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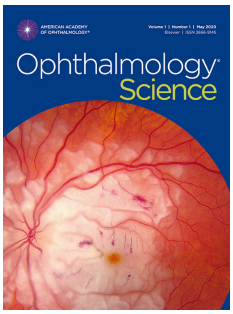

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Phase 1 Clinical Trial of Elamipretide in Intermediate Age-Related Macular Degeneration and High-Risk Drusen: ReCLAIM HRD Study

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Running head: ReCLAIM: Elamipretide in Intermediate AMD and High-Risk Drusen

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Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well tolerated in patients with intermediate age-related macular degeneration and high-risk drusen, with positive effect on visual function, particularly under low luminance conditions.

Abstract

Purpose: To assess safety, tolerability, and feasibility of subcutaneous administration of mitochondrial-targeted drug elamipretide in patients with intermediate age-related macular degeneration (AMD) and high-risk drusen (HRD) and to perform exploratory analyses of change in visual function.

Design: Phase 1, single-center, open-label, 24-week clinical trial with preplanned HRD cohort.

Participants: Adult patients, age ≥ 55 years, with intermediate AMD and HRD.

Methods: Participants received subcutaneous elamipretide 40 mg daily, with safety and tolerability assessed throughout the study. Ocular assessments included normal luminance best-corrected visual acuity (BCVA), low-luminance best-corrected visual acuity (LLVA), normal luminance binocular reading acuity (NLRA), low luminance binocular reading acuity (LLRA), spectral-domain optical coherence tomography (OCT), fundus autofluorescence (FAF), mesopic microperimetry, dark adaptation, and low-luminance questionnaire (LLQ).

Main Outcome Measure: The primary endpoint was safety and tolerability. Prespecified exploratory endpoints included changes from baseline in BCVA, LLVA, NLRA, LLRA, RPE-drusen complex (RPE-DC) volume by OCT, FAF, mesopic microperimetry, dark adaptation, and LLQ.

Results: Subcutaneous administration of elamipretide was highly feasible. All HRD participants (n=21) experienced ≥1 adverse event but all were mild (57%) or moderate (43%) with the most common events related to injection site reactions. There were no serious systemic AEs. One participant discontinued due to injection site reaction, one participant withdrew because they did

not wish to continue study visits, and one participant withdrew after experiencing transient visual impairment. Among the 18 participants who completed the study, mean change in BCVA from baseline to 24 weeks was +3.6 letters (P=0.014) and LLVA was +5.6 letters (P=0.004). Compared to baseline, mean NLRA improved by -0.11 logMAR units (P=0.001), and LLRA by –0.28 logMAR units (P<0.0001). There were significant improvements in 6 of 7 subscales of the LLQ (P<0.0015). No significant changes were observed for RPE-DC volume, FAF, mesopic microperimetry, and dark adaptation.

Conclusions: Elamipretide appears to be generally safe and well tolerated in patients with intermediate AMD and HRD. Exploratory analyses demonstrate a positive effect on visual function, particularly under low luminance conditions. Further study of elamipretide for treatment of intermediate AMD with HRD is warranted.

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision loss in individuals 65 and older,[1] with an expected increase in prevalence to 10% among those 50 years and older by the year 2050.[1,2] Severe vision loss occurs among patients who develop advanced dry AMD with central (i.e., foveal center-involving) geographic atrophy (GA) and those patients with untreated or undertreated neovascular AMD.[2] While decreased vision in setting of intermediate AMD and high-risk drusen (HRD) can occur in the setting of confluent, large-size drusen within the macula, the majority of HRD patients retain preserved central visual acuity. However, a significant number of HRD patients do experience difficulties with activities of daily living despite preserved best-corrected visual acuity.[3–7] Specifically, between 30-50% of HRD patients experience moderate to profound impairment in low luminance visual function and activities of daily living (e.g., driving at dusk, dim light reading, others).[8–10] While there is some evidence that supplements targeting enhancement of macular pigment might offer modest visual benefits,[11,12] these remain exploratory in nature. Thus, despite the progressive nature of AMD and associated visual dysfunction, there are currently no approved therapeutic agents that can improve vision (standard or low luminance) or that can alter the progression of AMD, in part because mechanisms of disease are not fully understood.[13]

