be able to administer the investigational medicinal product (IMP). Subjects must not have evidence of choroidal neovascularization (CNV) (by history or fluorescein angiography [FA]) in the study eye.

Methodology:

In this Phase 3, randomized, double-masked, parallel-group, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of once daily SC doses of elamipretide administered for 96 weeks as a treatment for subjects who have dry AMD, approximately 360 subjects will be randomized (2:1 ratio) to one of two groups, stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss, defined as an EZ-RPE thickness of 0µm assessed by SD-OCT and EZ mapping (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2):

- 96 weeks of once daily SC doses of 40 mg elamipretide OR
- 96 weeks of once daily SC doses of placebo

Screening Period: Screening will begin with the subject's signature of the Informed Consent Form (ICF), with the Screening Period lasting for a maximum of 28 days. Subjects will undergo Screening procedures as described in the Schedule of Assessments (SOA) (Appendix 1). Subjects who complete Screening and continue to meet all trial requirements, including all Inclusion Criteria and none of the Exclusion Criteria, may be randomized at the Baseline Visit (Day 1) and enter the Treatment Period.

Treatment Period: The Treatment Period begins on the day of the Baseline Visit (Day 1) and lasts for approximately 96 weeks. At the Baseline Visit (Day 1), following completion of all Baseline procedures as described in the SOA (Appendix 1), including reconfirming of eligibility, subjects will be randomized 2:1 to treatment with either elamipretide or placebo, stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2). Subjects (and caregivers if needed) will be provided with a dosing diary and trained on the procedure for administration of the IMP and recording of the location (alternating the injection site in one of the four abdominal quadrants or four thigh quadrants) and time (at approximately

the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration daily in the dosing diary. Subject (or trained caregiver) will administer IMP at the clinical trial site, unless otherwise specified.

Subjects will return to the clinical trial site for site visits at Week 4, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, and Week 96 for assessments, and to return used IMP to the clinical trial site, as instructed. On non-site visit days, subjects (or trained caregivers) will administer the IMP daily during the Treatment Period and record in the dosing diary. During the Treatment Period, subjects will continue to follow all trial requirements, including recording the location and time of the IMP administration daily in the dosing diary. The Treatment Period will conclude at Week 96 with a site visit to the clinical trial site when subjects will return all used and unused IMP.

Follow-up phone calls with the subject may be considered between scheduled site visits at approximately monthly intervals. During these calls, AEs should be assessed and documented in the source documents and eCRFs. Subject can be reminded of daily IMP administration and dosing diary completion.

An Unscheduled Visit may be conducted at any time based on the Investigator's discretion. Any assessments performed will be captured in the eCRF.

At the Week 96 Visit, subjects will have the option to enroll into a separate Open Label Extension (OLE) trial (ReTAIN/SPIAM-303) with elamipretide.

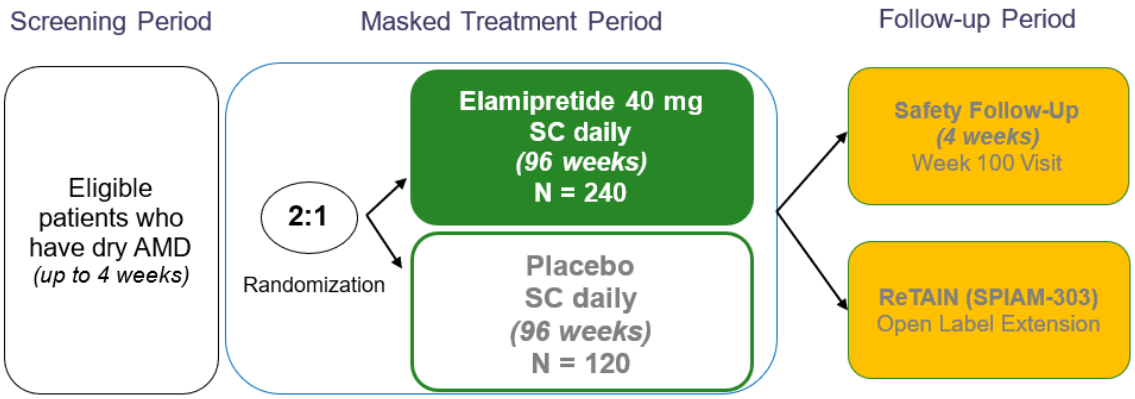
Safety Follow-Up Period: For subjects not enrolling in the ReTAIN, the 4-week Safety Follow-Up Period will begin after completion of the Week 96 Visit. Subjects will return to the clinical trial site at Week 100 for final safety assessments, as described in the SOA (Appendix 1) and return used and unused IMP not previously returned.

Subjects enrolling in ReTAIN immediately following the Week 96 Visit are not required to participate in the Safety Follow-Up Period. In this scenario, the Week 96 Visit will be the final site visit and all End of Study (EOS) procedures completed as outlined in the SOA (Appendix 1).

It is the intent that subjects who discontinue IMP at any time, and for any reason (such as due to an adverse event), will continue to be followed for all protocol-planned site visits through Week 96 and will have all assessments, including efficacy, performed accordingly. However, subjects who wish to withdraw consent from trial participation should be encouraged to complete an Early Discontinuation Visit as soon as possible and complete and report the observations as thoroughly as possible up to the date of withdrawal of consent.

The end of the trial is defined as Last Subject Last Visit. For subjects who are not participating in ReTAIN and do not discontinue the trial early, the EOS Visit will be at Week 100. For subjects who discontinue the trial, the EOS Visit will occur at the same visit as the Early Discontinuation Visit following the SOA (Appendix 1). For subjects participating in ReTAIN, the EOS Visit is defined as Week 96.

ReNEW (SPIAM-301) Design Schematic



Site Visit Schedule:

All subjects will be required to participate in Site Visits 1-11. A Safety Follow-Up Visit (Site Visit 12) will be required for subjects who do not choose to participate in ReTAIN. Subjects discontinuing IMP at any time, and willing to continue participation in the trial, will remain in the trial and have all possible trial assessments completed according to the SOA (Appendix 1). Subjects may continue treatment in ReTAIN after completing the trial through Site Visit 11 (Week 96).

SPIAM-301 Site Visit Schedule

Period	Screening Visit	Baseline Visit and Treatment Period	Safety Follow-Up Period
Site Visit Number	1	2 to 11	12
Day/Week	Day -28 to Day -1	Day 1 to Week 96	Week 100

Planned Duration of Trial and Treatment Period:

The trial duration is up to 104 weeks, which includes up to a 4-week Screening Period, a 96-week Treatment Period, and a 4-week Safety Follow-Up Period (for those not participating in the ReTAIN).

Inclusion Criteria

A subject must meet all the inclusion criteria at the Screening and Baseline Visit (unless otherwise specified) to be eligible for inclusion in the trial.

1. Adults ≥ 55 years of age with at least 1 eye with dry AMD with photoreceptor loss, as determined at the Screening Visit by the presence of extrafoveal GA, as determined by the Reading Center primarily by FAF. For this trial, extrafoveal GA is defined as:
    a. well-demarcated area(s) of GA
    b. All GA lesions must be at least 150 µm from foveal center

Note: The fellow eye may have any of the following: no AMD, AMD without GA, AMD with GA, CNV AMD, or foveal GA (ongoing treatment with anti-angiogenic and/or complement inhibitor therapies in the fellow eye is allowable)

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 ≥ 0.50 mm^2 and ≤ 10.16 mm^2 AND
    b. reside completely within the FAF 30- or 35-degree image
3. BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) score of ≥ 55 letters in the study eye
4. LL BCVA by ETDRS score of ≥ 10 letters in the study eye
5. LLD (defined as the difference between BCVA and LL BCVA) of > 5 letters in the study eye
6. 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:

7. Able to administer IMP or have an appropriate designee who can administer the IMP (i.e., a capable family member or a caregiver)
8. Able to provide informed consent and willing to comply with all site visits, examinations, daily IMP administrations and dosing diary entries, and other conditions of the trial protocol
9. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 28 days after the last dose of IMP:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject; Subject agrees to use a highly effective method of contraception should they become sexually active
    b. Relationships with male partners who have been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit)
    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system

    Note: Non-childbearing potential is defined as surgical sterilization (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).
10. Male subjects with female partners of childbearing potential must be willing to use a highly effective method of contraception (e.g., abstinence, dual method of

contraception) from the date they sign the ICF until 28 days after the last dose of IMP

Exclusion Criteria:

Subjects who meet *any* of the following criteria at the Screening and Baseline Visit (unless otherwise specified) will be excluded from the trial:

Ocular Conditions – Study Eye:

1. The absence of observable hyper-FAF at the margins of the GA in the study eye, as determined at the Screening Visit by the Reading Center
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. Evidence of exudative AMD or CNV by history or FA in the study eye, as determined by the Reading Center
4. Presence of retinal vein occlusion in the study eye
5. Presence of vitreous hemorrhage in the study eye
6. History of retinal detachment in the study eye
7. History of macular hole (stages 2 to 4) in the study eye
8. Presence of an epiretinal membrane and/or vitreomacular traction in the study eye that causes distortion of the retinal contour
9. Presence of any retinal pathology in the study eye that prohibits outer retinal quantification and EZ mapping, as determined at the Screening Visit by the Reading Center
10. At the Screening Visit, advanced glaucoma resulting in a cup to disc ratio of > 0.8 in the study eye
11. History of glaucoma filtration surgery or uncontrolled glaucoma at Baseline Visit in the opinion of the Investigator OR currently using > 2 medications (Minimally invasive glaucoma surgeries (e.g., MIGS) are allowable)

    Note: Combination medications count as 2 medications.
12. Presence of visually significant cataract OR presence of significant posterior capsular opacity in the setting of pseudophakia

    Note: 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 clinical 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 2010)

13. 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
14. Ocular incisional or laser surgery (including cataract surgery) in the study eye within 90 days before the Baseline Visit
15. YAG laser capsulotomy in the study eye within 30 days before the Baseline Visit
16. Aphakia in the study eye
17. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery in the study eye
18. Prior treatment with Visudyne® (verteporfin) ocular photodynamic therapy, external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy in the study eye
19. History of subthreshold laser treatment or other forms of photobiomodulation for AMD in the study eye
20. Intravitreal drug delivery in the past 60 days or 5-half-lives from the Baseline Visit of the injected drug whichever is longer (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye
21. Intravitreal drug delivery of a complement inhibitor in the past 6 months from the Baseline Visit in the study eye
22. Concurrent disease in the study eye that could require medical or surgical intervention during the trial

Ocular Conditions – <u>Either Eye</u>:

23. Presence of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion) in either eye
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. Has a history of a systemic eosinophilic illness and/or an eosinophil count >1,000 cells x10^6/L at the Screening Visit
29. History of solid organ transplant
30. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the trial or might confound trial results
31. 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)
32. eGFR of < 30 mL/min at the Screening Visit (using the CKD-EPI 2021 formula)

General Conditions:

33. Participation in other investigational drug or device clinical trials within 30 days or 5 half-lives (whichever is longer) of Screening; or is currently enrolled in a non-interventional clinical trial that, in the opinion of the Investigator, may be potentially confounding to the results of the current trial
34. Women who are pregnant, planning to become pregnant, or breastfeeding/lactating
35. History of allergy to fluorescein that is not amenable to treatment
36. Inability to comply with trial or follow-up procedures
37. Inability to obtain CFP, FAF, and FA of sufficient quality to be analyzed and interpreted
38. Active malignancy or any other cancer from which the subject has been cancer-free for < 2 years. Localized squamous or non-invasive basal cell skin carcinomas are allowed, if appropriately treated prior to Screening
39. History of allergic reaction to the IMP or any of its components
40. Prior participation in any elamipretide trial

Safety Variables:

AEs, vital signs, physical examinations, clinical evaluations (ocular and non-ocular), and clinical laboratory evaluations will be assessed.

Investigational medicinal product (IMP), dosage, and mode of administration:

Elamipretide will be supplied as a sterile 5.0 mL single-patient, multi-dose glass vial containing 3.5 mL of elamipretide solution (elamipretide [80 mg/mL], phosphate buffer, and benzyl alcohol) for a once daily 40 mg SC administration.

Reference therapy, dosage and mode of administration:

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

Concomitant Treatment Restrictions or Requirements:

The use of any other investigational drugs except elamipretide is prohibited during the conduct of the current trial. All attempts should be made to keep all medications, including over-the-counter treatments, vitamins, or supplements, constant during the trial.

The 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) is prohibited during the conduct of the current trial.

No new treatment should be initiated in the study eye, including intravitreal injections, unless in response to an AE. There are no restrictions on local delivery (including intravitreal injections) in the fellow eye.

No investigational devices are permitted during the conduct of the current trial.

Statistical Methods

Determination of Sample Size

Assuming a 15% study dropout by Week 48, a sample size of 360 subjects with a 2:1 treatment randomization provides > 90% power to detect a mean difference in the rate of change in the macular area of photoreceptor loss of -0.8 mm^2 at Week 48, at a two-sided alpha level of 0.05. Results from a prior trial (2:1 randomization) yield an estimated mean difference of -1.01 mm^2 (standard error 0.3346 mm^2) in change from baseline of the macular area of photoreceptor loss at Week 48, among 120 subjects with baseline GA of at least 0.50 mm^2. Additional details of power calculations will be provided in the SAP.

General Considerations

Data will be tabulated (by treatment group) using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and using frequencies and percentages for discrete variables. Inferential statistics will be presented where specified. This SAP will detail how missing values are to be handled, windows for site visits, and how other analysis considerations will be addressed.

Primary Efficacy Endpoint and Estimand

The primary endpoint is the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) in the study eye at Week 48.

