An Open-Label, Phase 1 Clinical Study to Evaluate the Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Intermediate Age-Related Macular Degeneration

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Study Phase:	Phase 1
Product Name:	Elamipretide (MTP-131) sterile solution
IND Number:	114,234
Formulation:	Subcutaneous
Study No.:	SPIAM-101
Sponsor:	Stealth BioTherapeutics, Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466
Sponsor Contact:	W. Douglas Weaver, MD, Chief Medical Officer 617-600-6888
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Role in Study	Name	Address and Telephone Number
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Sponsor Medical Monitor	W Douglas Weaver, MD	Stealth BioTherapeutics, Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 +1 (617) 600-6888

1. SYNOPSIS

Investigational Drug Product:	elamipretide (MTP-131)
Active Ingredient:	elamipretide (MTP-131)
Study Title:	An Open-Label, Phase 1 Clinical Study to Evaluate the Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Intermediate Age-Related Macular Degeneration
Study Number:	SPIAM-101
Study Phase:	Phase 1
Study Objectives:	The primary objective of this study is: • To evaluate the safety and tolerability of subcutaneous (SC) injections of elamipretide in subjects with intermediate age-related macular degeneration (AMD)
	The secondary objectives of this study are: • To evaluate the feasibility of administration of SC injections of elamipretide in subjects with intermediate AMD • To evaluate the changes from baseline in physical/ophthalmic examinations
Study Design:	This is an open-label, Phase 1 single-center study in approximately 40 evaluable subjects who have 1 eye with intermediate AMD, including a high-risk drusen without geographic atrophy (GA) cohort and a noncentral GA cohort. Cohort 1: High-risk drusen is defined as the presence of at least 1 large (≥ 125 μm) druse or multiple medium-size (between 63 and 124 μm) drusen. Cohort 2: Noncentral GA is defined as evidence of GA with cumulative area ≥1.27 mm^2 (approximately 0.5 disc area [DA]) by fundus autofluorescence (FAF), which spares the fovea (defined as retinal pigment epithelium and outer retina intact by spectral domain-optical coherence tomography [SD-OCT]). The study eye of eligible subjects must fall into one of the two cohorts, as defined above, cannot have choroidal neovascular (CNV) AMD or advanced central GA, and may not have previously received antiangiogenic therapies (in addition to meeting other specified inclusion/exclusion criteria). The AMD disease status of the fellow eye is not restricted: the fellow eye may have intermediate AMD with high-risk drusen, advanced central GA, or CNV AMD, and the fellow eye is allowed to receive antiangiogenic therapies. Written informed consent will be obtained from all subjects before the Screening visit. The screening examination will be performed no more than 14 days before the Baseline visit. Data to be collected from the screening examination will include significant and/or ongoing medical and ocular history, vital sign measurements, physical examination, routine blood samples for hematology, chemistry, and urinalysis, ECG, manifest refraction, measurement of best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale completed twice, intraocular pressure measurement, slit-lamp examination, dilated fundus examination, fundus photography, spectral domain optical coherence tomography (SD-OCT), FAF, fluorescein angiography*, best-corrected low-luminance (LL) visual acuity completed twice, mesopic microperimetry, dark adaptometry, and Low-Luminance Questionnaire. Women of childbearing potential will have a serum pregnancy test. *Fluorescein angiography assessments done as

	standard of care and completed within 90 days prior to dosing are allowed to be used for screening purposes. After the screening examination, relevant data will be reviewed by the PI or designee to confirm study eligibility. Eligible subjects will return for the Baseline (Day 0) visit, at which time qualified subjects will be assigned to study treatment. Each subject will be assigned into 1 of the 2 study disease cohorts, after determination of the subject's disease state in the Screening Period. Elamipretide will be supplied as 40 mg/1 mL of sterile solution for SC injection. The dose of elamipretide will be 40 mg administered as a once daily 1.0 mL SC injection. At the time of initial study drug administration, training on the proper SC administration of the study drug solution (by the subject, regular caregiver, or his/her appropriate designee) will occur. Subjects will be trained using a standard script explaining the importance of proper administration of study drug on a daily basis for the 24-week Study Treatment Period. The first dose may be given by a qualified member of the study team, by the subject, or caregiver at the PIs discretion. The option of a visiting nurse to oversee the study drug administration will be discussed with the subject and provided, as needed. Safety and tolerability will be measured throughout the Study Treatment Period, while exploratory anatomical and physiologic endpoints will be measured at time points as specified in the Schedule of Events. Visits will occur at: Day 7 (± 3 days), Week 4 (± 7 days), Week 8 (± 7 days), Week 12 (± 7 days), Week 16 (± 7 days), Week 20 (± 7 days), and Week 24 (± 7 days), with phone calls to collect safety information completed at Week 2 (± 4 days), Week 6 (± 4 days), Week 10 (± 4 days), Week 14 (± 4 days), Week 18 (± 4 days), and Week 22 (± 4 days). Ocular imaging will be read by an independent reading center and findings uploaded to the electronic data capture (EDC) system on a regular basis throughout the study. After completion of the 24-week Study Treatment Period, subjects will continue to be monitored for safety during the 4-week Follow-Up Period. A post-study drug follow-up visit is scheduled at Week 28 (± 7 days). Study procedures, their timing, and additional details are found in the Schedule of Events (Table 3).
Investigational Product, Dose and Mode of Administration:	Elamipretide will be supplied as 40 mg/1 mL of sterile solution for SC injection. The dose of elamipretide will be 40 mg administered as a once daily 1.0 mL SC injection. Study drug will be administered at approximately the same time each day by SC injection in the abdomen (rotating clockwise around the 4 abdominal quadrants), and may be administered by any of the following individuals: the clinical site staff, designated caregiver, or the subject. Refer to dosing instructions document for more details.
Study Population:	Subjects who have intermediate AMD confirmed clinically and by the PI or designee's interpretation of standard imaging procedures will be enrolled in 1 of 2 disease cohorts: 1. Intermediate age-related macular degeneration - high-risk drusen without GA cohort or 2. Intermediate age-related macular degeneration - noncentral GA cohort.
Inclusion Criteria:	For this study, only 1 eye of an eligible subject will be designated as the study eye. However, all specified ophthalmic testing will be performed on both eyes

	at each time point. A potential subject must meet the following criteria to be eligible for inclusion in the study**:** **Intermediate AMD – noncentral GA disease cohort:** 1. Adults ≥ 55 years of age with 1 eye with intermediate AMD –noncentral GA. For this study, noncentral GA is defined as well-demarcated area(s) of GA with a cumulative area ≥ 1.27 mm^2 (approximately 0.5 DA) by FAF, which spares the fovea (defined as retinal pigment epithelium and outer retina intact by SD-OCT). 2. Geographic atrophy may be multifocal, but the cumulative GA lesion size must be: a. ≥ 1.27 mm^2 (approximately ≥ 0.5 DA) and ≤ 10.16 mm^2 (approximately ≤ 4 DA). b. Must reside completely within the FAF imaging field (field 2 to 30-degree image centered on the fovea). 3. Presence of measurable hyperautofluorescence adjacent to the discrete foci of GA. OR **Intermediate AMD – high-risk drusen without GA disease cohort:** 4. ≥ 55 years of age with one eye with intermediate AMD – high-risk drusen without GA. 5. High-risk drusen is defined as presence of either at least 1 large (≥ 125 μm) druse or multiple medium-size (between 63 and 124 μm) drusen. **General (both disease cohorts)**: 6. No evidence of choroidal neovascularization (CNV) (active or prior history) in the macula of the study eye. 7. Able to provide informed consent and willing to comply with all study visits and examinations. 8. Women of childbearing potential who are not pregnant or nursing and have a negative serum pregnancy test at screening. 9. Best-corrected visual acuity assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters ≥ score of 55 (Snellen equivalent ≥ 20/70). 10. Low-luminance visual acuity deficit (defined as difference between BCVA and LL visual acuity) > 5 letters. 11. Has at least two Low-Luminance Questionnaire sub scale results, in which one of the abnormal subscales is either general dim light vision or dim light reading. 12. The fellow eye may have intermediate AMD without noncentral GA (i.e., high-risk drusen), intermediate AMD with noncentral GA, CNV neovascular AMD, or central GA. Ongoing treatment with antiangiogenic therapies in the fellow eye is allowable. 13. No evidence of visually significant cataract **OR** pseudophakia without evidence of posterior capsular opacity. 14. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and able to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment 15. Able to administer SC study drug solution as demonstrated at screening or able to have a care provider or appropriate designee who can administer the study drug (i.e. a capable family member or a care giver).

	16. If of childbearing potential or in a relationship with a partner of childbearing potential, are able to abstain from sex or use acceptable contraception during the study and for 3 months after dosing. a. For men: Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. The subject also agrees to use an acceptable method of contraception should they become sexually active. Subjects must use a condom with spermicide from the date of informed consent until at least 3 months after the last dose of study drug. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. b. For women: abstinence is only acceptable when it is in line with the preferred and usual lifestyle of the subject. The subject agrees to use an acceptable method of contraception should they become sexually active. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days before the Screening visit or confirmed via sperm analysis), barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system are acceptable methods. 17. Ability and willingness to undertake all scheduled visits and assessments. When both eyes are eligible for the study, only one eye (study eye) will be included. In that case, the eye with the greater LL visual acuity deficit will be chosen for inclusion. Data will be collected to assess potential effects of study drug on the fellow eye.
Exclusion Criteria:	A subject with study eye that meets any of the following criteria will be excluded from the study: **Ocular conditions – <u>study eye</u>** 1. Age-related macular degeneration with any evidence of central GA (i.e. involving the fovea). 2. Atrophic retinal disease due to causes other than AMD. 3. Presence or diagnosis of exudative AMD or choroidal neovascularization in the study eye. 4. History of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion). 5. Presence of vitreous hemorrhage. 6. History of retinal detachment or macular hole (stage 3 or 4) in the study eye. 7. Presence of macular pucker. 8. History of uncontrolled glaucoma, defined as advanced cup-to-disc ratio > 0.7 and intraocular pressure > 25, with or without topical antihypertensive eye drops; treatment of ocular hypertension or controlled glaucoma are not criteria for exclusion. 9. History of advanced guttae indicative of Fuchs endothelial dystrophy. 10. Presence of visually-significant cataract **OR** presence of significant posterior capsular opacity in the setting of pseudophakia. 11. Presence of significant keratopathy that would cause scattering of light or alter visual function, especially in LL conditions. 12. Ocular incisional surgery (including cataract surgery) in the study eye within 3 months before Day 0. 13. Aphakia.

