



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

ReCLAIM High-Risk Drusen Study

Michael J. Allingham, MD, PhD, Priyatham S. Mettu, MD, Scott W. Cousins, MD

Purpose: To assess safety, tolerability, and feasibility of subcutaneous administration of the 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 ≥ 55 years of age 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 OCT, fundus autofluorescence (FAF), mesopic microperimetry, dark adaptation, and low-luminance questionnaire (LLQ).

Main Outcome Measures: The primary end point was safety and tolerability. Prespecified exploratory end points included changes from baseline in BCVA, LLVA, NLRA, LLRA, retinal pigment epithelium (RPE)-drusen complex (DC) volume by OCT, FAF, mesopic microperimetry, dark adaptation, and LLQ results.

Results: Subcutaneous administration of elamipretide was highly feasible. All participants with HRD ($n = 21$) experienced 1 or more adverse events (AEs), but all were mild (57%) or moderate (43%), with the most common events related to injection site reactions. No serious systemic AEs occurred. One participant discontinued because of injection site reaction, 1 participant withdrew because they did not wish to continue study visits, and 1 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 with baseline, mean NLRA improved by -0.11 logarithm of the minimum angle of resolution (logMAR) units ($P = 0.001$), and LLRA by -0.28 logMAR units ($P < 0.0001$). Significant improvements were found in 6 of 7 subscales of the LLQ ($P < 0.0015$). No significant changes were observed for RPE-DC volume, FAF, mesopic microperimetry, or dark adaptation.

Conclusions: Elamipretide appeared to be generally safe and well tolerated in treating 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. *Ophthalmology Science* 2022;2:100095 © 2022 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.ophtalmologyscience.org

Age-related macular degeneration (AMD) is the leading cause of vision loss in individuals 65 years of age and older,¹ with an expected increase in prevalence to 10% among those 50 years of age and older by the year 2050.^{1,2} Severe vision loss occurs among patients in whom advanced dry AMD with central (i.e., foveal center-involving) geographic atrophy (GA) develops and those patients with untreated or undertreated neovascular AMD.² Although decreased vision in the setting of intermediate

AMD and high-risk drusen (HRD) can occur in the setting of confluent, large drusen within the macula, most patients with HRD retain preserved central visual acuity. However, a significant number of patients with HRD do experience difficulties with activities of daily living, despite preserved best-corrected visual acuity (BCVA).³⁻⁷ Specifically, between 30% and 50% of patients with HRD 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} Although some evidence suggests that supplements targeting enhancement of macular pigment may offer modest visual benefits,^{11,12} these remain exploratory. Thus, despite the progressive nature of AMD and associated visual dysfunction, there are currently no therapeutic agents approved that can improve vision (standard or low luminance) or that can alter the progression of AMD, in part because the 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 represent major mechanisms of disease, particularly at the retinal pigment epithelium (RPE).^{19,23,32–36} In histopathologic 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 increase progressively with more advanced stages of disease.^{19,32,37} Further, other accepted risk factors for AMD developing—including cigarette smoking, complement dysregulation, and lipofuscin accumulation within RPE (although 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 in support of certain energy-intensive cell functions. However, mitochondria also play roles in regulation of calcium signaling, reactive oxygen species generation, and key metabolic pathways such as glutamate recycling.^{39–41} Thus, although the specific mechanisms by which dysfunctional mitochondria mediate AMD pathobiology are not known, disrupted cellular bioenergetics, increased reactive oxygen species production, loss of other mitochondrial functions, or a combination thereof 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 adenosine triphosphate 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 the 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 2 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 HRD without GA. The present report details the findings of the HRD cohort; results of the NCGA cohort are included in a separate report.

Methods

Study Design

This was a phase 1, single-center, 24-week, open-label clinical trial ([ClinicalTrials.gov](https://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). After informed consent and study enrollment, prospective participants underwent a screening assessment (≤ 14 days before the baseline visit) to verify study eligibility, which included physical and ophthalmic examination, measurement of ETDRS scale BCVA under normal-luminance (i.e., standard light) and low-luminance conditions, spectral-domain OCT, fundus autofluorescence (FAF), fluorescein angiography, and administration of a low-luminance questionnaire (LLQ; adapted from Owsley, et al⁸; see [Supplemental Materials 1](#)).

Participants

A detailed list of eligibility criteria is included in [Supplemental Materials 2](#). Key inclusion and exclusion criteria are summarized below.

Inclusion Criteria. Men and nonpregnant or nursing women 55 years of age or older with 1 eye with intermediate AMD with high-risk drusen without GA were eligible. High-risk drusen were defined as the presence of either at least 1 large ($\geq 125 \mu\text{m}$) drusen or multiple medium (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 of 55 ETDRS letters or more (i.e., Snellen equivalent, $\geq 20/70$); (3) low-luminance visual acuity (LLVA) deficit of more than 5 letters, wherein the LLVA deficit is defined as the difference between BCVA and LLVA; and (4) at least 2 LLQ abnormal subscale scores indicating impairment, wherein 1 of the abnormal subscales is either general dim-light vision or dim-light reading (wherein abnormal subscale was defined as $\geq 50\%$ 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 LLVA 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 resulting from causes other than AMD. Additional macular or retinal exclusion criteria in the study eye included: presence of diabetic retinopathy, macular pathologic features (i.e., hole, pucker), history of retinal detachment, and presence of vitreous hemorrhage. Nonmacular exclusion criteria in the study eye included: uncontrolled glaucoma; advanced guttae indicative of Fuchs endothelial dystrophy; visually significant cataract; or 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-vascular endothelial growth factor] 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, vitritis, or both; history of uveitis; and 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 of < 30 ml/minute were excluded from study participation.