The primary analysis of rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) will be conducted using a linear mixed effects model assuming time as continuous and linear. The model will include treatment (elamipretide or placebo) and baseline macular area of photoreceptor loss as fixed effects, time (trial week, continuous assuming linearity), the time × treatment interaction term as well as the baseline × time interaction term. Correlation between the repeated measurements of the same subject will be accounted for by allowing an unstructured covariance matrix for the residuals. Additional details of the model, including alternative variance-covariance structure (if convergence cannot be attained) and denominator degrees of freedom will be specified in the SAP.

The outcome is the change in macular area of photoreceptor loss from baseline to each time point during the Treatment Period through Week 48. The primary comparison is the difference in least-square means between elamipretide and placebo at Week 48 for the ITT population. The treatment policy strategy will be applied to all intercurrent events. Analyses using the other estimand strategies will also be conducted and detailed in the SAP.

Analysis Populations:

Statistical analysis will be performed in the following populations:

- Safety Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed as treated.

- Intent-to-Treat (ITT) Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed according to the treatment group to which they were randomized.
- Week 48 Per-Protocol (W48PP) Population – Includes all ITT subjects without major protocol violations/deviations on and before Week 48. Details for protocol violations/deviations that would lead to exclusion for the W48PP analysis will be specified in the SAP.
- Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations. Details for protocol violations/deviations that would lead to exclusion for the PP analysis will be specified in the SAP.
- Pharmacokinetic (PK) Population – Includes all trial subjects who have at least one PK sample taken during their participation.

Subject Disposition

Subject disposition (including the number and percent of subjects randomized, receiving randomized treatment, included in each analysis population, completing the trial, or prematurely discontinuing [along with reasons for discontinuation]) will be tabulated by treatment group. The number and percentage of subjects by exposure duration will be tabulated.

Baseline Characteristics

Subject's age, gender, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized. Medical history will be listed.

Safety Analyses

Safety data analysis will be conducted for 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), treatment-emergent serious adverse events (TESAEs), drug-related TEAEs, and TEAEs 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.

Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) will be formed to provide ongoing safety oversight for the trial and will be provided unmasked safety data. The members of DMC must not be involved with the trial in any other way (e.g., they cannot be trial

investigators) and must have no competing interests that could affect their roles with respect to the trial. A separate charter will be established that will outline the frequency of meetings and the roles and responsibilities of all members. A DMC recommendation will be communicated to the Sponsor as described in the DMC charter.

Trial Scientific Review Committee

A Trial Scientific Review Committee (TSRC) managed by the Sponsor is the primary advisory group throughout the trial, providing scientific leadership, and helping ensure trial integrity via review of in-stream, masked, aggregate data. A separate charter will be established to outline the frequency of the meetings, committee member roles, and a complete list of their responsibilities.

2. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
AMD	Age-related macular degeneration
ATP	Adenosine triphosphate
AUC_{0-24}	Area under the plasma concentration curve from baseline to 24 hours post-dose
BCVA	Best-Corrected Visual Acuity
BMI	Body mass index
CFP	Color fundus photography
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration
CNV	Choroidal neovascularization
CRF/eCRF	Case report form / Electronic Case Report Form
DC	Discontinuation
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ETC	Electron Transport Chain
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	Ellipsoid zone
EZ-RPE	Ellipsoid Zone – Retinal Pigment Epithelium
FA	Fluorescein angiography
FAF	Fundus autofluorescence
GA	Geographic atrophy
GCP	Good Clinical Practice
HRD	High-risk drusen
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Integrated Response Technology
ISR	Injection site reaction
ITT	Intention-to-treat
IV	Intravenous
LLD	Low Luminance (BCVA) Deficit

Term	Definition
LL BCVA	Low Luminance Best-Corrected Visual Acuity
LL RA	Low Luminance Reading Acuity
LL VA	Low Luminance Visual Acuity
LS	Least Square
MAR	Missing at random
mg/day	milligrams/day
mg/mL	milligrams/milliliter
MI	Missing imputation
MIGS	Minimally invasive glaucoma surgery
MNAR	Missing not at random
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mtDNA	Mitochondrial DNA
OCT	Optical coherence tomography
OLE	Open-label extension
ONL	Outer nuclear layer
PBS	Placebo saline
PK	Pharmacokinetic(s)
PopPK	Population PK
PP	Per protocol
PR	Photoreceptor
PT	Preferred term
RBC	Red blood cell
ROS	Reactive oxygen species
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	Spectral domain-optical coherence tomography
SBT	Stealth BioTherapeutics
SC	Subcutaneous
SMMP	Safety Management and Medical Monitoring Plan
SOA	Schedule of Assessments
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSRC	Trial Scientific Review Committee
USA	United States of America
VEGF	Vascular endothelial growth factor
VILL-33	Vision Impairment in Low Luminance Questionnaire
WBC	White blood cell
µm	Microns or micrometers

4. INTRODUCTION

This pivotal trial will be conducted in strict accordance with the current versions of the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH GCP guidelines, the Declaration of Helsinki, and all applicable laws and regulations. For detailed information on elamipretide and the nonclinical and clinical studies conducted to date, please refer to the most recent edition of the elamipretide Investigator's Brochure (IB).

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

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 55 or older in the developed world (Bressler 2003; Vitale 2020). It is estimated that more than 11 million Americans have AMD, and prevalence in the United States is projected to increase up to 50% to 22 million by the year 2050 (Pennington 2016; Pascolini 2012). Age is particularly associated with increased risk for AMD, with the incidence of both early and advanced AMD increasing sharply starting in middle age (Bressler 2003; Friedman 2004; Chew 2014). Other risk factors include smoking, genetics, cardiovascular health, and diet. Mitochondrial dysfunction, which has been similarly associated with aging, smoking, obesity, and cardiovascular health, is known to precede clinical symptoms of AMD and increase commensurate with AMD disease progression (Feher 2006; Karunadharma 2010; Terluk 2015).

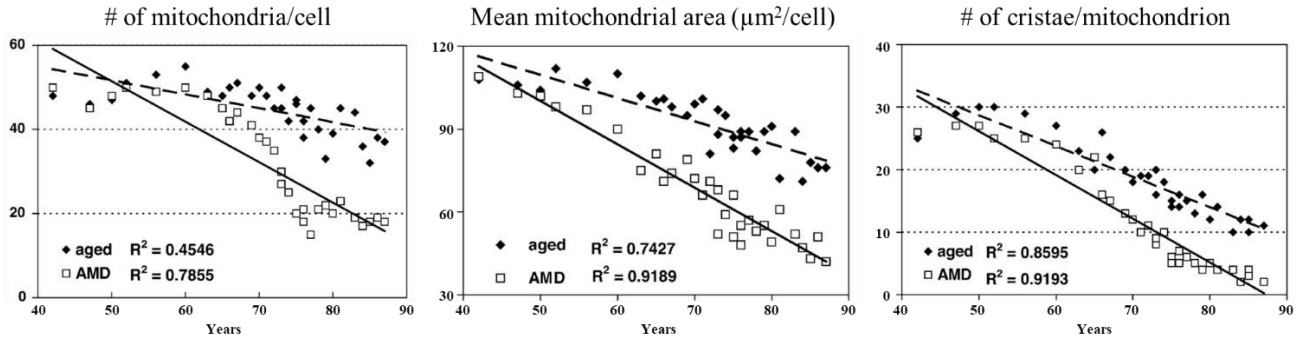
The eye is the highest consumer of mitochondrial ATP in the brain, due to the intensive bioenergetics required to support visual function (Wong-Riley 2010). Mitochondrial-mediated oxidative stress is considered a likely contributing factor to the underlying pathologic processes of AMD, with reactive 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. 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 2006; Decanini 2007; Ethen 2007; Owsley 2007; Nordgaard 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 disease pathology.

It is well-established that mitochondrial dysfunction precedes and increases commensurate with clinical signs and symptoms of dry AMD (Karunadharma 2010; Terluk 2015). Signs and symptoms of mitochondrial dysfunction in human RPE from AMD and from age- and sex-matched controls show markedly reduced number of mitochondria and mean mitochondrial area in cells from AMD patients as well as altered mitochondrial morphology characterized by a significantly reduced number of cristae per mitochondria (Feher 2006) (Figure 1). Disruption of

normal cristae architecture is highly indicative of mitochondrial dysfunction, since the cristae house the electron transport chain (ETC) which is the site of mitochondrial oxidative phosphorylation and ATP production.

Figure 1 Degenerative changes in RPE mitochondria in AMD vs. non-diseased aged eyes



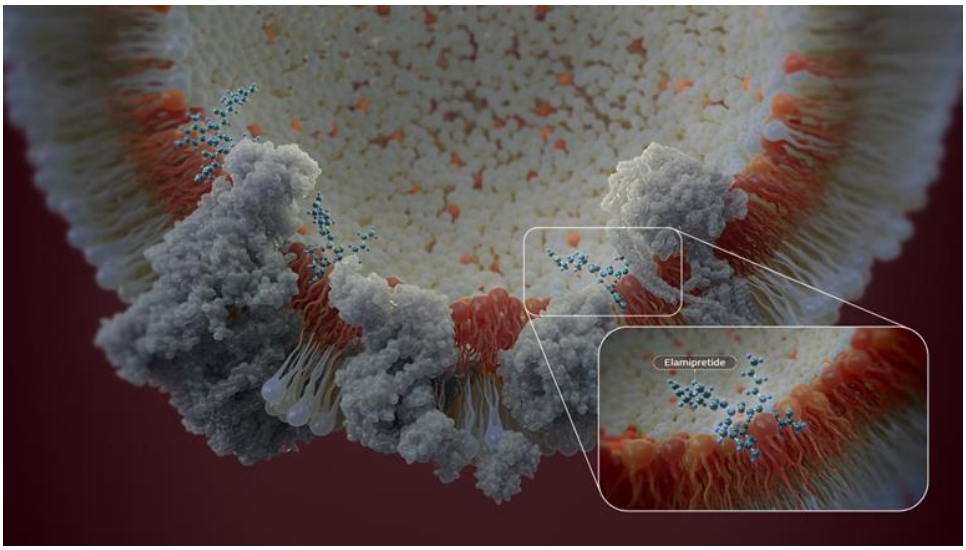
Photoreceptor dysfunction in dry AMD can be quantified by changes in the ellipsoid zone (EZ), which is the mitochondrial-rich layer of the photoreceptors, and the associated loss of photoreceptor cells leading to (and correlated with) progressive loss of visual function. Notably, EZ loss or attenuation has been shown to predict areas of geographic atrophy (GA) onset by two to three years (Pasricha 2021; Sarici 2022), confirming that photoreceptor dysfunction precedes the loss of underlying RPE. EZ loss has been associated with GA progression (Abraham 2022), and there is emerging data suggesting that attenuation of GA progression may mitigate EZ loss (Mai 2022). Longitudinal studies have also demonstrated that the EZ loss-to-GA boundary distance (EZ-GA gap) is prognostic for future GA progression rates and has been concurrently validated in multiple structure-function correlation studies in dry AMD (Pfau 2020).

4.2. Elamipretide

Elamipretide is a first-in-class mitochondrial protective agent that has been shown to improve cell viability and organ function across a spectrum of diseases including ophthalmic, cardiovascular, renal, metabolic, skeletal muscle, neurodegenerative, and genetic mitochondrial disease (Manczak 2010; Birk 2013; Dai 2013; Eirin 2014; Siegel 2013). Elamipretide is an aromatic-cationic tetrapeptide that readily penetrates cell membranes and transiently localizes to the inner membrane of the mitochondria, where it binds reversibly to cardiolipin.

Elamipretide has been shown to influence mitochondrial structure and function via its interaction with cardiolipin. Elamipretide diffuses across the outer mitochondrial membrane and, when proximate with the inner mitochondrial membrane, its positively-charged residues interact electrostatically with the anionic headgroups of cardiolipin, increasing local concentration levels, and its nonpolar side chains interact hydrophobically with the acyl chains (Figure 2) (Mitchell 2020). This electrostatic/hydrophobic binding modulates the surface electrostatics of the inner membrane to facilitate increases in lipid packing, membrane curvature and membrane surface area. The consequences of the effects of elamipretide on the inner mitochondrial membrane include augmenting cristae formation, improving the assembly/activity of membrane protein complexes, and ultimately normalizing oxidative phosphorylation in diseased states despite disease-induced cardiolipin deficit (Mitchell 2020; Allen 2020).

Figure 2 Elamipretide Interaction with Cardiolipin



In addition to improving ETC structure and function and reducing deleterious ROS production, elamipretide has also been shown to normalize or improve other cardiolipin-mediated processes which help the mitochondria adapt to stress or disease. Across multiple genetic and non-genetic disease models, elamipretide has been shown to improve mitochondrial dynamics and quality control through the cardiolipin-mediated processes of fission, fusion, and mitophagy, improve the importation of proteins and enzymes via the cardiolipin-mediated translocase of the outer membrane channel/translocase of the inner membrane "TIM/TOM" complex, signal transcription of certain stress proteins, and improve mitochondrial networking.

4.2.1. Elamipretide Risk/Benefit Assessment

The Investigator's Brochure describes in detail the risks and potential benefits of treatment with elamipretide and should be referenced by the Investigator. A brief overview of the risks and benefits is provided in the following sections. The risk/benefit assessment is considered supportive of the clinical development of elamipretide in patients with AMD.

4.3. Relevant AMD Development Efforts

4.3.1. Nonclinical Data

Elamipretide is efficacious in preclinical models of eye disease. For example, in cultured cells, elamipretide has been shown to reduce glucose- and peroxide-induced oxidative stress, apoptosis and to improve cell survival in human retinal endothelial cells (Li 2011), human trabecular meshwork cells (Chen 2011), and human retinal pigmented epithelial cells (Liang 2010). 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 2013). Elamipretide given to diabetic mice not only prevented but also corrected visual function loss (Alam 2012). Elamipretide given to mice with age-related visual decline and disease due to neural dysfunction mitigated and reversed decline in visual acuity and contrast sensitivity (Alam 2022).

