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ReCLAIM-2: A Randomized Phase II Clinical Trial Evaluating Elamipretide in Age-related Macular Degeneration, Geographic Atrophy Growth, Visual Function, and Ellipsoid Zone Preservation

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Objective: This study evaluated the safety and efficacy of elamipretide in dry age-related macular degeneration (AMD) with noncentral geographic atrophy (GA).

Design: ReCLAIM-2 was a prospective, phase II, randomized, placebo-controlled, double-masked, multicenter trial (NCT03891875).

Subjects: Patients aged ≥55 years with ≥1 eye with dry AMD with GA were enrolled.

Methods: Administration of daily subcutaneous elamipretide 40 mg was investigated in subjects for 48 weeks followed by a 4-week follow-up period.

Main Outcome Measures: The primary efficacy end points were the mean change from baseline (BL) in low-luminance best-corrected visual acuity (LL BCVA) and the change in square root (Sqrt) converted GA area from BL as measured by OCT. Additional predefined end points included ellipsoid zone (EZ) integrity preservation assessment and categorical changes in LL BCVA. The primary safety end point was the incidence and severity of adverse events.

Results: Of the 176 patients randomized, there were 117 and 59 patients in the elamipretide and placebo groups, respectively. Although elamipretide did not meet statistical significance for the primary end points (mean change in LL BCVA and mean change in Sqrt converted GA area), elamipretide produced a 43% reduction in the mean progression from BL in the macular percentage of total EZ attenuation/loss (i.e., complete loss of EZ band; nominal $P = 0.0034$) and 47% reduction in the mean progression of macular percentage of partial EZ attenuation/degradation (i.e., EZ-retinal pigment endothelium thickness of ≤20 microns; nominal $P = 0.0040$) versus placebo at week 48. Elamipretide treatment was also associated with significantly more patients experiencing a ≥10 letter gain in LL BCVA versus placebo (14.6% vs. 2.1%; nominal $P = 0.0404$). Adverse events were reported in 86% of those receiving elamipretide and 71% of the placebo group with the most common events being injection site reactions (e.g., pruritus, injection site pain, bruising, and erythema).

Conclusions: While the primary end points were not met in this phase II study, elamipretide treatment was associated with a slowing of progressive EZ degradation/loss, a surrogate for photoreceptor damage. These findings have important clinical relevance since EZ attenuation/photoreceptor loss precedes and predicts the progressive pathological changes associated with vision loss and AMD. The EZ attenuation/loss end point will serve as the regulatory approved primary end point in the elamipretide phase III clinical development program.

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Age-related macular degeneration (AMD) affects ∼11 million Americans and is the leading cause of irreversible blindness in people aged ≥50 years.[1] Age-related macular degeneration prevalence (United States) is estimated to increase to >20 million patients by 2050.[2] Age-related macular degeneration preferentially affects the macular (central) region of the retina and is characterized as early, intermediate, or late stages based on number, location, and

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size of drusen with hyperpigmentary or hypopigmentary changes and the presence or absence of geographic atrophy (GA) or macular neovascularization (MNV). Late stages of nonexudative or dry AMD are characterized by GA, which has a major negative impact on vision-related quality of life[3] and accounts for 20% and 25% of legal blindness in the United States and United Kingdom, respectively.[4,5]

The pathophysiology of dry AMD is thought to involve multiple converging pathways, including lipid metabolism, complement activation, and mitochondrial injury.[6] Because of the multifactorial etiology involved, effective disease management may require treatment of multiple targets that may differ across different stages of disease.[7] Although the multifaceted pathophysiology of dry AMD is complex and not fully understood, investigations confirm that the root cause of irreversible vision loss is photoreceptor death; therefore, protecting photoreceptors from damage and delaying their degeneration are key to the successful treatment of clinical symptoms and disease progression.[8]

Photoreceptor dysfunction/loss in dry AMD can be quantified by changes in the ellipsoid zone (EZ), which is thought to correspond to the mitochondria-rich layer of the photoreceptors, and the associated loss of photoreceptor cells leading to (and correlated with) progressive loss of visual function.[9-11] These observed EZ changes are typically associated with the eventual loss of the retinal pigment endothelium (RPE) and the underlying choriocapillaris leading to areas of GA. Notably, EZ loss or attenuation has been shown to predict areas of GA, as well as precede its onset by 2 to 3 years.[10,12] Ellipsoid zone loss has been associated with GA progression, and there are emerging data suggesting that a reduction in EZ loss may mitigate GA progression.[9,13-15] Longitudinal studies have also demonstrated that the EZ loss-to-GA boundary distance is prognostic for future GA progression rates.[14,16] Accordingly, it has been postulated that imaging photoreceptor degeneration may serve not only as a prognostic biomarker, but as attractive clinical end points in dry AMD since they are accurate, with high prognostic validity, and have been concurrently validated in multiple structure-function correlation studies in dry AMD.[16]

Patients with dry AMD usually report or present early in the course of the disease with visual function impairments including difficulty reading or limited vision at night or in reduced lighting conditions.[17,18] Research has demonstrated a clear link between visual function and EZ integrity measures, including EZ-RPE thickness, EZ total attenuation burden (i.e., macular area/percentage of total EZ [tEZ] loss), EZ partial attenuation burden (i.e., macular area/percentage of partial EZ [pEZ] attenuation/degradation based on EZ-RPE measurement of $\leq$20 microns), and EZ reflectivity index.[19] This early loss of low-luminance best-corrected visual acuity (LL BCVA) occurs despite relative preservation of best-corrected visual acuity (BCVA) in the absence of foveal atrophy.[20] Low-luminance visual dysfunction has been shown to be predictive of subsequent best-corrected visual dysfunction in eyes with GA.[21] Low-luminance BCVA is also significantly associated with patient-reported visual quality of life.[22] Accordingly, the preservation of LL BCVA is an important and relevant clinical end point for dry AMD.[21] Notably, in the setting of intermediate AMD, degeneration of EZ-RPE thickness and reflectivity is strongly associated with loss of mesopic and scotopic light sensitivity,[16] which in turn is associated with LL BCVA decline.[23]

