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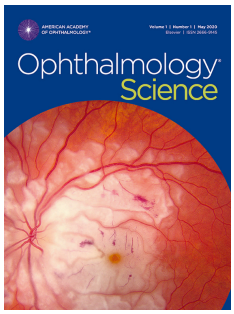

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Phase 1 Clinical Trial of Elamipretide in Dry Age-Related Macular Degeneration and Noncentral Geographic Atrophy: ReCLAIM NCGA Study

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Running head: ReCLAIM: Elamipretide in Dry AMD and NCGA

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Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well tolerated in patients with dry age-related macular degeneration and noncentral geographic atrophy, 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 dry age-related macular degeneration (AMD) and noncentral geographic atrophy (NCGA) and to perform exploratory analyses of change in visual function.

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

Participants: Adult patients, age ≥ 55 years, with dry AMD and NCGA.

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), and patient self-reported function by low luminance questionnaire (LLQ).

Main Outcome Measures: The primary endpoint was safety and tolerability. Prespecified exploratory endpoints included changes in BCVA, LLVA, NLRA, LLRA, GA area, and LLQ.

Results: Subcutaneous administration of elamipretide was highly feasible. All participants (n=19) experienced ≥ 1 non-ocular adverse events (AEs), but all AEs were either mild (73.7%) or moderate (26.3%); no serious AEs were noted. Two participants exited the study due to AEs (conversion to neovascular AMD (n=1); intolerable injection site reaction (n=1)), one participant discontinued due to self-perceived lack of efficacy, and one participant chose not to continue with study visits. Among participants completing the study (n=15), mean change (standard deviation (SD)) in BCVA from baseline to week 24 was +4.6 (5.1) letters (P=0.0032), while mean change (SD) in LLVA was +5.4 (7.9) letters (P=0.0245). While there was minimal change

in NLRA, mean change (SD) in LLVA was -0.52 (0.75) logMAR units (*P*=0.005). Mean change (SD) in GA area (SQRT) from baseline to week 24 was 0.14 (0.08) mm by FAF and 0.13 (0.14) mm by OCT. Improvement was observed in LLQ for dim light reading and general dim light vision.

Conclusions: Elamipretide appears to be well tolerated without serious AEs in patients with dry AMD and NCGA. Exploratory analyses demonstrate possible positive effect on visual function, particularly under low luminance. A Phase 2b trial is underway to further evaluate elamipretide in dry AMD and NCGA.

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 50 years and older, affecting an estimated 11 million individuals in the United States, with AMD prevalence expected to double to 22 million individuals by 2050 (10% of those 50 years and older).[1,2] The most profound visual impairment occurs in untreated neovascular AMD or in advanced dry AMD with foveal center-involving geographic atrophy (GA), both of which can cause severe central vision loss.[1] However, patients with patients with noncentral GA (NCGA) (as well as patients with high-risk drusen) also experience significant visual impairment.[3–7] In spite of good best-corrected visual acuity (i.e., often 20/40 or better), these patients frequently 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] Low luminance vision impairment affects up to 50% of NCGA patients,[9,10] thus representing a significant clinical unmet need.

An emerging body of evidence suggests an important role for retinal mitochondrial dysfunction in AMD pathobiology.[11–13] Multiple risk factors associated with AMD—including cigarette smoke, lipofuscin accumulation within retinal pigment epithelium (RPE), and complement dysregulation—have been identified as triggers of mitochondrial dysfunction.[14–16] Oxidant-induced modifications as well as mutations in mitochondrial DNA of RPE cells are more prevalent in human eyes with AMD than in eyes of age-matched controls, and the morphology of RPE mitochondria in eyes with AMD is often enlarged and dysmorphic (indicating dysfunction), as compared to RPE mitochondria of control eyes.[13,16,17] Additionally, certain genetic mitochondrial disorders, especially maternal inherited diabetes and deafness (MIDD) and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), often develop GA or other signs of macular degeneration.[18–20] The mechanisms of visual impairment in the

setting of mitochondrial dysfunction have not been clearly elucidated but may be related to alterations in cellular bioenergetics (i.e., diminished ATP production) and/or aberrant oxidant production at the RPE and/or photoreceptors, leading to altered phototransduction, impaired visual cycle, or insufficient metabolic support.[11,16,21]