4.3.1.1. Elamipretide improved retinal mitochondrial function, prevented disease progression, and improved visual function in models of dry AMD

Elamipretide has been assessed in several dry AMD models, which are summarized in Table 1.

Table 1 Elamipretide in other preclinical dry AMD models

Model	Result	Reference
Human iPSC-RPE cell model of AMD ("AMD in a Dish" model	Elamipretide enhanced RPE cell viability, decreased expression of genes that activate the complement system and enhanced expression of genes that regulate the complement system.	Fields 2022
Blue light model of retinal damage	Elamipretide preserved photoreceptor function as shown by preservation of cone function, PR/ONL thickness and ONL nuclei.	Data on File
RPE cells cultured from dry AMD donor eyes	Elamipretide improved mitochondrial function (maximal respiration and spare respiratory capacity) and cell viability, protected against oxidative stress and reduced ROS for AMD donor cells at baseline.	Kapphahn 2017
Hydroquinone-induced AMD mouse model	Elamipretide prevented disease progression (maintained normal membrane thickness, mitochondrial morphology and RPE ultrastructure) and reversed symptoms of disease (drusen-like deposit formation).	Cousins 2016
Aged mouse fed high fat diet AMD model	Elamipretide improved B-wave amplitude, in most cases restoring it to normal, suggesting an improvement in photoreceptor function and improved visual acuity, reduced or eliminated sub-RPE deposits and improved RPE mitochondrial morphology.	Cousins 2016

4.3.2. Clinical Data

The safety and efficacy of parenterally administered elamipretide was evaluated in multiple patient populations. These included patients with acute and chronic cardiovascular diseases, primary mitochondrial myopathy (PMM) (ongoing Phase 3 clinical trial), Barth syndrome, skeletal muscle mitochondrial dysfunction, Friedreich's ataxia (ongoing investigator sponsored Phase 2a clinical trial), and dry AMD. Additionally, the efficacy of elamipretide topical solution was evaluated in the clinic in patients with Leber's hereditary optic neuropathy (LHON), diabetic macular edema (DME), AMD and Fuchs' corneal endothelial dystrophy (Fuchs).

In dry AMD, the safety and efficacy of parenterally administered elamipretide was evaluated in SPIAM-101, an open-label, Phase 1 clinical trial that enrolled 40 patients with GA and/or drusen, and SPIAM-202, a Phase 2 clinical trial that enrolled 176 patients with GA.

4.3.2.1. SPIAM-101

SPIAM-101 was an open-label single-center trial to evaluate the safety, tolerability, and efficacy of subcutaneously injected elamipretide in a total of approximately 40 evaluable subjects with either high-risk drusen (HRD) without GA or GA.

At Week 24, patients in HRD (n= 21) and GA (n= 19) groups showed improvement in BCVA and LL BCVA, as well as improvements in Low Luminance Reading Acuity (LL RA) and

functional questionnaires (VFQ-39 and LLQ). (Table 2) (Mettu 2022; Allingham 2022). In the GA cohort, 53% of subjects showed >5 letter LL BCVA improvement, 33% of subjects showed >10 letter LL BCVA improvement, and 7% showed > 15 letters LL BCVA improvement.

Table 2 SPIAM-101: Summary of Changes in Visual Function Parameters in HRD and GA Cohorts

	HRD Only Cohort (n=21, average age 71.6, 61.9% female)		**GA Cohort** (n=19, average age 76.0, 57.9% female)	
	Baseline (SD)	Mean Change at Week 24 (SD) (n=18)	Baseline (SD)	Mean Change at Week 24 (SD) (n= 15)
BCVA	79.6 (7.3 letters)	3.6 (6.4 letters) (p=0.03)	73.7 (9.5 letters)	4.6 (5.1 letters) (p=0.003)
LL BCVA	63.7 (9.8 letters)	5.6 (7.8 letters) (p=0.006)	43.9 (19.8 letters)	5.4 (7.9 letters) (p=0.019)

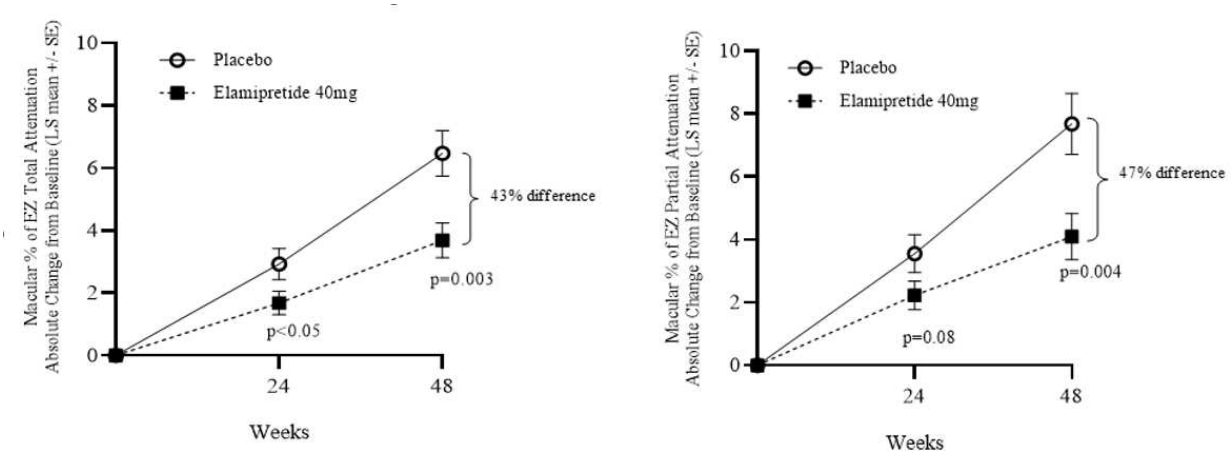
A post-hoc analysis of the GA cohort showed that the baseline photoreceptor health was predictive of patients most likely to respond to therapy. The analysis showed that macular percentage of total EZ attenuation (r = -0.72; p = 0.002) and baseline pan-macular EZ-RPE volume (r = 062; p = 0.01) were significantly correlated to change in LL BCVA from baseline to week 24. Eyes gaining 2 lines or more had significantly less macular total EZ attenuation at baseline (9.0% vs 27%; p = 0.03) and significantly less percentage area of macular GA (4.7% vs 15.6%; p = 0.004).

4.3.2.2. SPIAM-202

SPIAM-202 was a double-masked, randomized, placebo-controlled, multi-center, Phase 2 clinical trial which evaluated the safety, tolerability, and efficacy of daily subcutaneously injected elamipretide 40 mg in 176 adult (≥ 55 years of age) subjects (elamipretide n=117; placebo n=59) with at least one eye with noncentral GA.

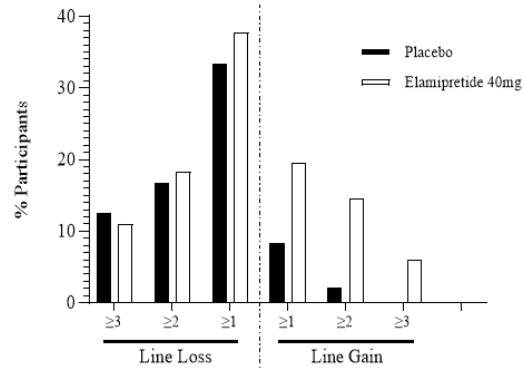
While SPIAM-202 did not meet its primary efficacy endpoints of mean change in LL BCVA and GA area, pre-specified, exploratory endpoints in SPIAM-202 showed that treatment with elamipretide at Week 48 was associated with a significant reduction (43%) in photoreceptor loss (defined as the percentage of the macular area where the EZ-RPE thickness is 0µm), with a (Least-Square) LS mean change from baseline of 3.69% in the elamipretide group versus 6.47% in the placebo group (P=0.003) (Figure 3). Elamipretide was similarly associated with 47% less progression in macular percentage of partial EZ attenuation (defined as the percentage of the macular area where the EZ-RPE thickness is < 20 µm), with a LS mean change of 4.10% in the elamipretide group versus 7.68% in the placebo group (P=0.004) (Figure 3).

Figure 3 SPIAM-202: Macular Percentage of EZ Total and Partial Attenuation for Elamipretide and Placebo (mITT)



Elamipretide was associated with significantly more subjects experiencing a ≥ 2-line gain at Week 48 in LL BCVA vs. placebo (14.63% elamipretide vs. 2.08% placebo; P=0.04) (Figure 4). The percentage of subjects at Week 48 experiencing a >1-line gain on elamipretide was higher compared to placebo, trending towards significance (19.51% vs. 8.33% respectively, p=0.17). All patients who experienced a >3-line gain were randomized to elamipretide (Figure 4).

Figure 4 Summary of Safety



The mITT population was used for the analysis, placebo n=48 and elamipretide n=82. Statistical analysis showing nominal significance levels

4.3.2.3. Clinical Trial Safety Findings

Elamipretide was assessed following single and multiple IV and SC doses in 16 completed clinical pharmacology trials and 14 completed clinical trials in over 1,000 subjects (in total) with heart failure, acute coronary syndrome, acute kidney injury, primary mitochondrial myopathy, age-related skeletal muscle dysfunction, Barth syndrome and dry AMD. Dose levels studied ranged from approximately 0.7 mg/day to 300 mg/day. There were no apparent differences between the safety profiles of IV infusion or SC elamipretide dosing routes except for injection site reactions. Generally, elamipretide has been well-tolerated. The most common side effect is

injection site reactions which have been characterized as mild to moderate with resolution typically occurring within hours of drug administration. Duration of exposure ranged from single dose to >4-years of once-daily SC dosing.

Please see the most recent Investigator's Brochure for more information.

4.4. Discussion of Trial Design and Control

The ReNEW (SPIAM-301) trial is a phase 3, randomized, double-masked, parallel-group, placebo-controlled clinical trial to evaluate the efficacy, safety, and pharmacokinetics of a once daily subcutaneous (SC) injection of elamipretide in subjects who have dry AMD. Subjects will be randomized (2:1) to 40 mg SC of elamipretide or placebo for up to 96 weeks of treatment by a central randomization and stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss, defined as an EZ-RPE thickness of 0µm assessed by SD-OCT and EZ mapping (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2).

The Trial Design Schematic is presented in Appendix 2.

4.5. Rationale for Selection of Doses in the Trial

The dose and route of administration (40 mg by once daily SC injection) for the current trial was chosen based on the safety and efficacy observed in previous clinical trials, as well as systemic exposure comparisons to nonclinical toxicology studies.

A 24-week safety and efficacy trial in AMD subjects (SPIAM-101) demonstrated that dosing at 40 mg/day SC was associated with a favorable benefit-risk profile. A 48-week safety and efficacy and safety trial (SPIAM-202) in subjects with GA secondary to AMD demonstrated that dosing at 40 mg/day SC was well-tolerated and associated with a reduction in photoreceptor loss and functional improvement by categorical changes in LL BCVA. No exposure-response relationships have been identified, and nonclinical exposure to elamipretide and its two major metabolites at the systemic no-observed-adverse-effect-level (NOAEL) in chronic rat and dog trials provide adequate safety margins for a clinical dose of 40mg/day SC elamipretide, even in subjects with severe renal impairment. The maximum dose of elamipretide in subjects with an eGFR ≥ 30 mL/min in chronic studies should generally be no more than 80 mg/day. Safety margins for a 40 mg/day dose are expected to be retained at an eGFR ≥ 20 mL/min in this study.

5. TRIAL OBJECTIVES

5.1. Primary Objective

- Evaluate the efficacy of once daily subcutaneous (SC) injections of elamipretide in subjects who have dry age-related macular degeneration (AMD)

5.2. Secondary Objectives

- Evaluate the safety and tolerability of once daily SC injections of elamipretide
- Evaluate the pharmacokinetic (PK) profile of elamipretide and its metabolites

6. INVESTIGATIONAL PLAN

6.1. SPIAM-301 Overall Trial Design

This Phase 3, randomized, double-masked, parallel-group, placebo-controlled trial will randomize approximately 360 subjects who have dry AMD.

Subjects will be randomized (2:1 ratio) to one of two treatment groups, stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2):

- 96 weeks of single daily SC doses of 40 mg elamipretide OR
- 96 weeks of single daily SC doses of placebo

Subjects who complete the trial will have the option to enroll into a separate open-label extension (OLE) trial (ReTAIN/SPIAM-303) with elamipretide.

6.1.1. Screening Period

Screening will begin with the subject's signature of the Informed Consent Form (ICF), with the Screening Period lasting for a maximum of 28 days. Subjects will undergo Screening procedures as described in the SOA (Appendix 1). Subjects who complete Screening and continue to meet all trial requirements, including all Inclusion Criteria and none of the Exclusion Criteria, will be randomized and enter the Treatment Period.

6.1.2. Treatment Period

The Treatment Period begins on the day of the Baseline Visit (Day 1) and lasts for approximately 96 weeks. At the Baseline Visit (Day 1), following completion of all described Baseline procedures as described in the SOA (Appendix 1), including reconfirming eligibility, subjects will be randomized 2:1 to treatment with either elamipretide or placebo and stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2). Subjects (and caregivers if needed) will be provided with a dosing diary and trained on the procedure for administration of the IMP and recording of the location (alternating the injection site in one of the four abdominal quadrants or four thigh quadrants) and time (at approximately the same time each day

e.g., early morning, noon, or early afternoon]) of the IMP administration daily in the dosing diary. Subject (or trained caregiver) will administer IMP at the clinical trial site, unless otherwise specified.

Subjects will return to the clinical trial site for site visits at Week 4, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, and Week 96, and to return used IMP to the clinical trial site, as instructed. On non-site visit days, subjects (or trained caregivers) will administer the IMP daily during the Treatment Period and record in the dosing diary. During the Treatment Period, subjects will continue to follow all trial requirements, including recording the location and time of the IMP administration daily in the dosing diary. The Treatment Period will conclude at Week 96 with a site visit to the clinical trial site when subjects will return all used and unused IMP.