Although approaches targeting the complement system have successfully slowed the progression of GA in clinical trials, attenuation of GA progression has not been associated with either improved visual function or attenuation of progressive visual dysfunction in these clinical programs, including after long term (24-month) follow-up.[24-26] For therapeutic agents to improve clinical outcomes, they should target photoreceptor function before vision loss is beyond rescue. Therefore, it is important to assess end points measuring photoreceptor EZ integrity. Elamipretide is a first-in-class mitochondria-targeting peptide that restores mitochondrial structure and function.[27,28] This agent increases mitochondrial energy generation in affected cells and organs and reduces the generation of reactive oxygen species.[24-26] Elamipretide stabilizes the mitochondrial electron transport chain structure and function. This leads to an increased production of adenosine triphosphate, decreased production of mitochondrial reactive oxygen species, and reduction in cellular apoptosis and necrosis.[24-26] Preclinical study results suggest the potential for positive effects of elamipretide on AMD.[29] Elamipretide improves cell-survival in human retinal endothelial cells, trabecular meshwork cells, and retinal pigmented epithelial cells, as well as reduces glucose- and peroxide-induced oxidative stress and apoptosis.[30-32] When given subcutaneously to diabetic rats, elamipretide reduced oxidative stress, prevented apoptosis, and reduced VEGF-2 receptor expression and retinal leakage of Evans Blue dye.[33] Elamipretide also prevented and corrected visual function loss in diabetic mice.[34]

The open-label phase I ReCLAIM elamipretide study reported vision improvement in 2 prespecified subgroups, in high-risk drusen without GA and in GA.[35,36] The objectives of this placebo-controlled phase II study (ReCLAIM-2) were to evaluate the safety and efficacy of elamipretide in patients with GA secondary to AMD.

Methods

Study Design

In this United States-based, phase II, randomized, placebo-controlled, double-masked, multicenter, safety and efficacy trial (ReCLAIM-2) (ClinicalTrials.gov identifier NCT03891875), patients with $\geq$1 eye with dry AMD and GA were included (see below). Visit 1 (screening visit) was performed no >14 days before the baseline (BL) visit (visit 2, day 1). Patient distribution is provided in the Consolidated Standards of Reporting Trials Flow Diagram (Fig 1). Eligible patients returned for the BL visit, at which time they each were assigned a subject number and corresponding treatment according to the randomization code. Subjects were randomized (interactive response system) in a 2:1 ratio to receive either elamipretide 40 mg or placebo, following the provision of oral and written detailed instructions by a trained health care professional, administered with the pen injector delivery system as a single daily self-administered