Elamipretide is a first-in-class investigational drug and mitochondria-targeted tetrapeptide that has been previously evaluated in mitochondrial diseases such as primary mitochondrial myopathy and Barth syndrome.[22] Elamipretide increases cellular ATP production and reduces mitochondria-derived oxidants in affected cells by stabilizing the structure and function of the mitochondrial electron transport chain.[23–26] Elamipretide's mechanism of action suggests that it could modulate the mitochondrial-mediated pathophysiologic processes involved in dry AMD.[24,27] The ReCLAIM study was a phase 1 clinical trial with the primary objective to evaluate the safety and tolerability of elamipretide in two preplanned cohorts of patients with dry AMD: 1) patients with dry AMD and noncentral, fovea-sparing GA (NCGA); and 2) patients with intermediate AMD: high-risk drusen (HRD) without GA. Exploratory objectives included evaluation of changes from baseline in measures of visual function and in GA area. The study protocol prespecified relevant inclusion criteria for each cohort and that the two cohorts would be analyzed separately. This report will detail the findings of the NCGA cohort; results of the high-risk drusen cohort will be included in a companion report.

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

For the NCGA cohort, males and females ≥ 55 years of age with dry AMD and NCGA were eligible for enrollment, with a single eye designated as study eye. NCGA was defined as well-demarcated area(s) of GA by FAF, sparing the foveal center (i.e., center having intact RPE and outer retinal ellipsoid zone layer) by OCT. The cumulative GA lesion size (solitary or multifocal) was required to be: 1) ≥ 1.27 mm^2 (approximately ≥ 0.5 disc area) and < 10.16 mm^2 (approximately < 4 disc area); and 2) to reside completely within the FAF imaging field (30 degree image centered on the fovea). There were no other size requirements for a single GA lesion as long as the above specified size criteria were met. Participants were also required to have: 1) detectable rim area hyper-autofluorescence adjacent to the area of GA by FAF; 2) no evidence of choroidal neovascularization (active or prior history) in the study eye; 3) normal luminance BCVA ≥ 55 ETDRS letters score (i.e., Snellen equivalent ≥ 20/70); 4) low-luminance

visual acuity (LLVA) deficit > 5 letters, wherein LLVA deficit is defined as the difference BCVA and LLVA; and 5) at least two low luminance questionnaire (LLQ) abnormal subscale scores indicating impairment, wherein one of the abnormal subscales was either general dim light vision or dim light reading (where 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 central GA (i.e., involving the foveola by OCT), diagnosis of neovascular AMD, 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 daily 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.

Best-corrected binocular reading acuity (BCRA) 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 BCRA was done by standardized illumination using several different standard MNREAD charts (MNREAD 1-W, 2-W, and 3-W charts; Precision Vision, Lasalle, IL). Charts were rotated at visits throughout the study, and a single chart was not utilized at consecutive visits, to reduce the likelihood of learning effect. 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. 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 BCRA, with MNREAD 1-W, 2-W, and 3-W charts again rotated at visits throughout the study, and a single chart was not utilized at consecutive visits, to reduce the likelihood of learning effect. For LLRA, 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. If participants were unable to read the 1.3 logMAR line (i.e., largest font size) using the 2.0-log unit neutral density filter, then LLRA was repeated using a 1.0-log unit neutral density filter. The final adjusted logMAR value for measurements obtained with 1.0-log unit neutral density filter was derived by adding 1.9 to the measured value, such that the adjusted logMAR value ranged between 1.4 logMAR (smallest font size) to 3.2 logMAR (largest font size).

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.