Study Drug and Evaluations

The study drug elamipretide was administered as a 40-mg (1-ml) subcutaneous injection in the abdominal area once daily for 24 weeks, beginning at baseline. The 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 was 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 (AEs) 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, although only 1 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 BCVA (ETDRS letter score) under normal luminance (BCVA) and low luminance (LLVA) were performed at screening and baseline, during the active treatment period (weeks 1, 4, 8, 12, 16, 20, and 24), and at follow-up (week 28). Best-corrected visual acuity 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-luminance binocular reading acuity (NLRA) and low-luminance binocular reading acuity (LLRA) were measured at baseline, during study treatment (weeks 4, 8, 12, 16, 20, and 24), and at follow-up (week 28). Assessment of NLRA was carried out 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 method⁴⁶ 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 or fewer mistakes within 30 seconds. This approach was undertaken to optimize test-retest consistency and to reduce subjectivity related to assessment of reading error measurements. The MNREAD reading chart comprises 19 distinct font sizes ranging from -0.5 logarithm of the minimum angle of resolution (logMAR; smallest font size; Snellen equivalent, 20/6) to 1.3 logMAR (largest font size; Snellen equivalent, 20/400), with a total range in values of 1.9 logMAR.

Low-luminance binocular reading acuity was performed in the same fashion as NLRA, with MNREAD 1-W, 2-W, and 3-W charts rotated among 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 (range, -0.5 to 1.3 logMAR), with 1 word or fewer mistakes within 30 seconds.

Additional tests including mesopic microperimetry, dark adaptometry, FAF, and spectral-domain OCT were performed at baseline; weeks 4, 8, 12, 16, 20, and 24; and follow-up (week 28). Mesopic microperimetry (MAIA microperimeter; iCare) was performed as previously described.⁴⁷ The mean 95% bicurve ellipse area, the mean threshold for reduced retinal sensitivity, and the number of loci with reduced retinal sensitivity as defined by < 25 dB or < 14 dB less than 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 obtained at baseline and week 24. Segmentation of spectral-domain OCT images was used to quantify the RPE-drusen complex (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 images was performed by masked graders.

The LLQ (adapted from Owsley et al⁵; see [Supplemental Material 1](#)) was administered at baseline as described and was repeated at weeks 12 and 24 and at follow-up (week 28). The 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. The 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 reflects the lowest functional level; the mean value was determined for the applicable items comprising each subscale.

End Points

The primary study end point was safety and tolerability as assessed by the incidence and severity of AEs and changes from baseline in vital sign measurements, electrocardiograms, clinical assessments, and clinical laboratory evaluations. Assessment of AEs was performed at each study visit and included both investigator-assessed and participant-reported events. Exploratory efficacy end points reported in the present study include changes from baseline in BCVA, LLVA, NLRA, and LLRA; OCT (to determine changes in RPE-DC) volume; FAF; and LLQ score. Mesopic microperimetry and dark adaptometry were performed to assess retinal sensitivity and recovery of dim light vision after 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 numbers. Safety and efficacy variables are summarized descriptively. All participants who received 1 dose or more of study drug were included in assessment of safety as part of the intention-to-treat analysis. Exploratory efficacy end points were assessed in participants who completed the 24-week treatment period. All statistical analyses and reporting were performed using SAS System software version 9.4 (SAS Institute). Continuous variables analyzed in this study were summarized by the number of nonmissing observations and mean, standard deviation (SD), median, minimum, and maximum values. For each continuous variable, statistical analysis of mean change from baseline value was assessed by a 1-sample *t* test and signed-rank test for parametric and nonparametric 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 4 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 4 metrics; $P < 0.0167$ for the second lowest *P* value among the 4 metrics; $P < 0.025$ for the next to highest *P* value among the 4 metrics; and $P < 0.05$ for the highest *P* value among the 4 metrics.⁵⁰

Results

Study Participants

A total of 21 participants were included in the high-risk drusen cohort (Table 1). Most were women (13/21), the mean age was 71 years, and most (20/21) were White. One participant had large drusen, pigment, and reticular

Table 1. Characteristics of Participants in the High-Risk Drusen Study Cohort (n = 21)

Characteristic	Data
Age (yrs)	
Mean \pm SD	70.9 \pm 8.5
Range	59–87
Sex	
Female	13 (61.9)
Male	8 (38.1)
Ethnicity	
Hispanic/Latino	1 (4.8)
White	20 (95.2)
Former smoker*	8 (38.1)
Baseline BCVA	79.4 \pm 7.4
Baseline LLVA	63.8 \pm 10.0

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

Data are presented as no. (%) or mean \pm SD, unless otherwise indicated.

*No participants were current smokers.

pseudodrusen; 1 participant had medium drusen, pigment, and reticular pseudodrusen; 5 participants had large drusen and pigment; 2 participants had medium drusen and pigment; 4 participants had large drusen and reticular pseudodrusen; 1 participant had large drusen and subretinal hyperreflective material; 1 participant had medium drusen and subretinal hyperreflective material; 5 participants had large drusen; and 1 participant 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) because of intolerable injection site reaction, 1 participant withdrew from the study (at week 12) because they did not wish to continue with study visits, and 1 participant withdrew after experiencing transient visual impairment (after week 12). Mean \pm SD baseline BCVA and LLVA values were 79.4 \pm 7.4 and 63.8 \pm 10.0, respectively.