Risk factors associated with intermediate AMD and HRD include aging,[14,15] genetic polymorphisms (e.g., complement factor H),[16] systemic health factors, and environmental risk factors (especially cigarette smoking).[14,17,18] Development of therapies for AMD is challenging, in part because disease pathogenesis is multifactorial, including: mitochondrial dysfunction,[19,20] abnormal lipid metabolism and transport,[21,22] oxidant injury,[23] complement overactivity,[24] inflammation,[25] accumulation of bisretinoids,[26] diminished autophagy,[27] and other mechanisms

of disease. A substantial body of evidence suggests that mitochondrial dysfunction plays a major role in AMD pathobiology [28–33] with numerous preclinical investigations demonstrating that mitochondrial dysfunction and oxidant-induced cellular injury represents a major mechanism of disease, particularly at the RPE.[19,23,32–36] In histopathology studies, AMD is also associated with damage to RPE mitochondrial DNA, and the effect occurs early in the course of the disease.[32] Human RPE isolated from patients with AMD exhibit mitochondrial dysmorphology and markers of oxidative damage, and these are noted to progressively increase with more advanced stages of disease.[19,32,37] Further, other accepted risk factors for developing AMD—including cigarette smoking, complement dysregulation and lipofuscin accumulation within RPE (though the relative importance and contribution of lipofuscin to dry AMD is still debated[31,38]) —have been shown to cause mitochondrial dysfunction in RPE cell culture models and in rodent models of AMD-like sub-RPE deposit formation.[30,31,33] Collectively, these findings provide a strong rationale for the development of mitochondria targeted therapies for treatment of AMD.

Mitochondria are most well known as producers of adenosine triphosphate (ATP) in support of certain energy-intensive cell functions. However, mitochondria also play roles in regulation of calcium signaling, reactive oxygen species (ROS) generation, and key metabolic pathways such as glutamate recycling.[39–41] Thus, while the specific mechanisms by which dysfunctional mitochondria mediate AMD pathobiology are not known, disrupted cellular bioenergetics, increased ROS production, and/or loss of other mitochondrial functions may lead to dysfunction at the RPE and photoreceptors, with subsequent disruption of the visual cycle, phototransduction, or normal metabolism of affected cells.[28,31,37]

Elamipretide is a first-in-class mitochondria-targeted tetrapeptide drug that increases cellular ATP production and reduces mitochondria-derived oxidants in affected cells by stabilizing the

structure and function of the mitochondrial electron transport chain.[42–45] This mechanism of action suggests that elamipretide could improve mitochondrial dysfunction within RPE and retina, ameliorating this component of AMD pathobiology.[36,43] The ReCLAIM study was a phase 1 clinical trial with a primary objective of evaluating the safety and tolerability of subcutaneously administered elamipretide in patients with nonexudative AMD, with exploratory analyses for changes in measures of visual function and disease progression. The ReCLAIM study included two prespecified cohorts of patients with nonexudative AMD: 1) patients with dry AMD and noncentral, fovea-sparing GA (NCGA); and 2) patients with intermediate AMD and high-risk drusen (HRD) without GA. The present report details the findings of the HRD cohort; results of the NCGA cohort are included in a separate report.

Materials and Methods

Study Design

This was a Phase 1, single-center, 24-week, open-label clinical trial (ClinicalTrials.gov Identifier: NCT02848313). The study was conducted in accordance with ICH GCP Guidelines and the tenets of the Declaration of Helsinki and was approved by the Duke Health Institutional Review Board (Durham, NC). Following informed consent and study enrollment, prospective participants underwent a screening assessment (≤ 14 days prior to the baseline visit) to verify study eligibility, which included physical and ophthalmic examination, measurement of Early Treatment Diabetic Retinopathy Study (ETDRS) scale best-corrected visual acuity (BCVA) under normal luminance (i.e., standard light) and low luminance conditions, spectral-domain optical coherence tomography (OCT), fundus autofluorescence (FAF), fluorescein angiography, and low-luminance questionnaire (LLQ) (adapted from Owsley, *et al.*,[8] see Supplement 1).

Participants

Detailed list of eligibility criteria is included in Supplement 2. Key inclusion and exclusion criteria are summarized below.

Inclusion criteria

Males and nonpregnant or nursing females ≥ 55 years of age with 1 eye with intermediate AMD with high-risk drusen without GA were eligible. High-risk drusen was defined as the presence of either at least 1 large (≥125 μm) drusen or multiple medium-size (63-124 μm) drusen. Participants were also required to have: 1) no evidence of choroidal neovascularization (active or prior history) in the study eye; 2) normal luminance BCVA ≥ 55 ETDRS letters score (i.e., Snellen equivalent ≥ 20/70); 3) low-luminance visual acuity (LLVA) deficit > 5 letters, wherein LLVA deficit is defined as the difference BCVA and LLVA; and 4) at least two LLQ abnormal subscale scores indicating impairment, wherein one of the abnormal subscales was either general dim light vision or dim light reading (wherein abnormal subscale was defined as ≥ 50% of questions in that subscale with answers of 3 (some difficulty) or 4 (a lot of difficulty) with specific low luminance tasks or functions). The fellow eye was permitted to have any stage of AMD: intermediate AMD with high-risk drusen, AMD with NCGA, neovascular AMD, or advanced AMD with center-involving GA. Ongoing treatment with anti-vascular endothelial growth factor therapies in the fellow eye was permitted.