Follow-up phone calls with the subject may be considered between scheduled site visits at approximately monthly intervals. During these calls, AEs should be assessed and documented in the source documents and eCRFs. If any concerns arise, the subject should have an Unscheduled Visit conducted. Subject can be reminded of daily IMP administration and dosing diary completion.

An Unscheduled Visit may be conducted at any time based on the Investigator's discretion. Any assessments performed will be captured in the eCRF.

At the Week 96 Visit, subjects will have the option to enroll into a separate OLE trial (ReTAIN) with elamipretide.

6.1.3. Safety Follow-Up Period

For subjects not enrolling in ReTAIN, the 4-week Safety Follow-Up Period will begin after completion of the Week 96 Visit. Subjects will return to the clinical trial site at Week 100 for final safety assessments, as described in the SOA (Appendix 1) and return all used and unused IMP not previously returned.

Subjects enrolling in ReTAIN immediately following the Week 96 Visit are not required to participate in the Safety Follow-Up Period. In this scenario, the Week 96 Visit will be the final site visit and all End of Study (EOS) procedures completed as outlined in the SOA (Appendix 1).

It is the intent that subjects who discontinue IMP at any time, and for any reason (such as due to an adverse event), will continue to be followed for all protocol-planned site visits through Week 96 and will have all assessments, including efficacy, performed accordingly. However, subjects who wish to withdraw consent from trial participation should be encouraged to complete an Early Discontinuation Visit as soon as possible and complete and report the observations as thoroughly as possible up to the date of withdrawal of consent.

The end of the trial is defined as Last Subject Last Visit. For subjects who are not participating in ReTAIN and do not discontinue the trial early, the EOS Visit will be at Week 100. For subjects who discontinue the trial, the EOS Visit will occur at the same visit as the Early Discontinuation Visit following the SOA (Appendix 1). For subjects participating in ReTAIN, the EOS Visit is defined as Week 96.

6.2. Schedule of Visit Assessments

The Schedule of Assessments (SOA) includes an up to 4-week Screening period, a 96-week double-masked Treatment Period, and a 4-week Safety Follow-Up Period.

Trial procedures and their timing are summarized in the SOA (Appendix 1) and Trial Design Schematic (Appendix 2).

A signed and dated ICF will be obtained from the subject before any Screening procedures are conducted. A copy of the signed ICF will be given to the subject.

All assessments during each site visit will be documented in the source documents and eCRFs.

A complete medical history will be obtained during the Screening Visit (Site Visit 1) within four weeks before the first dosing of IMP at the Baseline Visit (Day 1). The subject's medical history will be recorded in the Medical History section of the 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 9.3.1). The subject's ocular history should be recorded in the source documents and eCRF.

Subjects will undergo the following screening procedures which may be completed all on the same day or on separate days if logistics don't permit, as long as all procedures are completed during the Screening Period.

Trial Days are relative to the Baseline Visit, and thus Day 1 is the first day of treatment with double-masked IMP, while Day -1 is the day immediately prior.

6.2.1 Screening Visit/Period: Day -28 to Day -1

The following procedures will be performed:

- Review and sign the ICF
- Record demographics (age, gender, ethnicity, race)
- Review all inclusion and exclusion criteria
- Record medical/surgical history, including ocular history (as described in Section 6.3.1)
- Record prior/concomitant medication/procedures, including supplements and vitamins (as described in Section 6.3.1)
- Assess for any pre-treatment events and record as medical history or AE (as described in Section 9.3.1)
- Complete a physical examination (as described in Section 6.3.2)
- Collect vital signs (including height) and weight (as described in Section 6.3.3)
- Complete 12-lead resting Electrocardiogram (ECG) (as described in Section 6.3.6)
- Draw blood and collect urine for clinical laboratory testing and urinalysis (as described in Appendix 3 and Section 6.3.4)
- Complete serum pregnancy test (only for women of childbearing potential, as described in Section 6.3.5)
- Ocular assessments (as described in Section 6.3.10)
  - Refraction
  - BCVA
  - LL BCVA
  - RA at standard luminance
  - LL RA
  - Slit lamp exam
  - Intraocular pressure (IOP)
  - Dilated fundus exam

  - Spectral-domain optical coherence tomography (SD-OCT)
  - Color fundus photography (CFP)
  - Fundus autofluorescence (FAF)
  - Fluorescein angiography (FA)

6.2.2 Baseline Visit (Day 1)

Note: Subjects who have been deemed eligible during Screening Period will return for Baseline Visit and the following procedures will be performed. At Baseline Visit, the IMP administration will occur after the completion of all Visit procedures.

- Review and ensure all Inclusion Criteria and Exclusion Criteria continue to be met
- Assess AEs (as described in Section 9.3.1) related to a trial procedure and/or meet seriousness criteria that occurred since the signing of the ICF, including Injection Site Reactions (ISRs) (as described in Section 6.3.9) after first dose is given
- Update medical/surgical history, including ocular history, during the Screening Period (as described in Section 6.3.1)
- Update concomitant medication/procedures, including supplements and vitamins (as described in Section 6.3.1)
- Complete a physical examination (as described in Section 6.3.2)
- Collect vital signs and weight (as described in Section 6.3.3)
- Draw blood and collect urine for clinical laboratory testing, biomarker analysis, and urinalysis (as described in Section 6.3.4 and Appendix 3)
- Complete urine pregnancy test (only for women of childbearing potential) (as described in Section 6.3.5)
- Complete the following questionnaires as described in Section 6.3.10):
  - Vision Impairment in Low Luminance Questionnaire (VILL-33)
  - EQ-5D-5L
- Ocular assessments (as described in Section 6.3.10)
  - Refraction
  - BCVA
  - LL BCVA
  - RA at standard luminance
  - LL RA
  - Slit lamp exam
  - IOP
  - Dilated fundus exam

- SD-OCT
- CFP
- Fundus autofluorescence (FAF)

If the subject meets all Inclusion Criteria and none of the Exclusive Criteria and has completed all baseline assessments, the subject will be randomized (as described in Section 8.5).

Following Randomization:

- Dispense IMP and ancillary supplies
- Provide subject with the dosing diary and train subject (or caregiver, if needed) on the procedure for IMP administration and recording of the location (alternating the injection site in one of the four abdominal quadrants or four thigh quadrants) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration daily in the dosing diary
- Administer by subject (or trained caregiver) the first dose of IMP, recording the location, date, and time of the IMP administration in the dosing diary; IMP administration should occur after completion of all visit procedures

6.2.3 Site Visits: Week 4, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, and Week 96/EOT Visits

Subjects will return to the clinical trial site for site visits and perform procedures, as described in the Schedule of Assessments (Appendix 1) for that visit. On days of site visits to the clinical trial sites during the Treatment Period, the IMP should be administered at the clinical trial site (except Week 36). The IMP administration should occur after completion of all visit procedures. During this double-masked Treatment Period, subjects (or trained caregivers) will administer assigned IMP daily, and record the location, date, and time of the IMP administration in the dosing diary.

During these site visits:

- Collect all used IMP and assess compliance
- Collect all unused IMP (Week 96 only)
- Update concomitant medication/procedures, including supplements and vitamins (as described in Section 6.3.1)
- Assess AEs (as described in Section 9.3.1), including ISRs (as described in Section 6.3.9)
- Complete a physical examination at Weeks 48 and 96 (as described in Section 6.3.2)
- Collect vital signs and weight (as described in Section 6.3.3)
- Complete 12-lead resting Electrocardiogram (ECG) (as described in Section 6.3.6) at Weeks 48 and 96
- Draw blood and collect urine for clinical laboratory testing, biomarker analysis (Weeks 24 and 48 only), and urinalysis (as described in Section 6.3.4 and Appendix 3)

- Complete urine pregnancy test (only for women of childbearing potential, as described in Section 6.3.5)
- Draw blood for PK analysis (as described in Section 6.3.8):
  - Week 4: pre-dose (within 1 hour of dosing), 15 min. post-dose (± 5 min.), 30 min. post-dose (± 5 min.), and 90 min. post-dose (± 15 min.)
  - Week 36: 4 hours post-dose (± 90 min.)

    Note: The Week 36 dose will be administered at home (not at site visit)
- Complete the following questionnaires (as described in Section 6.3.10):
  - VILL-33 – Weeks 48 and 96 only
  - EQ-5D-5L – Weeks 24, 48, 72, and 96 only
- Ocular assessments (as described in Section 6.3.10):
  - Refraction
  - BCVA
  - LL BCVA
  - RA at Standard Luminance
  - LL RA
  - Slit lamp exam
  - IOP
  - Dilated fundus exam
  - SD-OCT (excluding Week 4)
  - CFP (Weeks 24, 48, 72, and 96)
  - FAF (Weeks 24, 48, 72, and 96)
  - FA (Week 48 and 96)
- Dispense IMP and ancillary supplies (excluding Week 96)
- Administer (by subject or their trained caregiver) IMP (excluding Week 36, where IMP will be administered at home), recording the location, date, and time of the IMP administration in the dosing diary
- Remind women of childbearing potential and male subjects with female partners of childbearing potential to use a highly effective method of contraception until 28 days after the last dose of IMP
- Schedule next site visit according to the SOA (Appendix 1)
- Determine if the subject will enroll in ReTAIN (Week 96 only)

Follow-up phone calls with the subject may be considered between scheduled site visits at approximately monthly intervals. During these calls, AEs should be assessed and recorded in the

source documents and eCRFs. If any concerns arise, the subject should have an Unscheduled Visit conducted.

6.2.4 Safety Follow-Up/Week 100/EOS Visit and Early Discontinuation Visit

Subjects will return to the clinical trial site for the final safety assessments (unless enrolling in ReTAIN immediately following the Week 96 Visit), as described in the SOA (Appendix 1) and return all used and unused IMP not previously returned.

- Collect all used and unused IMP and assess compliance (Early Discontinuation Visit only)
- Update concomitant medication/procedures, including supplements and vitamins (as described in Section 6.3.1)
- Assess AEs (as described in Section 9.3.1), including ISRs (as described in Section 6.3.9)
- Complete a physical examination (as described in Section 6.3.2) (Early Discontinuation Visit only)
- Collect vital signs and weight (as described in Section 6.3.3)
- Complete 12-lead resting Electrocardiogram (ECG) (as described in Section 6.3.6) (Early Discontinuation Visit only)
- Draw blood and collect urine for clinical laboratory testing, biomarker analysis (Early Discontinuation Visit Only if prior to Week 48), and urinalysis as outlined in Appendix 3 (and as described in Section 6.3.4)
  - If the assessment is being undertaken as an Early Discontinuation Visit prior to Week 36, draw blood for random PK testing as described in Section 6.3.8
  - If the Early Discontinuation Visit is after Week 36, a random PK sample is not needed
- Complete serum pregnancy test (only for women of childbearing potential) (as described in Section 6.3.5)
- Complete the following questionnaires (as described in Section 6.3.10):
  - VILL-33 (Early Discontinuation Visit Only)
  - EQ-5D-5L (Early Discontinuation Visit Only)
- Ocular assessments (as described in Section 6.3.10):
  - Refraction
  - BCVA
  - LL BCVA
  - RA at Standard Luminance
  - LL RA

  - Slit lamp exam
  - IOP
  - Dilated fundus exam
  - SD-OCT
  - CFP
  - FAF
  - FA (Early Discontinuation Visit Only)
- If an Early Discontinuation Visit, remind women of childbearing potential and male subjects with female partners of childbearing potential to use a highly effective method of contraception until 28 days after the last dose of IMP

6.3. Description of Trial Procedures

The following sections describe trial procedures occurring during the trial. Trial procedures and their timing are summarized in the Schedule of Assessments (Appendix 1).

6.3.1. Medical/Surgical History and Concomitant Medications/Procedures

Medical history and any concomitant medications will be recorded during the Screening Visit. At the Baseline Visit (Day 1), 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 site visit from Screening Visit until EOS.

All ocular history with details regarding condition(s) and allergies, date(s) of onset, and whether condition(s) currently exist should be noted. Significant medical history, any medical history including surgical and medical procedures within the past 30 days, and all ongoing/active medical history should also be recorded on the eCRF with details regarding condition(s) and allergies, date(s) of onset, and whether condition(s) currently exist, as well as past surgical and medical procedures and all current medications.

6.3.2. Physical Examination

A physical examination will be performed at the Screening, Baseline, Week 48, and Week 96 Visits. The examination will include a review of the following systems: head, ears, nose, throat, general appearance, skin, chest, heart, abdomen, extremities, and nervous system.

6.3.3. Vital Signs and Weight

During all site visits, the vital signs measurements and weight will be collected. This will include temperature, respiratory rate, sitting blood pressure (recorded after at least 5 minutes of rest and prior to blood draw), heart rate and weight. The equipment should be properly calibrated/certified. If possible, the same equipment and evaluator should be used throughout the trial period. Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed and bladder empty. Height will only be measured at the Screening Visit.

6.3.4. Clinical Laboratory Testing

All standard blood (can be taken non-fasting) 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 any clinically significant events. Any clinically significant event must be followed and reported (see Section 9 for AEs and abnormal laboratory values).

A blood sample will also be collected for the mitochondrial DNA (mtDNA) biomarker at the Baseline, Week 24, and Week 48 Site Visits at USA clinical trial sites only.

Detailed instructions for blood sample collection will be provided to clinical trial sites in the Laboratory Manual.

Clinical laboratory assessments performed are listed in Appendix 3.