Feasibility and Compliance

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

Safety and Tolerability

Adverse events are summarized in Table 2. All patients experienced at least 1 AE, but all were either mild (57%) or moderate (43%) in intensity. The most common treatment-emergent AEs 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 1 participant discontinued study drug because of intolerance

Table 2. Adverse Events* in Patients with High-Risk Drusen (n = 21)

Event	No. (%)
All treatment-emergent AEs	
Any treatment-emergent AE	21 (100)
Injection site reactions	
Pruritus	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 AEs in the study eye	
Any treatment-emergent AE	10*
Eye disorders	
Retinal hemorrhage	2 (9.5)
Borderline glaucoma	1 (4.8)
Eyelid pruritus	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

AE = adverse event.

*Ten total ocular AEs occurred in 8 participants; 2 participants each experienced 2 AEs during the study (1 participant experienced reduced visual acuity and visual impairment; 1 participant experienced neovascular age-related macular degeneration and retinal hemorrhage).

to injection site reaction. No deaths occurred in the study, and 1 treatment-emergent serious AE (urinary calculus) occurred that was of moderate intensity, was not considered related to the study drug, and resolved with full recovery of the participant. Eight participants experienced an AE in the study eye (2 participants each experienced 2 AEs): 1 participant showed conversion to neovascular

AMD and retinal hemorrhage, 1 participant showed mild intraretinal hemorrhage, 1 participant showed reduced visual acuity and visual impairment, 1 participant showed borderline glaucoma, 1 participant showed eyelid pruritus, 1 participant showed meibomian gland dysfunction, 1 participant showed posterior capsular opacification, and 1 participant showed punctate keratopathy. Of the 2 participants who experienced retinal hemorrhage in the study eye, the first was a mild intraretinal hemorrhage outside the arcades that was not consistent with choroidal neovascularization, diabetes, or retinal vein occlusion and that was attributed to longstanding hypertension. This was not considered related to the study drug. The second participant with intraretinal hemorrhage was diagnosed concurrently with new choroidal neovascularization resulting from neovascular AMD at the final week 28 study visit (4 weeks after having stopped study drug per protocol). This individual subsequently received intravitreal anti-vascular endothelial growth factor 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. Similarly, this was not considered related to the study drug.

As noted above, 1 participant experienced 2 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 with baseline, whereas others were stable or improved compared with baseline (−17 letters BCVA, −8 letters LLVA, NLRA was unchanged at 0.1 logMAR, and LLRA was improved by +0.3 logMAR). No change in clinical examination or imaging findings was found. The participant voluntarily decided to withdraw from the study at the week 12 visit. At this participant's standard-of-care follow-up visit 1 month later, BCVA had recovered to baseline. These AEs were considered mild and possibly related to the 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 2 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 these were considered mild in intensity and possibly related to the study drug.

Exploratory Efficacy End Points

Mean ± SD BCVA at baseline was 79.4 ± 7.4 letters compared with 82.0 ± 6.9 letters 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 with baseline were evident by week 4, which was maintained

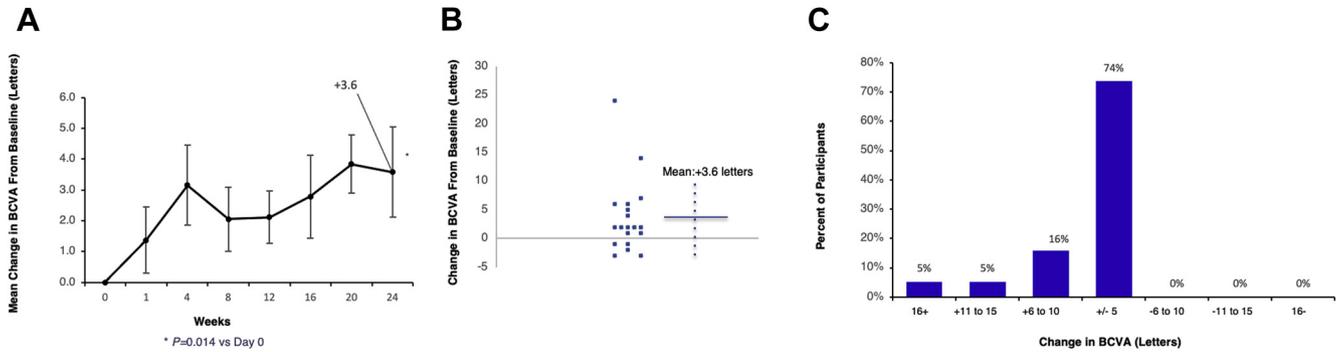


Figure 1. Effects of elamipretide on best-corrected visual acuity (BCVA). **A**, Line graph showing the mean change in BCVA (ETDRS letters) from baseline (day 0) over the 24-week active study period. Bars indicate standard deviation (SD). * $P = 0.014$, Holm method threshold for statistical significance of $P < 0.05$. **B**, Scatterplot showing change in BCVA (ETDRS letters) from baseline at week 24. Horizontal solid line indicates mean value; vertical dashed line indicates SD. **C**, Bar graph showing the percentage of study participants by categorical change in BCVA (ETDRS letters) from baseline at week 24.

throughout the study period with a mean increase of 3.6 ± 6.4 letters at week 24 ($P = 0.014$, Holm method threshold for statistical significance of $P < 0.05$; Fig 1A). Scatterplot and categorical analyses showed that 14 of 18 patients experienced an increase in BCVA, 5 of 18 patients (26.3%) achieved a more than 5-letter improvement in BCVA, 2 of 18 patients (10.5%) achieved a more than 10-letter increase in BCVA, and 1 of 18 patients (5.3%) achieved a more than 15-letter increase in BCVA (Fig 1B, C). No participants showed a more than 5-letter decrease in BCVA.