	14. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery. 15. Prior treatment with Visudyne® (verteporfin), external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy. 16. History of prophylactic subthreshold laser treatment for retinal disease. 17. Previous intravitreal drug delivery (e.g. intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye. **Ocular conditions – <u>either eye</u>** 18. Active uveitis and/or vitritis (grade trace or above) in either eye. 19. History of idiopathic or autoimmune-associated uveitis in either eye. 20. Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. **Systemic conditions** 21. Known to be immunocompromised or receiving systemic immunosuppression therapy. 22. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the study or might confound study results. 23. Estimated glomerular filtration rate < 30 mL/min, by Modification of Diet of Renal Disease (MDRD). **General** 24. Participation in other investigational drug or device clinical trials during and/or within 30 days before enrollment, or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion. 25. History of allergy to fluorescein that is not amenable to treatment. 26. Inability to comply with study or follow-up procedures. 27. Inability to obtain color fundus photograph, FAF, and fluorescein angiography of sufficient quality to be analyzed and interpreted. 28. History of allergic reaction to the investigational drug or any of its components.
Planned Duration of Treatment:	Up to 30 weeks of study participation; including up to 2 weeks for screening before Baseline (Day 0) study enrollment, a 24-week period on study drug, and a 4-week safety Follow-up Period. Screening Period: 2 weeks Study Treatment Period: 24 weeks Follow-up Period: 4 weeks
Primary Safety and Tolerability Endpoints:	• The incidence and severity of AEs • Changes from baseline in vital sign measurements • Changes from baseline in ECGs • Changes from baseline in clinical evaluations • Changes from baseline in clinical laboratory evaluations

Secondary Endpoints for Both Noncentral GA and High Risk Drusen Without GA:	• Compliance of administration of subcutaneous elamipretide • Number of home health visits necessary for subject or caregiver to learn how to inject elamipretide • Change in fundus hyperautofluorescence • Change from baseline in LL visual acuity • Change from baseline in mesopic light sensitivity by microperimetry • Change in dark adaptometry • Change in drusen volume ("retinal pigment epithelium – drusen complex", as measured by automated segmentation) by SD-OCT • Change in fundus photography • Change in BCVA • Change in speed reading at standard light • Change in speed reading at low light • Change in LL visual function by the Low-Luminance Questionnaire • Change in National Eye Institute VFQ-39 score
Secondary Endpoints for High Risk Drusen Without GA:	• Change in drusen volume ("retinal pigment epithelium – drusen complex", as measured by automated segmentation) by SD-OCT.
Sample Size and Statistical Methods:	For this Phase 1 study, the sample size of 40 evaluable subjects is reasonably sized for demonstrating clinical safety and tolerability. An equal enrollment (1:1) of approximately 20 subjects per cohort (cohort 1: 20 and cohort 2: 20) is targeted, but subject availability may dictate the actual enrollment ratio between the cohorts. **General Methods:** Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, and minimum and maximum). Discrete variables will be summarized by frequencies and percentages. All study data are to be displayed in the data listings. Importantly, tabulated data will be presented for each Cohort as well as the Total Sample (i.e., data from both cohorts pooled together). All data are to be displayed in the data listings, sorted by subject and visit, or where appropriate. Each listing will have indication of which cohort each subject was assigned to. **Analysis Populations:** All subjects who receive at least 1 dose of study drug will be included in the safety population. In general, subjects in the safety population are expected to have received active study drug and so will be identified as such. **Baseline Characteristics and Disposition** Baseline demographic and other non-eye specific characteristics will be presented by disease cohort. Subject disposition summaries will include the number of subjects treated (i.e., in the Safety population). The number and percentage of subjects who complete or discontinue from the study will be summarized by reason. Subject's age, sex, weight, and other demographic characteristics will be recorded and summarized. Medical history will be listed. **Safety Analyses:** Adverse events will be summarized by system organ class and preferred term, presenting the number and percentage of subjects having adverse events. Adverse Events attributed to an individual eye or both eyes will be

	characterized by specific study cohort. Severity and relationship to study drug will be listed as appropriate. **Efficacy Analyses:** Changes in endpoints will be presented by time point for each cohort as well as pooled. For continuous data of the by-cohort outcomes, a mixed model for repeated measures (MMRM) will be used, with fixed effects for cohort, baseline covariate, study visit, the cohort-by-visit interaction, and random effects for subject. For continuous data for the pooled outcomes, an MMRM with fixed effects for baseline covariate and study visit, and random effects for subject will be used. Plots of the Least Square Mean (LSMean) values over time will be presented for each endpoint. **Interim Analysis** This is an open-label study, and thus monitoring of data outcomes over the course of the study may be performed. In addition, an interim analysis may be performed on partial or all data when the first 20 subjects have completed through 24 weeks of treatment. The interim analysis may be performed by the Sponsor or their designee. Assessments of both safety and efficacy endpoints will be performed utilizing similar methods as are planned for the final analysis. Additional details of all statistical analyses will be included in a separate statistical analysis plan.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS

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

Abbreviation	Definition or Explanation
AE	Adverse event
ACS	Acute coronary syndrome
ADL	Activity of daily living
AKI	Acute kidney injury
AMD	Age-related macular degeneration
APOE	Apolipoprotein E
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration time-curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration time-curve from 0 to 24 hours
BCVA	Best-corrected visual acuity
CHF	Congestive heart failure
C_{max}	Maximum plasma concentration
CNV	Choroidal Neovascular
DA	Disc area
DDI	Drug-Drug Interaction
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERG	Electroretinogram
ETC	Electron transport chain
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus autofluorescence
GA	Geographic atrophy
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgE	Immunoglobulin E
IL5	Interleukin 5
IMP	Investigational Medicinal Product
IOP	Intraocular pressure
IRB	Institutional Review Board
ISR	Injection Site Reaction
IV	Intravenous

Abbreviation	Definition or Explanation
LL	Low-luminance
LLQ	Low-Luminance Questionnaire
LS Mean	Least Square Mean
M1, M2	Major metabolite of elamipretide (MTP-131)
MDRD	Modification of Diet in Renal Disease
MMP	Matrix metalloproteinase
MMRM	Mixed Model for Repeated Measures
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NOAEL	No-observed-adverse-effect-level
NV	Neovascular
PCI	Percutaneous coronary intervention
PK	Pharmacokinetics
PI	Principal Investigator
PT	Preferred term
PTRA	Percutaneous transluminal renal angioplasty
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SC	Subcutaneous
SD-OCT	Spectral domain-optical coherence tomography
SOC	System organ class
STEMI	ST-segment elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
UFH	Unfractionated heparin
VFQ-39	Visual Function Questionnaire-39

4. INTRODUCTION

This study will be conducted in strict accordance with the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guideline, and all applicable laws and regulations. For detailed information on the study drug and the nonclinical and clinical studies conducted to date, please refer to the most recent edition of the elamipretide Investigator's Brochure[1].

Mitochondria are organelles responsible for generating adenosine triphosphate (ATP) by a series of redox reactions through the electron transport chain (ETC) and ATP synthase. Mitochondria normally produce a small amount of reactive oxygen species including superoxide anions and hydrogen peroxide as physiological byproducts of electron transport and ATP production. Under conditions of metabolic or genetic stress, mitochondria can become a major endogenous source of reactive oxygen species such as superoxide anions, peroxynitrite, and hydroxyl radicals. Increased oxidative damage to the inner membrane of the mitochondria leads to imbalances in the electron transport chain, resulting in further increased superoxide and hydrogen peroxide production, which in turn can initiate a vicious cycle of further damage to membrane and mitochondrial proteins and mitochondrial DNA. Excess production of oxidants can damage mitochondrial proteins and lipids to a point that triggers mitochondria to activate signaling pathways that mediate nonlethal cellular injury.2 The biology of nonlethal injury at the retinal pigment epithelium (RPE) includes cytosolic actin aggregate formation, cell membrane blebbing at the basal aspect of the RPE, vimentin upregulation, decreased matrix metalloproteinase (MMP)-2 activity, and other mediators of sub-RPE deposit formation that are relevant to the pathobiology of drusen formation, the hallmark feature of early age-related macular degeneration (AMD).3 Additionally, compromised mitochondrial function in the photoreceptors of the neurosensory retina can adversely affect photodetection and phototransduction by limiting the efficiency of photon capture at the photoreceptors. This can result in diminished visual acuity, particularly in low-luminance (LL) conditions, where efficiency of photon capture is necessary for optimal visual function.

4.1. Disease Background

4.1.1. Age-related Macular Degeneration

Age-related macular degeneration (AMD) is a progressive degenerative disorder of the retina affecting 30% of people over age 65 and is the most common cause of blindness in the elderly in the developed world.[4] Early and intermediate stages of dry AMD are characterized by formation of drusen-lipid-rich deposits under the RPE.[5,6] No treatments are currently available to regress drusen or to prevent drusen progression into geographic atrophy (GA). Dry AMD/drusen pathogenesis is multifactorial, and requires aging[7] plus interaction among genetic,[8-11] systemic health,[12] and environmental risk factors (dietary fats, smoking).[13,14] Multiple paradigms have been proposed to explain how risk factors contribute to deposits, including lipid accumulation in

Bruch's membrane, complement activation, and formation of toxic byproducts of the visual cycle function.

4.1.2. Age-Related Macular Degeneration With Mitochondrial Abnormalities

Emerging evidence suggests an association between mitochondrial dysfunction and dry AMD pathobiology. Patients with inherited mitochondrial diseases develop maculopathy similar in appearance to dry AMD. In histopathology specimens, mitochondria are located along the basal aspect of RPE, often near drusen, and specifically, mitochondria in RPE with drusen are reduced approximately 50% as compared to age-matched controls and exhibit pathologic morphology, especially vacuolization. Moreover, RPE mitochondrial DNA in AMD eyes exhibit more oxidative damage as compared with aged control eyes without AMD. Taken together, these findings raise the possibility that mitochondrial dysfunction may play a pathologic role in dry AMD.

4.1.3. Age-Related Macular Degeneration Trigger Factors Causing Mitochondrial Dysfunction

Cigarette smoke and hydroquinone, a potent toxicant in cigarette smoke, have been epidemiologically associated with dry AMD, and in preclinical models, both have been identified as biochemical triggers of RPE cellular injury related to dry AMD. Hydroquinone mediates RPE injury by disruption of the mitochondrial ETC, producing mitochondrial dysfunction.[15] Emerging evidence suggests that mitochondrial dysfunction may also be associated with other established triggers of dry AMD. Abnormal lipid metabolism can alter fatty acid and cholesterol content of the mitochondrial inner membrane, compromising ETC function.[16,17] Disruption of phagolysosomes (i.e., by lipofuscin or inflammasome) can promote accumulation of damaged mitochondria since normal phagolysosomal function is required for clearance of dysfunctional mitochondria (mitophagy).[18,19] Even complement dysregulation has been associated with decreased retinal ATP production.[20] Taken together, these observations suggest that various AMD triggers may directly or indirectly induce mitochondrial dysfunction as a shared pathogenic mechanism.

4.1.4. Mitochondrial Dysfunction and Rationale for Mitochrondria-targeted Drugs

Although mitochondria have been suggested as a source of reactive oxidants in AMD,[21-25] 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. Preclinical studies suggest that many AMD triggers induce mitochondrial dysfunction (decreased ATP, calcium flux dysregulation, loss of mitochondrial membrane potential [$\Delta\Psi_m$], superoxide overproduction), leading to activation of specific signaling molecules (ASK1→ p38 MAPK → pHSP25, or pERK and pJNK), followed by activation of mediators of deposit formation (cytoskeleton disruption, actin aggregates, loss of ZO-1, blebbing, decreased MMP-14, decreased MMP-2, increased collagen IV, increased expression of vimentin), all of which will precede and contribute to sub-RPE deposits (as degraded blebs

contributing phospholipids, cytosolic proteins and degraded organelles, collagen accumulation and vimentin accumulation). It is hypothesized that prevention or reversal of mitochondrial dysfunction by specific mitochondria-targeting molecules may prevent and perhaps reverse pre-existing deposit biochemistry at the RPE, restoring physiologic function of the RPE and promoting clearance of drusen deposits in dry AMD. In turn, mitochondria-targeted therapies may facilitate improved visual function in affected eyes and may prevent progression to vision-threatening AMD disease, neovascular AMD and GA.