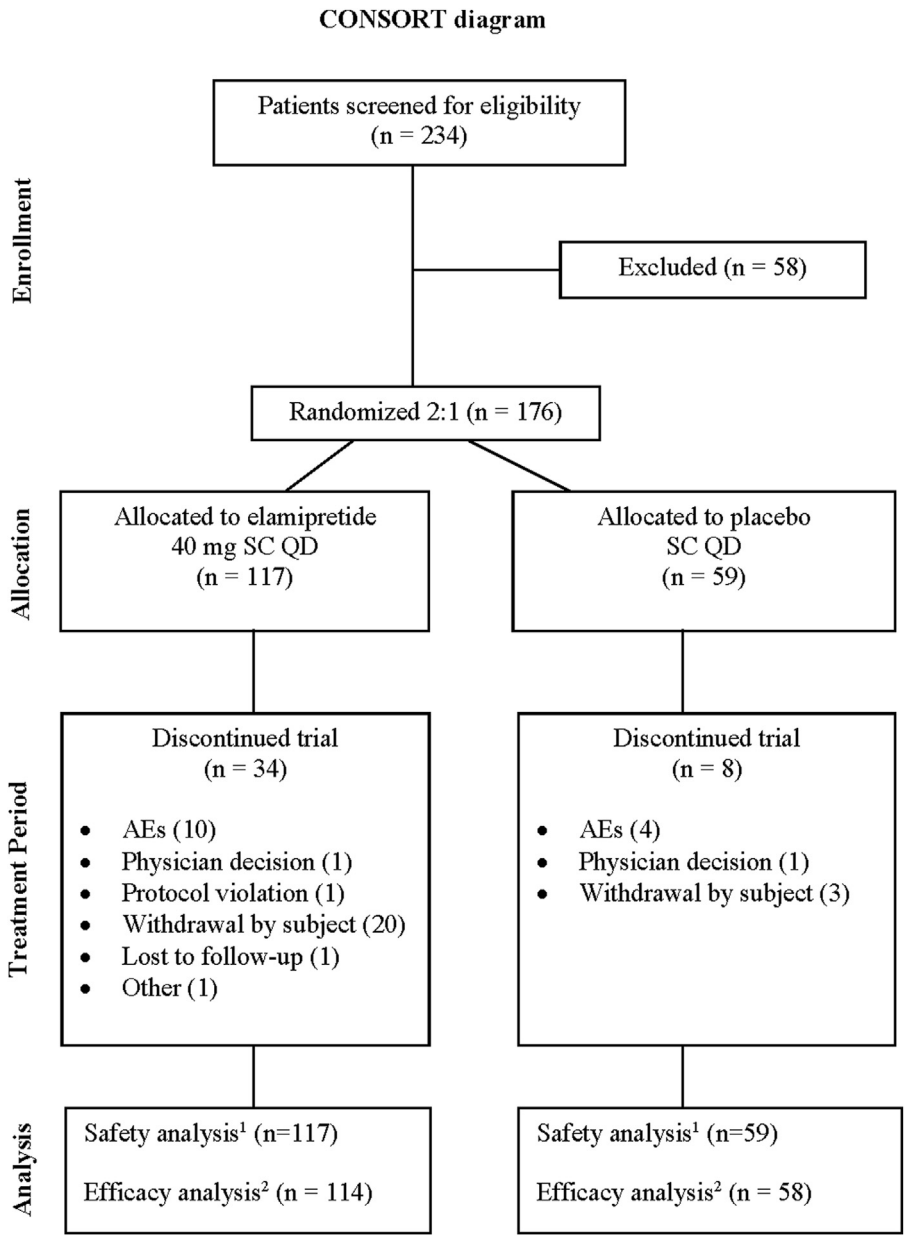

Figure 1. CONSORT study flow diagram. AE = adverse event; CONSORT = Consolidated Standards of Reporting Trials; QD = daily; SQ = subcutaneous.

subcutaneous injection, rotating clockwise around the 4 quadrants of the abdomen. This dose was chosen based on the systemic exposure and safety profiles of elamipretide in the ReCLAIM-1 trial.[35,36] Patients were treated for 48 weeks, with assessments at day 1 and weeks 4, 8, 12, 24, 36, and 48 (total visits 2−8) plus a final safety follow-up visit 4 weeks after the last day of study treatment (week 52; visit 9). Patient diaries and vial counts were used and reviewed to verify compliance. Trial personnel, subjects, and the Sponsor study team were masked to treatment until the database was locked. Investigators were instructed to contact the Sponsor prior to unmasking any subject's treatment unless in the instance of a medical emergency. In case of an immediate medical emergency, or if directed by the Sponsor, and only if the information was required by the Investigator to manage a subject's adverse event (AE), was a subject's treatment assignment to be unmasked prematurely. In cases of medical emergency, the Investigator could unmask a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor was to be notified as soon as possible regarding the reason for unmasking, and source documentation was required. The Sponsor designated contract research organization was to control and document, according to the appropriate Standard Operating Procedures, the disclosure of treatment assignments, and treatment identity. These procedures ensured that no masked staff (contract research organization, trial site staff, Sponsor) would have premature access to the subjects' treatment assignments.

The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including

the Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonisation Good Clinical Practice Guideline, and the Declaration of Helsinki. Institutional review board/ethics committee approval was obtained and all patients provided written informed consent. Investigators were responsible for monitoring the safety of subjects who entered the trial and for alerting the Sponsor or its designee to any event that seemed unusual, even if this event was considered to be an unanticipated benefit to the subject. The Investigator was responsible for facilitating the appropriate medical care of subjects during the trial and for an AE/adverse device event, should one have occurred.

Patients

Key Inclusion Criteria. The original protocol specified that adults ≥55 years of age with 1 eye with dry AMD and GA were eligible for study entry. However, a subsequent amendment to the protocol limited inclusion to patients with noncentral GA. Noncentral GA and area were determined primarily by fundus autofluorescence (FAF) and all noncentral GA lesions were required to be ≥150 μm from foveal center with preserved outer retinal structural details, as confirmed by the central reading center Boston Imaging Research Center, Boston, MA. Noncentral GA was required to be ≥0.05 mm^2 and ≤10.16 mm^2 in size and reside completely within the FAF 30- or 35-degree image. In the study eye, patients could not have evidence of MNV by history, OCT, or fluorescein angiography; or had a BCVA by ETDRS score of ≥55 letters, an LL BCVA by ETDRS score of ≥10 letters, or an LL BCVA deficit (defined as the difference between BCVA and LL BCVA) of >5 letters. The fellow eye was allowed to have AMD with or without GA, MNV, central GA, or no pathology.

Key exclusion criteria for the study eye consisted of absence of observable hyper-FAF at the margins of the GA (only for lesions ≥0.25 mm^2), and atrophic retinal disease of causality other than AMD including myopia-related maculopathy and monogenetic macular dystrophies, such as pattern dystrophy and adult-onset Stargardt disease. Presence or diagnosis of exudative AMD or MNV, presence of retinal vein occlusion or vitreous hemorrhage, history of retinal detachment or macular hole, presence of an epiretinal membrane that causes distortion of the retinal contour, vitreomacular traction, or advanced glaucoma in the study eye were also not allowed. Full inclusion/exclusion criteria are summarized in Appendix 1 (available at https://www.ophthalmologyscience.org).