Mean \pm SD LLVA at baseline was 63.8 ± 10.0 letters compared with 68.4 ± 11.5 letters 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 a mean increase of 5.6 ± 7.8 letters at week 24 ($P = 0.004$, Holm method threshold for statistical significance of $P < 0.025$; Fig 2A). Nine of 18 participants (50%) achieved a more than 5-letter improvement, 3 of 18 participants (16.7%) achieved a more than 10-letter improvement, and 2

of 18 participants (11.1%) achieved a more than 15-letter increase in LLVA. One participant showed a decline of more than 5 letters in LLVA (Fig 2B, C).

Mean \pm SD NLRA at baseline was 0.01 ± 0.18 logMAR compared with -0.08 ± 0.186 logMAR at week 24, with mean increase of -0.11 ± 0.15 logMAR ($P = 0.001$, Holm method threshold for statistical significance of $P < 0.0167$), equivalent to an approximately 1-line gain in NLRA (Fig 3). Improvement in NLRA was evident by week 4 and was maintained at weeks 8 through 24. Mean \pm SD LLRA was 0.39 ± 0.23 logMAR at baseline compared with 0.11 ± 0.21 logMAR at week 24, a mean increase of -0.28 ± 0.17 logMAR ($P < 0.0001$, Holm method threshold for statistical significance of $P < 0.0125$), equivalent to an approximately 3-line gain in LLRA (Fig 4). Improvement in LLRA was evident by week 4 and was maintained at weeks 8 through 24.

For the LLQ, subscale scores at week 24 as well as change in subscale score at week 24 from baseline are included in Table 3. Using Holm method thresholds for statistical significance to correct for multiple comparisons

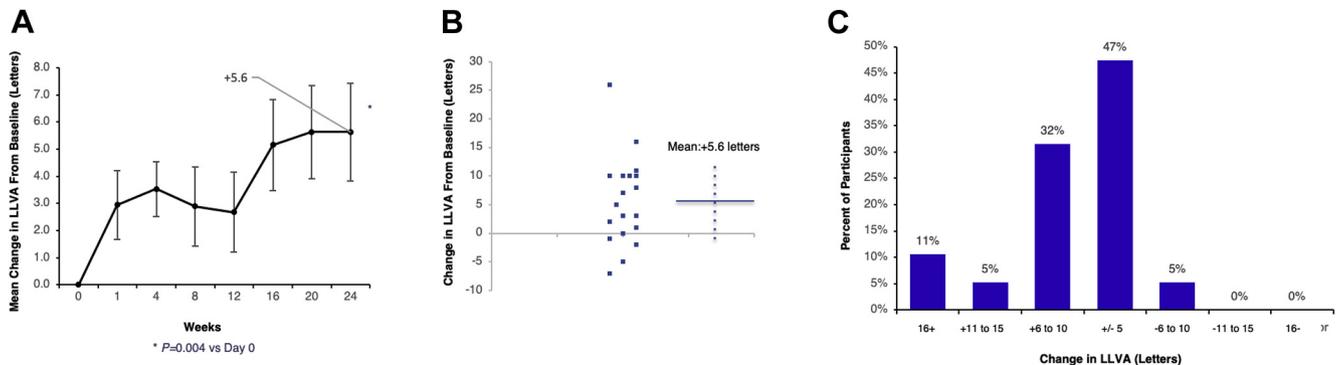


Figure 2. Effects of elamipretide on low-luminance best-corrected visual acuity (LLVA). **A**, Line graph showing the mean change in LLVA (ETDRS letters) from baseline (day 0) over the 24-week active study period. Bars indicate standard deviation (SD). * $P = 0.004$, Holm method threshold for statistical significance of $P < 0.025$. **B**, Scatterplot showing the change in LLVA (ETDRS letters) from baseline at week 24. Horizontal solid line indicates mean value; vertical dashed line indicates SD. **C**, Bar graph showing the percentage of study participants by categorical change in LLVA (ETDRS letters) from baseline at week 24.