4.1.5. Visual Dysfunction and Deficit in Low-Luminance Activities of Daily Living

It is often assumed, incorrectly, that patients with early AMD, characterized by the presence of drusen, are not visually impaired because they retain good high-contrast (best-corrected) visual acuity and activities of daily living (ADLs) in photopic (bright-light) conditions. However, many drusen patients manifest severely reduced LL vision, defined both as loss of visual function under LL conditions and poor scores on inventories of LL ADLs.[26-29] For example, 50% of patients with large drusen demonstrate loss of > 10 letters of visual acuity when measured under LL conditions (reading black letters on dark gray background)[30]. Studies have also shown that drusen patients experience decreased foveal sensitivity to dim light and delayed dark adaptation.[31,32] These deficits translate into impaired LL ADLs: loss of reading in imperfect lighting, reduced mobility in dimly lit areas, impaired night driving, increased sensitivity to glare, and reduced night-time socialization. Because parafoveal rods in AMD eyes with drusen can die,[33] dark adaption defects may reflect either loss or reversible dysfunction of rods. However, since drusen eyes usually have normal cone density,[33] LL deficits most likely represent physiologic cone dysfunction rather than anatomic cone loss.

4.1.6. Low-Luminance Deficit – Photoreceptor Mitochondrial Dysfunction and Rationale for Mitochondria-targeted Drugs

Photoreceptor mitochondria may become susceptible to dysfunction in the setting of RPE injury and subRPE deposit formation, as a result of compromised RPE metabolism. ATP is crucial for outer segment membrane biogenesis and for transport of structural proteins.[34,35] Mitochondria also regulate local calcium flux. Accordingly, the ellipsoid has high mitochondria density. The presynaptic terminal also has high mitochondria density. This is not surprising: ATP is required for glutamate endocytosis and vesicle localization, which is crucially related to the graded glutamate release for vision.[36] Also, ATP is required to maintain calcium balance by ATP-dependent ion pumps. Thus, photoreceptor mitochondrial dysfunction, induced by exposure to AMD trigger factors in the setting of RPE injury and deposit formation, may contribute to LL acuity deficit because of deficient ATP and abnormal calcium flux regulation required for (a) outer segment function and (b) presynaptic neurotransmitter vesicle dynamics. Therefore, mitochondria-targeted drugs that reverse mitochondrial dysfunction in retinal photoreceptors may improve visual function by restoring ATP production and in turn boosting efficiency of retinal photon capture, improving LL acuity deficit.

4.1.7. Elamipretide – a Novel Mitochondria-targeted Drug

Elamipretide is a novel tetrapeptide drug that accumulates within mitochondria and facilitates restoration of normal mitochondrial function.[37-39] Cardiolipin is a specialized phospholipid found in mitochondria that is a vital component of the inner mitochondrial membrane, maintaining the structural integrity of the ETC.[40] In doing so, cardiolipin maintains the efficiency of the redox reactions essential for generating the transmembrane potential and proton-motive force for production of ATP. In the setting of excess oxidant generation, cardiolipin is susceptible to peroxidation; peroxidized cardiolipin is ineffective at maintaining the structural integrity of the ETC. As a result, the ETC is much less efficient, accumulation of free electrons leads to a vicious cycle of oxidant generation, transmembrane potential is decreased, ATP production diminishes, and calcium flux is perturbed. Elamipretide binds to peroxidized CL,[41] optimizing its function, and restoring transmembrane potential, ATP production, and normal calcium flux, while reducing superoxide generation. Elamipretide has been found to be effective in cell culture systems of oxidant and toxic injury and in animal models of ischemia-reperfusion, heart failure, and renal disease[42-45] to reverse mitochondrial dysfunction and to ameliorate mediated pathology. Elamipretide is bioavailable after systemic injection and readily penetrates tissues and cells.

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

4.1.8. Elamipretide in Preclinical Models of Dry Age-related Mitochondrial Degeneration

In *in vitro* studies of RPE cell culture, elamipretide has been found to reverse mitochondrial dysfunction, and prevent activation of signaling cascades that activate biochemical mediators of deposit formation. Elamipretide has also been recently studied in 2 relevant mouse models of dry AMD: an acute model of subRPE deposit formation after repetitive exposure to periocular hydroquinone in young C57BL6J wild-type mice and a chronic model of subRPE deposit formation in aged (> 16 months) apolipoprotein E (APOE) 4 transgenic mice fed a high fat plus cholate diet. Both models are characterized by RPE mitochondrial dysfunction, evidence of photoreceptor mitochondrial dysfunction, RPE cellular injury evident by cytosolic actin aggregate formation, loss of ZO-1 junctions, increased vimentin expression, basal cell membrane blebbing, and decreased MMP-2 activity, all of which mediate formation of subRPE deposits Presence of deposits is also associated with RPE mitochondrial dysmorphology (i.e., vacuolization). The APOE4 mouse model is also characterized by dysfunction of the neurosensory retina, which is evident by a diminished a-wave (photoreceptor activation) as well as diminished b-wave (photoreceptor – bipolar cell synapse) by electroretinogram (ERG). In both models, systemic (i.e., SC) daily treatment of mice with elamipretide reversed mitochondrial dysfunction, downregulated biochemical mediators, and promoted regression of subRPE deposits (unpublished preclinical data). Moreover, elamipretide treatment reversed

neurosensory retinal dysfunction, restoring normal a-wave and b-wave amplitudes on ERG. This striking effect on retinal and visual function represents the first observed reversal of established retinal dysfunction in the APOE4 transgenic mouse model.

Taken together, the profound unmet need to identify a treatment for dry AMD, a disease without any known effective therapy, the strong rationale for mitochondrial-targeted drugs in dry AMD, the well-established mechanism of action and clinical safety profile for the novel tetrapetide drug elamipretide, and notably the profound beneficial effects of elamipretide treatment to reverse subRPE deposit formation and restore retinal function in mouse models of dry AMD, collectively provide compelling evidence to support the clinical development of elamipretide for the treatment of patients with intermediate (early dry) AMD.

4.2. Elamipretide Risk/Benefit Assessment

4.2.1. Potential Risks and Benefits

Major metabolites of elamipretide, M1 and M2, have been qualified in toxicology studies in both rat and dog. M1 and M2 have been demonstrated to be pharmacologically inactive in a model of mitochondrial dysfunction in reperfusion injury where elamipretide demonstrates statistically significant reduction in damage.

In previous clinical studies of elamipretide, the most frequent treatment emergent adverse events (TEAEs) reported are injection site reactions, headache, nausea, and eosinophilia, as reported in both placebo and elamipretide-treated groups. All TEAEs should be treated by the Principal Investigator (PI) per standard of care. Monthly lab collections will be used to monitor for signs of eosinophilia. Specifically, collection of blood for hematology, chemistry, Immunoglobulin E (IgE), and Interleukin 5 (IL5) testing and urine for urinalysis.

In a preclinical fertility study, elamipretide, administered by daily SC injection before cohabitation, through mating and implantation at doses of 2, 6, and 20 mg/kg, had no adverse effects on fertility in male and female rats. In a preclinical gestational study, daily intravenous (IV) infusion of elamipretide to mated female rats and rabbits was associated with maternal toxicity characterized by reduced food consumption and body weight gain at high doses but no developmental toxicity. In rats, the maternal no-observed-adverse-effect-level (NOAEL) was 3 mg/kg/day, and the developmental NOAEL was 10 mg/kg/day. In rabbits, the maternal NOAEL was 5 mg/kg/day, and the developmental NOAEL was 50 mg/kg/day. As a precaution against any potential reproductive risks, this study mandates pregnancy testing for women of childbearing potential and the use of effective contraception for all participants of childbearing potential or having partners with childbearing potential during trial participation. Subjects enrolled in the study will be required to follow the contraceptive restrictions described in Section 9.8.44. Women who are pregnant or breastfeeding are excluded from study participation. It is possible that this drug may cause harm to a fetus or embryo. Furthermore, the safety of receiving elamipretide during breastfeeding is not known.

Elamipretide was not associated with any end organ toxicity and all clinical findings were reversible. No significant toxicity was observed at 3 mg/kg/hour in rats and dogs, infused continuously for 12 hours with elamipretide or after 90 days dosing of elamipretide by SC injection (6mg/day in rat; 20 mg/day in dog).

In animal studies, evidence of drug-induced histamine release syndrome was seen with cutaneous vasodilation, redness of the face, and pinna and muscle twitching noted in association with variable increases in plasma histamine. Mild and moderate histaminergic-like reactions occurred at elamipretide time to maximum plasma concentration (T_{max}), where maximum plasma concentration (C_{max}) was > 16,500 ng/mL in rat [30 mg/kg/day] and > 3500 ng/mL [10 mg/kg/day] in dog and resolved spontaneously after approximately 4 hours post dose. This phenomenon was best characterized in the cardiovascular dog study where minimal decreases in blood pressure and a reflex increase in heart rate and peripheral vasodilation were clearly associated with increases in plasma histamine at doses of elamipretide > 10 mg/kg/day. At SC doses > 300 mg/kg/day in the rat or > 40 mg/kg in the dog, convulsions were observed when C_{max} plasma concentrations of elamipretide were approximately 200,000 ng/mL and approximately 60,000 ng/mL in the rat and dog, respectively.

In human volunteers, 2 clinical studies have assessed the safety and pharmacokinetics (PK) of elamipretide. At doses of up to 80 mg/day administered as a SC injection for up to 7 days, no subject experienced symptoms of histamine release. Plasma concentrations reached time to T_{max} at approximately 0.75 hours postdose and mean C_{max} at 80 mg/day on Day 7 was 1643 ng/mL. The daily dosage level for this study (40 mg) is below the dosage range utilized in these prior safety studies. Nonetheless, close monitoring of study subjects receiving elamipretide for clinical signs related to a histaminergic response, including local injection site reactions, is warranted. Antihistamines should be considered if clinically significant histaminergic-like reactions occur.

In rats, dose levels above 100 mg/kg/day were associated with metabolic acidosis, electrolyte loss, hypocalcaemia, and hypophosphatemia. In human subjects, early clinical data suggested a treatment-related lowering in serum sodium levels. Expansion of the clinical study population has not demonstrated hyponatremia; however, close monitoring of study subjects receiving elamipretide for clinical and laboratory signs of hyponatremia will be conducted. Treatment for the condition is fluid restriction.

Elamipretide and its 2 metabolites, M1 and M2, are excreted primarily through the kidneys. Patients with renal dysfunction will have higher exposure to the drug and its metabolites. A clinical study conducted in subjects with varying degrees of renal function (normal renal function and mild, moderate, and severe renal impairment) assessed the safety and PK of elamipretide and metabolites after IV administration of elamipretide (0.25 mg/kg/hour for 1 hour) for 7 days. As expected, PK variables were impacted by renal function in a proportional manner; exposure (as the area under the plasma concentration-time curve from 0 to 24 hours [$AUC_{0\text{-}24h}$]) to elamipretide in the severe renal impairment group was approximately 2.3 times higher than in the normal renal function group, while C_{max} was 1.08 times higher. Elamipretide,

M1, and M2 had reached steady-state by 7 days of dosing. Anticipated C_{max} and AUC_{0-24h} after daily exposure to elamipretide at 40 mg/day by SC injection are shown in Table 2.

Table 2: Anticipated Mean C_{max} and Mean AUC_{0-24} Hours of elamipretide, M1 and M2 After Administration of elamipretide at 40 mg/day SC

Analyte	PK Parameter	Renal Function (GRF mL/min)			
		Normal (>90)	Mild Impairment (60-89)	Moderate Impairment (30-59)	Severe Impairment (<30)
elamipretide	C_{max} (ng/mL)	1320	1337	1426	1426
	AUC_{0-24h} ng.hr/mL	3810	5372	6782	8649
M1	C_{max} (ng/mL)	436	577	577	774
	AUC_{0-24h} ng.hr/mL	3200	6560	7328	12544
M2	C_{max} (ng/mL)	88.8	189	273	612
	AUC_{0-24h} ng.hr/mL	1410	3469	5288	11844

Abbreviations: AUC_{0-24h} = area under the plasma concentration-time curve from 0 to 24 hours; C_{max} = maximum plasma concentration; GFR = glomerular filtration rate.