Study Objectives and End Points

The primary efficacy end points were changes from BL in LL BCVA and in square root (Sqrt) converted GA area as measured by OCT. Geographic atrophy was assessed by FAF and OCT with results yielding nearly exactly the same values. Secondary efficacy end points included changes in EZ integrity, defined as the macular percentage of tEZ attenuation, (i.e., EZ to RPE thickness of 0 microns [i.e., EZ absence]) and the macular percentage of pEZ attenuation (i.e., EZ to RPE thickness of ≤20 microns), categorical changes from BL in LL BCVA, changes from BL in low-luminance reading acuity, BCVA, and GA area as measured by FAF. For clarity, the EZ integrity measures reported here are not evaluating the actual thickness of the EZ band or the reflectivity/brightness of the EZ band. As noted, this measurement reflects the distance between the EZ band and the RPE band. Total EZ attenuation as noted above reflects complete loss of the EZ visualization. Partial EZ attenuation reflects abnormal thinning of the distance between the EZ and RPE (≤20 microns) that is often seen in degenerative outer retinal diseases (i.e., hydroxychloroquine toxicity, dry AMD). All EZ integrity end points were analyzed at the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research at the Cole Eye Institute of the Cleveland Clinic. All other imaging end points were analyzed by the Boston Image Reading Center. Additional predefined end points included change in central 1-mm and 2-mm mean EZ-RPE thickness, National Eye Institute Visual Function Questionnaire score, reading acuity at standard light, and visual function by the Low-Luminance Questionnaire. For efficacy end points, the unit of analysis was the study eye; in cases where both eyes were eligible for analysis, the study eye was the eye with the worse LL BCVA as determined at BL (right eye was the study eye for equal LL BCVA). Ellipsoid zone integrity was measured as previously described on spectral-domain OCT utilizing expert certified reader validation of a machine learning enhanced multilayer segmentation platform that provided panmacular assessment of the EZ and RPE location.[10,11] As previously described, initial automated segmentation generated panmacular segmentation of the EZ and RPE bands with an interpretable output.[37] Each B-scan was then reviewed by a certified expert reader for segmentation accuracy. Any segmentation errors were corrected as needed. An additional senior certified reader provided a sequential read oversight for segmentation consistency. This system is able to be used on both Cirrus (Zeiss) and Spectralis (Heidelberg) OCT scans (Appendix 2 SD-OCT protocol, available at www.ophthalmologyscience.org). All certified readers went through intensive training on recognition of EZ loss and degradation patterns and segmentation performance. This training consisted of >200 hours of hands-on training. The reading environment was standardized for lighting and displays. Internal quality control has demonstrated high consistency and agreement between certified readers and ground truth using both purely manual segmentation (without preplaced segmentation lines) and semiautomated segmentation as performed in this study across multiple retinal diseases. The intraclass correlation coefficients for the methodology used for this clinical trial are included from an independent dry AMD test set used for reading center quality control purposes in Supplement Table 1 (available at www.ophthalmologyscience.org) and demonstrate excellent agreement between multiple certified readers and ground truth (intraclass correlation coefficients 0.967−0.988) with both purely manual assessment approaches and using the semiautomated approach to measurements, as described for this trial.

The primary safety objective was to evaluate the safety/tolerability of elamipretide. Safety/tolerability evaluations included assessment of the incidence and severity of AEs/adverse device effects, incidence of conversion to MNV, changes from BL in vital sign measurements, electrocardiograms, clinical evaluations, clinical laboratory evaluations, slit lamp examination, and dilated fundus examination.

Statistical Analysis

Safety and efficacy variables were summarized descriptively. The safety population included all patients receiving ≥1 dose of investigational product. Efficacy was assessed in all randomized patients receiving ≥1 dose of study treatment and having ≥1 post-BL value for LL BCVA or GA area on OCT. A sample size of 180 patients provides ≥80% power to detect a 5-letter (1-line) difference in mean change from BL in LL BCVA between drug and placebo, assuming a standard deviation (SD) of 11 letters, at a 2-sided alpha-level of 0.10, and provides approximately 80% power to detect a 30% difference in the change from BL in Sqrt transformed total GA area by OCT between drug and placebo, assuming a SD of 0.2 mm/year, and an average change of 0.33 mm/year, at a 2-sided alpha-level of 0.1. The EZ assessments were designated as predefined exploratory end points and were not

adjusted for multiplicity. The analyses of these assessments are exploratory in nature, and only nominal *P* values were reported, accordingly. These exploratory end points are intended for research purposes and the generation of new hypotheses.

For continuous data, a mixed model for repeated measures was used for each eye separately (study eye), with fixed effects for the treatment arm, study visit, treatment arm-by-visit interaction, BL as a covariate, BL-by-visit interaction, random effect for subject, and using an unstructured covariance structure. The primary time point for analysis was week 48 (end of treatment visit) and the modified intention-to-treat population was the primary analysis population. A family-wise alpha level of 0.1 was maintained for the primary end point family, using Hochberg's procedure at the primary time point of 48 weeks.

Results

Patients

There were 176 patients randomized in the study (elamipretide n = 117; placebo n = 59). Of these, 114 and 59 patients, respectively, were included in the modified intention-to-treat populations. Forty-two patients (elamipretide n = 34 [29%]; placebo n = 8 [14%]) discontinued the study early and the remaining patients completed the study to 48 weeks. Subjects discontinuing the investigational drug, but willing to continue participation in the trial, remained in the trial and had all possible trial assessments completed per the schedule of assessments (with the exception of pharmacokinetic sampling), according to the visit schedule. The most common reasons for early discontinuation were withdrawal by subject (elamipretide n = 20; placebo n = 3) and AEs (elamipretide n = 10; placebo n = 4) (Table 1). The mean age was 76 years in both treatment arms and the mean (SD) BL BCVA values (letters) were 75.8 (9.09) and 76.6 (7.90), while LL BCVA values (letters) were 53.4 (16.17) and 58.8 (10.70) for the elamipretide and placebo groups, respectively. Twenty-seven patients (elamipretide n = 18; placebo n = 9) with central GA were included prior to a protocol amendment which limited enrollment to patients with noncentral GA only. Baseline ocular parameters were generally similar between treatment groups, although patients in the elamipretide group tended to have greater disease burden at BL as reflected by greater LL deficit, tEZ attenuation, and pEZ attenuation and lower central 1 mm mean EZ-RPE thickness compared with the placebo group (Table 2).