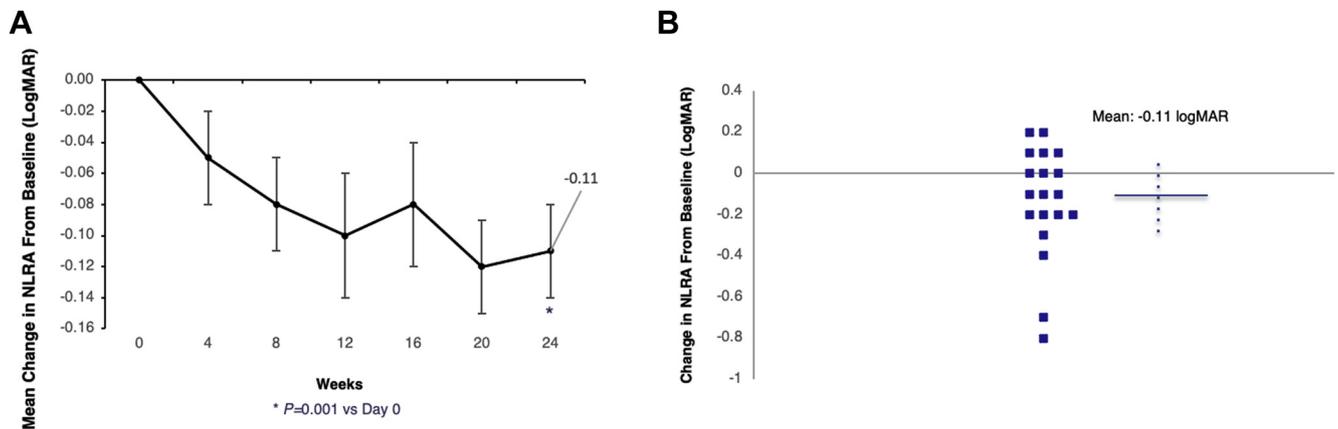


Figure 3. Effects of elamipretide on normal luminance reading acuity (NLRA). **A**, Line graph showing the mean change in NLRA (logarithm of the minimum angle of resolution [logMAR]) from baseline (day 0) over the 24-week active study period. Bars indicate standard deviation (SD). * $P = 0.001$, Holm method threshold for statistical significance of $P < 0.0167$. **B**, Scatterplot showing change in NLRA (logMAR) from baseline at week 24. Horizontal solid line indicates mean value; vertical dashed line indicates SD.

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, and 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. Fundus autofluorescence images were assessed at 24 weeks as compared with baseline, and no appreciable change in hyperautofluorescence signal and no appreciable development of new hypoautofluorescence indicating GA were observed at week 24.

To assess potential alterations in retinal sensitivity, mesopic microperimetry was performed. The mean 95% bicurve ellipse area 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; $P = 0.1901$). No significant change was found in the mean

threshold for reduced retinal sensitivity, nor in the number of loci with reduced retinal sensitivity as defined by < 25 dB or < 14 dB less than normal values. The usefulness 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 showed a mean \pm 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 to week 24.

Discussion

Along the spectrum of AMD, the most profound vision loss occurs in patients experiencing central vision loss resulting from GA or from inadequately treated or advanced neovascular AMD, and this effect is evident by BCVA under

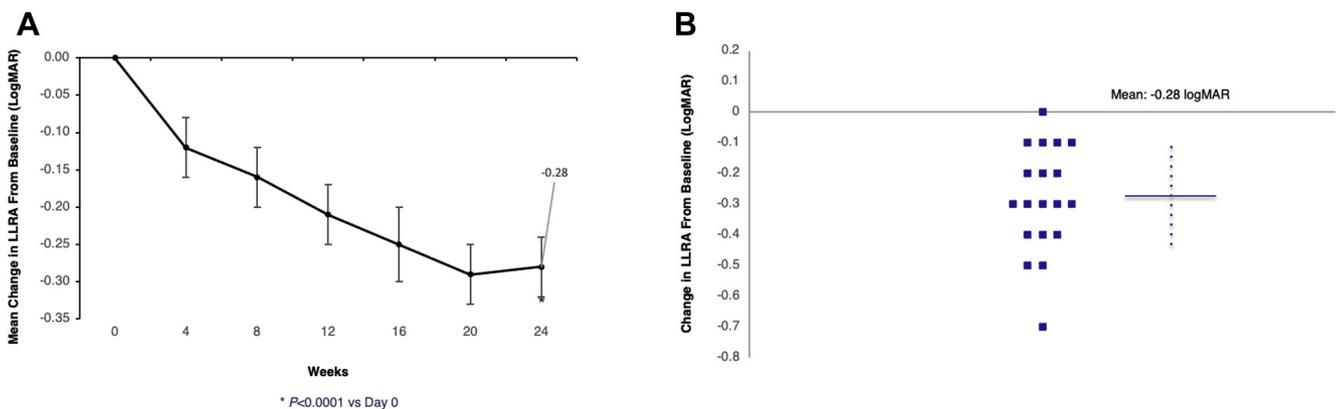


Figure 4. Effects of elamipretide on low luminance reading acuity (LLRA). **A**, Line graph showing the mean change in LLRA (logarithm of the minimum angle of resolution [logMAR]) from baseline (day 0) over the 24-week active study period. Bars indicate standard deviation (SD). * $P < 0.0001$, Holm method threshold for statistical significance of $P < 0.0125$. **B**, Scatterplot showing change in LLRA (logMAR) from baseline at week 24. Horizontal solid line indicates mean value; vertical dashed line indicates SD.