Safety and tolerability of elamipretide was not affected by renal function. Subjects with glomerular filtration rates < 30 mL/minute will be excluded from the study and anticipated plasma PK of the active compound or inactive metabolites are expected to remain within mandated toxicity margins.

Generally, injection of SC elamipretide resulted in mild or moderate injection site reactions (ISRs), frequently characterized by erythema, induration, bruising, pruritus, pain, and/or urticaria. Injection site reactions were reported intermittently across multiple studies with elamipretide, with most subjects experiencing ISRs beginning upon first administration of elamipretide and continuing throughout treatment, with resolution of the ISRs typically occurring the day of last elamipretide administration. The resolution of ISRs, however, has occurred as late as 14 days after the end of elamipretide treatment in one subject. The site may be requested to acquire photographs of the injection site reaction and provide them to the sponsor. The subject will be consented to allow these photographs to be collected and transferred to sponsor for analysis.

Given the potential benefit of a first-in-any-class treatment for patients with dry AMD, the overall risk benefit balance is therefore considered to be acceptable.

4.2.1.1. Safety Studies - Non-clinical Studies

Toxicology studies in rats and dogs showed that elamipretide has an acceptable profile that permits clinical investigations in humans for the proposed duration of the study.

In non-clinical safety studies in rats and dogs, no safety issues relevant to either IV infusion or SC administration at therapeutic doses were identified during the non-clinical evaluation of elamipretide. Elamipretide did not cause end-organ toxicity at any dosage tested in either rats or dogs. Systemic toxicity at high doses was manifested primarily by acute and transient clinical signs, which may have been mediated by histaminergic-like reactions. Effects were associated with maximum elamipretide C_{max} and were rapidly reversible as the plasma concentrations of elamipretide and histamine decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory, or central nervous system function; off-target non-adverse effects were limited to a transient decrease of blood pressure and heart rate, which is thought to be consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to C_{max} for elamipretide; thus, the safety margin is estimated based on C_{max}, and not area under the plasma concentration-time curve (AUC). The plasma elamipretide threshold concentration for clinically relevant adverse effects appears to be approximately 20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures in this trial.

Elamipretide was negative for genotoxicity in the full battery of tests and caused no significant hemolysis or inhibition of receptor binding. Elamipretide was not associated with adverse effects on fertility or embryo-fetal development.

No formal immunotoxicity studies have been performed. As a tetrapeptide, the immunogenic potential of the drug is expected to be low.

4.2.1.2. Human Safety

To date, 17 clinical trials have been completed with parenteral elamipretide, including 14 clinical studies with the IV formulation and 3 studies with the SC formulation. In 11 clinical pharmacology trials completed, the primary objective was not to treat a disease state (9 trials with the IV formulation and 2 trials with the SC formulation).

Eight of the 11 clinical pharmacology trials evaluated single doses of IV or SC elamipretide, and three trials evaluated multiple doses of IV and SC elamipretide (SPISC-101 and SPISC-102 evaluated both single and multiple dose SC elamipretide). Parenteral administration of elamipretide was assessed following single and multiple IV and SC doses in approximately 200 healthy subjects in 11 completed clinical pharmacology studies. Single IV doses ranged from 0.005 mg/kg/hour to 0.25 mg/kg/hr, typically administered over 4 hours, while 0.25 mg/kg/hr administered over 1 hour daily for 7 days was the multiple-dose regimen studied. Single SC doses ranged from 2 mg to 80 mg administer as 0.5 or 1 mL injections, while multiple-dose regimen of 6 mg to 80 mg administered as 0.25, 0.5, or 1 mL injections daily for 7 days were studied.

No safety concerns have been identified with administration of IV or SC elamipretide for up to seven days. In these studies, the only systemic adverse event reported in over 5% of subjects was headache (7.3%). Nausea and hyponatraemia were each reported in 3.0% of the subjects. All

other events were reported with incidence of <2.0%. The majority of TEAEs were assessed by the investigator to be of mild severity, resolved without sequelae and did not require intervention. There were no significant findings for group mean clinical laboratory, vital sign, ECG, or physical examination parameters within or across trials.

The SC formulation of elamipretide has been studied in both single- and multiple-dose trials in healthy volunteers and patient populations. Generally, injection of SC elamipretide resulted in mild or moderate injection site reactions, frequently characterized by erythema, induration, bruising, pruritus, pain, and/or urticaria. Injection site reactions were reported intermittently across dosing with elamipretide, with most subjects experiencing ISRs beginning upon first administration of elamipretide and continuing throughout treatment, with resolution of the ISRs typically occurring the day of last elamipretide administration. The resolution of ISRs, however, has occurred as late as 14 days after the end of elamipretide treatment in one subject.

In subjects with renal impairment, exposure, as measured by AUC, to elamipretide and both of its metabolites (M1 and M2) increased proportionally to the degree of renal impairment. However, there was no evidence of increased toxicity as a consequence of impaired renal function. Similarly, in the Drug-Drug Interaction (DDI) studies carried out to date, co-administration of elamipretide with aspirin, with clopidogrel, or with unfractionated heparin (UFH) did not indicate a change in the nature, severity or frequency of AEs to the safety profile of either elamipretide or the comparator.

Elamipretide, administered by parenteral routes, was also assessed in completed studies in multiple patient populations including subjects with stable congestive heart failure (CHF), acute coronary syndrome (ACS) subjects who were undergoing primary percutaneous coronary intervention (PCI) and stenting for ST-segment elevation myocardial infarction (STEMI), subjects with acute kidney injury (AKI) undergoing percutaneous transluminal renal angioplasty (PTRA), subjects with genetically confirmed mitochondrial disease with signs and symptoms of mitochondrial myopathy and/or exercise intolerance, and subjects over 60 years of age with evidence of skeletal muscle mitochondrial dysfunction. Single and multiple IV and SC doses of elamipretide were assessed with generally no notable differences between the elamipretide and placebo arms in the frequency or severity of adverse events, except for ISRs with SC elamipretide administration. Additionally, eosinophilia was reported as an adverse event and laboratory data demonstrated elevations (>0.45 cells $x10^9$/L) in eosinophils beginning at approximately 28 days after initiation of elamipretide treatment in numerous subjects. These laboratory findings have not been reported to be associated with any systemic clinical manifestations of eosinophilia. In general, these elevations were demonstrated to have returned to within normal range or to baseline levels at the follow-up visit. There were no other identified safety concerns in these trials with respect to other clinical laboratory results, physical examinations, vital signs, ECG data between the elamipretide and placebo. In general, the safety profile of systemic elamipretide was consistent with the pre-existing, comorbid medical conditions.

Across all studies, both IV and SC formulations, there has been no reported pregnancies. There have been no exposures during lactation, no overdoses, and no abuses or misuses reported.

4.2.2. Conclusions

In summary, based on the clinical and non-clinical study data, acceptable safety risks are expected for the current study.

5. OBJECTIVES

5.1. Primary Objective

The primary objective of the study is:

- To evaluate the safety and tolerability of SC injections of elamipretide in subjects with intermediate AMD

5.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the feasibility of administration of SC injections of elamipretide in subjects with intermediate AMD
- To evaluate the changes from baseline in physical/ophthalmic examinations

6. INVESTIGATIONAL PLAN

6.1. Summary of Study Design

This is an open-label, Phase 1, single-center study in a total of approximately 40 evaluable subjects who have either: 1 eye with intermediate AMD - high-risk drusen without GA or 1 eye with intermediate AMD with noncentral GA. The study will thus include two predefined study disease cohorts: high-risk drusen cohort and noncentral GA cohort.

The disease cohort high-risk drusen, is defined as presence of either at least 1 large (≥ 125 μm) druse or multiple medium-size (between 63 and 124 μm) drusen.

The disease cohort noncentral GA, is defined as evidence of GA with cumulative area ≥ 1.27 mm^2 (approximately 0.5 disc area [DA]) by fundus autofluorescence (FAF), which spares the fovea (defined as retinal pigment epithelium and outer retina intact by SD-OCT).

Eligible subjects may have intermediate AMD with either high-risk drusen or noncentral GA in the study eye but without CNV AMD in the study eye. The fellow eye (not the study eye) is allowed to receive antiangiogenic therapies and may have advanced central GA, advanced central GA, or CNV AMD, and the fellow eye is allowed to receive antiangiogenetic therapies. .

Eligible subjects identified during the screening process will return for the Baseline (Day 0) visit, at which time they will be enrolled into the study and will begin receiving the 40 mg dose of elamipretide administrated subcutaneously once daily.

Written informed consent will be obtained from all subjects before the Screening visit.

The screening examination will be performed no more than 14 days before the Baseline visit. Data to be collected from the screening examination will include significant and/or ongoing medical and ocular history, vital sign measurements, physical examination, routine blood samples for hematology, chemistry, and urinalysis, ECG, manifest refraction, measurement of best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale completed twice, intraocular pressure measurement, slit-lamp examination, dilated fundus examination, fundus photography, SD-OCT, FAF, fluorescein angiography*, best-corrected low-luminance (LL) visual acuity completed twice, mesopic microperimetry, dark adaptometry, and Low-Luminance Questionnaire. Women of childbearing potential will have a serum pregnancy test.

*Fluorescein angiography assessments done as standard of care and completed within 90 days prior to dosing are allowed to be used for screening purposes.

After the screening examination, relevant data will be reviewed by the PI or designee to confirm study eligibility.

Each subject will be assigned into 1 of the 2 predefined study disease cohorts. Elamipretide will be supplied as 40 mg/mL of sterile solution for SC injection. The dose of elamipretide will be 40 mg administered as a once daily 1.0 mL SC injection.

At the time of study drug administration, training on the proper administration of subcutaneous drug solution (by the subject, regular caregiver, or his/her appropriate designee) will occur. Subjects will be trained using a standard script explaining the importance of proper administration of the drug on a daily basis for the 24-week Study Treatment Period. The first dose may be given by a qualified member of the study team, by the subject, or caregiver at the PIs discretion. The option of a visiting nurse to oversee the study drug administration will be discussed with the subject and provided, as needed.

Safety and tolerability will be measured throughout the Study Treatment Period, while exploratory anatomical and physiologic endpoints will be measured at time points as specified in the Schedule of Events (Table 3). Visits will occur at: Baseline (Day 0), Day 7 (± 3 days), Week 4 (± 7 days), Week 8 (± 7 days), Week 12 (± 7 days), Week 16 (± 7 days), Week 20 (± 7 days), and Week 24 (± 7 days), with phone calls to collect safety information completed at Week 2 (± 4 days), Week 6 (± 4 days), Week 10 (± 4 days), Week 14 (± 4 days), Week 18 (± 4 days), and Week 22 (± 4 days).

Ocular imaging will be read by an independent reading center and findings uploaded to the electronic data capture (EDC) system on a regular basis throughout the study.

After completion of the 24-week Study Treatment Period, subjects will continue to be monitored for safety during the 4-week Follow-Up Period. A post-study drug follow-up visit is scheduled at Week 28 (±4 days).

6.2. Schedule of Events

Study procedures and their timing are summarized in the Schedule of Events (Table 3). A list of all clinical laboratory tests to be performed is found in Appendix C.