Participants were also required to have either no visually significant cataract or pseudophakia without posterior capsular opacity, along with sufficiently clear ocular media, adequate pupillary dilation, fixation to permit quality fundus imaging, and ability to cooperate sufficiently for adequate ophthalmic visual function testing and anatomic assessment. When both eyes were

eligible for the study, the eye with the greater low luminance visual acuity deficit was chosen for inclusion.

Exclusion criteria

Exclusion criteria included any of the following ocular conditions in the study eye: AMD with any evidence of GA, where GA is defined as a well demarcated area of hypoautofluorescence on FAF corresponding to an area of choroidal hypertransmission and loss of RPE and outer retina on OCT, based on the assessment of the investigator; diagnosis of neovascular AMD or presence of choroidal neovascularization; or macular atrophy due to causes other than AMD. Additional macular / retinal exclusion criteria in the study eye included: presence of diabetic retinopathy, macular pathology (i.e., hole, pucker), history of retinal detachment, presence of vitreous hemorrhage. Nonmacular exclusion criteria in the study eye included: uncontrolled glaucoma, advanced guttae indicative of Fuchs endothelial dystrophy; visually significant cataract, presence of significant posterior capsular opacity in the setting of pseudophakia, aphakia, or significant keratopathy that would alter visual function, especially in low light conditions. Prior treatment exclusion criteria in the study eye included previous intravitreal injection of pharmacologic agents or implants (including anti-angiogenic (anti-VEGF) drugs and corticosteroids), prior vitreoretinal surgery (including vitrectomy surgery and submacular surgery), prior treatment with macular laser, verteporfin, external-beam radiation therapy, or transpupillary thermotherapy, or any ocular incisional surgery (including cataract surgery) in the study eye in the 3 months preceding the baseline visit. Additional exclusion criteria included the presence of any of the following ocular conditions in either eye: active uveitis and/or vitritis, history of uveitis, active infectious disease (conjunctivitis, keratitis, scleritis, endophthalmitis, etc.). Finally, individuals known to be immunocompromised, individuals receiving systemic immunosuppression for any

disease, and individuals with estimated glomerular filtration rate < 30 mL/minute were excluded from study participation.

Study Drug and Evaluations

The study drug elamipretide was administered as a 40mg (1 mL) subcutaneous injection in the abdominal area once daily for 24 weeks, beginning at baseline. Study drug was either self-administered by the participant or by a caregiver, following training by study personnel at the initial baseline visit. Participants were 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 could be given by a qualified member of the study team, by the participant, or caregiver at the investigator's discretion. The option of a home health nurse making visit(s) to the participant and caregiver to oversee and verify proper study drug administration was offered to each participant and provided to participants, as needed, and the number of nurse visits was recorded for each participant. Assessments for safety and tolerability were performed throughout the 24-week treatment period and at the follow-up visit (Week 28). Adverse events were assessed by the investigator for severity and relationship to study drug. Participants were asked to complete a diary documenting study drug administration and compliance. Compliance was assessed by study personnel assessment of participant diary and inventory of used study drug vials over the course of the active treatment period.

For ocular assessments, while only one eye of each eligible participant was designated as the study eye, all specified ophthalmic testing was performed on both eyes at each time point. Assessments for best-corrected visual acuity (ETDRS letter score) under normal luminance (BCVA) and low luminance (LLVA) were performed at screening and baseline, during active

treatment period (Weeks 1, 4, 8, 12, 16, 20, 24), and at follow-up (Week 28). BCVA and LLVA were measured as the correct number of letters read using standard ETDRS charts, lighting, and procedures. For LLVA, participants were fitted with trial frames with their best-corrected refraction and a 2.0-log unit neutral density filter to replicate low-luminance conditions under standardized ambient lighting.

Normal light binocular reading acuity (NLRA) and low luminance binocular reading acuity (LLRA) were measured at baseline, during study treatment (Weeks 4, 8, 12, 16, 20, 24), and at follow-up (Week 28). Assessment of NLRA was done by standardized illumination using several different standard MNREAD charts (MNREAD 1-W, 2-W and 3-W charts; Precision Vision, Lasalle, IL) with charts rotated throughout the study to prevent a learning effect. To calculate reading acuity, we used an adaptation of Gordon Legge's initially reported method[46] as follows: participants were fitted with trial frames with best-corrected near acuity lenses in standardized ambient lighting conditions, and results were recorded as the smallest font size read correctly with ≤1 word mistake within 30 seconds. This approach was undertaken to optimize test-retest consistency and reduce subjectivity related to assessment of reading error measurements. The MNREAD reading chart is comprised of 19 distinct font sizes ranging from -0.5 logMAR (smallest font size, Snellen equivalent 20/6) to 1.3 logMAR (largest font size, Snellen equivalent 20/400), total range in logMAR values of 1.9.