6.3.5. Pregnancy Tests

For women of childbearing potential, pregnancy testing by assessment of serum beta human chorionic gonadotrophin (β-hCG) will be performed at the time of the Screening Visit and at trial conclusion (i.e., Safety Follow-Up or Early Discontinuation Visit), unless a subject continues in ReTAIN; in that case, a subject follows the ReTAIN Schedule of Assessments after Week 96. Women of childbearing potential will have a urine pregnancy test at the Baseline Visit (Day 1) and all site visits during the Treatment Period, and the results of the Baseline Visit (Day 1) pre-dose pregnancy test must be evaluated before randomization to ensure eligibility.

Women who are considered not to be of childbearing 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 source documents.

6.3.6. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained after the subject has rested quietly for 5 minutes in the supine position. ECG intervals (PR, RR, QRS, QT, available QTc), heart rate and ECG findings will be recorded for each subject and submitted to a central reading center for evaluation. A single method for corrected QT interval (e.g. QTcF) will be calculated for all subjects. ECGs will be performed before vital signs are assessed and collection of blood samples for laboratory testing.

6.3.7. Dosing Diary

Subjects will be asked to complete a dosing diary documenting IMP compliance with daily dosing. Clinical trial site personnel will review the completed dosing diary at each site visit and if necessary, retrain the subject (or their trained caregiver) on proper administration of IMP and dosing diary entries.

6.3.8. Pharmacokinetic (PK) Sampling

To characterize the PK of elamipretide, PK sampling will be conducted at defined time points. PopPK modeling will identify and characterize the influence of demographic factors (e.g., age, gender, race), health status, drug-drug interaction and other covariates on the PK of elamipretide. The PK sampling schedule is as follows:

- Week 4: pre-dose (within 1 hour of dosing), 15 min. post-dose (± 5 min.), 30 min. post-dose (± 5 min.), and 90 min. post-dose (± 15 min.)
- Week 36: 4 hours post-dose (± 90 min.)

  Note: The Week 36 dose will be administered at home (not at site visit)
- Early Discontinuation Visit (prior to Week 36): Random PK sample (one sample at any time during visit)

Samples should be collected as close to nominal as possible.

If a subject has permanently discontinued IMP but remains in the trial to collect protocol-specified assessments, PK samples scheduled at a given site visit do not need to be collected if the date of treatment discontinuation is ≥7 days before the site visit.

6.3.9. Injection Site Reaction (ISR) Review

A thorough ISR review will be conducted at each site visit. ISRs will be graded for severity as described in Section 9.10.1.1. If interventions are utilized in the treatment of ISRs, they should be recorded as a Concomitant Medication. During the subject's site visit, the clinical trial site staff should ask the subject whether they believe the intervention was beneficial.

6.3.10. Other Assessments

Subjects will undergo several examinations to establish the subject's baseline disease and change in disease over time. The following assessments with be performed within 28 days before Day 1 and at various times throughout the trial, as described in the SOA (Appendix 1). All ophthalmic testing is conducted on each eye at each time point. Reading Acuity and LL Reading Acuity testing is conducted on both eyes simultaneously.

All clinical trial site certification, equipment certification and all images collected will be managed by a central Reading Center.

- BCVA, LL BCVA, RA, LL RA and refraction will be assessed as detailed in their respective procedures' manuals. Clinical trial site staff will be trained and certified in these procedures.
- Slit lamp biomicroscopy will be performed to examine the eyelid, conjunctiva, cornea, lens, iris, and anterior chamber. 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 the source documents and corresponding eCRF.
- IOP will be measured by Goldmann applanation tonometry or Tono-pen. The same method for each individual subject should be used throughout the trial, if possible. IOP measurement must be performed prior to dilation. If IOP is >35 mmHg as measured with a Tono-pen, IOP should be measured again by Goldmann applanation tonometry.
- Dilated fundus examination will be performed to examine the vitreous, retina, macula, choroid, optic nerve, and blood vessels. Findings which are deemed clinically

significant by the Investigator will be documented on the source documents and corresponding eCRF.

- CFP of the posterior segment for safety assessment of the RPE, choroid, neuro-retinal structure, retinal vessels, optic nerve, and vitreous, 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 CNV will all be performed as outlined in the imaging manual.

Both VILL-33 and EQ-5D-5L questionnaires are to be completed prior to any ophthalmology evaluations.

- VILL-33 (Appendix 4) is a self-completed questionnaire assessing patient-reported difficulties under low luminance and low contrast conditions. The VILL-33 questionnaire includes 33 items which focus on visual impairment and vision-related quality of life under challenging luminance and contrast conditions.
- EQ-5D-5L (Appendix 5) is a self-completed general quality of life questionnaire assessing mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall assessment of health.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

The inclusion and exclusion criteria for participation are provided below. All screening assessments must be completed during the Screening Period but may be performed on different days. Screening assessments should not be repeated and subjects cannot be re-screened without the Sponsor's documented approval. If a subject is re-screened, they will maintain their original screening number. Subjects may only be enrolled into the trial one time.

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

7.1. SPIAM-301 Eligibility

7.1.1. Subject Inclusion Criteria

A subject must meet all the inclusion criteria at the Screening and Baseline Visit (unless otherwise specified) to be eligible for inclusion in the trial.

1. Adults ≥ 55 years of age with at least 1 eye with dry AMD with photoreceptor loss, as determined at the Screening Visit by the presence of extrafoveal GA, as determined by the Reading Center primarily by FAF. For this trial, extrafoveal GA is defined as:
    a. well-demarcated area(s) of GA
    b. All GA lesions must be at least 150 µm from foveal center

    Note: The fellow eye may have any of the following: no AMD, AMD without GA, AMD with GA, CNV AMD, or foveal GA (ongoing treatment with anti-angiogenic therapies and/or complement inhibitor therapies in the fellow eye is allowable)

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 ≥ 0.50 mm^2 and ≤ 10.16 mm^2 AND
    b. reside completely within the FAF 30- or 35-degree image
3. BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) score of ≥ 55 letters in the study eye
4. LL BCVA by ETDRS score of ≥ 10 letters in the study eye
5. LLD (defined as the difference between BCVA and LL BCVA) of > 5 letters in the study eye
6. 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:

7. Able to administer IMP or have an appropriate designee who can administer the IMP (i.e., a capable family member or a caregiver)
8. Able to provide informed consent and willing to comply with all site visits, examinations, daily IMP administrations and dosing diary entries, and other conditions of the trial protocol
9. Women of childbearing potential must agree to use 1 of the following methods of contraception from the date they sign the ICF until 28 days after the last dose of IMP:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject; Subject agrees to use a highly effective method of contraception should they become sexually active
    b. Relationships with male partners who have been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit)
    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system

Note: Non-childbearing potential is defined as surgical sterilization (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).

10. Male subjects with female partners of childbearing potential must be willing to use a highly effective method of contraception (e.g., abstinence, dual method of contraception) from the date they sign the ICF until 28 days after the last dose of IMP

7.1.2. Subject Exclusion Criteria

Subjects who meet *any* of the following criteria at the Screening and Baseline Visit (unless otherwise specified) will be excluded from the trial:

Ocular Conditions – Study Eye:

1. The absence of observable hyper-FAF at the margins of the GA in the study eye at the Screening Visit by the Reading Center
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. Evidence of exudative AMD or CNV by history or FA in the study eye, as determined by the Reading Center
4. Presence of retinal vein occlusion in the study eye
5. Presence of vitreous hemorrhage in the study eye
6. History of retinal detachment in the study eye
7. History of macular hole (stages 2 to 4) in the study eye
8. Presence of an epiretinal membrane and/or vitreomacular traction in the study eye that causes distortion of the retinal contour
9. Presence of any retinal pathology in the study eye that prohibits outer retinal quantification and EZ mapping, as determined at the Screening Visit by the Reading Center
10. At the Screening Visit, advanced glaucoma resulting in a cup to disc ratio of > 0.8 in the study eye
11. History of glaucoma filtration surgery or uncontrolled glaucoma at Baseline Visit in the opinion of the Investigator OR currently using > 2 medications (Minimally invasive glaucoma surgeries (e.g., MIGS) are allowable)

Note: Combination medications count as 2 medications.

12. Presence of visually significant cataract OR presence of significant posterior capsular opacity in the setting of pseudophakia

Note: 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 clinical 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 2010)

13. 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
14. Ocular incisional or laser surgery (including cataract surgery) in the study eye within 90 days before the Baseline Visit
15. YAG laser capsulotomy in the study eye within 30 days before the Baseline Visit
16. Aphakia in the study eye

17. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery in the study eye
18. Prior treatment with Visudyne® (verteporfin) ocular photodynamic therapy, external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy in the study eye
19. History of subthreshold laser treatment or other forms of photobiomodulation for AMD in the study eye
20. Intravitreal drug delivery in the past 60 days or 5-half-lives from the Baseline Visit of the injected drug whichever is longer (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye
21. Intravitreal drug delivery of a complement inhibitor in the past 6 months from the Baseline Visit in the study eye
22. Concurrent disease in the study eye that could require medical or surgical intervention during the trial

Ocular conditions – <u>Either Eye</u>:

23. Presence of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion) in either eye
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. Has a history of a systemic eosinophilic illness and/or an eosinophil count >1,000 cells x10^6/L at the Screening Visit
29. History of solid organ transplant
30. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the trial or might confound trial results
31. 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)
32. eGFR of < 30 mL/min at the Screening Visit (using the CKD-EPI 2021 formula)

General Conditions:

33. Participation in other investigational drug or device clinical trials within 30 days or 5 half-lives (whichever is longer) of Screening; or is currently enrolled in a non-interventional clinical trial that, in the opinion of the Investigator, may be potentially confounding to the results of the current trial
34. Women who are pregnant, planning to become pregnant, or breastfeeding/lactating

35. History of allergy to fluorescein that is not amenable to treatment
36. Inability to comply with trial or follow-up procedures
37. Inability to obtain CFP, FAF, and FA of sufficient quality to be analyzed and interpreted
38. Active malignancy or any other cancer from which the subject has been cancer-free for < 2 years. Localized squamous or non-invasive basal cell skin carcinomas are allowed, if appropriately treated prior to screening
39. History of allergic reaction to the investigational drug or any of its components
40. Prior participation in any elamipretide trial

7.2. Concomitant Treatment Restrictions or Requirements

The use of any other investigational drugs except elamipretide is prohibited during the conduct of the current trial. All attempts should be made to keep all medications, including over-the-counter treatments, vitamins, or supplements, constant during the trial.

The 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) is prohibited during the conduct of the current trial.

No new treatment should be initiated in the study eye, including intravitreal injections unless in response to an AE. There are no restrictions on local delivery (including intravitreal injections) in the fellow eye.

No investigational devices are permitted during the conduct of the current trial.

7.3. Criteria for Subject, Site, or Trial Discontinuation

7.3.1. Discontinuation of Subjects

7.3.1.1. Discontinuation of Subjects from Trial

Subjects must discontinue from the trial for the following reasons:

- Investigator Decision
  - The Investigator decides that the subject should be discontinued from the trial for any reason.
- Subject Decision
  - The subject requests to be withdrawn from the trial.
  - Subjects who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.
  - Preferably the subject should withdraw consent in writing and, if the subject refuses or is physically unavailable, the clinical trial site should document and sign the reason for the subject's failure to withdraw consent in writing.
- Sponsor Decision

  - The Sponsor or its designee terminates the trial or terminates the subject's participation in the trial for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

- Adverse Event
  - If the Investigator decides that the subject should be withdrawn from the trial because of an AE or a clinically significant laboratory value, the IMP is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.
- Lost to Follow-Up
  - The subject is lost to follow-up after a reasonable number of attempts to contact the subject (including documented phone calls and/or e-mails, and a certified letter) have been completed.

In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. In the event of missing data, the investigator should include an assessment of whether the reason for the missing data is response-related (i.e., disease state, treatment, etc.).

Upon discontinuation, an assessment of disease or drug association should be conducted. This can be an answer of definitely, probably, possibly, or not at all to two questions:

1. Is any reason for discontinuation associated with the treatment, for example, through side-effect or ISRs, or perceived lack of efficacy?
2. Is any reason for discontinuation associated with severity (or lack of severity) of AMD?

7.3.1.2. Discontinuation of Subjects from IMP

Subjects must discontinue IMP for the following reasons:

- Adverse Event
  - If the Investigator decides that the subject should be withdrawn from IMP because of an AE, the IMP is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.
- Pregnancy
  - If a subject becomes pregnant while enrolled in the trial.

For these subjects, it is the intent that subjects who discontinue IMP at any time, or for any reason, will continue to be followed for all protocol-planned site visits through completion and will have all assessments, including efficacy, performed accordingly, if agreed by the subject and Investigator.

7.3.2. Discontinuation of Clinical Trial Site Participation

Clinical trial site participation must be discontinued if the Sponsor or its designee, the Investigator, the Regulatory Authority, or the Ethics Committee (EC) deems it necessary for

medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.3.3. Discontinuation of the Trial

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

7.4. Dose Adjustments and Interruptions

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. Apart from emergency situations, the Investigator is responsible for contacting the Sponsor or designee prior to interrupting the subject's daily trial drug dosing regimen.

There are no dose adjustments for mild or moderate renal impairment. For subjects with an eGFR < 20 mL/min during the treatment period, IMP should be interrupted, and the Medical Monitor should be notified. Treatment with IMP may be resumed if the eGFR increases to ≥ 20 mL/min pending an evaluation of the etiology of renal impairment and provided that the renal function is anticipated to remain stable. Otherwise, IMP should be permanently discontinued.

8. INVESTIGATIONAL MEDICINAL PRODUCT MATERIALS AND MANAGEMENT

8.1. Treatments Administered

The ReNEW (SPIAM-301) trial is a phase 3, randomized, double-masked, parallel-group, placebo-controlled clinical trial to evaluate the efficacy, safety, and pharmacokinetics of a once daily subcutaneous (SC) injection of elamipretide in subjects who have dry AMD. Subjects will be randomized (2:1) to 40 mg SC of elamipretide or placebo for up to 96 weeks of treatment by a central randomization and stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss (High Strata ≥ 5.1mm^2, Low Strata < 5.1mm^2).