Table 3. Low-Luminance Questionnaire Scores at Week 24

Subscale Score	Observed Score at Week 24					Change from Baseline at Week 24					P Value	Holm Threshold		
	No.	Mean	Standard Deviation	Median	Minimum	Maximum	No.	Mean	Standard Deviation	Median			Minimum	Maximum
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

ADL = activity of daily living.
*Denotes statistical significance

standard luminance conditions, the most frequently used measure of assessing visual function. However, BCVA generally has poor sensitivity to detect visual dysfunction in patients with HRD because these patients frequently retain preserved central visual acuity under standard lighting conditions.⁴⁷ Instead, patients with HRD experience debilitating visual impairment in low-light conditions, which can have profound effects on nighttime activities and can also increase the risk of nighttime falls and injury.^{4,7,8} Thus, measures of visual function in dim lighting conditions (e.g., LLVA) seem to be more useful for characterization of visual difficulties in patients with intermediate AMD and HRD.^{47,51}

Decreased LLVA 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 or the neurosensory retina, or both, 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 that has been shown to prevent or reverse mitochondrial dysfunction in a number of preclinical models.^{43,52,53} Elamipretide localizes to mitochondria where it reversibly binds to cardiolipin, a unique phospholipid localized to the hairpin turn of mitochondrial cristae, where it is required for normal morphologic features of the cristae and the electron transport complex.^{44,45,53,54} Elamipretide has been shown to bind cardiolipin in dysfunctional mitochondria and to restore normal adenosine triphosphate 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 sub-RPE deposits, improved mitochondrial morphologic features, and restoration of electroretinography amplitudes, all of which provided compelling support for the current clinical trial.³⁶

The current study demonstrated that subcutaneous daily elamipretide is generally well tolerated in patients with AMD with most AEs related to local injection site reactions. These events were all mild to moderate in severity, and only 1 participant discontinued study drug because of injection site reaction. One serious AE (urinary calculus) occurred that was not related to the study drug. Ocular AEs were all of mild or moderate intensity, and only 2 ocular AEs in the study eye were considered possibly related to the 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 with that previously observed in other clinical trials of elamipretide.^{55,56}

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

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 resulting from very good normal-light visual function at baseline in this cohort. Larger and statistically significant gains were noted in low-luminance visual function end points (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 end points. Additionally, significant improvements were noted in 6 of the

7 subscales of the LLQ at week 24, consistent with the observed improvements in visual acuity end points.

The current study is limited by a 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. No statistically significant improvements were found in drusen volume (RPE-DC on OCT), dark adaptometry, or mesopic microperimetry. Thus, improvements in the exploratory visual end points must be interpreted with caution. Nevertheless, elamipretide showed good feasibility, safety, and tolerability in participants with intermediate AMD and HRD. The natural history of 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} A relative lack exists of clinical trials targeting the HRD stage of AMD compared with more advanced stages of the disease. Given the encouraging safety profile and findings in some exploratory end points, a future study of elamipretide in patients with HRD is strongly justified.

Acknowledgments

The authors thank James A. Shiffer, RPh, and Bret Fulton, RPh, for writing and formatting assistance with the manuscript.

Footnotes and Disclosures

Originally received: May 20, 2021.

Final revision: October 29, 2021.

Accepted: December 6, 2021.

Available online: December 22, 2021. Manuscript no. D-21-00087

Duke Center for Macular Diseases, Department of Ophthalmology, Duke Eye Center, Duke University School of Medicine, Durham, North Carolina.

Presented in part at: Association for Research in Vision and Ophthalmology Annual Meeting, April-May 2019, Vancouver, Canada; and American Society of Retina Specialists Annual Meeting, July 2019, Chicago, IL.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): M.J.A.: Consultant – Stealth BioTherapeutics; Financial support – Stealth BioTherapeutics, Ocuphire Pharma

P.S.M.: Consultant and Financial support – Stealth BioTherapeutics

S.W.C.: Consultant – Stealth BioTherapeutics; Financial support – Stealth BioTherapeutics, Bausch & Lomb, Lineage Cell Therapeutics, Merck

Supported by Stealth BioTherapeutics, Newton, Massachusetts. The sponsor participated in the design of the study, conducting the study, data collection, data management, and data analysis. Following authors' preparation of the manuscript, the sponsor reviewed the manuscript prior to submission. However, the authors retained full and final control over data collection, data analysis, manuscript writing and content, and final decision to submit manuscript for publication.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Duke University approved the study. All

research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Allingham, Mettu, Cousins

Analysis and interpretation: Allingham, Mettu, Cousins

Data collection: Allingham, Mettu, Cousins

Obtained funding: N/A

Overall responsibility: Allingham, Mettu, Cousins

Abbreviations and Acronyms:

AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **DC** = drusen complex; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **HRD** = high-risk drusen; **logMAR** = logarithm of the minimum angle of resolution; **LLQ** = low-luminance questionnaire; **LLRA** = low-luminance binocular reading acuity; **LLVA** = low-luminance best-corrected visual acuity; **NCGA** = noncentral, fovea-sparing geographic atrophy; **NLRA** = normal-luminance binocular reading acuity; **RPE** = retinal pigment epithelium; **SD** = standard deviation.

Keywords:

Dry age-related macular degeneration, Elamipretide, Mitochondrial dysfunction, Phase 1 clinical trial, Retina.

Correspondence:

Scott W. Cousins, MD, DUMC Box 3802, 2351 Erwin Road, Durham, NC 27710. E-mail: scott.cousins@duke.edu.