LLRA was performed in the same fashion as NLRA, with MNREAD 1-W, 2-W, and 3-W charts rotated between visits to prevent a learning effect, except that a 2.0-log unit neutral density filter was added to trial frames with best-corrected near acuity lenses to replicate low-luminance conditions. Results were recorded as the smallest font size read correctly (logMAR value ranging between -0.5 to 1.3) with ≤ 1-word mistake within 30 seconds.

Additional tests including mesopic microperimetry, dark adaptometry, fundus autofluorescence (FAF), and spectral domain optical coherence tomography (SD-OCT) were performed at baseline and Weeks 4, 8, 12, 16, 20, 24 and follow-up (Week 28). Mesopic microperimetry (MAIA microperimeter, iCare) was performed as previously described.[47] The mean 95% bicurve ellipse area (BCEA), the mean threshold for reduced retinal sensitivity, and the number of loci with reduced retinal sensitivity as defined by <25dB or <14dB below normal values were quantified. Dark adaptometry (AdaptDx, Maculogix) was performed and the rod intercept was calculated as previously described.[48] with some modification. Participants were initially exposed to 100% bleach. If participants could not recover from 100% bleach defined as inability to detect the stimulus after 20 minutes, testing was repeated at 75% bleach. For FAF, reading center graders evaluated changes in hyperautofluorescence patterns in images taken at baseline and week 24. Segmentation of SD-OCT was used to quantify the retinal pigment epithelium-drusen complex (RPE-DC) as previously described,[49] The RPE-DC was defined as the volume extending from the inner aspect of the RPE plus drusen material to the outer aspect of Bruch's membrane. Evaluation of FAF and OCT was performed by masked graders.

Low luminance questionnaire (LLQ) (adapted from Owsley, *et al.*,[8] see Supplement 1) was performed at baseline as described and was subsequently repeated at weeks 12 and 24, and at follow-up (week 28). LLQ was scored and analyzed as previously described.[8] In brief, items in the LLQ had a difficulty response scale and corresponding scores: (1) no difficulty at all; (2) a little difficulty; (3) some difficulty; and (4) a lot of difficulty. option of "X", does not apply to me, was included in case a particular item was not applicable for a participant, and in this case, the item was not included in determining the subscale score. The subscale score was calculated by scaling each item response from 0 to 100, wherein 100 reflects the highest functional level

and 0 the lowest functional level; the mean value was determined for the applicable items comprising each subscale.

Endpoints

The primary study endpoint was safety and tolerability as assessed by the incidence and severity of adverse events and changes from baseline in vital sign measurements, ECGs, clinical assessments, and clinical laboratory evaluations. Assessment of adverse events was performed at each study visit and included both investigator-assessed and participant-reported events. Exploratory efficacy endpoints reported in the present study include changes from baseline in BCVA, LLVA, NLRA, and LLRA, OCT (to determine changes in retinal pigment epithelium-drusen complex (RPE-DC) volume, FAF, and LLQ. Mesopic microperimetry and dark adaptometry were performed to assess retinal sensitivity and recovery of dim light vision following bright light stress, respectively.

Statistical Analysis

For this phase 1, open-label study, a sample size of 40 evaluable participants was considered sufficient to allow preliminary assessment of safety and tolerability, based on precedent set by prior phase 1 studies of similar nature and design. The HRD and NCGA cohorts were preplanned by study design and were enrolled with approximately equal number. Safety and efficacy variables are summarized descriptively. All participants who received ≥1 dose of study drug were included in assessment of safety as part of intention-to-treat analysis. Exploratory efficacy endpoints were assessed in participants who completed the 24-week treatment period. All statistical analyses and reporting were performed using the SAS® System Version 9.4 (SAS, Cary, NC). Continuous variables analyzed in this study were summarized by the number of non-

missing observations (N), mean, standard deviation (SD), median, minimum, and maximum values. For each continuous variable, statistical analysis of mean change from baseline value was assessed by one-sample t-test and signed-rank test for parametric and non-parametric analysis, respectively. To correct for multiple comparisons for changes in metrics from baseline, the Holm method was applied to determine the statistically significant threshold (*P* value) for the α level (Type I error rate) for each metric, based on the *P* value threshold $P<0.05$ for the metric with the highest *P* value.[50] For example, using the Holm method, for the four metrics BCVA, LLVA, NLRA, and LLVA, the *P* values were ordered from lowest to highest to identify the statistically significant threshold for each: $P<0.0125$ for the lowest *P* value among the four metrics; $P<0.0167$ for the second lowest *P* value among the four metrics; $P<0.025$ for the next to highest *P* value among the four metrics; and $P<0.05$ for the highest *P* value among the four metrics.[50]