8.2. Materials and Supplies

Elamipretide and placebo will be supplied as a sterile 5.0 mL single-patient, ready to use, multi-dose glass vial. Elamipretide vials will contain 3.5 mL of elamipretide solution (elamipretide [80 mg/mL], phosphate buffer, and benzyl alcohol) for a once daily 40 mg SC injection.

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

The placebo and elamipretide multi-dose supplies will be dispensed and stored according to the Pharmacy Manual.

The placebo and elamipretide multi-dose materials are to be stored refrigerated at 2 to 8°C (36 to 46°F) in a secure area. Temperature records must be maintained, and temperature excursions

reported as soon as they are discovered. The Sponsor must be notified in the case of an excursion so that a disposition decision can be made.

Additional information including the count of materials dispensed, returns, temperature monitoring, etc. will be provided in the Pharmacy Manual.

Until IMP is administered to trial subjects, it is the sole property of Stealth Biotherapeutics Inc.

8.3. Investigational Medicinal Product Accountability

The IMP will be assigned to each subject through an Integrated Response Technology (IRT). All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused elamipretide supplies. These records should contain the dates and quantity:

- Received at clinical trial site
- Administered to each subject
- Dispensed to each subject
- Returned from each subject
- Disposed of at the clinical trial site or returned to the Sponsor or designee

The clinical trial site monitor is responsible for ensuring the clinical trial site will provide written approval for the destruction or return of used and unused elamipretide supplies following reconciliation of all clinical supplies.

8.4. Treatment Compliance

During the Treatment Period, IMP will be administered once daily by the subject (or caregiver). A dosing diary will be used to document daily IMP administration.

8.5. Randomization

The randomization will be based on a 2:1 ratio of elamipretide to matching placebo, stratified by SD-OCT device type (Heidelberg SPECTRALIS®, ZEISS CIRRUS®) and baseline macular area of photoreceptor loss (High Strata $\geq 5.1mm^2$, Low Strata $< 5.1mm^2$). The randomization will be centrally administered through an IRT.

8.6. Masking and Unmasking Procedures

Trial personnel and subjects will be masked to treatment until the database is locked at the end of the trial, unless noted below.

The Investigator will contact the Sponsor Medical Monitor prior to unmasking any subject's treatment sequence 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, a subject's treatment assignment may be unmasked prematurely using the computerized system. 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

IRT system and also included in the source documents. The name of the individual who broke the masking must be included in the source documents.

The Emergency Unblinding function within the IRT system is used to reveal the unmasked treatment assigned to a specific subject. This function is only available to Site Investigators and Sponsor Medical Monitor. Once unmasked, the subject will not continue in the trial. Site Investigators users will only have access to subjects associated with their corresponding clinical trial site.

The study unmasking for the primary analysis at 48 weeks will be limited to firewalled team members, only on an as-needed basis. All other trial personnel, including subjects, clinical trial site staff, Sponsor, and Reading Center members in the "masked" role will remain masked until the end of study. A document outlining the masking strategy, including the roles and responsibilities of the individuals participating in the unmasking analysis, will be provided prior to the unmasking.

9. EFFICACY AND SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

For efficacy endpoints, unless otherwise specified, 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 Visit (Day 1). If both eyes have equal LL BCVA at baseline, then the right eye will be the study eye.

9.1. Efficacy Endpoints

Endpoints (comparing elamipretide to placebo)

9.1.1. Primary Endpoints

- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 48

9.1.2. Secondary Endpoints

- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 72
- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 96
- Proportion of subjects gaining ≥ 10 letters (2 lines) in Low Luminance Best-Corrected Visual Acuity (LL BCVA) from baseline at Week 48
- Proportion of subjects gaining ≥ 15 letters (3 lines) in LL BCVA from baseline at Week 48

9.1.3. Exploratory Efficacy Endpoints

- Proportion of subjects gaining ≥ 10 letters (2 lines) in LL BCVA from baseline at Weeks 72 and 96

- Proportion of subjects gaining ≥ 15 letters (3 lines) in LL BCVA from baseline at Weeks 72 and 96
- Rate of change in photoreceptor loss to geographic atrophy (GA) area ratio assessed by SD-OCT and EZ mapping at Weeks 48, 72, and 96
- Change in LL BCVA letter score assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart from baseline at Weeks 48, 72, and 96
- Rate of change in the macular area of partial photoreceptor loss (defined as an EZ-RPE thickness of ≤20µm) assessed by SD-OCT and EZ mapping at Weeks 48, 72, and 96
- Change in Best-Corrected Visual Acuity (BCVA) letter score assessed by the ETDRS chart from baseline at Weeks 48, 72, and 96
- Change in LL BCVA Deficit (LLD, defined as the difference between BCVA and LL BCVA) assessed by the ETDRS chart from baseline at Weeks 48, 72, and 96
- Proportion of subjects losing < 10 letters (2 lines) in LL BCVA from baseline at Weeks 48, 72, and 96
- Proportion of subjects losing < 15 letter (3 lines) in LL BCVA from baseline at Weeks 48, 72, and 96
- Rate of change in square root-transformed GA area as assessed by SD-OCT at Weeks 48, 72, and 96
- Change in Low Luminance Reading Acuity (LL RA) from baseline at Weeks 48, 72, and 96
- Change in Reading Acuity at standard light from baseline at Weeks 48, 72, and 96
- Change in the Vision Impairment in Low Luminance (VILL-33) Questionnaire from baseline at Weeks 48, 72, and 96
- Change in the EQ-5D-5L score from baseline at Weeks 48, 72, and 96
- Change in mtDNA copy number from baseline at Weeks 24 and 48
- Change in mtDNA deletion mutation frequency from baseline at Weeks 24 and 48
- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping, in fellow eyes with GA at Weeks 48, 72, and 96

9.2. Pharmacokinetic (PK) Endpoints

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) modeling.

9.3. Safety Endpoints

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 adverse events (AEs)
- Vital sign measurements

- Physical examination
- Clinical evaluations (ocular and non-ocular)
- Clinical laboratory evaluations

9.3.1. Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The safety profile will be assessed through the recording, reporting, and analyzing of Aes, clinical evaluations, and laboratory tests.

The AE reporting period begins when the subject signs the ICF. For those not continuing in ReTAIN, the reporting period continues through the Safety Follow-Up Period, ending at the Safety Follow-Up Visit (Week 100). For subjects continuing in ReTAIN, the reporting period ends at Week 96.

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every site visit and the evaluation must be documented. Clinical trial site personnel will report any AE, whether observed by the Investigator (or designee), or reported by the subject.

The Investigator is responsible for promptly documenting and reporting all AEs in the subject's eCRF and applicable forms.

Should the IMP be discontinued due to an AE deemed probably or possibly related to the IMP (per Section 9.10.1.2), reinitiating (re-challenge) of the IMP may be possible, after consultation with the Sponsor. For all subjects, it is the intent that subjects who discontinue IMP at any time, and for any reason, will continue to be followed for all protocol-planned site visits through the completion of the Treatment Period and will have all endpoints, including efficacy, collected.

The reporting period for AEs is described in Section 9.10.3.

9.4. Pre-Treatment Adverse 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.

9.5. Medical History Conditions

Pre-treatment events or diagnoses not related to a trial procedure and/or not 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.

9.6. Medical and Surgical Procedures

Medical or surgical procedures (including hospitalizations) scheduled (or considered for planning) prior to the subject's signing the ICF, 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.

9.7. 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.

When reporting an abnormal laboratory finding as an AE or SAE, 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.

9.8. Symptomatic Overdose

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

9.9. Serious Adverse Events (SAEs)

A SAE is any AE that:

- Results in death.
- Is life-threatening. The term "life-threatening" refers to a situation in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a medically important event or reaction.

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 that worsens and meets the criteria for a SAE should be reported as a SAE. The start date of the SAE should be the date the AE worsened to meet the criteria for a SAE.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the subject's eCRF.

As part of the routine medical monitoring, the medical monitor (or designee) will review all SAEs reported in the ReNEW (SPIAM-301) trial, looking for any safety data trends or trial IMP-related issues.

9.10. Recording of Adverse Events (AEs)

Complete and accurate data on all AEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis on the subject's eCRF. All SAEs must be reported in the subject's eCRF.

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

Investigators should use the AE 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 rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if this is available, rather than a list of signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnea, rales, and cyanosis'). However, signs and symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.
- Provisional 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 rather than the procedure itself.

9.10.1. Investigator Assessments

9.10.1.1. Severity

Severity, which is a description of the intensity of manifestation of the AE, is distinct from the regulatory definition of *seriousness*.

For all AE's including ISR's, the Investigator is required to grade the severity of each AE according to the following guidelines:

- **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 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.

9.10.1.2. Relationship to the Investigational Medicinal Product (IMP)

Investigators must systematically assess the causal relationship of AEs to the IMP or 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, 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.
- **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, the event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, and there is no reasonable response on withdrawal.

9.10.1.3. Outcome of an Adverse Event (AE)

Investigators must follow all AEs and SAEs until the clinical trial's Safety 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.

9.10.1.4. Investigator Injection Site Reaction (ISR) Assessment

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

- The ISR should be assessed for severity per the guidelines in Section 9.10.1.1.
- Any ISR that meets any of the criteria of a SAE (Section 9.9) should be reported within 24 hours of the clinical trial site first becoming aware of the event (as outlined in Section 9.11).
- 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 which reoccur following a subsequent SC injection, only one 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.

ISRs are common and can lead to patient discomfort. The Investigator is expected to use their clinical judgement regarding treatments for ISRs. Clinical trial sites are encouraged to monitor ISRs between site visits. If ISRs are persistent and/or increase in severity, the Medical Monitor should be contacted to discuss mitigation strategies. Any medications necessary for treatment of the ISR signs and/or symptoms must be recorded on the subject's eCRF. The subject will be asked whether they believe the intervention was beneficial.

9.10.2. Adverse Events of Special Interest (AESI)

AEs related to hypersensitivity and/or allergic reactions will be summarized as AESIs in this trial. The Investigator should inform the Sponsor of any potential AEs related to hypersensitivity and/or allergic reaction; more information may be requested to further characterize these events as necessary. ISRs will be recorded and reported as described in Section 9.10.1.4 and do not fall under the category of AESI described here. Additional details will be outlined in the Safety Management and Medical Monitoring Plan (SMMP).

9.10.3. Adverse Event (AE) Reporting Period

The AE reporting period begins when the subject signs the ICF. For those not continuing in ReTAIN, the reporting period continues through the Safety Follow-Up Period, ending at the Safety Follow-Up Visit (Week 100). For subjects continuing in ReTAIN, the reporting period ends at Week 96. Note that findings that occur between the time the 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 a SAE or is related to a trial procedure.

Treatment-emergent AEs (TEAEs) are defined as AEs that occur after the first IMP administration. TEAEs will be summarized per treatment group.

As previously mentioned, after trial completion, all SAEs with an ongoing/unknown outcome will be followed up until resolution or stabilization. Additional information on SAEs, obtained after database lock, will reside solely in the safety database. Furthermore, the Investigator shall immediately notify the Sponsor if, after completion of the trial, the Investigator learns of an SAE and other promptly reportable AEs in a subject suspected of having a causal relationship with the IMP.

9.11. Serious Adverse Event (SAE) Expedited Reporting

In the event of a SAE occurring during the reporting period, the Investigator must immediately (within 24 hours after becoming aware of the SAE) inform the Sponsor by telephone or e-mail as detailed in the eCRF completion guidelines. Reporting responsibilities for SAEs are detailed in the SMMP.

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

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

Within 24 hours, the relationship of the event to the IMP (e.g., the causality according to the Investigator) should be provided.

For the expedited reporting evaluation, SAEs considered possibly or probably related are processed as related and SAEs considered unrelated or unlikely related are processed as unrelated.

All SAE reports should be processed according to the SMMP.

The Investigator/Reporter must provide follow-up information as available and as requested by the Sponsor.

9.11.1. Pregnancy and Contraception

For women of childbearing potential (or male subjects with female partners of childbearing potential), highly effective methods of contraception must be adhered to from the date they sign the ICF until 28 days after the last dose of IMP. Highly effective methods of contraception are defined as the usage by the female 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. Male subjects with pregnant partners must use a condom from the start of treatment until 28 days after the last dose of IMP. Sperm or egg donation by subjects is not permitted from the start of treatment until 28 days after the last dose of IMP.

Any pregnancy in a subject or partner of a male subject during the trial and until the last Safety Follow-Up Visit must be reported, even if no AE has occurred, as detailed in the SMMP. 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.

The Investigator must notify the Sponsor of any pregnancy using the Pregnancy Notification Form and the reporting procedure as described in the SMMP. Investigators must actively follow up, document, and report on the outcome of every pregnancy, even if the subject is withdrawn from the trial, as detailed in the SMMP.

9.11.2. Responsibilities to Regulatory Authorities, Investigators and Ethics Committees

The Sponsor or its designee 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 site-specific requirements related to the reporting of SAEs involving his/her subjects to the Ethics Committee/Institutional Review Board (EC/IRB) 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 EC's/IRB's approval to continue the trial. In particular, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered IMP ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of these Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety reports directly to the 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 site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

The sponsor will report SUSARs in accordance with Regulation 536/2014 and the related detailed Guidelines.

10. 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 subjects and trial centers, as appropriate.
- Sponsor start-up training to instruct the Investigators and trial coordinators. This training will give instructions on the protocol, the completion of the eCRFs, and trial procedures.
- Make periodic visits to the trial centers in accordance with the Monitoring Plan.
- Be available for consultation and stay in contact with the clinical trial site staff by e-mail, telephone, and/or virtual meetings.
- 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 CRO designee will periodically monitor subject data recorded on eCRFs against the source documents at the clinical trial site. The trial may be audited by the Sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participating subjects in the trial, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the trial. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ECs with direct access to original source documents.