Table 3: Schedule of Events

Days/Weeks	Screening Period[a]	Study Treatment Period														Follow up visit	Early Termination
	Screening (Day -14 to Day -1)	Day 0[b] Baseline	Day 7 (± 3 days)	Week 2 (± 4 days)	Week 4 (± 7 days)	Week 6 (± 4 days)	Week 8 (± 7 days)	Week 10 (± 4 days)	Week 12 (± 7 days)	Week 14 (± 4 days)	Week 16 (± 7 days)	Week 18 (± 4 days)	Week 20 (± 7 days)	Week 22 (± 4 days)	Week 24 (± 7 days) End of Study	Week 28 (± 7 days) FU Visit	Early Termination/ Discontinuation Visit
Visit	**1**	**2**	**3**		**4**		**5**		**6**		**7**		**8**		**9**	**10**	
Informed consent	X																
Eligibility	X	X															
Demographics[h]	X																
Medical/ Ocular history[j]	X	X															
Vital signs[c]	X	X	X		X		X		X		X		X		X	X	X
Physical examination[d]	X														X		X
Blood for safety[e]	X				X		X		X		X		X		X	X	X
Urinalysis	X				X		X		X		X		X		X	X	X
IgE	X				X		X		X		X		X		X	X	X
IL5	X				X		X		X		X		X		X	X	X
Pregnancy testing (serum)	X														X		X
ECG[f]	X														X		X
Adverse events[g]	X	X	X	X	X	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	X	X	X	X

Days/Weeks	Screening Period[a]	Study Treatment Period														Follow up visit	Early Termination
	Screening (Day -14 to Day -1)	Day 0[b] Baseline	Day 7 (± 3 days)	Week 2 (± 4 days)	Week 4 (± 7 days)	Week 6 (± 4 days)	Week 8 (± 7 days)	Week 10 (± 4 days)	Week 12 (± 7 days)	Week 14 (± 4 days)	Week 16 (± 7 days)	Week 18 (± 4 days)	Week 20 (± 7 days)	Week 22 (± 4 days)	Week 24 (± 7 days) End of Study	Week 28 (± 7 days) FU Visit	Early Termination/ Discontinuation Visit
Refraction	X				X						X				X		X
BCVA	X[k]	X	X		X		X		X		X		X		X	X	X
Best-corrected low-luminance VA	X[k]	X	X		X		X		X		X		X		X	X	X
IOP	X	X			X		X		X		X		X		X	X	X
Slit lamp exam	X	X	X		X		X		X		X		X		X	X	X
Dilated fundus exam	X	X			X		X		X		X		X		X	X	X
Fundus photography	X								X						X		X
Spectral-domain optical coherence tomography	X	X			X		X		X		X		X		X	X	X
Fundus autofluorescence	X	X			X		X		X		X		X		X	X	X
Fluorescein angiography[i]	X																
Mesopic microperimetry	X	X			X		X		X		X		X		X	X	X
Dark adaptometry	X	X			X		X		X		X		X		X	X	X

Days/Weeks	Screening Period[a]	Study Treatment Period													Follow up visit	Early Termination
	Screening (Day -14 to Day -1)	Day 0[b] Baseline	Day 7 (± 3 days)	Week 2 (± 4 days)	Week 4 (± 7 days)	Week 6 (± 4 days)	Week 8 (± 7 days)	Week 10 (± 4 days)	Week 12 (± 7 days)	Week 14 (± 4 days)	Week 16 (± 7 days)	Week 18 (± 4 days)	Week 20 (± 7 days)	Week 22 (± 4 days)	Week 24 (± 7 days) End of Study	Week 28 (± 7 days) FU Visit	Early Termination/ Discontinuation Visit
Reading Speed at standard light		X			X		X		X		X		X		X	X	X
Reading Speed at low light		X			X		X		X		X		X		X	X	X
Low-Luminance Questionnaire	X	X							X						X	X	X
VF Questionnaire-39		X							X						X	X	X
Dispense study drug and Subject diary		X	X		X		X		X		X		X				
Study drug accountability			X		X		X		X		X		X		X	X	X
Telephone screen[g]				X		X		X		X		X		X			

Abbreviations: BCVA = best-corrected visual acuity; ECG = electrocardiogram; VA = visual acuity.
Note: All ophthalmic testing is conducted on both eyes at each time point.

a. Screening procedures may be completed on more than one day, as long as all procedures are completed during the Screening Period.
b. The day of enrollment is defined as study Day 0.
c. Vital sign measurements include temperature, respiratory rate, sitting blood pressure after resting for 5 minutes, and pulse and weight.
d. Physical examination will include general appearance, skin, chest, heart, abdomen, extremities, and nervous system.
e. Blood for safety will consist of hematology panel and clinical chemistry.
f. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.
g. Telephone screens for safety events will occur at weeks intervening study visits: Week 2, Week 6, Week 10, Week 14, Week 18, and Week 22.
h. Demographic will collect date of birth, subject initials, sex, race, ethnicity, eye color, and history of smoking.

i. Fluorescein Angiography completed for reasons of standard of care and within 90 days prior to first dose can be used for screening purposes.
j. All ocular history will be collected. For all other body systems, only significant history and ongoing issues will be collected.
k. BCVA and BCVA LL repeated twice at screening

6.2.1. Screening Period

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

A complete medical history will be obtained during the Screening Period within 14 days before the first study drug administration on Day 0. The following will be collected:

- All ocular history
- Significant medical history
- Any ongoing medical history

The subject's medical history will be recorded on the Medical History section of the electronic case report form (eCRF). Any AEs reported from the time of signed ICF until the first dose of study drug should be recorded on the Medical History section of the eCRF. Any SAEs during this time will be reported on the AE eCRF and SAE paperwork completed within 24 hours of the PI learning of the SAE.

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

6.2.2. Study Treatment Period

Once the screening procedures are completed and the subject meets eligibility criteria, the subject will be assigned by the investigator into 1 of 2 study disease cohorts: intermediate AMD - high-risk drusen without GA cohort or intermediate AMD - noncentral GA cohort.

The dose of elamipretide will be 40 mg administered as a once daily 1.0 mL SC injection. Study site personnel will instruct the subject and/or the subject's caregiver or his/her appropriate designee on the techniques for drawing up the solution into the syringe and administering the study drug subcutaneously into the abdomen. The subject and/or the subject's caregiver or his/her appropriate designee will be instructed on rotating the SC injection site clockwise around the four abdominal quadrants from previous injection sites. The first injection will be given at the study center by a qualified study staff member, the subject, or the subject's caregiver under the supervision of the study site personnel. Study drug will be administered daily for the 24-week Study Treatment Period and should be administered at approximately the same time every day.

Assessments for safety and tolerability will be measured according to the Schedule of Events (Table 3). Visits will occur at: Day 7 (± 3 days), Week 4 (± 7 days), Week 8 (± 7 days), Week 12 (± 7 days), Week 16 (± 7 days), Week 20 (± 7 days), and Week 24 (± 7 days), with phone calls to collect safety information completed at Week 2 (± 4 days), Week 6 (± 4 days), Week 10 (± 4 days), Week 14 (± 4 days), Week 18 (± 4 days), and Week 22 (± 4 days). Subjects will be instructed to return all used and unused vials of study drug at subsequent visits.

6.2.3. Follow-up Period

A follow-up visit will occur 4 weeks after the last dose of study drug administration. Assessments will be collected according to the Schedule of Events (Table 3).

Subjects withdrawing from the study will be asked to complete the Early Discontinuation visit assessments (Table 3).

6.3. Study Assessments

6.3.1. Physical Examination

A physical examination should occur within 14 days before Day 0, at the end of the Study Treatment Period (Week 24), and at the Early Termination visit (for subjects who withdraw early from the study). The physical examination will include an assessment of general appearance, skin, chest, heart, abdomen, extremities, and the nervous system.

6.3.2. Vital Sign Measurements

Vital sign measurements (temperature, respiratory rate, sitting blood pressure after resting for 5 minutes, and pulse) and weight will be collected within 14 days before Day 0, at every visit during the Study Treatment Period, the Follow-up Period, and Early Termination (for subjects who withdraw early from the study). All vital sign measurements are to be obtained with the patient in a position that is consistent throughout the study.

6.3.3. 12-lead Electrocardiogram

A 12-lead ECG should be obtained within 14 days before Day 0, at the end of the Study Treatment Period (Week 24), and Early Termination (for subjects who withdraw early from the study). All scheduled ECGs must be performed after the subject has rested for at least 5 minutes in the supine position and before any blood draws.

6.3.4. Clinical Laboratory Testing

Samples for hematology, serum chemistry, and urinalysis assessments will be collected and measured as described in Table 3 and Appendix C.

All laboratory results must be reviewed for clinically significant events. Any clinically significant event must be followed and reported as required by the protocol (see Section 9.6 for AEs and abnormal laboratory values).

6.3.4.1. Hematology

Blood samples for hematology assessments will be obtained within 14 days before Day 0, at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Early Termination (for subjects who withdraw early from the study).

6.3.4.2. Blood Chemistry

Blood samples for chemistry assessments will be obtained within 14 days before Day 0, at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Early Termination (for subjects who withdraw early from the study).

6.3.4.3. Urinalysis

A urine sample for urinalysis will be obtained within 14 days before Day 0, at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Early Termination (for subjects who withdraw early from the study).

6.3.4.4. Immunoglobulin E (IgE)

A blood sample for IgE testing will be obtained within 14 days before Day 0, at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Early Termination (for subjects who withdraw early from the study).

6.3.4.5. Interleukin 5 (IL5)

A blood sample for IL5 testing will be obtained within 14 days before Day 0, at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and Early Termination (for subjects who withdraw early from the study).

6.3.4.6. Pregnancy Testing

If the subject is female and of child bearing potential, pregnancy testing by assessment of serum beta-human chorionic gonadotrophin (β-HCG) will be conducted within 14 days before Day 0, at Week 24, and at Early Termination (for subjects who withdraw early from the study).

Female subjects who are considered not to be of child bearing potential must have a history of being post-menopausal (no menses for 12 months without an alternative medical cause), tubal ligation or other surgical sterilization such as hysterectomy or bilateral oophorectomy that is clearly documented in the subject's source documents.

6.3.5. Concomitant Medications

All concomitant medications started on or after Day 0 should be recorded in the eCRF at every visit. For additional details see Section 7.5.2.

6.3.6. Subject Diary

Subjects will be asked to complete Subject Diary documenting study drug compliance. Study site personnel will review the Subject Diary at each visit and retrain the subject on administration of study drug if necessary.

6.3.7. Adverse Events

Subjects will be monitored for any untoward medical events (AEs or SAEs) from the time when the subject signs the informed consent and continuing through the 28 (± 7 days) days after last administration of study drug.

New protocol-related AEs (caused by any intervention required by the protocol) and updates on all AEs ongoing or with an unknown outcome must be recorded until the last subject visit required by the protocol. Additional details can be found in Section 9.3.1.

6.3.8. Low-Luminance Questionnaire and Visual Function Questionnaire-39

The LLQ is a vision-related quality of life scale assessing mainly mesopic and scotopic functioning. Subjects will be asked 36 questions about problems that involve his/her vision under different lighting conditions (see Appendix D). Subjects will be asked to complete this questionnaire within 14 days before Day 0, Day 0, Week 12, Week 24, and Week 28 and at the Early Termination visit (for subjects who withdraw early from the study).

The VFQ-39 is designed to assess health-related quality of life of subjects with visual impairment and includes: general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, color vision, and peripheral vision (see Appendix E). Subjects will be asked to complete questionnaire at Day 0, Week 12, Week 24, and Week 28 and at the Early Termination visit (for subjects who withdraw early from the study).

6.3.9. Other Study Assessments

Subjects will undergo a number of examinations to establish the subject's baseline disease and change in disease over time.

Best-corrected ETDRS visual acuity testing has become the gold standard for test for BCVA. The test should be conducted under standardized lighting conditions. The BCVA testing using the ETDRS chart will be conducted within 14 days before Day 0 (repeated twice) and at every visit. Subjects will also undergo testing for LL visual acuity testing within 14 days before Day 0 (repeated twice) and at every visit. IOP will be measured by Goldmann tonometry and recorded within 14 days before Day 0 and at every visit except Day 7. Refraction testing will be performed within 14 days of Day 0, Week 4, Week 16, and Week 24. It will also be complete at Early Termination (for subjects that withdraw early from the study).