References

- Klein R, Klein BEK. The prevalence of age-related eye diseases and visual impairment in aging: current estimates. *Invest Ophthalmol Vis Sci.* 2013;54(14):ORSF5–ORSF13.
- Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. *Eye Vis (Lond).* 2016;3:34.
- Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. *Ophthalmology.* 1997;104(10):1677–1691.
- Owsley C, McGwin G, Jackson GR, et al. Cone- and rod-mediated dark adaptation impairment in age-related maculopathy. *Ophthalmology.* 2007;114(9):1728–1735.
- Sunness JS, Rubin GS, Broman A, et al. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology.* 2008;115(9):1480–1488–2.
- Wu Z, Ayton LN, Luu CD, Guymer RH. Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration. *JAMA Ophthalmol.* 2015;133(4):442–448.
- Hsu ST, Thompson AC, Stinnett SS, et al. Longitudinal study of visual function in dry age-related macular degeneration at 12 months. *Ophthalmol Retin.* 2019;3(8):637–648.
- Owsley C, McGwin G, Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. *Invest Ophthalmol Vis Sci.* 2006;47(2):528–535.
- Holekamp N, Wykoff CC, Schmitz-Valckenberg S, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the prospective Proxima A and B clinical trials. *Ophthalmology.* 2020;127:769–783.
- Chakravarthy U, Bailey CC, Johnston RL, et al. Characterizing disease burden and progression of geographic atrophy secondary to age-related macular degeneration. *Ophthalmology.* 2018;125(6):842–849.
- Nolan JM, Power R, Stringham J, et al. Enrichment of macular pigment enhances contrast sensitivity in subjects free of retinal disease: Central Retinal Enrichment Supplementation Trials—report 1. *Invest Ophthalmol Vis Sci.* 2016;57(7):3429–3439.
- Murray IJ, Makridaki M, van der Veen RLP, et al. Lutein supplementation over a one-year period in early AMD might have a mild beneficial effect on visual acuity: the CLEAR Study. *Invest Ophthalmol Vis Sci.* 2013;54(3):1781–1788.
- Brown GC, Brown MM, Sharma S, et al. The burden of age-related macular degeneration: A value-based medicine analysis. *Trans Am Ophthalmol Soc.* 2005;103:173–186, 13.
- Jonasson F, Fisher DE, Eiriksdottir G, et al. Five-year incidence, progression, and risk factors for age-related macular degeneration: the age, gene/environment susceptibility study. *Ophthalmology.* 2014;121(9):1766–1772.
- Klein R. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol.* 2011;129(1):75–80.
- Restrepo NA, Spencer KL, Goodloe R, et al. Genetic determinants of age-related macular degeneration in diverse populations from the PAGE study. *Invest Ophthalmol Vis Sci.* 2014;55(10):6839–6850.
- Klein BEK, McElroy JA, Klein R, et al. Nitrate-nitrogen levels in rural drinking water: is there an association with age-related macular degeneration? *J Environ Sci Health A Tox Hazard Subst Environ Eng.* 2013;48(14):1757–1763.
- Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration. *Arch Ophthalmol.* 2000;118(3):351–358.
- Karunadharm PP, Nordgaard CL, Olsen TW, Ferrington DA. Mitochondrial DNA damage as a potential mechanism for age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2010;51(11):5470–5479.
- Nordgaard CL, Karunadharm PP, Feng X, et al. Mitochondrial proteomics of the retinal pigment epithelium at progressive stages of age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2008;49(7):2848–2855.
- Fujihara M, Bartels E, Nielsen LB, Handa JT. A human apoB100 transgenic mouse expresses human apoB100 in the RPE and develops features of early AMD. *Exp Eye Res.* 2009;88(6):1115–1123.
- Cousins SW, Espinosa-Heidmann DG, Alexandridou A, et al. The role of aging, high fat diet and blue light exposure in an experimental mouse model for basal laminar deposit formation. *Exp Eye Res.* 2002;75(5):543–553.
- Espinosa-Heidmann DG, Suner IJ, Catanuto P, et al. Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry AMD. *Invest Ophthalmol Vis Sci.* 2006;47(2):729–737.
- Hagstrom SA, Ying G-S, Pauer GJT, et al. Pharmacogenetics for genes associated with age-related macular degeneration in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology.* 2013;120(3):593–599.
- Ardeljan C, Ardeljan D, Abu-Asab M, Chan C-C. Inflammation and cell death in age-related macular degeneration: an immunopathological and ultrastructural model. *J Clin Med.* 2014;3(4):1542–1560.
- Sparrow JR, Wu Y, Nagasaki T, et al. Fundus autofluorescence and the bisretinoids of retina. *Photochem Photobiol Sci.* 2010;9(11):1480–1489.
- Ferrington DA, Sinha D, Kaamiranta K. Defects in retinal pigment epithelial cell proteolysis and the pathology associated with age-related macular degeneration. *Prog Retin Eye Res.* 2016;51:69–89.
- Brown EE, Lewin AS, Ash JD. *Mitochondria: potential targets for protection in age-related macular degeneration.* In: *Advances in Experimental Medicine and Biology.* 1074. New York: Springer LLC; 2018:11–17.
- Mettu PS, Wielgus AR, Ong SS, Cousins SW. Retinal pigment epithelium response to oxidant injury in the pathogenesis of early age-related macular degeneration. *Mol Aspects Med.* 2012;33(4):376–398.
- Ferrington DA, Kapphahn RJ, Leary MM, et al. Increased retinal mtDNA damage in the CFH variant associated with age-related macular degeneration. *Exp Eye Res.* 2016;145:269–277.
- Kaamiranta K, Uusitalo H, Blasiak J, et al. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. *Prog Retin Eye Res.* 2020;79:100858.
- Terluk MR, Kapphahn RJ, Soukup LM, et al. Investigating mitochondria as a target for treating age-related macular degeneration. *J Neurosci.* 2015;35(18):7304–7311.
- Marin-Castaño ME, Csaky KG, Cousins SW. Nonlethal oxidant injury to human retinal pigment epithelium cells causes cell membrane blebbing but decreased MMP-2 activity. *Invest Ophthalmol Vis Sci.* 2005;46(9):3331–3340.