For assessment of geographic atrophy (GA), OCT of the macula and FAF were performed at screening, baseline, during study treatment (weeks 4, 8, 12, 16, 20, 24), and at follow-up (week 28), with measurement of GA area assessed on each imaging modality performed by masked graders, who were masked to the date of performance / study visit. For FAF, masked graders demarcated the margins of GA lesions, defined as discrete regions of hypoautofluorescence within the FAF imaging field (field 2- to 30-degree image centered on the fovea), determined lesion areas, and determined the cumulative GA lesion area (in square millimeters). For OCT, graders assessed OCT B-scan images to identify the margins of GA lesion, defined as the presence of choroidal hypertransmission, absence or disruption of RPE, and overlying photoreceptor loss (ellipsoid zone loss, absence of external limiting membrane, outer nuclear layer thinning). GA margin was identified as the transition point between intact and disrupted or absent / attenuated RPE. OCT B-scans were registered to OCT infrared images, and the margin points were identified on infrared images to determine the cumulative GA area (in square millimeters). Square root transformation (SQRT) was performed on GA area measurements to eliminate the dependence of growth rates on baseline GA lesion measurements.

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, LLRA, LLQ, and GA area.

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. As mentioned, the HRD and NCGA cohorts were preplanned by study design. 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. As this was an open-label study without a control or comparator group, analyses of exploratory efficacy endpoints were limited to descriptive analyses. Analyses of change in each metric from baseline to 24 weeks were limited to participants who completed the 24-week study period. Missing data was not imputed (e.g., by last observation carried forward) to avoid making assumptions about the outcomes of study participants that did not complete the study. 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. Statistical analysis of mean change from baseline value was assessed by signed-rank test. Pearson's correlation coefficient was utilized to assess the correlation between GA area at baseline and the change in LLVA at week 24 from baseline. 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.[28] 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.[28]

Results

Study Participants

A total of 19 participants were included in the NCGA cohort (**Table 1**). The mean age was 76 and the majority were female (11/19) and current or former smokers (11/19). Of the 19 enrolled, 15 participants completed the 24-week treatment period. Of the four individuals who did not complete the study, one participant discontinued participation due to study drug intolerance in the form of pruritis and discomfort at injection site (prior to the week 4 visit), one participant was discontinued by study investigator due to conversion to neovascular AMD (just after the week 8 visit), one participant chose to withdraw from the study due to the participant's perceived lack of efficacy of the study drug (at week 12), and one participant withdrew from the study (at week 20) because they did not wish to continue with study visits.

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 2.5 (1.02) visits. Mean (SD) treatment compliance across the 24-week active study drug period was 97.3 (6.7) %.

Safety and Tolerability

Adverse events are summarized in **Table 2.** All study participants experienced at least one adverse event, which were all either or mild (73.7%) or moderate (26.3%) in intensity. The most common treatment-emergent adverse events were injection site reactions, defined as a local reaction at the site of subcutaneous administration (including pruritus, erythema, discomfort, swelling, induration, and bruising). In most cases, these reactions were mild, self-limited and/ or amenable to local treatment; one participant discontinued study drug due to intolerance to injection-site reaction, pruritis, which in this instance was considered moderate intensity. There were two treatment-emergent serious adverse events and no deaths in the study. Both serious adverse events, urinary tract infection [n=1] and sepsis [n=1], occurred in the same participant, were of moderate intensity, and were not considered related to study drug; both events resolved with full recovery of the participant. Two study participants experienced ocular adverse events in the study eye; conversion to neovascular AMD [n=1] (moderate intensity) and vitreous floaters [n=1] (mild intensity), but both events were not considered related to study drug (**Table 2**). As noted above, the participant with conversion to neovascular AMD was withdrawn from the study by the study investigator. Two participants reported an ocular adverse event in the nonstudy eye, both of which were of mild intensity and not related to study drug.

Exploratory Efficacy Endpoints

Mean (SD) normal luminance BCVA was 77.9 (12.7) letters at week 24, as compared to 73.7 (9.5) letters at baseline. Normal luminance BCVA over the course of the study period are summarized in **Figure 1.** Among the 15 participants who completed the active study period, the mean change in BCVA from baseline progressively increased over time, with a mean (SD) increase of 4.6 (5.1) letters (P=0.0032, Holm method threshold for statistical significance

P<0.0125) at week 24 (**Figure 1A, 1B**). Six of 15 participants (40%) had at least a 6-letter increase in BCVA at week 24, and two of 15 participants (13.3%) had greater than 10-letter increase in BCVA at week 24; no individuals had greater than 5-letter decrease in BCVA (**Figure 1B, 1C**).