The anterior segment of the eye by slit lamp biomicroscopy and regions of the vitreous, retina, choroid, optic nerve, and blood vessels will be examined by dilated ophthalmoscopy which will occur within 14 days before Day 0 and at every visit. The subject will have eye drops placed to dilate the pupils. Fundus photography of the posterior segment will be obtained within 14 days before Day 0, at Week 12, at Week 24, and at Early Termination (for subjects that withdraw early from the study). SD-OCT of the macula will be obtained within 14 days before Day 0, Day 0, and at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and at Early

Termination (for subjects that withdraw early from the study). Fundus autofluorescence imaging of the retinal pigment epithelium and neurosensory retina will be performed within 14 days of Day 0 and at every visit with the exception of Day 7, and at Early Termination (for subjects who withdraw early from the study).

Fluorescein angiography (FA) will be used to examine the circulation of the retina and choroid using fluorescein dye and a specialized camera to trace the dye. Subjects will receive an IV injection of fluorescein dye in order to highlight the blood vessels in the back of the eye. During the procedure, subjects should be observed for any adverse reactions to the dye. FA will be obtained within 14 days before Day 0. Fluorescein angiography completed for standard of care within 90 days prior to first dose can be used as the screening assessment.

Mesopic microperimetry will be used to measure retinal sensitivity, and dark adaptometry will be used to measure the absolute thresholds of rod sensitivity for the evaluation of night blindness. Both mesopic microperimetry and dark adaptometry and will be performed within 14 days before Day 0 and at all visits except for Day 7.

To assess the subject's reading difficulty and reading performance, a reading speed test will be administered under standard lighting conditions and under low luminance conditions at Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, and at the Early Termination visit (for subjects who withdraw early from the study).

7. STUDY POPULATION

7.1. Number of Subjects Planned

A total of approximately 40 evaluable subjects will receive study drug: approximately 20 subjects who have 1 eye with intermediate AMD – high risk drusen without GA, and approximately 20 subjects with noncentral GA. Subjects will receive elamipretide 40 mg administered as a once daily 1.0 mL SC injection.

7.2. Study Population

Subjects who have the following retinal diseases confirmed clinically and by standard imaging studies will be enrolled in 1 of 2 disease cohorts:

- Intermediate AMD - high-risk drusen without GA

  or

- Intermediate AMD - noncentral GA

7.2.1. Inclusion Criteria

For this study, only 1 eye of an eligible subject will be included and designated as the study eye. However, all specified ophthalmic testing will be performed on both eyes at each time point. A potential subject must meet the following criteria to be eligible for inclusion in the study**:**

Intermediate AMD – noncentral GA disease cohort:

1. Adults ≥ 55 years of age with 1 eye with intermediate AMD – noncentral GA. For this study, noncentral GA is defined as well-demarcated area(s) of GA with a cumulative area ≥ 1.27 mm^2 (approximately 0.5 DA) by FAF, which spares the fovea (defined as retinal pigment epithelium and outer retina intact) by SD-OCT.
2. Geographic atrophy may be multifocal, but the cumulative GA lesion size must be

   (A) ≥ 1.27 mm^2 (approximately ≥ 0.5 DA) and ≤ 10.16 mm^2 (approximately ≤ 4 DA) and

   (B) must reside completely within the FAF imaging field (field 2 to 30 degree image centered on the fovea).
3. Presence of measurable hyperautofluorescence adjacent to the discrete foci of GA.

OR

Intermediate AMD – high-risk drusen without GA disease cohort:

4. ≥ 55 years of age with one eye with intermediate AMD – high-risk drusen without GA.
5. High-risk drusen is defined as presence of either at least 1 large (≥ 125 μm) druse or multiple medium-size (between 63 and 124 μm) drusen.

General (both disease cohorts):

6. No evidence of choroidal neovascularization (active or prior history) in the macula of the study eye.
7. Able to provide informed consent and willing to comply with all study visits and examinations.
8. Women of childbearing potential who are not pregnant or nursing and have a negative serum pregnancy test at screening.
9. Best-corrected visual acuity by ETDRS letters ≥ score of 55 (Snellen equivalent ≥ 20/70).
10. Low-luminance visual acuity deficit (defined as difference between BCVA and LL visual acuity) > 5 letters.
11. Has at least two Low-Luminance Questionnaire sub scale results, in which one of the abnormal subscales is either general dim light vision or dim light reading.
12. The fellow eye may have intermediate AMD without noncentral GA (i.e., high-risk drusen), intermediate AMD with noncentral GA, CNV neovascular AMD, or central GA. Ongoing treatment with antiangiogenic therapies in the fellow eye is allowable.

13. No evidence of visually significant cataract **OR** pseudophakia without evidence of posterior capsular opacity.
14. Sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and able to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment.
15. Able to administer SC study drug solution as demonstrated at screening or able to have a care provider or appropriate designee who can administer the study drug (i.e., a capable family member or a caregiver).
16. If of childbearing potential or in a relationship with a partner of childbearing potential, are able to abstain from sex or use acceptable contraception during the study and for 3 months after dosing.
    a. For men: abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. The subject also agrees to use an acceptable method of contraception should they become sexually active. Subjects must use a condom with spermicide from the date of informed consent until at least 3 months after the last dose of study drug. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
    b. For women: abstinence is only acceptable when it is in line with the preferred and usual lifestyle of the subject. The subject agrees to use an acceptable method of contraception should they become sexually active. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days before the Screening visit or confirmed via sperm analysis), barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system are acceptable methods.
17. Ability and willingness to undertake all scheduled visits and assessments.

When both eyes are eligible for the study, only 1 eye will be included. In that case, the eye with the greater LL visual acuity deficit will be chosen for inclusion. Data on the fellow eye will be collected to assess potential effects of study drug on the fellow eye.

7.2.2. Exclusion Criteria

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

Ocular conditions – <u>study eye</u>

1. Age-related macular degeneration with any evidence of central GA (i.e., involving the fovea).
2. Atrophic retinal disease because of causes other than AMD.
3. Presence or diagnosis of exudative AMD or choroidal neovascularization in the study eye.

4. History of diabetic retinopathy (a history of diabetes mellitus without retinopathy is not a criterion for exclusion).
5. Presence of vitreous hemorrhage.
6. History of retinal detachment or macular hole (stage 3 or 4) in the study eye.
7. Presence of macular pucker.
8. History of uncontrolled glaucoma, defined as advanced cup-to-disc ratio > 0.7 and IOP > 25, with or without topical antihypertensive eye drops; treatment of ocular hypertension or controlled glaucoma are not criteria for exclusion.
9. History of advanced guttae indicative of Fuchs endothelial dystrophy.
10. Presence of visually significant cataract **OR** presence of significant posterior capsular opacity in the setting of pseudophakia.
11. Presence of significant keratopathy that would cause scattering of light or alter visual function, especially in LL conditions.
12. Ocular incisional surgery (including cataract surgery) in the study eye within 3 months (i.e. 90 days) before Day 0.
13. Aphakia.
14. History of vitrectomy surgery, submacular surgery, or any vitreoretinal surgery.
15. Prior treatment with Visudyne ® (verteporfin), external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy.
16. History of prophylactic subthreshold laser treatment for retinal disease.
17. Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation) in the study eye.

Ocular conditions – <u>either eye</u>

18. Active uveitis and/or vitritis (grade trace or above) in either eye.
19. History of idiopathic or autoimmune-associated uveitis in either eye.
20. Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

Systemic conditions

21. Known to be immunocompromised or receiving systemic immunosuppression.
22. Any disease or medical condition that in the opinion of the Investigator would prevent the subject from successfully participating in the study or might confound study results.
23. Estimated glomerular filtration rate < 30 mL/minute, by MDRD.

General

24. Participation in other investigational drug or device clinical trials during and/or within 30 days before enrollment, or planning to participate in any other investigational drug or device clinical trials within 30 days of study completion.
25. History of allergy to fluorescein that is not amenable to treatment.
26. Inability to comply with study or follow-up procedures.

27. Inability to obtain color fundus photograph, FAF, and fluorescein angiography of sufficient quality to be analyzed and interpreted.
28. History of allergic reaction to the investigational drug or any of its components.

7.3. Discontinuation

7.3.1. Discontinuation of Subjects

Subjects may be discontinued for the following reasons:

- Investigator decision
  - The Investigator decides that the subject should be discontinued from the study for any reason.
- Subject decision
  - The subject requests to be withdrawn from the study.
    - 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 site should document and sign the reason for the subject's failure to withdraw consent in writing.
  - The subject is lost to follow-up after a reasonable number of attempts to contact the subject (including documented phone calls and/or emails, and a certified letter) have been completed.
- Sponsor decision
  - The Sponsor or its designee stops the study or stops the subject's participation in the study 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 because of an AE or because of a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

Any subject withdrawing from the study will be asked to complete the Early Termination visit assessments (see Table 3).

7.3.2. Discontinuation of Study Sites

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

7.3.3. Discontinuation of the Study

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

7.4. Replacement of Subjects

In order to ensure that a sufficient number of subjects are available for assessment of primary and secondary endpoints, subjects that are not able to be compliant, i.e. less than 80% compliance, with administration of the IP will be replaced. Replacement of subjects will be assessed and confirmed on a case by case basis by the sponsor.

7.5. Other Medications and Therapies

7.5.1. Prohibited Medications

The use of any other investigational drug except elamipretide is prohibited during the conduct of the current trial.

Prohibited medications include:

- Medications known to be toxic to the lens, retina, or optic nerve. Examples include deferoxamine, chloroquine, hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines, ethambutol, and aminoglycosides.
- Any ophthalmic topical medications will be reviewed and deemed safe and approved by the investigator. Topical drops for treatment of elevated intraocular pressure are allowed, including for ongoing / intermittent application of artificial tears / lubricating ointments for the treatment of mild ocular surface disease / dry eye.
- Systemic medications (prescription or non-prescription) for the treatment of ocular conditions may be used if deemed safe and appropriate by both the Investigator and Sponsor.

7.5.2. Concomitant Medications

All medications, including over-the-counter treatments, vitamins, or supplements, must have been unchanged and constant for at least 1 month before the Baseline (Day 0) visit. All concomitant medications will be recorded in the source data and the eCRF. Changes in dosages

of current therapeutic agents during the conduct of the study will be discouraged, unless medically necessary or required to treat an AE.

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

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

8. STUDY DRUG

8.1. Study Drug Administration

Approximately 40 evaluable subjects will receive study drug administered as a single daily SC injection containing 40 mg elamipretide for 24 weeks. Study drug will be administered daily in the subject's abdomen (rotating clockwise around the four abdominal quadrants) by a caregiver or the subject.

Study drug injection will occur at the study site on Day 0. Subjects will be trained on the procedure for administration of study drug. The first dose may be given by a qualified member of the study team, by the subject, or caregiver at the PIs discretion, a designated, trained caregiver is also able to administer the study drug. The subject will be instructed to administer study drug on a daily basis at approximately the same time each day. The option of a visiting nurse to oversee the study drug administration will be discussed with the subject and provided, as needed.

8.2. Materials and Supplies

Study drug elamipretide will be dispensed, stored, and administered according to the Manual of Procedures. Subjects will be provided with syringes and any other supplies necessary for injection.

8.2.1. Elamipretide

Elamipretide drug product will be provided as a sterile solution for administration by SC injection. Each single-use vial is filled with 1 mL of drug product containing the equivalent of 40 mg elamipretide (added as MTP-131 acetate) in an isotonic, unpreserved, clear, colorless solution.