34. Cano M, Wang L, Wan J, et al. Oxidative stress induces mitochondrial dysfunction and a protective unfolded protein response in RPE cells. *Free Radic Biol Med*. 2014;69:1–14.
35. Espinosa-Heidmann DG, Sall J, Hernandez EP, Cousins SW. Basal laminar deposit formation in APO B100 transgenic mice: complex interactions between dietary fat, blue light, and vitamin E. *Invest Ophthalmol Vis Sci*. 2004;45(1):260–266.
36. Cousins SW, Saloupis P, Brahmajoti MV, Mettu PS. Mitochondrial dysfunction in experimental mouse models of sub-RPE deposit formation and reversal by the mito-reparative drug MTP-131. ARVO Annual Meeting; May 2016.
37. Riazi-Esfahani M, Kuppermann BD, Kenney MC. The role of mitochondria in AMD: current knowledge and future applications. *J Ophthalmic Vis Res*. 2017;12(4):424–428.
38. Rudolf M, Vogt SD, Curcio CA, et al. Histologic basis of variations in retinal pigment epithelium autofluorescence in eyes with geographic atrophy. *Ophthalmology*. 2013;120(4):821–828.
39. Lavialle M, Aumann G, Anlauf E, et al. Structural plasticity of perisynaptic astrocyte processes involves ezrin and metabotropic glutamate receptors. *Proc Natl Acad Sci U S A*. 2011;108(31):12915–12919.
40. Derouiche A, Haseleu J, Korf H-W. Fine astrocyte processes contain very small mitochondria: glial oxidative capability may fuel transmitter metabolism. *Neurochem Res*. 2015;40(12):2402–2413.
41. Derouiche A, Pannicke T, Haseleu J, et al. Beyond polarity: functional membrane domains in astrocytes and Müller cells. *Neurochem Res*. 2012;37(11):2513–2523.
42. Nickel A, Kohlhaas M, Maack C. Mitochondrial reactive oxygen species production and elimination. *J Mol Cell Cardiol*. 2014;73:26–33.
43. Kapphahn R, Terluk M, Ebeling M, et al. Elamipretide protects RPE and improves mitochondrial function in models of AMD. *Invest Ophthalmol Vis Sci*. 2017;58:1954.
44. Birk AV, Chao WM, Bracken C, et al. Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis. *Br J Pharmacol*. 2014;171(8):2017–2028.
45. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol*. 2014;171(8):2029–2050.
46. Calabrèse A, Cheong AMY, Cheung S-H, et al. Baseline MNREAD measures for normally sighted subjects from childhood to old age. *Invest Ophthalmol Vis Sci*. 2016;57(8):3836–3843.
47. Chandramohan A, Stinnett SS, Petrowski JT, et al. Visual function measures in early and intermediate age-related macular degeneration. *Retina*. 2016;36(5):1021–1031.
48. Jackson GR, Scott IU, Kim IK, et al. Diagnostic sensitivity and specificity of dark adaptometry for detection of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2014;55(3):1427.
49. Farsiu S, Chiu SJ, O’Connell RV, et al. Quantitative classification of eyes with and without intermediate age-related macular degeneration using optical coherence tomography. *Ophthalmology*. 2014;121(1):162–172.
50. Menyhart O, Weltz B, Györfy B. MultipleTesting.com: a tool for life science researchers for multiple hypothesis testing correction. *PLoS One*. 2021;16(6):e0245824.
51. Cocce KJ, Stinnett SS, Luhmann UFO, et al. Visual function metrics in early and intermediate dry age-related macular degeneration for use as clinical trial endpoints. *Am J Ophthalmol*. 2018;189:127–138.
52. Alam NM, Iv WCM, Wong AA, et al. A mitochondrial therapeutic reverses visual decline in mouse models of diabetes. *DMM Dis Model Mech*. 2015;8(7):701–710.
53. Szeto HH, Liu S, Soong Y, Birk AV. Improving mitochondrial bioenergetics under ischemic conditions increases warm ischemia tolerance in the kidney. *Am J Physiol Renal Physiol*. 2015;308(1):F11–F21.
54. Liu S, Soong Y, Seshan SV, Szeto HH. Novel cardiolipin therapeutic protects endothelial mitochondria during renal ischemia and mitigates microvascular rarefaction, inflammation, and fibrosis. *Am J Physiol Renal Physiol*. 2014;306(9):F970–F980.
55. Karaa A, Haas R, Goldstein A, et al. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology*. 2018;90(14):E1212–E1221.
56. Butler J, Khan MS, Anker SD, et al. Effects of elamipretide on left ventricular function in patients with heart failure with reduced ejection fraction: the PROGRESS-HF phase 2 trial: effects of elamipretide in heart failure. *J Card Fail*. 2020;26(5):429–437.
57. Daubert MA, Yow E, Dunn G, et al. Novel mitochondria-targeting peptide in heart failure treatment. *Circ Hear Fail*. 2017;10(12):e004389.
58. Chew EY, Clemons TE, Agrón E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132(3):272–277.