Results

Study Participants

A total of 21 participants were included in the high-risk drusen cohort (**Table 1**). The majority were female (13/21), mean age was 71, and most (20/21) were Caucasian. One participant had large drusen, pigment and reticular pseudodrusen (RPD); 1 had medium drusen, pigment and RPD; 5 had large drusen and pigment; 2 had medium drusen and pigment; 4 had large drusen and RPD; 1 had large drusen and subretinal hyperreflective material (SHRM); 1 had medium drusen and SHRM; 5 hard large drusen; and 1 had medium drusen. Eighteen of the 21 participants completed the 24-week treatment period. One participant in the HRD cohort discontinued the study early (at week 8) due to intolerable injection site reaction. One participant withdrew from the study (at week 12) because they did not wish to continue with study visits,

and one participant withdrew after experiencing transient visual impairment (following week 12). Mean baseline (SD) BCVA and LLVA values were 79.4 (7.4) and 63.8 (10.0), respectively.

Feasibility and Compliance

Subcutaneous administration of elamipretide was highly feasible following proper instruction of participants and caregiver by study personnel and health nurse home visits to instruct and verify proper drug administration. The mean (SD) number of home visits required to ensure proper subcutaneous administration of elamipretide was 2.2 (0.54) visits. Mean (SD) treatment compliance across the 24-week active study drug period was 98.4 (4.0) %.

Safety and Tolerability

Adverse events are summarized in **Table 2.** All patients experienced at least one adverse event but all were either mild (57%) or moderate (43%) in intensity. The most common treatment-emergent adverse events were related to the injection site and included pruritus, erythema, induration and bruising. In most cases, these reactions were either self-limited or amenable to local treatment. Only one participant discontinued study drug due to intolerance to injection-site reaction. There were no deaths in the study, and there was one treatment emergent serious adverse event (urinary calculus), which was of moderate intensity, was not considered related to study drug, and resolved with full recovery of the participant. Eight participants experienced an adverse event in the study eye (two participants each experienced two adverse events): one participant had conversion to neovascular AMD and retinal hemorrhage, one participant had mild intraretinal hemorrhage; one participant had reduced visual acuity and visual impairment; one participant had borderline glaucoma, one participant had eyelid pruritis, one participant had meibomian gland dysfunction, one participant had posterior capsular opacification, and one

participant had punctate keratopathy. Of the two participants who experienced retinal hemorrhage in the study eye, the first was a mild intraretinal hemorrhage outside the arcades which was not consistent with choroidal neovascularization (CNV), diabetes, or retinal vein occlusion and which was attributed to the patient's longstanding hypertension. This was not considered related to study drug. The second participant with intraretinal hemorrhage was concurrently diagnosed with new CNV due to neovascular AMD at the final week 28 study visit (4 weeks after having stopped study drug per protocol). This individual subsequently received intravitreal anti-VEGF therapy as part of standard of care. Risk factors for the development of neovascular AMD in this participant included large drusen and pigmentary changes in the study eye and prior diagnosis of neovascular AMD in the fellow eye. This was similarly not considered related to study drug.

As noted above, one participant experienced two ocular AEs of reduced visual acuity and visual impairment in the study eye at the week 12 study visit. In this individual, measures of visual function were stable through the week 8 study visit. At week 12, some visual function measures were decreased compared to baseline while others were stable or improved compared to baseline (-17 letters BCVA; -8 letters LLVA; NLRA was unchanged at 0.1 logMAR and LLRA was improved by +0.3 logMAR). There was no change in clinical exam or imaging. The participant voluntarily decided to withdraw from the study at the week 12 visit. At this participant's standard of care follow up visit one month later, BCVA had recovered to baseline. These AEs were considered mild and possibly related to study drug. Among other study eye AEs, one was considered moderate in intensity (punctate keratopathy), and all others were mild in intensity.

Eight participants reported an ocular AE in the nonstudy eye. Six of these were considered mild in intensity and two were considered of moderate intensity. Two AEs, reduced visual acuity and

visual impairment, occurred in the same participant who experienced these AEs in the study eye and were considered mild in intensity and possibly related to study drug.

Exploratory Efficacy Endpoints

Mean (SD) BCVA at baseline was 79.4 (7.4) letters compared to 82.0 (6.9) at week 24. Effects of the study drug on standard luminance BCVA are summarized in **Figure 1.** Among study participants completing the 24-week treatment period, improvement in BCVA compared to baseline were evident by week 4 which was maintained throughout the study period with mean increase of 3.6 (6.4) letters at week 24 (P=0.014, Holm method threshold for statistical significance P <0.05) (**Figure 1A**). Scatterplot and categorical analyses showed that 14 of 18 patients experienced an increase in BCVA, 5 of 18 (26.3%) had a greater than 5-letter improvement in BCVA, 2 of 18 (10.5%) had a greater than 10-letter increase and 1 of 18 (5.3%) had a greater than 15-letter increase in BCVA. (**Figure 1B, 1C**). No participants had a greater than 5-letter decrease in BCVA.