Efficacy for Visual Function and GA

Elamipretide did not meet the primary end points as the change from BL to week 48 in LL BCVA (least squares [LSs] mean [SD] −3.0 letters [1.20] vs. −4.4 letters [1.59] for elamipretide and placebo, respectively; $P = 0.49$), and for Sqrt transformed GA area as measured by OCT (0.312 mm [0.0230] vs. 0.275 mm [0.0304]; $P = 0.34$) were not statistically significantly different between the elamipretide and placebo groups at week 48 (Fig 2). There were also no significant differences between the elamipretide and placebo groups for the LS mean (SD) change from BL to week 48 for the secondary end points of low-luminance reading acuity (0.024 [0.0359] vs. 0.069 [0.0468]), BCVA (−3.3 [0.77] vs. −2.6 [1.00]; $P = 0.5642$) and change in GA area as measured by FAF (1.099 [0.0.0761] vs. 0.958 [0.1013]; $P = 0.2672$). As opposed to the results of mean change in LL BCVA (primary end point), elamipretide treatment was associated with nominally significantly more patients experiencing a ≥2-line gain (≥10 letter) in LL BCVA versus placebo (14.6% vs. 2.1%; $P = 0.0404$) (Fig 3).

Efficacy for EZ Preservation

Elamipretide was associated with significantly less progression of tEZ attenuation. Specifically, the LS mean change from BL to week 48 for macular percentage of tEZ attenuation (i.e., EZ-RPE thickness of 0 μm across macular cube) was 43% lower (3.69% [0.562] vs. 6.47% [0.737]; nominal $P = 0.0034$) in favor of the elamipretide group (Fig 4). Similarly, the LS mean change from BL to week 48 for pEZ attenuation (i.e., EZ-RPE thickness ≤20 μm across macular cube) was 47% lower (4.10% [0.737] vs. 7.68% [0.969]; nominal $P = 0.0040$) in the elamipretide group versus placebo. A post hoc analysis showed that LL BCVA changes were correlated with the change in tEZ attenuation ($r = -0.352$, nominal $P < 0.0001$). A separate post hoc analysis identified a significant correlation between BL central 1-mm EZ-RPE thickness and change in LL BCVA at week 48 ($r = 0.26$, nominal $P = 0.02$) in the elamipretide treatment group.

Table 1. Reasons for Discontinuation

Reason for Discontinuation	Elamipretide n (%)	Placebo n (%)	Overall n (%)
Subjects leaving study early	34 (29.1)	8 (13.6)	42 (23.9)
Related to coronavirus diease 2019	5 (4.3)	0	5 (2.8)
Reason for early discontinuation			
Adverse event	10 (8.5)	4 (6.8)	14 (8.0)
Lost to follow-up	1 (0.9)	0	1 (0.6)
Physician decision	1 (0.9)	1 (0.7)	2 (1.1)
Protocol violation	1 (0.9)	0	1 (0.6)
Withdrawal by subject	20 (17.1)	3 (5.1)	23 (13.1)
Other	1 (0.9)	0	1 (0.6)

Table 2. Patient Disposition and Baseline Characteristics (mITT Population)*

Characteristic	Elamipretide (n = 114)	Placebo (n = 58)
Age, yrs	76.0 (8.4)	75.8 (8.8)
LL BCVA	53.4 (16.17)	58.8 (10.70)
BCVA	75.8 (9.10)	76.6 (7.90)
LL deficit	22.4 (12.34)	17.8 (8.07)
Sqrt GA area by OCT, mm	1.47 (0.76)	1.38 (0.68)
GA area by OCT, mm^2	2.73 (2.42)	2.37 (2.17)
OCT GA distance to fovea	0.49 (0.37)	0.45 (0.35)
Extrafoveal/foveal GA, n (%)	96 (84)/18 (16)	49 (84)/9 (16)
Multifocal/unifocal GA, n (%)	85 (73)/32 (27)	43 (74)/15 (26)
Total EZ attenuation, %	16.01 (12.46)	12.20 (8.75)
Partial EZ attenuation, %	25.94 (19.58)	20.82 (15.29)
Central 1 mm mean EZ-RPE thickness	16.97 (12.66)	18.85 (12.11)

BCVA = best-corrected visual acuity; EZ = ellipsoid zone; GA = geographic atrophy; LL = low-luminance; mITT = modified intent-to-treat; RPE = retinal pigment epithelium; SD = standard deviation; Sqrt = square root.
*Mean ± (SD) unless otherwise indicated.