Elamipretide should be store in the refrigerator at a temperature of 2 to 8°C or 35.6 to 46.6°F.

A Manual of Procedures will be provided to the study center sites detailing dispensing directions, training materials for subjects, and Subject Diary. IP accountability will be documented in the study EDC system.

8.3. Study Drug Logistics and Accountability

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

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

The clinical monitor responsible for the study site will provide written approval for the destruction or return of used and unused study drug vials following reconciliation of all clinical supplies.

8.4. Study Drug Compliance

During the Study Treatment Period, study drug will be administered by the subject or caregiver. Subjects will be instructed to return all used and unused vials of study drug to the clinic at each visit.

8.5. Method of Assigning Study Drug

At Day 0, after eligibility criteria have been confirmed, a treatment cohort will be assigned to each subject. This is an open label non-comparative study and not randomized.

Subjects will be dispensed study drug at each study site visit. Each kit will be labeled with information including the following:

- Protocol number
- Sponsor name
- Storage conditions
- Directions for use
- Investigational caution statement

8.6. Rationale for Dose Selection

The dose and route of administration (i.e., 40 mg in 1.0 mL by SC injection) for the current study has previously been tested in a clinical trial involving healthy subjects. The dose for the current study was chosen based on the systemic exposure profile, as well as the safety observed in previous clinical trials.

The plasma elamipretide threshold concentration for clinically relevant adverse effects appears to be approximately 20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than

the maximum anticipated human exposures for the selected dosage in this study. In healthy human adults, systemic exposure (in terms of mean AUC_{0-24} on Day 7) to elamipretide after repeat SC injection at 40 mg in 1 mL was 3810 ng.hour/mL, while mean C_{max} on Day 7 was 1320 ng/mL. No accumulation of elamipretide was seen after repeat dosing for 7 consecutive days. Neither metabolite of elamipretide (M1 and M2) is active or implicated in toxicology.

In a completed Phase 1 trial (SPISC-101), elamipretide given subcutaneously to healthy subjects at doses up to 40 mg in 1 mL once daily for 7 consecutive days was well tolerated, with no systemic safety issues. Local injection site reactions were limited to transient, local erythema, and occasional pruritus or swelling, which resolved quickly without sequelae and without intervention.

8.7. Continued Access to Investigational Medicinal Product

Elamipretide will not be made available to subjects at the conclusion of their participation in the study.

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

9.1. Primary Safety Measures

The primary safety and tolerability endpoints for the study are:

- The incidence and severity of AEs
- Changes from baseline in vital sign measurements
- Changes from baseline in ECGs
- Changes from baseline in clinical evaluations
- Changes from baseline in clinical laboratory evaluations

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

9.2. Secondary Efficacy Measures

Secondary efficacy measures include:

Both Noncentral GA and High risk drusen without GA:

- Compliance of administration of SC elamipretide
- Number of home health visits for subject or caregiver to learn how to inject elamipretide
- Change in fundus hyperautofluorescence

- Change from baseline in LL visual acuity
- Change from baseline in mesopic light sensitivity by microperimetry
- Change in dark adaptometry
- Change in drusen volume ("RPE – drusen complex", as measured by automated segmentation) by SD-OCT
-
- Change in BCVA
- Change in reading speed at standard light
- Change in reading speed at low light
- Change in LL visual function by the LLQ
- Change in NEI VFQ-39 score
- Change in fundus photography

High Risk Drusen Without GA:

- Change in drusen volume ("RPE – drusen complex", as measured by automated segmentation) by SD-OCT

9.3. Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The Investigator is responsible for facilitating the appropriate medical care of subjects during the study, in the event of adverse event (AE).

The Investigator remains responsible for following, through an appropriate health care option, of AEs that are serious, considered related to the study drug or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained.

Comprehensive assessment of any apparent toxicity experienced by study subjects will be performed throughout the course of the study, from the date of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject. The reporting period for AEs is described in Section 9.8.2.

9.3.1. Adverse Events

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

Adverse Events may include the following:

- Suspected adverse drug reactions: side effects known or suspected to be caused by the study drug.
- Other medical experiences, regardless of their relationship with the study drug, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing, or physical examination findings.
- Events occurring as a result of protocol interventions (pre- or post-IMP administration)
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity. The Sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

9.4. Pre-study Drug Events

Untoward events and/or incidental diagnoses that occur prior to study drug administration are by definition, unrelated to the study drug. Pre-study drug events or incidental diagnoses will be recorded on the past medical history eCRF. However, if a pre-study drug event is assessed by the Investigator as related to a study procedure and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF and followed as per protocol guidelines noted in Section 9.7 and 9.8.

9.5. Baseline Medical Conditions

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

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

9.6. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs. However, abnormal laboratory findings or other objective measurements should be reported on the AE pages of the eCRF that:

- Meet the criteria for a SAE

- Result in discontinuation of the IMP
- Require medical intervention or
- Are judged by the Investigator to be clinically significant changes from baseline

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

9.7. Serious Adverse Events

An SAE is any AE from this study that:

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

Important medical events may be considered as SAEs when, based upon medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered a SAE and all such cases should be reported in an expedited manner as described in Section 9.8.3.3.

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

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

9.8. Recording of Adverse Events

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined in Section 9.8.2) will be recorded on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs must be additionally documented and reported using the study specific SAE Report Form.

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

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

Whenever possible, recognized medical terms should be used to describe AEs rather than lay terms (for example, “influenza” rather than “flu”), and abbreviations should be avoided.

Adverse events should be described using a specific clinical diagnosis, if available, rather than a list of signs or symptoms (for example, “congestive heart failure” rather than “dyspnea, rales, and cyanosis”). However, signs and symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.

Provisional diagnoses (e.g., “suspected myocardial infarction”) are acceptable, but should be followed up with a definitive diagnosis if later available. Similarly, a fatal event with an unknown cause should be recorded as “death of unknown cause.”

In cases of surgical or diagnostic procedures, the condition or illness leading to the procedure is considered the AE rather than the procedure itself.

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

9.8.1. Investigator Assessments

9.8.1.1. Severity/Intensity

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

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

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

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

9.8.1.2. Relationship to the Investigational Medicinal Product (IMP)

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

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, 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 study drug.

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

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

9.8.2. Adverse Event Reporting Period

The AE reporting period begins when the subject signs the ICF and continues through the clinical study's post study drug follow-up period, defined as 28 (± 7 days) days after last administration of study drug.

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

Within the study, all subjects who took at least 1 dose of IMP, whether they completed the study drug period or not, should enter the 28-day period as defined above.

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

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

9.8.3. Serious Adverse Event Expedited Reporting

In the event a SAE occurs during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor as detailed in the Clinical Trial Pharmacovigilance Procedural Manual.

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

- Investigator/Reporter with full contact information
- Subject identification details (study number, site number, subject number)
- Study drug administration details (dose and dates)
- Event verbatim terms, a brief description of signs/symptoms/diagnosis and the date of onset
- Seriousness criteria(ion) met
- Relationship of the event to the study drug (e.g., the causality according to the Investigator)

Reporting procedures and timelines are the same for any new follow-up information on a previously reported SAE.

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

The names, addresses, telephone and fax numbers for SAE back-up reporting (paper), are included in the Safety Reporting Plan.

The Investigator/Reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow

the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

9.8.4. Pregnancy and Contraception

Any pregnancies occurring during the study and within the three months after the last dose of study drug must be reported to the Investigator. In addition, women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 3 months after the last dose of study drug:

- Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.
- Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days before the Screening visit or confirmed via sperm analysis).
- Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

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

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to from the date of informed consent and for at least 3 months (i.e. 90 days) after last dose of study drug. Highly effective methods of contraception are defined as the usage by the female partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the study) 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 with spermicide from the start of study drug until at least 3 months after the last dose of study drug. Sperm or egg donation by subjects is not permitted from the start of study drug until 3 months after the study drug was administered.

Only pregnancies considered by the Investigator as related to study drug (e.g., resulting from an interaction between study drug and a contraceptive drug) are considered AEs unto themselves. However, all pregnancies with an estimated conception date that occurred during the AE reporting period, as defined in Section 9.8.2, must be recorded in the AE section of the eCRF. For this study, this applies to pregnancies in female subjects and in female partners of male subjects.

The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Form and the back-up reporting procedure as described in the Clinical Trial Pharmacovigilance Procedural Manual. Investigators must actively follow up, document, and report on the outcome of all pregnancies.

The Investigator must notify the Sponsor of these outcomes using Section II of the Pregnancy Form and submit the information using the back-up reporting procedure. Any abnormal outcome must be reported in an expedited manner as described in Section 9.8.3.3, while normal outcomes must be reported within 45 days from delivery.

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

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

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

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving subjects to the IRB that approved the study.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study, or alter the IRB's approval/favorable opinion to continue the study. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reaction [SUSARs]). The Investigator should place copies of the safety reports in the Investigator site file.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports to the CRO for distribution to the site and will maintain records of these notifications. The Investigator will be responsible for promptly notifying the concerned independent IRB of any safety reports provided by the Sponsor and or filing copies of all related correspondence in the site file.

9.9. Appropriateness of Measurements

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

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

In addition, the Sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

10.1. Data Capture System

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

Electronic case report form data will be encoded and stored in a clinical study database. Data managed by a central vendor, such as laboratory test data or ECG data, 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 site in that site's study file. Paper documentation provided by the subject may include, for example, a paper diary to collect subject reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

For this Phase 1, open label study, a sample size of 40 evaluable subjects is considered sufficient. The sample size of the study is based on precedent set by prior Phase 1 studies of similar nature and design. It is considered sufficient to provide for preliminary assessment of safety and tolerability.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

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

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

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

Subject's age, sex, weight, history of smoking, eye color, and other demographic characteristics will be recorded and summarized by disease cohort. Medical history will be listed.

11.2.2. Subject Disposition

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

11.2.3. Subject Characteristics

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

11.2.4. Concomitant Therapy

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

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

11.2.5. Study Drug Compliance

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

11.2.6. Endpoints and Methodology

11.2.6.1. General Considerations

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by disease cohort.

11.2.6.2. Analysis Populations

All subjects who receive at least 1 dose of study drug 40 mg (40 mg/1 mL of sterile solution for subcutaneous injection) will be included in the safety population.

Efficacy data will be summarized by disease group.

All presentations and analysis will be provided for the safety population.

The details of all analyses will be described in the statistical analysis plan.

11.2.7. Efficacy Analyses

For primary and secondary efficacy endpoints, the change from baseline in all continuous endpoints will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) by disease cohort. Categorical variables will be described using frequencies and percentages.

11.2.8. Interim Analysis

This is an open-label study, and thus monitoring of data outcomes over the course of the study may be performed. In addition, an interim analysis may be performed when 20 subjects have completed through 24 weeks of treatment. All data from all subjects up to these interim analyses may be included in the assessments.

These interim analysis will be performed by the Sponsor or their designee. Assessments of both safety and efficacy endpoints will be performed utilizing similar methods as are planned for the final analyses.

11.2.9. Safety Analyses

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

11.2.9.1. Adverse Events

The number and percentage of subjects experiencing 1 or more AEs will be summarized by disease group, relationship to study drug, and severity. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Adverse events will be summarized by SOC, PT, and disease cohort.

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

11.2.9.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

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

11.2.9.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, 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.

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

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each cohort. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of study.

11.2.9.4. Vital Signs

Vital signs data will be summarized by changes from baseline values for each disease cohort 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.

11.2.9.5. Other Safety Parameters

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

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

12.1. Informed Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study 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 study.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The ICF will also request approval for ISR photographs to be taken and provided to the sponsor for surveillance use.