Sponsor, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this trial are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations, and guidelines as applicable.

Sponsor has implemented technical and organizational security measures to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data in compliance with GDPR where required.

10.1. Data Capture System

An electronic data capture system (EDC) will be used in this trial. The clinical trial site will maintain separate sources for the data entered by the clinical trial site into the Sponsor-provided EDC system.

Case report form (CRF) 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 clinical trial site in the Investigator Site File. Paper documentation provided by the subject may include, for example, a paper dosing diary to collect daily dosing compliance, quality of life questionnaires for self-completion and/or through administration by the trial center staff.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

Assuming a 15% study dropout by Week 48, a sample size of 360 subjects with a 2:1 treatment randomization provides > 90% power to detect a mean difference in the rate of change in the macular area of photoreceptor loss of -0.8 mm^2 at Week 48, at a two-sided alpha level of 0.05. Results from a prior trial (2:1 randomization) yield an estimated mean difference of -1.01 mm^2 (standard error 0.3346 mm^2) in change from baseline of the macular area of photoreceptor loss at Week 48, among 120 subjects with baseline GA of at least 0.50 mm^2. Additional details of power calculations will be provided in the SAP.

11.2. Planned Database Locks

There are two planned database locks for this trial, one after all subjects have completed Week 48 and one at the end of the trial. The masking strategy is outlined in Section 8.6. Additional details of analysis timing and data cut will be provided in the SAP.

11.3. Statistical and Analytical Plans

11.3.1. General Considerations

Data will be tabulated (by treatment group) using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and using frequencies and percentages for discrete variables. Inferential statistics will be presented where specified. This SAP will detail how missing values are to be handled, windows for site visits, and how other analysis considerations will be addressed.

Statistical tests (where performed) will be 2-sided at the alpha=0.05 level of significance, except where otherwise noted.

11.3.2. Analysis Populations

Statistical analysis will be performed using the following populations:

- Safety Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed as treated.
- Intent-to-Treat (ITT) Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed according to the treatment group to which they were randomized.
- Week 48 Per-Protocol (W48PP) Population – Includes all ITT subjects without major protocol violations/deviations on and before Week 48. Details for protocol violations/deviations that would lead to exclusion for the W48PP analysis will be specified in the SAP.
- Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations. Details for protocol violations/deviations that would lead to exclusion for the PP analysis will be specified in the SAP.
- Pharmacokinetic (PK) Population – Includes all trial subjects who have at least one PK sample taken during their participation.

11.3.3. Subject Disposition

Subject disposition (including the number and percent of subjects randomized, receiving randomized treatment, included in each analysis population, completing the trial, or prematurely discontinuing [along with reasons for discontinuation]) will be tabulated by treatment group. The number and percentage of subjects by exposure duration will be tabulated.

11.3.4. Baseline Characteristics

Subject's age, gender, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized. Medical history will be listed.

11.3.5. Efficacy Analyses

Details regarding the final analyses will be included in a comprehensive SAP.

For efficacy endpoints, unless otherwise specified, 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 identified at baseline (see Section 9).

Efficacy analyses will be conducted on the ITT, W48PP, and PP populations.

11.3.5.1. Intercurrent Events and Estimand Strategy

The following events are recognized as intercurrent events:

- Discontinuation of IMP
- CNV conversion in study eye
- Complement therapy initiation in study eye

The intercurrent events will be handled with a treatment policy strategy whereby any measured value will be used as is for all primary and secondary endpoints.

The primary analysis will use the ITT population.

11.3.5.2. Primary Efficacy Endpoint and Estimand

The primary endpoint (see Section 9.1.1) is the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) in the study eye at Week 48.

The null and alternative hypotheses for the primary efficacy analysis are:

$$H_0: \mu_{ELAM} = \mu_{Placebo} \quad \text{vs} \quad H_a: \mu_{ELAM} \neq \mu_{Placebo}$$

Note: Here $\mu_{ELAM}, \mu_{Placebo}$ are the mean rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) at Week 48 in the elamipretide and placebo group, respectively.

The primary analysis of rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) will be conducted using a linear mixed effects model assuming time as continuous and linear. The model will include treatment (elamipretide or placebo) and baseline macular area of photoreceptor loss as fixed effects, time (trial week, continuous assuming linearity), the time × treatment interaction term as well as the baseline × time interaction term. Correlation between the repeated measurements of the same subject will be accounted for by allowing an unstructured covariance matrix for the residuals. Additional details of the model, including alternative variance-covariance structure (if convergence cannot be attained) and denominator degrees of freedom will be specified in the SAP.

The outcome is the change in macular area of photoreceptor loss from baseline to each time point during the Treatment Period through Week 48. The primary comparison is the difference in least-square means between elamipretide and placebo at Week 48 for the ITT population. The treatment policy strategy will be applied to all intercurrent events. Analyses using the other estimand strategies will also be conducted and detailed in the SAP.

The main model for the primary analysis using data (as observed) from all subjects in the ITT set assumes missing at random (MAR). To evaluate the robustness of the primary analysis, sensitivity analyses based on different analysis sets (e.g., W48PP set) and/or different approaches in handling missing data will be performed. Multiple imputation methods and other sensitivity analyses will be explored, and details will be provided in the SAP.

11.3.5.3. Secondary Efficacy Endpoints

Secondary endpoints, comparing elamipretide to placebo, will be alpha level protected in a hierarchical fashion, conditional upon the statistical significance of the primary endpoint, with the order outlined in Section 9.1.2 and below.

- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 72
- Rate of change in the macular area of photoreceptor loss (defined as an EZ-RPE thickness of 0µm) assessed by SD-OCT and EZ mapping at Week 96
- Proportion of subjects gaining ≥ 10 letters (2 lines) in LL BCVA from baseline at Week 48
- Proportion of subjects gaining ≥ 15 letters (3 lines) in LL BCVA from baseline at Week 48

The analysis of rate of change in the macular area of photoreceptor loss during the second year will be conducted using a linear mixed effects model assuming time as continuous and piece-wise linear, with linearity assumed between Baseline to Week 48, Week 48 to Week 72 and Week 72 to Week 96. All observed data through Week 96 will be utilized.

The analyses of proportion of subjects gaining in Low Luminance Best-Corrected Visual Acuity (LL BCVA) will be based on Cochran-Mantel-Haenszel test.

Further details including sensitivity analysis for the secondary efficacy endpoints will be provided in the SAP.

11.3.5.4. Exploratory Efficacy Endpoints

Exploratory endpoints are specified in Section 9.1.3.

The analysis of continuous endpoints will be conducted in the same manner as for the primary and key secondary endpoints comparing elamipretide to placebo. The analysis of proportion endpoints will be conducted in the same manner as the similar endpoints in secondary efficacy endpoints. Further details will be provided in the SAP.

11.3.5.5. Pharmacokinetic (PK) Endpoints

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) modeling.

11.3.5.6. Handling of Missing Data

All efforts will be made to minimize missing data. A full description of the imputation methods will be provided in the SAP. The SAP will include sample SAS code for implementation of the designated approaches.

11.3.6. Multiplicity

Secondary endpoints will be alpha-level protected in a hierarchical fashion conditional upon the statistical significance of the primary endpoint, with the order outlined in Section 11.3.5.3.

11.3.7. Subgroups of Interest

The primary endpoint will be evaluated for a set of pre-specified subgroups to support the proposed indication. These subgroups will be evaluated regardless of adherence to IMP.

Although subgroup analyses aim to assess for consistency with the overall results, they may have low power, especially if the subgroup is small or has a low number of events. Statistical models will be adjusted for the covariates used in the original analysis, subgroup, treatment, and treatment by subgroup interaction. Subgroup analyses will not be adjusted for multiplicity.

Categories of subgroups will include age, gender, race, ethnicity, iris pigmentation, region, visual function, and baseline area of photoreceptor loss (total EZ attenuation). Details for these subgroups, including additional subgroups of interest, will be defined in the SAP.

11.3.8. Pharmacokinetics (PK) Analyses

Elamipretide plasma concentration data collected on repeated occasions in all subjects (Week 4, Week 36, and Early Discontinuation Visit) will be used in a non-linear mixed effects model to assess the characteristics of elamipretide PK in the PK population.

The PK model will be generated and validated using data reported from historical, thorough PK studies. Where sufficient data allows, covariates will include age, gender, race, genotype, 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. Pharmacokinetic modeling will be performed using NONMEM computer software.

All model assumptions, validation and data analysis will be detailed in the PK Analysis Plan.

11.3.9. Safety Analyses

Safety data analysis will be conducted for 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), treatment-emergent serious adverse events (TESAEs), drug-related TEAEs, and TEAEs 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.

11.3.9.1. Adverse Events (AEs)

All AEs will be coded to SOC and PT using the latest Medical Dictionary for Regulatory Activities coding dictionary. All reported AEs will be listed, but only TEAEs will be summarized.

The incidence of all TEAEs, drug relationship with TEAEs, and severity of TEAEs will be summarized by treatment group. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once for each treatment group. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (i.e., considered related). Summary tables will be organized by SOC, then PT.

Local tolerability (e.g., pain/tenderness, erythema, induration/swelling, pruritus, etc.) of the injection site will be evaluated as AEs and summarized.

AESIs will also be evaluated and summarized separately.

11.3.9.2. Deaths and Other Serious Adverse Events (SAEs)

Listings will be provided for the following:

- Deaths
- SAEs
- AEs leading to discontinuation of double-masked IMP

11.3.9.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters included in Appendix 3 (including clinical hematology and chemistry laboratory parameters, and urinalysis) will include descriptive statistics of change relative to baseline where appropriate, and data listings of clinically significant abnormalities.

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged. Indicators of findings below or above limits of quantitation (BLQ or ALQ) will be included, and those limits recorded.

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 parameter and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of trial.

11.3.9.4. Vital Signs

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

Shift tables for heart rate and blood pressure (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.

11.3.9.5. Electrocardiogram

ECG data will be captured at Screening, Week 48, and Week 96 only.

Electrocardiogram results (normal versus abnormal) and an assessment of the clinical significance of any abnormalities, in the opinion of the Investigator, will be listed for individual subjects. Intervals of PR, RR, QRS, QT, heart rate, and the calculated corrected QT using a standardized method (e.g. QTcF) will also be listed.

11.3.9.6. Other Safety Parameters

The additional safety variables of slit lamp examination, IOP 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.

12. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The Investigator is responsible for identifying potential subjects that meet trial Inclusion/Exclusion Criteria. 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. This includes contemporaneously obtaining the appropriate signatures and dates on the current version of the ICF prior to the performance of any protocol procedures and prior to the administration of IMP.

12.2. Ethical Review

The Sponsor or its CRO designee must approve all ICFs before they are used at a clinical trial site. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of EC approval of the protocol and the ICFs must be provided to the Sponsor, or designee before the trial may begin at the clinical trial site.

12.3. Regulatory Considerations

This trial will be conducted in accordance with:

1. The ICH GCP Guideline [
2. E6]
3. Consensus ethics principles derived from international ethics guidelines, including the CIOMS International Ethical Guidelines
4. Regulation 536/2014 and related detailed guidelines
5. Applicable laws and regulations

The Investigator, Sponsor, or designee will promptly submit the protocol to applicable ECs, IRBs, Regulatory Authorities, and other Regulatory bodies as required. Some of the obligations of the Sponsor may be assigned to a third-party organization. Clinical trial sites will not commence enrollment until Regulatory Authority submission/approval and clinical trial site EC/IRB favorable opinion/approval are granted.

Subject data is pseudonymized. Each subject is assigned a number in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

12.3.1. Protocol Approval

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of their knowledge, the protocol accurately describes the planned design and conduct of the trial.

12.3.2. Final Report Approval

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

12.3.3. Trial Monitoring

The Investigators and institution(s) will permit trial-related monitoring of the eCRF data by the Sponsor, or their CRO designee by providing direct access to source data and documents. The clinical trial site monitor will verify the eCRFs 100% against the source documents. Deviations from the protocol regarding subject enrollment or trial conduct will be tracked. Serious or major protocol deviations may be reported to ECs, IRBs, Regulatory Authorities, and other Regulatory bodies as required. The clinical trial site monitor will visit the clinical trial site to qualify the site, initiate the trial, upon first subject randomized, and at agreed frequency throughout the trial, including closing the site at the end of the trial. Drug dispensing and clinical drug supply records will be verified at the clinical trial site by the clinical trial site 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. Additional site monitoring details will be documented in a Clinical Monitoring Plan.

12.3.4. Retention of Records

All trial-related material including source documents, eCRFs, Competent Authority, IRB/EC correspondence, and data analyses and any other documentation required by applicable laws and regulations will be maintained for a minimum of 15 years and up to 25 years after completion of the trial and/or duration required in accordance with regional/country-specific requirements and notification from the Sponsor that the data can be destroyed.

12.3.5. Disclosure of Information

Information concerning the IMP and patent application processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the trial only. It is understood by the Investigator that Sponsor 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. 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 of the results of this trial without first receiving written authorization from the Sponsor.

12.4. Review Committees

12.4.1. Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) will be formed to provide ongoing safety oversight for the trial and will be provided unmasked safety data. The members of DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. A separate charter will be established that will outline the frequency of meetings and the roles and responsibilities of all members. A DMC recommendation will be communicated to the Sponsor as described in the DMC charter.