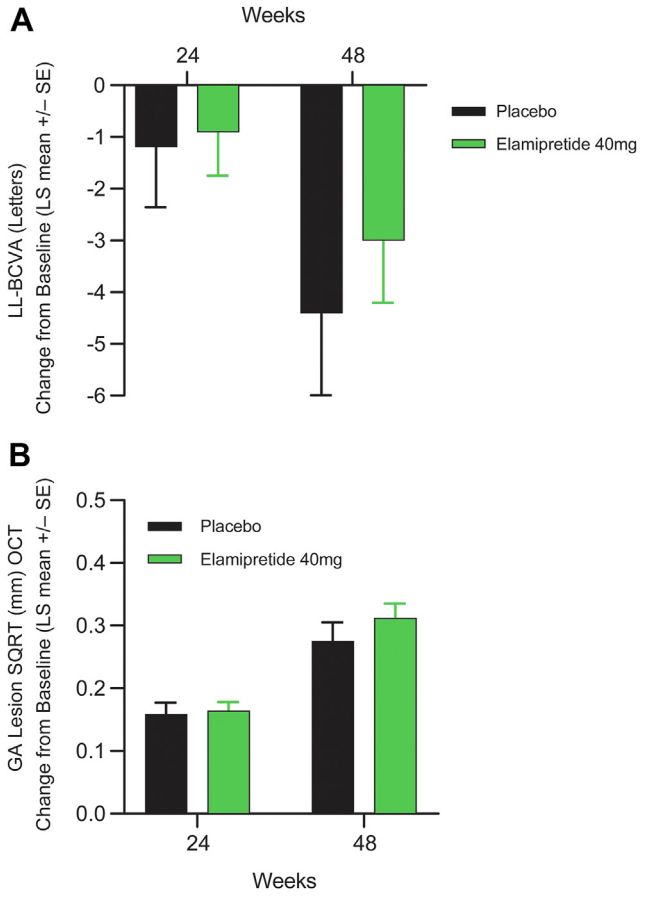

Figure 2. Mean change in LL-BCVA (**A**) and GA progression (**B**) least square means estimated from a mixed-effects model for repeated measures. The mITT population was used for the analysis, for LLVA, placebo n = 52 and 48 for 24 and 48 weeks, respectively while elamipretide n = 93 and 82, respectively. From GA assessment, placebo n = 48 and 45, for 24 and 48 weeks, respectively while elamipretide n = 89 and 76, respectively. GA = geographic atrophy; LL-BCVA = low-luminance best-corrected visual acuity; LLVA = low-luminance visual acuity; LS = least square; mITT = modified intent-to-treat; SE = standard error; SQRT = square root.

Representative EZ integrity maps are shown in Figure 5.

Safety

Adverse events were reported in 101 patients in the elamipretide group (86%) and in 42 of those receiving placebo (71%). The most common AEs were injection site reactions (ISRs), occurring more often in the elamipretide group than the placebo group (60% vs. 27%; Table 3). The most common ISRs were pruritus, injection site pain, bruising, erythema, induration, injection site mass, hypertrophy, and swelling, all occurring in >5% of those receiving elamipretide. The majority of ISRs were mild to moderate in intensity. Adverse events leading to treatment discontinuation occurred in 24.8% of patients in the elamipretide group and 15.2% of placebo-treated patients. The most common reason for early treatment discontinuation in the elamipretide group was ISRs (17.1%). There were no serious AEs or deaths in either treatment group that were considered related to study treatment.

Discussion

Geographic atrophy, a late stage of AMD, progresses over time and is associated with a loss of central vision.[21,37] Although the inhibition of GA progression has historically been used as a clinical end point in investigational trials of therapeutic agents, it has consistently been proven to be a challenging target to achieve.[38] Although we now have complement inhibitor agents to slow GA progression, to date these approaches have not demonstrated any favorable impact on visual function.[13,15] Therefore, there remains a significant unmet need to address the decline in visual function experienced by patients with GA secondary to AMD. Because of the complex pathophysiology of dry AMD, which involves multiple converging pathways, including complement activation, lipid metabolism, and mitochondrial injury,[6] effective disease management may require targeting multiple

pathways along the continuum of disease progression[7] that address different outcomes of interest.

In the ReCLAIM-2 study, changes from BL in either LL BCVA or Sqrt converted GA area were not significantly altered after 48 weeks of elamipretide therapy; however, analysis of progressive photoreceptor degeneration (assessed by tEZ and pEZ attenuation) was significantly impacted by elamipretide treatment. Previous studies suggest that the overall results of this study may be a function of time—noting that EZ attenuation has been shown to predict areas of GA growth by 2 to 3 years[12]—and the GA will grow into the area of preexisting photoreceptor loss (tEZ attenuation). This suggests that once EZ attenuation has progressed beyond a critical threshold, mitochondria-targeted therapeutic agents, such as elamipretide, could not alter the resulting trajectory of underlying RPE loss/GA formation. The results observed in the ReCLAIM-2 trial related to GA may not be unexpected when BL patient characteristics are considered since the trial was randomized and balanced on GA area at BL, with no a priori stratification for EZ parameters. In general, the mean tEZ attenuation area was approximately 2 times greater than and extending well beyond the area of GA, suggesting that there is extensive photoreceptor loss in areas with intact RPE. Therefore, it's reasonable to surmise that GA progression into surrounding retinal tissue may not be altered where there is no target for a mitochondrial therapy, such as elamipretide.

The root cause of vision loss in dry AMD is photoreceptor death; therefore, protection of photoreceptors from damage and delaying their degeneration are key approaches to successful management of dry AMD.[8] A regulatory agency and several professional organizations have confirmed that preventing photoreceptor damage/loss would be considered a clinically meaningful end point, given the established link between photoreceptor loss, visual function, and the importance of photoreceptor preservation.[40] The assessment of EZ attenuation as a marker of photoreceptor loss/dysfunction and a predictor of future GA progression has been well established across many diseases, including a link to visual function.[10,16,41,42] These measures of EZ integrity are important clinical end points for future clinical trials in dry AMD.[39]

In ReCLAIM-2, elamipretide was associated with significantly more patients experiencing a ≥2-line gain at week 48 in LL BCVA versus placebo. It was previously hypothesized, based on preclinical data, that elamipretide may protect and potentially restore photoreceptor function in dry AMD.[35] The improvements observed in categorical