Mean (SD) LLVA was 51.5 (21.8) letters at week 24, as compared to 44.0 (19.8) letters at baseline. LLVA over the course of the study period are summarized in **Figure 2.** Mean increase in LLVA from baseline was observed at all study visits throughout the study period, with a mean (SD) increase of + 5.4 (7.9) letters (*P*=0.0245, Holm method threshold for statistical significance *P*<0.025) at 24 weeks (**Figure 2A, 2B**). Eight of 15 participants (53.3%) had at least a 6-letter increase in LLVA, five of 15 participants (33.3%) had greater than 10-letter increase in LLVA, and one of 15 participants (6.7%) had greater than 15-letter increase in LLVA. (**Figure 2B, 2C**). Two of 15 participants (13.3%) had at least a 6-letter decrease in LLVA (**Figure 2B, 2C**).

Mean (SD) NLRA at week 24 (0.13 (0.26) logMAR) was not appreciably different from baseline (0.15 (0.25) logMAR); mean change from baseline -0.02 logMAR (*P*=0.55, Holm method threshold for statistical significance *P*<0.05). In contrast, mean (SD) LLRA at week 24 was 0.79 (0.97) logMAR as compared to baseline value of 1.28 (1.07) logMAR. Increase in LLRA was observed at all study visits throughout the study period, with a mean LLRA change from baseline in the smallest line read correctly of −0.52 logMAR at week 24 (*P*=0.005, Holm method threshold for statistical significance *P*<0.0167) (**Figure 3**), equivalent to an approximately 5-line gain in LLRA.

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 not statistically significant, though there were notable improvements in general dim light vision *(P*=0.0292) and dim light reading (*P*=0.0271) that trended toward clinical significance.

For change in GA lesion size, mean (SD) change in GA area at week 24 was increased at 0.50 (0.49) mm^2 by FAF and 0.45 (0.61) mm^2 by OCT. Mean (SD) change from baseline in GA area at week 24, measured by square root transformation (i.e., calculation performed to eliminate dependence of growth rates on lesion measurements), was increased at 0.14 (0.08) mm by FAF and 0.13 (0.14) mm by OCT. There was good correlation between baseline GA area (mm^2) by OCT and change in LLVA at week 24 from baseline (correlation coefficient: -0.6555; *P*=0.008). In general, eyes with smaller GA area at baseline experienced greater increase in LLVA at week 24, with all instances of ≥ 6-letter increase in LLVA (N=8) occurring in eyes with baseline GA area < 4 mm^2 (approximately 1.6 disc areas) and intact foveal ellipsoid zone.

Discussion

Dry AMD with geographic atrophy (GA) represents an advanced form of AMD disease, characterized by foci of cell death at the RPE, attenuation of underlying choriocapillaris, and loss of overlying and marginal photoreceptors.[12] While the disease is variably progressive, the extent of associated visual deficit is related to several factors, including size and location of GA relative to the fovea as well as the rate and direction of GA enlargement.[29] Progression of AMD disease produces increasing impairment in health-related quality of life (QoL), with a QoL in moderate AMD (i.e., AMD with NCGA) comparable to that following a moderate stroke and QoL in severe AMD (i.e., AMD with center-involving GA) similar to that found in patients with total renal failure on home dialysis.[30] Currently, there are no approved treatments to prevent GA, limit

its progression, or improve vision for affected patients. The lack of efficacious therapies for dry AMD carries significant public health and societal burden, estimated at a total financial cost (direct and indirect) of $30 billion.[30]

Declines in visual function experienced by dry AMD patients are especially apparent under low luminance conditions, including difficulty reading in dimly lit conditions and driving at dusk / nightfall or in poor ambient light environments.[8–10] These deficits in activities of daily living profoundly impact affected patients, in many cases causing loss of independence and social withdrawal. Low luminance vision dysfunction is quantified by clinical endpoints of LLVA and LLRA, which assess central cone-mediated function under standardized conditions.[10,31,32] Therapies that specifically improve low luminance visual function and boost LLVA and LLRA would thus represent a paradigm shift for AMD patients.