12.4.2. Trial Scientific Review Committee

A Trial Scientific Review Committee (TSRC) managed by the Sponsor is the primary advisory group throughout the trial, providing scientific leadership, and helping ensure trial integrity via review of in-stream, masked, aggregate data. A separate charter will be established to outline the frequency of the meetings, committee member roles, and a complete list of their responsibilities.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

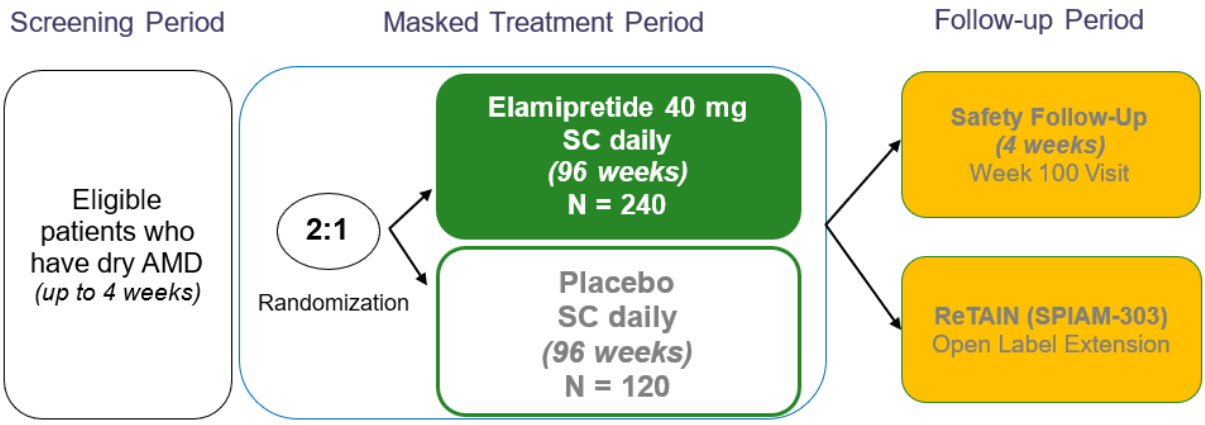
Days/Weeks	Screening Period[a]	Treatment Period[b]										Safety Follow-Up Period[c]	Early Discontinuation
	Screening (Day -28 to Day -1)	Day 1[d] BL	Wk 4 ± 7d	Wk 12 ± 7d	Wk 24 ± 7d	Wk 36 ± 7d	Wk 48 ± 7d	Wk 60 ± 7d	Wk 72 ± 7d	Wk 84 ± 7d	EOT/ EOS[e] Wk 96 + 7 days	EOS[e] Wk 100 ± 7 days	EOS Early Discontinuation Visit
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Procedures													
Informed Consent[f]	X												
Verify Inclusion/Exclusion Criteria	X	X											
Demographics	X												
Medical/Ocular History	X	X											
Vital Signs[g] and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[h]	X	X					X				X		X
Review of Injection Site Reactions[i]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X						X				X		X
Randomization		X											
Review AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP													
Dispense IMP		X	X	X	X	X	X	X	X	X			
IMP Administration[k]		X (daily administration)											
IMP Collection/Accountability			X	X	X	X	X	X	X	X	X	X[l]	X
Dosing Diary[m]		X (daily)											
Ophthalmology Evaluations													
Refraction	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X
LL BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X
Reading Acuity[n]	X	X	X	X	X	X	X	X	X	X	X	X	X

Days/Weeks	Screening Period[a]	Treatment Period[b]										Safety Follow-Up Period[c]	Early Discontinuation
	Screening (Day -28 to Day -1)	Day 1[d] BL	Wk 4 ± 7d	Wk 12 ± 7d	Wk 24 ± 7d	Wk 36 ± 7d	Wk 48 ± 7d	Wk 60 ± 7d	Wk 72 ± 7d	Wk 84 ± 7d	EOT/ EOS[e] Wk 96 + 7 days	EOS[e] Wk 100 ± 7 days	EOS Early Discontinuation Visit
Site Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
LL Reading Acuity[n]	X	X	X	X	X	X	X	X	X	X	X	X	X
Slip lamp exam	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundus exam	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X		X	X	X	X	X	X	X	X	X	X
Fundus Autofluorescence	X	X			X		X		X		X	X	X
Color Fundus Photography	X	X			X		X		X		X	X	X
Fluorescein Angiography	X						X				X		X
Questionnaires[o]													
Vision Impairment in Low Luminance Questionnaire (VILL-33)		X					X				X		X
EQ-5D-5L Questionnaire		X			X		X		X		X		X
Laboratory Assessments													
Blood for Safety[p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker Sample (USA clinical trial sites only)		X			X		X						X[q]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing (serum)[r]	X											X	X
Pregnancy Testing (urine)[s]		X	X	X	X	X	X	X	X	X	X		
PK[t]			X			X							X

Abbreviations: AE = adverse event; BCVA = Best-Corrected Visual Acuity; BL = baseline; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; IMP = investigational medicinal product; IOP = Intraocular pressure; ISR = injection site reaction; LL = low luminance; PK = pharmacokinetics; SD-OCT = Spectral domain-optical coherence tomography
Note: All ophthalmic testing is conducted on each eye at each time point. Reading Acuity and LL Reading Acuity testing is conducted on both eyes simultaneously.

a. Screening will begin with the subject's signature of the ICF. 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. Optional follow-up phone calls with the subject may be considered between scheduled site visits at approximately monthly intervals where site visits do not occur.
c. Subjects enrolling in ReTAIN/SPIAM-303 (Open Label Extension trial) within 28 days following the Week 96 Visit are not required to participate in the Safety Follow-Up Period, including the Week 100 Visit.
d. The first day of treatment is defined as Day 1. Trial days are relative to Day 1. Baseline assessments must be completed within 24 hours prior to receiving IMP.
e. For subjects who are not participating in ReTAIN and do not discontinue the trial, the EOS Visit will be the Week 100 Visit. For subjects who discontinue the trial, the EOS Visit will occur at the same visit as the Early Discontinuation Visit. For subjects participating in ReTAIN, the EOS Visit is defined as Week 96.
f. The current version of the ICF must be signed prior to any trial-related procedures being performed.
g. Vital sign measurements will be taken prior to blood draws and will include temperature, respiratory rate, sitting blood pressure (recorded after resting for 5 minutes), heart rate, and weight. Height will only be recorded at the Screening Visit.
h. Physical examination will include assessment of head, ears, nose, and throat, general appearance, skin, chest, heart, abdomen, extremities, and nervous system.
i. A thorough ISR review will be conducted for all subjects at each Treatment Period site visit. The subject will be asked whether they believe the intervention was beneficial.
j. ECGs will be performed after the subject has rested quietly for 5 minutes in the supine positions and will be performed before vital signs are assessed and collection of blood samples for laboratory testing.
k. IMP administration technique review will occur at all Treatment Period site visits except Week 96.
l. All remaining used and unused IMP should be collected at Week 100.
m. Daily IMP administration will be recorded and collected in the Dosing Diary.
n. Only performed in countries where translations are available.
o. Questionnaires to be completed prior to all ophthalmology evaluations.
p. Blood for safety labs can be taken in a non-fasting state and will consist of hematology and clinical chemistry panels.
q. A biomarker sample is only required for Early Discontinuation Visits prior to Week 48.
r. Serum pregnancy test will be done for women of childbearing potential at the Screening Visit and at trial conclusion, i.e., Week 100 Safety Follow-Up Visit or Early Discontinuation Visit, unless a subject continues in ReTAIN; in that case, a subject follows the ReTAIN Schedule of Assessments after Week 96.
s. Women of childbearing potential will have a urine pregnancy test at the Baseline Visit (Day 1) and all site visits during the Treatment Period, and the results of the Baseline Visit (Day 1) pre-dose pregnancy test must be evaluated before randomization to ensure eligibility.
t. PK samples will be collected at Week 4 pre-dose (within 1 hour of dosing), 15 min. post dose (±5 min.), 30 min. post-dose (±5 min.), and 90 min. post-dose (±15 min.). PK samples will also be collected at Week 36 4-hours post-dose (± 90 min). For the Week 36 Site Visit, the subject will administer IMP at home (not at site visit), approximately 4 hours ± 90 min before arriving at the clinical trial site. 1 random PK sample will also be collected in the event of an Early Discontinuation Visit (one sample at any time during visit), prior to Week 36.

APPENDIX 2. TRIAL DESIGN SCHEMATIC



APPENDIX 3. LIST OF CLINICAL LABORATORY TESTS TO BE PERFORMED

Hematology:	**Chemistry:**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
MCH	Direct bilirubin
MCHC	Indirect bilirubin
MCV	Bicarbonate
RBC morphology	Alkaline phosphatase (ALK-P)
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils (ANC, segmented %)	Aspartate aminotransferase (AST)
Lymphocytes (absolute, %)	Blood urea nitrogen (BUN)
Monocytes (absolute, %)	Gamma-glutamyl transpeptidase (GGTP)
Eosinophils (absolute, %)	Creatine kinase (CK)
Basophils (absolute, %)	Creatinine
Platelets	LDH
	Troponin I
Urinalysis:	Uric Acid
Specific Gravity	Phosphate
pH	Total Protein
Protein	Globulin
Glucose	Magnesium
Ketones	Calcium
Bilirubin	Glucose (non-fasting)
Urobilinogen	Hemoglobin A1c (HbA1c)
Blood	Albumin
Nitrites	Chloride
Leukocyte esterase	
Urine Pregnancy (women of childbearing potential)	**Other:**
	Serum Pregnancy (women of childbearing potential)
	mtDNA (USA clinical trial sites only)

APPENDIX 4. VISION IMPAIRMENT IN LOW LUMINANCE QUESTIONNAIRE (VILL-33)

Vision Impairment in Low Luminance (VILL)

This questionnaire asks about difficulties with your eyesight under challenging light conditions such as low lighting or low contrast and their impact on your daily life.

Please read each question carefully and choose the answer that best applies to you by marking it with an X.

If you wear GLASSES or use any other VISUAL AIDS (such as contact lenses or a magnifying glass), please answer the questions as they pertain to your eyesight while using them.

Please answer all questions and do not leave any rows blank.

Thank you.

In the past month, due to your EYESIGHT, how much difficulty did you have with the following activities:

		Couldn't do because of eyesight	A lot of difficulty	A little difficulty	No difficulty	Didn't do this for other reasons
1.	Adjusting to the dark when entering a dimly lit room? (e.g. a restaurant at night)	☐	☐	☐	☐	☐
2.	Recognizing small objects in dim lighting? (e.g. coins)	☐	☐	☐	☐	☐
3.	Recognizing people's faces outside at dusk?	☐	☐	☐	☐	☐
4.	Recognizing people or objects by candlelight?	☐	☐	☐	☐	☐
5.	Seeing things clearly close up when they are in the center of your vision?	☐	☐	☐	☐	☐
6.	Reading print which has a low contrast to its background?	☐	☐	☐	☐	☐
7.	Reading print which is not black? (e.g. grey)	☐	☐	☐	☐	☐
8.	Reading text on a digital display? (e.g. in the car, on an electronic radio)	☐	☐	☐	☐	☐

 2

In the past month, due to your EYESIGHT, how much difficulty did you have with the following activities:

		Couldn't do because of eyesight	A lot of difficulty	A little difficulty	No difficulty	Didn't do this for other reasons
9.	Reading print against a colorful background? (e.g. a brochure)	☐	☐	☐	☐	☐
10.	Reading a paperback novel in dim lighting?	☐	☐	☐	☐	☐
11.	Reading a newspaper in dim lighting?	☐	☐	☐	☐	☐
12.	Reading a menu in a dimly lit restaurant?	☐	☐	☐	☐	☐
13.	Reading labels or instructions on medicine bottles in good lighting?	☐	☐	☐	☐	☐
14.	Reading labels or instructions on medicine bottles in dim lighting?	☐	☐	☐	☐	☐
15.	Reading package labels or price tags in a shop?	☐	☐	☐	☐	☐
16.	Driving a car on a sunny day? (with or without sunglasses)	☐	☐	☐	☐	☐

 3

In the past month, due to your EYESIGHT, how much difficulty did you have with the following activities:

	Couldn't do because of eyesight	A lot of difficulty	A little difficulty	No difficulty	Didn't do this for other reasons
17. Driving a car along a road lined with trees on a sunny day? (with or without sunglasses)	☐	☐	☐	☐	☐
18. Driving a car at night?	☐	☐	☐	☐	☐
19. Driving a car at night in the rain?	☐	☐	☐	☐	☐
20. Reading street signs in time when driving by?	☐	☐	☐	☐	☐
21. Walking on uneven ground in the dark?	☐	☐	☐	☐	☐
22. Going out to do things at dusk? (e.g. visiting the supermarket or shops)	☐	☐	☐	☐	☐
23. Seeing steps or curbs in the dark?	☐	☐	☐	☐	☐
24. Getting your bearings in dimly lit or dark unfamiliar places?	☐	☐	☐	☐	☐

In the past month, due to your EYESIGHT, how often did you experience the following:

	Always	Often	Sometimes	Never	Does not apply to me
25. Felt blinded by oncoming cars at night?	☐	☐	☐	☐	☐
26. Felt blinded by the sun while driving a car? (with or without sunglasses)	☐	☐	☐	☐	☐
27. Felt unsafe as a pedestrian or cyclist at dawn or at night?	☐	☐	☐	☐	☐
28. Felt exhausted by reading in dim light?	☐	☐	☐	☐	☐
29. Needed additional lighting to see or read anything?	☐	☐	☐	☐	☐
30. Felt worried that your eyesight might get worse?	☐	☐	☐	☐	☐
31. Felt worried about losing your independence?	☐	☐	☐	☐	☐
32. Felt worried about the future?	☐	☐	☐	☐	☐
33. Felt worried that your lifestyle might change due to your eye condition?	☐	☐	☐	☐	☐

Fields highlighted in grey to be completed by the site personnel!

VILL administration mode: ☐ Subject self-completed

☐ Interviewer-administered

APPENDIX 5. EQ-5D-5L QUESTIONNAIRE

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g., work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