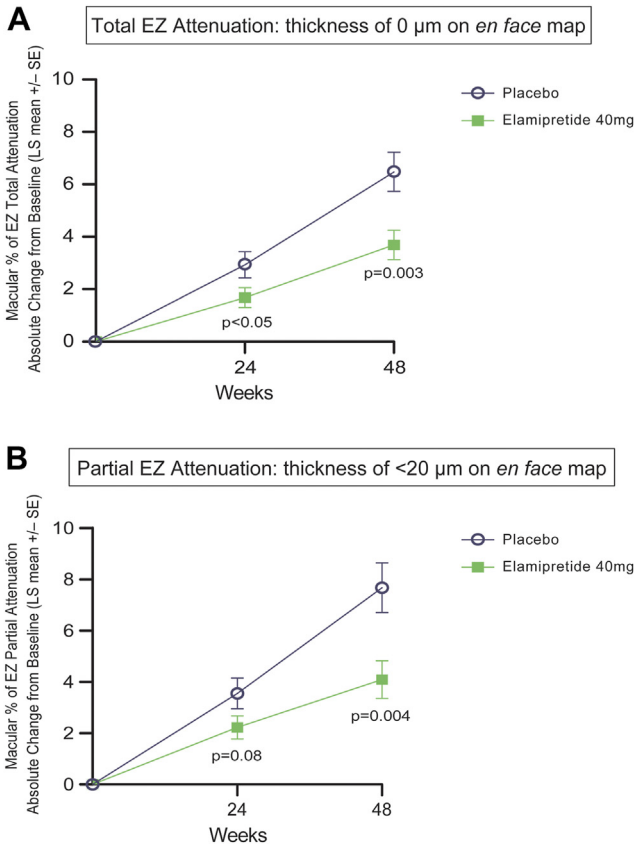

Figure 4. Total (**A**) and partial (**B**) EZ attenuation. Least square means estimated from a mixed-effects model for repeated measures. The mITT population was used for the analysis, for total attenuation, placebo n = 50 and 42 for 24 and 48 weeks, respectively while elamipretide n = 89 and 71, respectively. From partial attenuation, placebo n = 50 and 42, for 24 and 48 weeks, respectively while elamipretide n = 89 and 71, respectively. Statistical analysis showing nominal "*P* values." Macular percent refers to the percent of the macular area included within the SD-OCT scan (target is 6 mm × 6 mm). EZ = ellipsoid zone; LS = least square; mITT = modified intent-to-treat; SD-OCT = spectral-domian OCT; SE = standard error.

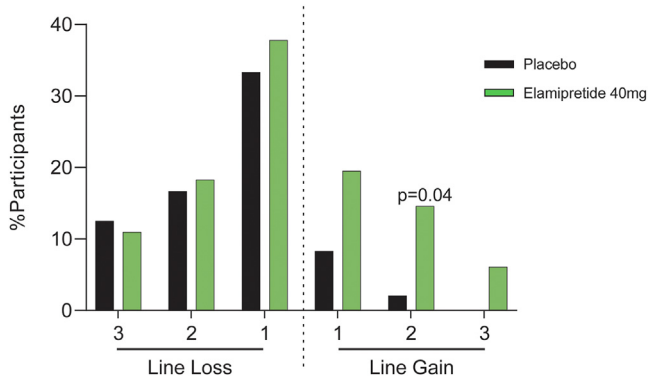

Figure 3. Categorical improvement in LLVA*. The mITT population was used for the analysis, placebo n = 48 and elamipretide n = 82. LLVA = low-luminance visual acuity; mITT = modified intent-to-treat. **P* value significant for 2-line change only.

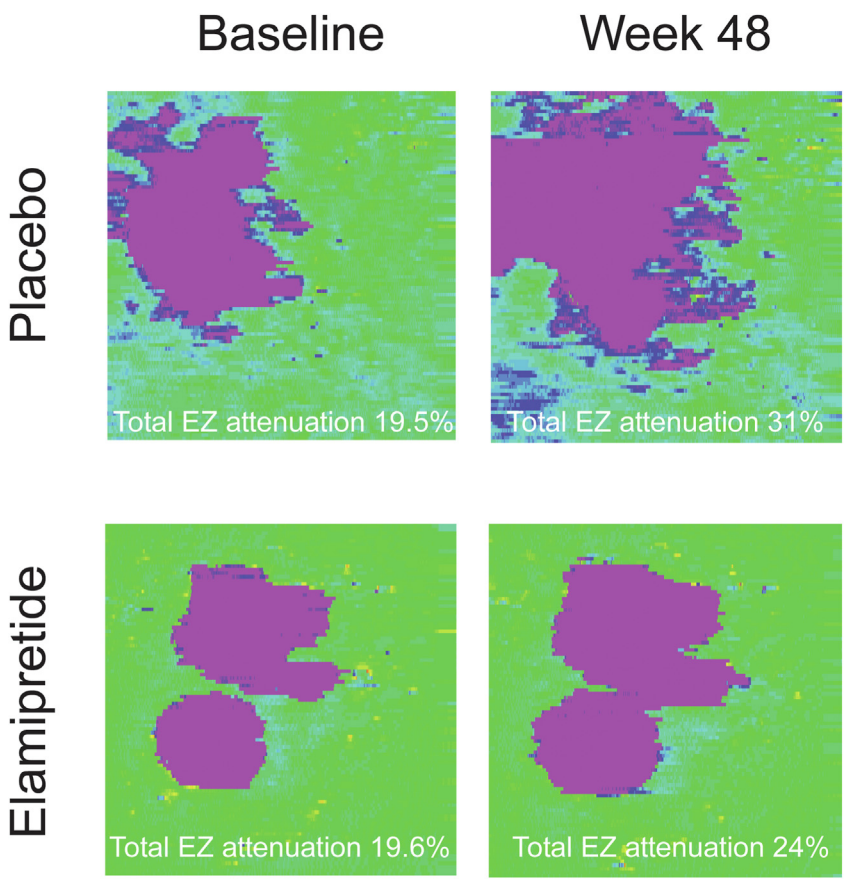

Figure 5. Representative EZ integrity maps (i.e., EZ-RPE thickness map of the macular cube). Pink represents total attenuation and blue represents partial attenuation. Maps were matched for degree of baseline tEZ attenuation and growth from baseline to week 48 in exemplary patients of the placebo treatment, and elamipretide treatment arms are illustrated demonstrating increased EZ loss in the foveal group at week 48 (i.e., increased are of pink) compared with the elamipretide group. The fovea is centrally located in the image. EZ = ellipsoid zone; RPE = retinal pigment endothelium; tEZ = total ellipsoid zone.