Mitochondrial dysfunction at the RPE and neurosensory retina, characterized by excessive production of cellular oxidants (superoxide, singlet oxygen, others) and diminished ATP production, appears to be an important contributor to AMD pathobiology.[11,13,21] RPE cells in eyes from patients with AMD exhibit mitochondrial dysmorphology and oxidative damage with the effect proportional to disease severity.[13,17,21] Preclinical mouse models of dry AMD, which are characterized by dysmorphic RPE and subRPE deposit formation, have abnormal RPE mitochondria along with biochemical evidence of mitochondrial dysfunction and increased superoxide production at the RPE.[27,33,34] Additionally, induction of the ApoE4 dry AMD mouse model triggers neurosensory retina mitochondrial dysfunction in the setting of diminished ERG amplitudes and disrupted photoreceptor-bipolar cell synapses.[27] These data strongly support mitochondrial dysfunction as a key disease paradigm for dry AMD.

The investigational drug elamipretide is a small peptide that reversibly binds cardiolipin, a phospholipid found only in the inner mitochondrial membrane that is responsible for establishing the cristae architecture and optimizing the function of the electron transport chain for ATP generation.[23–26] Binding of elamipretide to cardiolipin restores the efficiency of the electron transport chain in dysfunctional mitochondria, improving cellular respiration and ATP production and reducing production of oxidants.[23–26] The net effect is to restore niche cellular functions requiring high levels of ATP and to downregulate cellular response to injury pathways that are triggered by oxidants. Elamipretide has been shown to have significant activity in preclinical models of eye disease, with *in vitro* studies showing reduced oxidative stress, decreased apoptosis, and improved cell survival in cultured human RPE cells.[24,35] Further, in RPE cells cultured from dry AMD donor eyes, elamipretide treatment improved mitochondrial function, as measured by maximal respiration and spare respiratory capacity.[24] Finally, treatment of the ApoE4 mouse model of dry AMD, using a rigorous drug intervention strategy following induction of the model (as opposed to an pretreatment strategy prior to or concurrent with model induction), promoted reversal of mitochondrial dysfunction, regression of subRPE deposits, restoration of RPE cellular morphology, improvement in neurosensory retinal function by ERG, and restoration of phototransduction and synaptic integrity and function.[27] It was on the basis of these compelling preclinical data that the elamipretide clinical development program was initiated for dry AMD.

Results from the present phase 1 ReCLAIM study demonstrate that subcutaneous administration of elamipretide is generally well tolerated without serious drug-related adverse events (AEs) in patients with AMD and NCGA. Treatment-emergent adverse events, which were primarily comprised of injection site reactions, were mild or moderate in severity, with only one

participant discontinuing study participation due to injection site reaction (pruritis). There were two serious AEs (urinary tract infection [n=1] and sepsis [n=1]) that occurred in the same patient, but neither of these was deemed to be related to study drug, and both serious AEs resolved with recovery of the participant. Among ocular AEs occurring in the study eye (n=2), none were severe or thought to be related to study drug, and only one, conversion to neovascular AMD [n=1], led to study drug discontinuation. The overall safety profile of elamipretide was comparable to that previously observed in other clinical trials of elamipretide.[36,37]

Elamipretide dose and frequency was selected based on maximally tolerated subcutaneous dosing from prior safety studies in adults. While pharmacokinetics (PK) samples were not collected and analyzed in the present study, the PK profile of elamipretide administered via infusion has been characterized in other clinical trials (data on file, Stealth BioTherapeutics).[38] 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). Studies on the pharmacokinetics of subcutaneous elamipretide in AMD patients are included in the forthcoming Phase 2 clinical trial.

Exploratory efficacy endpoints suggest that elamipretide may have a possible positive benefit on visual function in dry AMD and NCGA, particularly under low luminance conditions. We observed increased mean change in both LLVA and LLRA that was evident at early visits (i.e., day 7 and week 4) and subsequently sustained over the duration of the study, suggestive of a possible drug treatment effect. The phenomenon of short-term learning effect has been described in studies of other measures of visual function (e.g., microperimetry) in dry AMD patients.[39] It is