Mean (SD) LLVA at baseline was 63.8 (10.0) letters compared to 68.4 (11.5) at week 24. Effects of the study drug on LLVA are summarized in **Figure 2**. Among study participants completing the 24-week treatment period, improved LLVA was noted at all time points with mean increase of 5.6 (7.8) letters at week 24 (P=0.004, Holm method threshold for statistical significance P <0.025) (**Figure 2A**). Nine of 18 participants (50%) had greater than 5-letter improvement, 3 of 18 (16.7%) had greater than 10-letter improvement and 2 of 18 (11.1%) had greater than 15-letter increase in LLVA. One participant had a decline of > 5 letters in LLVA. (**Figure 2B, 2C**).

Mean (SD) NLRA at baseline was logMAR 0.01 (0.18) compared to -0.08 (0.186) at week 24, with mean increase of -0.11 ± 0.15 (P=0.001, Holm method threshold for statistical significance

P <0.0167), equivalent to an approximately 1-line gain in NLRA **(Figure 3)**. Improvement in NLRA was evident by week 4 and was maintained at weeks 8 through 24. Mean (SD) LLRA was logMAR 0.39 (0.23) at baseline compared to 0.11 (0.21) at week 24, a mean increase of -0.28 (0.17) (*P*<0.0001, Holm method threshold for statistical significance *P* <0.0125), equivalent to an approximately 3-line gain in LLRA **(Figure 4)**. Improvement in LLRA was evident by week 4 and was maintained at weeks 8 through 24.

For the low luminance questionnaire (LLQ), subscale scores at week 24 as well as change in subscale scale at week 24 from baseline are included in **Table 3**. Using Holm method thresholds for statistical significance to correct for multiple comparisons of subscales on the LLQ, mean changes from baseline were statistically significant in 6 of 7 parameters (dim light reading; driving or riding in car; general dim light vision; light transitions and glare; other activities of daily living; peripheral vision) at Week 24.

Examination of anatomic changes was performed by segmentation of RPE-DC volume on OCT. Mean RPE-DC volume did not change significantly in any of the 9 fields of the ETDRS grid nor globally across the macula from baseline at Week 24. FAF was assessed at 24 weeks as compared to baseline, and no appreciable change in hyperautofluorescence signal, and no appreciable development of new hypoautofluorescence indicating GA was observed at Week 24.

To assess potential alterations in retinal sensitivity, mesopic microperimetry was performed. The mean 95% bicurve ellipse area (BCEA) was 8.06 log square minutes of arc at baseline and this parameter did not change significantly from baseline at Week 24 (mean 1.47-log square minutes of arc decrease; P=0.1901). There was no significant change in the mean threshold for reduced retinal sensitivity, nor in the number of loci with reduced retinal sensitivity as defined by <25dB

or <14dB below normal values. The utility of this endpoint was further limited by problematic test-retest variability present in nearly all participants.

Dark adaptometry was performed to assess recovery of dim light vision following bright light stress. In the HRD cohort, results were limited by the fact that no patient could recover from 100% bleach within 20 minutes. Participants had a mean (SD) dark adaptation time at a 75% bleach level of 7.121 (5.6128) minutes at the baseline visit, and this parameter did not change significantly from baseline at Week 24.

Discussion

Along the spectrum of AMD, the most profound vision loss occurs in patients experiencing central vision loss due to GA or due to inadequately treated or advanced neovascular AMD, and this effect is evident by best-corrected visual acuity (BCVA) under standard luminance conditions, the most frequently used measure of assessing visual function. However, BCVA generally has poor sensitivity to detect visual dysfunction in HRD patients since these patients frequently retain preserved central visual acuity under standard lighting conditions .[47] Instead, patients with HRD suffer from debilitating visual impairment in low-light conditions, which can have profound effects on nighttime activities and also increase risk of nighttime falls and injury.[4,7,8] Thus, measures of visual function in dim lighting conditions (e.g., low luminance visual acuity (LLVA)) appear to be more useful for characterization of visual difficulties in patients with intermediate AMD and HRD.[47,51]

Decreased low luminance visual acuity may be associated with impaired short-wavelength cone function and reduced retinal sensitivity that are evident in early and intermediate AMD disease.[47,51] Nevertheless, the mechanism(s) for low luminance visual impairment in AMD are

poorly understood, which has limited the development of therapies to treat visual dysfunction in affected patients. The results of the present study suggest that mitochondrial dysfunction, likely at the RPE and/or the neurosensory retina, is a major mediator of low luminance vision impairment, and that drugs targeting mitochondrial dysfunction may be effective to improve low luminance visual function.