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

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

12.2. Institutional Review Board

The Sponsor or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative site. The IRB will review the protocol as required.

The study site’s IRB should be provided with the following:

- The current Investigator’s Brochure and updates during the course of the study

- ICF
- Relevant curricula vitae

12.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

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

12.3.1. Protocol Approval

The Sponsor's 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 study.

12.3.2. Final Report Approval

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

12.3.3. Study Monitoring

The Investigators and institution(s) will permit study-related monitoring of the CRF data by Stealth BioTherapeutics, Inc., or their assignee by providing direct access to source data and/or documents. The study monitor will verify the eCRFs against the source documentation. This study will utilize risk based monitoring. What and how much data is being verified against the source is documented in the Monitoring and Communications Plan. Deviations from the protocol with regard to subject enrollment or study conduct will also be noted in the source documentation, and in the eCRF database. A Sponsor representative will visit the site to initiate the study, prior to the first administration of study drug for the first subject, and at agreed times throughout the study, including at the end of the study. Drug dispensing and clinical drug supply records will be 100% verified at the study site by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

12.3.4. Retention of Records

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

12.3.5. Disclosure of Information

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

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

13. AUDITS AND INSPECTIONS

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

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

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

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15. APPENDICES

Appendix A. SPONSOR'S PROTOCOL SIGNATURE PAGE

SPONSOR'S PROTOCOL SIGNATURE PAGE

An Open-Label, Phase 1 Clinical Study to Evaluate the Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Intermediate Age-Related Macular Degeneration

Study No.:	SPIAM-101
Sponsor:	Stealth BioTherapeutics, Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466
Protocol Date/Version:	20 June 2017 / v 7.0 FINAL

Printed name: W. Douglas Weaver, MD

Signature: W Douglas Weaver MD

Date: 06/21/2017

Appendix B. INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

An Open-Label, Phase 1 Clinical Study to Evaluate the Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Intermediate Age-Related Macular Degeneration

Study No.:	SPIAM-101
Sponsor:	Stealth BioTherapeutics, Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466
Protocol Date/Version:	20 June 2017 / v 7.0 FINAL

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

Investigator:

Printed name: _____

Signature: _____

Date: _____

Site address: _____

Appendix C. CLINICAL LABORATORY TESTS

Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase
Monocytes	Aspartate aminotransferase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Creatinine kinase
Urinalysis:	Calcium
Specific gravity	Glucose (non-fasting)
pH	Albumin
Protein	Chloride
Glucose	Bicarbonate
Ketones	Total protein
Blood	Estimated glomerular filtration rate calculated with the Modification Diet in Renal Disease equation
Pregnancy Test (Women of childbearing potential only)	
IgE	
IL5	

Appendix D. LOW-LUMINANCE QUESTIONNAIRE

Low Luminance Questionnaire

INSTRUCTIONS

Below you will find some statements about problems that involve your vision under different lighting conditions. After each question, you will find a list of possible answers. Please choose the response that best describes your situation at the present time *using your eye.*

Please answer all the questions as if you were wearing your glasses or contact lenses (if any) *with clear lenses (without yellow or other tints), except for the last two questions*. Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems under different lighting conditions and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer the following questions as though you were wearing them. "Does not apply to me" means that you do not perform this activity or you do not encounter this situation.

1. Do you have difficulty seeing in bright sunlight? (i.e. normal light without glare) ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty
   X – Does not apply to me

2. Do you have difficulty seeing in fluorescent lighting, like that found in stores and offices? ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty
   X – Does not apply to me

3. Do you have difficulty seeing at dusk or at dawn? (i.e. sunrise/sunset) ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty
   X – Does not apply to me

4. Do you have difficulty seeing at night? ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty
   X – Does not apply to me

5. Do you have difficulty seeing in candlelight? ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty
   X – Does not apply to me

6. Do you have difficulty reading books or newspapers in bright light? (i.e. normal light without glare) ☐

   1 – No difficulty at all
   2 – A little difficulty
   3 – Some difficulty
   4 – A lot of difficulty / stopped reading due to my vision
   X – Does not apply to me / stopped reading for other reasons

7. Do you have difficulty reading books or newspapers in dim light? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty / stopped reading due to my vision
X – Does not apply to me / stopped reading for other reasons

8. In dimly lit restaurants, do you have difficulty reading menus? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty / stopped going to restaurants due to my vision
X – Does not apply to me / stopped for other reasons

9. Do you have difficulty reading words printed on dark colored paper? ☐

1- No difficulty at all
2- A little difficulty
3- Some difficulty
4- A lot of difficulty
X- Does not apply to me

10. Do you have difficulty seeing to walk around in a darkened theater or darkened room? ☐

1- No difficulty at all
2- A little difficulty
3- Some difficulty
4- A lot of difficulty
X- Does not apply to me

11. In dimly lit places or at night, do you have difficulty seeing people's faces? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

12. Because of your vision, do you have difficulty going out for night time social events such as friend's homes, church, the theater or restaurants? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty / stopped because of my vision
X – Does not apply to me / do not socialize for other reasons

13. In dimly lit places or at night, do you have difficulty seeing colors? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

14. In dimly lit places or at night, do you have difficulty with depth perception? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

15. In dimly lit rooms with dark floors, do you have difficulty seeing furniture? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

16. In walking around in dimly lit places or at night, have you bumped into furniture, stumbled, tripped or fallen because of your vision (for example, going to the bathroom during the night)? ☐

1- None of the time
2- A little of the time
3- Some of the time
4- Most or all of the time
X- Does not apply to me / have fallen for other reasons

17. In dimly lit places or at night, do you depend on others to help you because of your vision? ☐

1- None of the time
2- A little of the time
3- Some of the time
4- Most or all of the time
X- Does not apply to me

18. When you visit other people's homes, do you have difficulty seeing because there is not enough light? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty / I do not visit other people due to my vision
X – Does not apply to me / I do not visit people for other reasons

19. Do you have difficulty seeing under kitchen counters, in cabinets or in closets because there is not enough light? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

20. Do you have difficulty with your peripheral vision in bright sunlight? (i.e. normal light without glare) ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

21. Do you have difficulty with your peripheral vision under dim lighting conditions? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

22. Do you have difficulty with your peripheral vision at night? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

23. Do you limit your driving in the daytime due to your vision? ☐

1- No difficulty at all
2- A little difficulty
3- Some difficulty
4- A lot of difficulty / stopped driving due to my vision
X- Does not apply to me / stopped for other reasons

24. Do you limit your driving at night due to your vision? ☐

1- No difficulty at all
2 - A little difficulty
3 - Some difficulty
4 - A lot of difficulty / stopped driving at night most or all the time

X -Does not apply to me / stopped for other reasons

25. While in a car at night, do you have difficulty seeing? ☐

1 - No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X - Does not apply to me

26 . While in a car at night, do you have difficulty seeing dark colored cars? ☐

1- No difficulty at all
2- A little difficulty
3- Some difficulty
4- A lot of difficulty
X- Does not apply to me

27. While in a car at night, do you have difficulty reading street signs? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

28. While in a car at night, do headlights from oncoming cars cause glare? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

29. While in a car at night, do you have difficulty recovering normal vision after being glared out by oncoming headlights? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty

X – Does not apply to me

30. While in a car at night in heavy rain, do you have difficulty seeing? ☐

1 - No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X - Does not apply to me

31. While in a car at dawn or dusk, does glare from the sun create difficulty seeing? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

32. While in a car driving through fog, do you have difficulty seeing?

1 - No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X - Does not apply to me

33. When entering a dimly lit room from the bright outdoors (or when entering a dark tunnel or driving on a road into shadows), does your eyesight take longer than normal getting adjusted to the change from bright into dim light? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

34. When leaving a dimly lit building into the bright outdoors (or leaving a dark tunnel or shadows into bright sunlight), does your eyesight take longer than normal getting adjusted to the change from dim into bright light? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me

35. While wearing dark sunglasses, do you have difficulty reading? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me / I do not wear dark sunglasses

36. While wearing dark sunglasses, do you have difficulty recognizing other people's faces? ☐

1 – No difficulty at all
2 – A little difficulty
3 – Some difficulty
4 – A lot of difficulty
X – Does not apply to me / I do not wear dark sunglasses

Table 1. Subscale Items

Subscale	Item Numbers
Control questions	1, 6, 20, 23, 30, 32
General dim light vision	2, 3, 4, 5, 13, 14, 15, 36
Dim light reading	7, 8, 9, 35
Driving or riding in car	24, 25, 26, 27
Other ADLs	11, 12, 18, 19
Mobility	10, 16, 17

Light transitions and glare	28, 29, 31, 33, 34
Peripheral vision	21, 22

Appendix E. VISUAL FUNCTIONING QUESTIONNAIRE-39

National Eye Institute's Visual Functioning Questionnaire

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.
Please answer all the questions as if you were wearing your glasses or contact lenses (if any).
Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible.
Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.
2. Please answer every question - unless you are asked to skip questions because they do not apply to you.
3. Answer the questions by circling the appropriate number.
4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

Excellent 1	Fair 4
Very Good 2	Poor 5
Good 3	

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

1

Excellent 1	Fair 4
Very Good 2	Poor 5
Good 3	Completely Blind 6

3. How much of the time do you worry about your eyesight?

None of the time 1	Most of the time 4
A little of the time 2	All of the time 5
Some of the time 3	

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

None 1	Severe 4
Mild 2	Very severe 5
Moderate 3	

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

8. How much difficulty do you have reading street signs or the names of stores?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

3

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

15. Are you currently driving, at least once in a while?

Yes 1 *Skip To Q 15c*	No 2

15a. IF NO: Have you never driven a car or have you given up driving?

Never drove 1 *Skip To Part 3, Q 17*	Gave up 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

Mainly eyesight 1 *Skip To Part 3, Q 17*
Mainly other reasons 2 *Skip To Part 3, Q 17*
Both eyesight and other reasons 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

PART 3: RESPONSES TO VISION PROBLEMS

17. Do you accomplish less than you would like because of your vision?

4

All of the time 1	A little of the time 4
Most of the time 2	None of the time 5
Some of the time 3	

18. Are you limited in how long you can work or do other activities because of your vision?

All of the time 1	A little of the time 4
Most of the time 2	None of the time 5
Some of the time 3	

19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:

All of the time 1	A little of the time 4
Most of the time 2	None of the time 5
Some of the time 3	

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me.	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

5

GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

No difficulty at all 1	Moderate difficulty 3
A little difficulty 2	Extreme difficulty 4
Stopped doing this because of your eyesight 5	
Stopped doing this for other reasons or not interested in doing this 6	

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

No difficulty at all	1	Moderate difficulty	3
A little difficulty	2	Extreme difficulty	4
Stopped doing this because of your eyesight	5		
Stopped doing this for other reasons or not interested in doing this	6		

7

ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

WELL-BEING/DISTRESS and DEPENDENCY

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

Patient's name: _____

Date _____

8

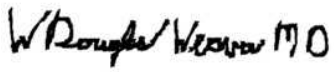
Signature Certificate

Document Reference: MGRLYNIE4JLBJ3STAIULSL

RightSignature
Easy Online Document Signing

W. Douglas Weaver
Party ID: J8RFJGJCHK9C3E76KVUZJA
IP Address: 50.203.117.38
VERIFIED EMAIL: doug.weaver@stealthbt.com

Electronic Signature:



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2017-06-21 06:58:29 -0700	Document signed by W. Douglas Weaver (doug.weaver@stealthbt.com) with drawn signature. - 50.203.117.38
2017-06-21 06:56:08 -0700	Document viewed by W. Douglas Weaver (doug.weaver@stealthbt.com). - 50.203.117.38
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