possible that short-term learning effect could have contributed to observed changes in LLVA and LLRA at early visits. However, as described in the methods, for LLRA (and NLRA), MNREAD charts were rotated at visits throughout the study, such that single chart was not utilized at consecutive visits, to reduce the likelihood of a testing-specific learning effect. Furthermore, as the methodology for LLVA testing does not include added psychovisual aspects beyond what is encountered in the testing of normal luminance BCVA, a learning effect specifically attributable to LLVA would be unexpected. The recent GA natural history study Proxima B (NCT02399072) demonstrated that patients with NCGA (with fellow eye intermediate AMD) had mean visual acuity loss of approximately 3-5 letters at the similar 6 month (24 week) assessment interval; there was neither a short-term learning effect for LLVA nor a spontaneous improvement in LLVA at later points for patients in this study.[9] This is of relevance since Proxima B had eyes of similar disease state and baseline LLVA as compared to those included in the NCGA cohort of the present ReCLAIM study.

In contrast, in the sham control arms of GATHER1, the Phase 2b/3 clinical trial of avacincaptad pegol (IVERIC Bio), mean change in LLVA from baseline to month 12 was -1.4 (standard error (SE) 3.3) in the sham group for the 2 mg arm and +3.0 (SE 3.4) for the sham group for the 4 mg arm.[40] In a natural history study of a cohort (n=8) of NCGA patients, Wu, et al., observed minimal change in LLVA from baseline to 12 months.[6] The findings from these studies suggest the possibility that LLVA may not substantially decline over time or may demonstrate short-term improvement in some dry AMD patients. Further, the coefficient of repeatability for LLVA in patients with intermediate AMD was found to be 9.34 letters by Chandramohan, et al.,[41] and approximately 6.5 letters and Wu and colleagues.[42] While the present study describes findings in a cohort of NCGA patients rather than intermediate AMD patients, visit-to-visit variation in

LLVA and LLRA must be taken into account when considering the potential for true differences attributable to study drug. The data from available and relevant literature highlight the importance of careful study design, endpoint measurement methodology, and patient selection in assessing change in low luminance visual function in AMD patients over time, and most importantly, underscore the critical need for a placebo control group to understand the true nature and magnitude of drug effect on low luminance visual function in NCGA patients.

With respect to effects on GA area, similarly, multiple caveats apply in interpreting observations, including the relatively short 24-week duration of the study, selection of NCGA patients, and the normal variability across AMD populations for changes in GA size over time. We observed mean increase in GA area (SQRT) of 0.14 mm by FAF and 0.13 mm by OCT. Previously published studies of GA natural history at 6 months (24 weeks) have included increases in GA area (SQRT) ranging from 0.17 – 0.19 mm.[9,43,44] The limitations inherent in making cross-trial comparisons to other studies preclude substantive conclusions for NCGA patients in ReCLAIM. If a reduced rate of GA progression is affirmed for elamipretide-treated patients in a placebo-controlled study, this would suggest the hypothesis that retinal and/or RPE mitochondrial dysfunction may contribute to progression of GA over time and would further suggest that rate of GA progression could serve as an additional clinical efficacy endpoint for mitochondria-targeted drugs. Further evaluation in a placebo-controlled study is needed to address this possibility.

While the study produced an acceptable safety profile as well as intriguing efficacy signals, care must be taken not to overinterpret the presented exploratory efficacy analyses. As we have noted, the lack of placebo control group represents the most significant limitation for this study in considering the implications of the efficacy analyses. As this was an open-label uncontrolled

Phase 1 safety with small sample size, there were also limitations in the statistical approach, as there were not prespecified rules for handling missing data. As such, efficacy analyses were restricted to the 15 participants who completed the study, to avoid making assumptions about the outcomes of those individuals who discontinued study participation. The inability to account for the impact of the four participants withdrawals on efficacy analyses represents an additional limitation of the present study. However, we did adjust analyses for multiple comparisons to determine appropriate thresholds for statistical significance, following which, the observed changes from baseline to week 24 for BCVA, LLVA, and LLRA remained statistically significant.

The observed, potentially positive effects of elamipretide on visual function are thus highly promising and provide substantial support and justification for further investigation of elamipretide in clinical trials of dry AMD. Based on the results of this prespecified cohort analysis of NCGA patients, a randomized, double-masked, multicenter Phase 2b clinical trial (ReCLAIM-2, NCT03891875) is ongoing to continue the evaluation of safety and efficacy of subcutaneous administration of elamipretide in patients with dry AMD with NCGA.