LL BCVA may support this conclusion. The ReCLAIM-2 data demonstrate that 48 weeks of elamipretide therapy resulted in significantly less progression of tEZ attenuation (a 43% reduction) and pEZ attenuation (a 47% reduction) relative to placebo, supporting the hypothesis that photoreceptor preservation is potentially achievable with elamipretide. Correlations observed in ReCLAIM and now in ReCLAIM-2, between both BL EZ integrity as well as elamipretide-mediated EZ preservation and elamipretide-mediated changes in visual function, support a conclusion that mitigation of progressive EZ attenuation may allay or potentially reverse progressive visual decline in dry AMD. These findings support the clinical relevance of these anatomical end points. These novel findings also support the potential utility of elamipretide, a mitochondria-targeted therapeutic for dry AMD, and support its continued development for amelioration, or even reversal, of the functional visual decline experienced by patients with this devastating disease.

As noted, more patients treated with elamipretide discontinued the ReCLAIM-2 study early as compared with placebo with the most common reasons being "withdrawal by subject" and "AEs." The initiation and duration of the trial was impacted by global events. Patients were randomized into treatment either just prior to or during the coronavirus disease 2019 pandemic, likely complicating the ability of patients to attend visits and leading to discontinuation of the study. This rate of discontinuation is consistent with that of other similar trials within the dry AMD sector conducted in the similar timeframe.[43-46] In addition to coronavirus disease 2019, ISRs, the most common reported AE, were a contributor to the discontinuation rate. The ISRs, a well-known event with subcutaneous elamipretide, were generally mild to moderate in nature and were self-resolving. However, ISRs in the setting of the coronavirus disease 2019 pandemic may have influenced patients' decisions to discontinue the study. During the conduct of the phase III development program, ISR mitigation strategies are available for investigators to offer their patients, if necessary, which will likely enhance tolerability, compliance, and maintenance within the study.

The results of ReCLAIM-2 provide evidence that elamipretide can beneficially alter EZ attenuation. While the ReCLAIM-2 trial did not meet its primary end points (i.e., mean change in LL BCVA and mean change in Sqrt transformed GA progression), the study did demonstrate

Table 3. Adverse Events (≥5%)

Event, n (%)	Elamipretide (n = 117)	Placebo (n = 59)
Total AEs	101 (86)	42 (71)
Serious AEs	18 (15)	6 (10)
Drug related AEs	0	0
Deaths	2 (1.7)*	0
Study eye converted to wet AMD/MNV	6 (5)	4 (7)
Injection site AEs	70 (60)	16 (27)
Pruritus	46 (39.3)	0
Pain	33 (28.2)	6 (10.2)
Bruising	15 (12.8)	11 (18.6)
Erythema	22 (18.8)	0
Hemorrhage	17 (14.5)	4 (6.8)
Induration	16 (13.7)	3 (5.1)
Hypertrophy	10 (8.5)	4 (6.8)
Mass	13 (11.1)	0
Swelling	11 (9.4)	0
Eosinophil count increased	7 (6.0)	0
Pneumonia	6 (5.1)	1 (1.7)
Urinary tract infection	4 (3.4)	7 (11.9)
Arthralgia	1 (0.9)	3 (5.1)

AE = adverse event; AMD = age-related macular degeneration; COVID-19 = coronavirus disease 2019; MNV = macular neovascularization; SD = standard deviation.
Displayed as mean ± (SD).
*One COVID-19 and 1 respiratory failure, deemed unrelated to drug.

biologic activity and suggest that the mitochondria-targeting agent, elamipretide, should be further evaluated for treatment of dry AMD in stages where the necessary structural elements (photoreceptors, RPE, and associated mitochondria) are still viable and capable of functional improvement.

Overall, the results from this phase II clinical trial have informed the design criteria, end point selection (EZ integrity related, non-GA), and patient disposition (smaller GA lesion size, more intact retinal structures) for follow-on clinical trials to investigate elamipretide in dry AMD. The incorporation and implementation of the EZ integrity analyses into ReCLAIM-2 have served to build additional substantive and exploratory evidence that justifies the use of EZ integrity measures as a primary efficacy end point to evaluate the structural and functional outcomes in dry AMD patients. The ongoing phase III elamipretide clinical trial program (ReNEW and ReGAIN) will investigate and report the results that chronic elamipretide therapy will have in this dry AMD population.

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This article contains supplemental material. The following should appear as supplemental material: Table S1, Appendix 1, Appendix 2.

Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **BL** = baseline; **EZ** = ellipsoid zone; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **ISR** = injection site reaction; **LL BCVA** = low-luminance best-corrected visual acuity; **LS** = least square; **MNV** = macular neovascularization; **pEZ** = partial ellipsoid zone; **RPE** = retinal pigment endothelium; **SD** = standard deviation; **Sqrt** = square root; **tEZ** = total ellipsoid zone.

Keywords:
Age-related macular degeneration, Elamipretide, Ellipsoid zone, Geographic atrophy, Visual acuity.

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