Elamipretide is a small tetrapeptide drug which has been shown to prevent or reverse mitochondrial dysfunction in a number of preclinical models.[43,52,53] Elamipretide localizes to mitochondria where its reversibly binds to cardiolipin, a unique phospholipid localized to the hairpin turn of mitochondrial cristae where it is required for normal morphology of the cristae and the electron transport complex.[44,45,53,54] Elamipretide has been shown to bind cardiolipin in dysfunctional mitochondria and restore normal ATP generation, respiration and reactive oxygen species generation.[44,45,53,54] Elamipretide has been studied in multiple preclinical models relevant to AMD where it has been shown to ameliorate mitochondrial dysfunction in RPE.[36,43] Specifically, elamipretide has been shown to prevent mitochondrial dysfunction and improve mitochondrial respiration in cultured RPE cells isolated from AMD donor eyes. Finally, elamipretide was found to reverse morphologic, biochemical and functional signs of AMD pathobiology in the ApoE4 mouse model of AMD,[36] including regression of subRPE deposits, improved mitochondrial morphology, and restoration of ERG amplitudes, all of which provided compelling support for the current clinical trial.[36]

The current study demonstrates that subcutaneous daily elamipretide is generally well tolerated in patients with AMD with the majority of adverse events related to local injection site reactions. These events were all mild to moderate in severity and only one participant discontinued study drug due to injection site reaction. There was one serious AE (urinary calculus) which was not

related to study drug. Ocular AEs were all of mild or moderate intensity and only two ocular AEs in the study eye were considered possibly related to study drug, reduced visual acuity (n=1) and visual impairment (n=1), both of which occurred in the same participant. Overall, the safety profile of elamipretide was comparable to that previously observed in other clinical trials of elamipretide.[55,56]

Exploratory efficacy endpoints suggest that elamipretide may have a positive benefit on visual function in intermediate AMD with HRD. While pharmacokinetics (PK) samples were not collected and analyzed in this study, the PK profile of elamipretide has been extensively characterized in other clinical trials (data on file, Stealth BioTherapeutics).[57] In rabbit PK studies, subcutaneous dosing of elamipretide (1 mg / kg) produced measurable drug levels at the choroid, RPE, and retina at C_{max} (30 min). The measured concentrations are expected to be therapeutic, based on the exposure-response data from the mouse model of HQ-induced oxidative injury (data on file, Stealth BioTherapeutics).

Small but statistically significant improvements in both BCVA and NLRA were observed in participants with HRD. These gains may have been limited by a ceiling effect due to very good normal light visual function at baseline in this cohort. Larger and statistically significant gains were noted in low luminance visual function endpoints (LLVA and LLRA). Gains in visual function evident as early as day 7, increased further by week 4 and were maintained across the study period for all visual function endpoints. Additionally, significant improvements were noted in 6 out of the 7 subscales of the LLQ at week 24, consistent with the observed improvements in visual acuity endpoints.

The current study is limited by small sample size and the fact that it was an open-label study without placebo control. In addition, the improvements in BCVA and LLVA may have been influenced by a highly responsive subset of participants with a substantially greater benefit. There were not statistically significant improvements in drusen volume (RPE-DC on OCT), dark adaptometry, or mesopic microperimetry. Thus, improvements in the exploratory visual endpoints must be interpreted with caution. Nevertheless, elamipretide showed good feasibility, safety and tolerability in participants with intermediate AMD and HRD. The natural history AMD is one of progressive vision loss in affected patients, with a high prevalence of low luminance visual dysfunction in intermediate AMD with HRD.[7,58] There is a relative lack of clinical trials targeting the HRD stage of AMD compared to more advanced stages of the disease. Given the encouraging safety profile and findings in some exploratory endpoints, a future study of elamipretide in HRD patients is strongly justified.

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Figure Legends

Figure 1. Effects of elamipretide on best-corrected visual acuity (BCVA). (A) Mean change in BCVA (ETDRS letters) from Baseline (Day 0) over 24-week active study period; bars indicate standard deviation (SD). * (P=0.014, Holm method threshold for statistical significance P <0.05). (B) Scatterplot for change in BCVA (ETDRS letters) from Baseline at week 24. Horizontal solid line: mean value; vertical dashed line: SD. (C) Percentage of study participants by categorical change in BCVA (ETDRS letters) from Baseline at week 24.

Figure 2. Effects of elamipretide on low luminance best-corrected visual acuity (LLVA). (A) Mean change in LLVA (ETDRS letters) from Baseline (Day 0) over 24-week active study period; bars indicate standard deviation (SD). * (P=0.004, Holm method threshold for statistical significance P <0.025). (B) Scatterplot for change in LLVA (ETDRS letters) from Baseline at week 24. Horizontal solid line: mean value; vertical dashed line: SD. (C) Percentage of study participants by categorical change in LLVA (ETDRS letters) from Baseline at week 24.

Figure 3. Effects of elamipretide on normal luminance reading acuity (NLRA). Mean change in NLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate standard deviation (SD). * (P=0.001, Holm method threshold for statistical significance P <0.0167). (B) Scatterplot for change in NLRA (logMAR) from Baseline at week 24. Horizontal solid line: mean value; vertical dashed line: SD.