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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*=0.0032 for mean change value at week 24 vs. Baseline, Holm method threshold for statistical significance *P*<0.0125. (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*=0.0245 for mean change value at week 24 vs. Baseline, 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 low luminance reading acuity (LLRA). Mean change in LLRA (logMAR) from Baseline (Day 0) over 24-week active study period; bars indicate standard deviation (SD). ***P*=0.005 for mean change value at week 24 vs. Baseline, Holm

588 method threshold for statistical significance $P<0.0167$.

Table 1. Characteristics of patients with noncentral geographic atrophy (NCGA)

Characteristic	N=19
Age, mean (SD) (range)	76.0 (8.22) (64, 96)
Sex, n (%)	
Female	11 (57.9)
Male	8 (42.1)
Ethnicity, n (%)	
Hispanic/Latino	1 (5.3)
Caucasian	18 (94.7)
Former smoker*, n (%)	11 (57.9)
Baseline BCVA, mean (SD)	73.7 (9.5)
Baseline LLVA, mean (SD)	43.9 (19.8)
Baseline NCGA area by FAF, mean (SD)	3.46 (3.39)
Baseline NCGA area by OCT, mean (SD)	3.28 (3.23)

*Former smoker - no participants were active smokers
SD= standard deviation; BCVA= best-corrected visual acuity; LLVA= low luminance visual acuity; FAF= fundus autofluorescence; OCT= spectral domain-optical coherence tomography

Table 2. Adverse events (AEs) in patients with noncentral geographic atrophy

Event	N=19
All Treatment-emergent events, n (%)	
Any treatment-emergent AE	19 (100)
Injection site reactions	
Pruritis	17 (89.5)
Erythema	14 (73.7)
Induration	14 (73.7)
Bruising	13 (68.4)
Hemorrhage	7 (36.8)
Pain	6 (31.6)
Urticaria	4 (21.1)
Extravasation	2 (10.5)
Swelling	1 (5.3)
Upper respiratory tract infection	3 (15.8)
Headache	2 (10.5)
Dizziness	2 (10.5)
Pyrexia	2 (10.5)
Nausea	2 (10.5)
Gastroenteritis, viral	2 (10.5)
AE by maximum intensity	
Mild	14 (73.7)
Moderate	5 (26.3)
Related to study drug	18 (94.7)

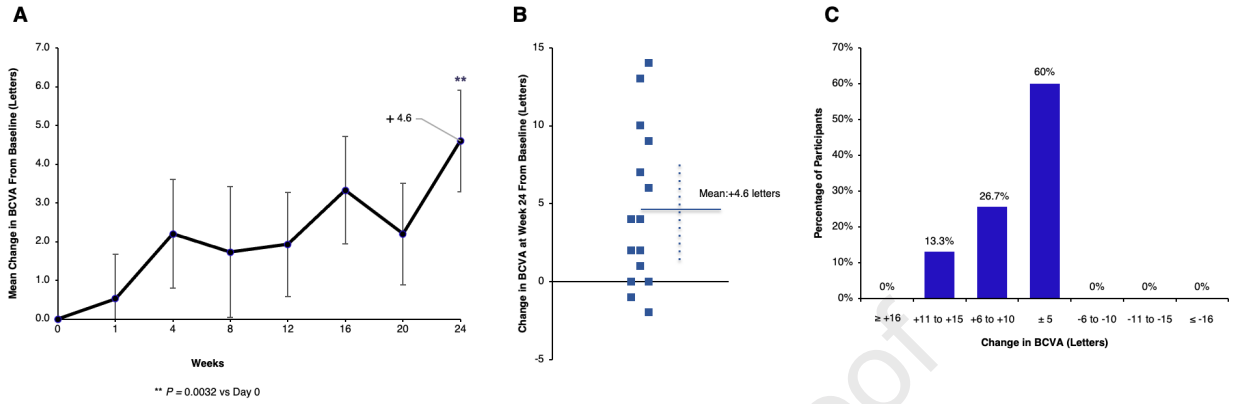
AE leading to study drug discontinuation	2 (10.5)
Any serious systemic AE*	
Urinary traction infection	1 (5.3)
Sepsis	1 (5.3)
All treatment-emergent ocular events in study eye, n (%)	
Any treatment-emergent ocular AE	2 (10.5)
Neovascular AMD	1 (5.3)
Vitreous floaters	1 (5.3)
AE by maximum intensity	
Mild	1 (5.3)
Moderate	1 (5.3)
Related to study drug	0
AE leading to study drug discontinuation	2 (10.5)
Any serious ocular AE	0