610 **Figure 4.** Effects of elamipretide on low luminance reading acuity (LLRA). Mean change in
611 LLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate
612 standard deviation (SD). * (P<0.0001, Holm method threshold for statistical significance P
613 <0.0125). (B) Scatterplot for change in LLRA (logMAR) from Baseline at week 24. Horizontal
614 solid line: mean value; vertical dashed line: SD.

Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well tolerated in patients with intermediate age-related macular degeneration and high-risk drusen, with positive effect on visual function, particularly under low luminance conditions.

Tables and Figure Legends

Table 1. Characteristics of participants in the high-risk drusen study cohort

Characteristic	N=21
Age, mean (SD) (range)	70.9 (8.5) (59, 87)
Sex, n (%)	
Female	13 (61.9)
Male	8 (38.1)
Ethnicity, n (%)	
Hispanic/Latino	1 (4.8)
Caucasian	20 (95.2)
Former smoker*, n (%)	8 (38.1)
Baseline BCVA, mean (SD)	79.4 (7.4)
Baseline LLVA, mean (SD)	63.8 (10.0)

*Former smoker; no participants were current smokers

SD= standard deviation; BCVA= best-corrected visual acuity; LLVA= low luminance visual acuity

Table 2. Adverse events (AEs)* in patients with high-risk drusen

Event	N=21
All Treatment-emergent events, n (%)	
Any treatment-emergent AE	21 (100)
Injection site reactions	
Pruritis	21 (100)
Erythema	16 (76.2)
Induration	16 (76.2)
Bruising	16 (76.2)
Pain	9 (42.9)
Hemorrhage	6 (28.6)
Urticaria	5 (23.8)
Upper respiratory tract infection	7 (33.3)
Headache	2 (9.5)
Myalgia	2 (9.5)
Increased intraocular pressure	2 (9.5)
Procedural nausea	2 (9.5)
Seasonal allergy	2 (9.5)
AE by maximum intensity	
Mild	11 (52.4)
Moderate	10 (47.6)
Related to study drug	21 (100)
AE leading to study drug discontinuation	1 (4.8)
Any serious systemic AE	1 (4.8)
Urinary Calculus	1 (4.8)

All treatment-emergent ocular events in the study eye, n (%)	
Any treatment-emergent AE	10*
Eye disorders	
Retinal hemorrhage	2 (9.5)
Borderline glaucoma	1 (4.8)
Eyelid pruritis	1 (4.8)
Meibomian gland dysfunction	1 (4.8)
Neovascular age-related macular degeneration	1 (4.8)
Posterior capsular opacification	1 (4.8)
Punctate keratitis	1 (4.8)
Visual acuity reduced	1 (4.8)
Visual impairment	1 (4.8)
AE by maximum intensity	
Mild	9 (42.8)
Moderate	1 (4.8)
Possibly related to study drug	2 (9.5)
Visual acuity reduced	1 (4.8)
Visual impairment	1 (4.8)
AE leading to study drug discontinuation by investigator	0
Any serious AE	0

* There were 10 total ocular AEs in 8 participants; two participants each experienced two AEs during the study (one participant experienced reduced visual acuity and visual impairment; one participant experienced neovascular AMD and retinal hemorrhage).

Table 3. Low Luminance Questionnaire Scores at Week 24

Subscale Score	**Observed Score at Week 24**						**Change from Baseline at Week 24**							
	n	Mean	SD	Median	Minimum	Maximum	n	Mean	SD	Median	Minimum	Maximum	*P* value	Holm threshold
Dim light reading	18	58.9	20.34	56.3	31.3	87.5	18	15.8	14.34	12.5	-6.3	43.8	**0.0001**	0.0083
Driving or riding in car	18	63.5	26.54	68.8	25.0	100.0	18	16.4	18.77	12.5	-12.5	75.0	**0.0013**	0.025
General dim light vision	18	71.1	22.09	75.0	34.4	100.0	18	15.6	15.17	12.5	-6.3	56.3	**0.0003**	0.010
Light transitions and glare	18	62.6	21.69	65.0	25.0	95.0	18	17.4	13.98	15.0	-5.0	45.0	**<0.0001**	0.0071
Mobility	18	74.6	21.60	83.3	41.7	100.0	18	9.6	20.27	8.3	-16.7	66.7	0.0526	0.05
Other ADLs	18	76.3	21.00	81.3	37.5	100.0	18	17.8	17.95	12.5	-6.3	68.8	**0.0004**	0.012
Peripheral vision	18	74.3	27.79	75.0	25.0	100.0	18	17.8	20.12	12.5	-12.5	50.0	**0.0012**	0.017

SD= standard deviation; ADLs= activities of daily living