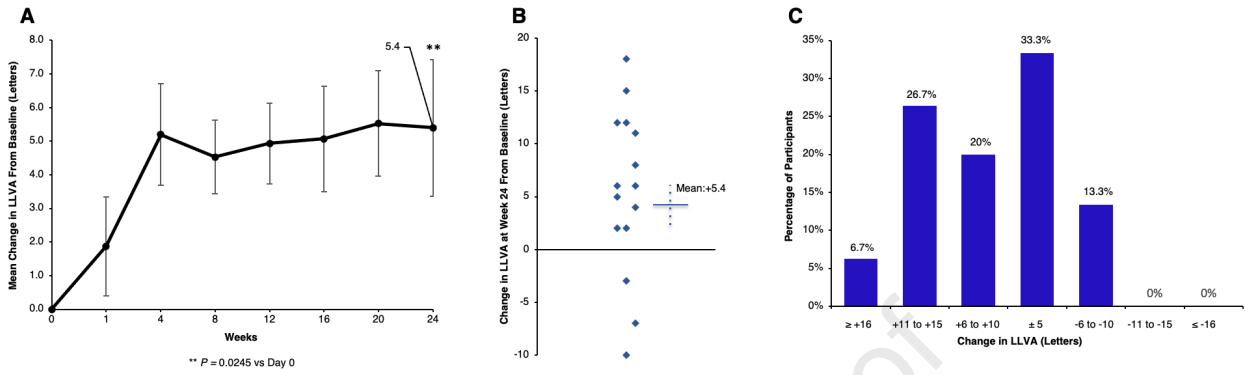
*Both serious systemic AEs occurred in the same participant.

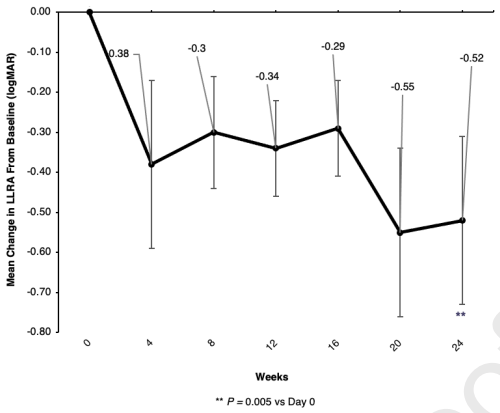
Table 3. Low Luminance Questionnaire Scores at Week 24

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
Dim light reading	15	40.8	16.00	37.5	25.0	81.3	15	7.1	11.30	6.3	-12.5	25.0	0.0292
Driving or riding in car	15	48.9	26.86	37.5	25.0	93.8	15	4.2	14.11	0.0	-25.0	31.3	0.2719
General dim light vision	15	58.4	20.38	53.1	31.3	93.8	15	7.7	12.10	6.3	-18.8	25.0	0.0271
Light transitions and glare	15	51.0	20.98	45.0	25.0	95.0	15	6.7	13.71	5.0	-25.0	30.0	0.0807
Mobility	15	71.1	22.02	75.0	25.0	100.0	15	2.8	16.57	0.0	-25.0	33.3	0.5266
Other ADLs	15	64.6	24.96	68.8	25.0	100.0	15	10.4	20.82	12.5	-37.5	43.8	0.0731
Peripheral vision	15	61.7	32.55	50.0	25.0	100.0	15	5.8	24.03	0.0	-50.0	50.0	0.3630

SD= standard deviation; ADLs= activities of daily living







Precis: In this Phase 1 study, subcutaneous elamipretide was generally safe and well-tolerated in patients with dry age-related macular degeneration and noncentral geographic atrophy, with possible positive effect on visual function, particularly under low luminance conditions.