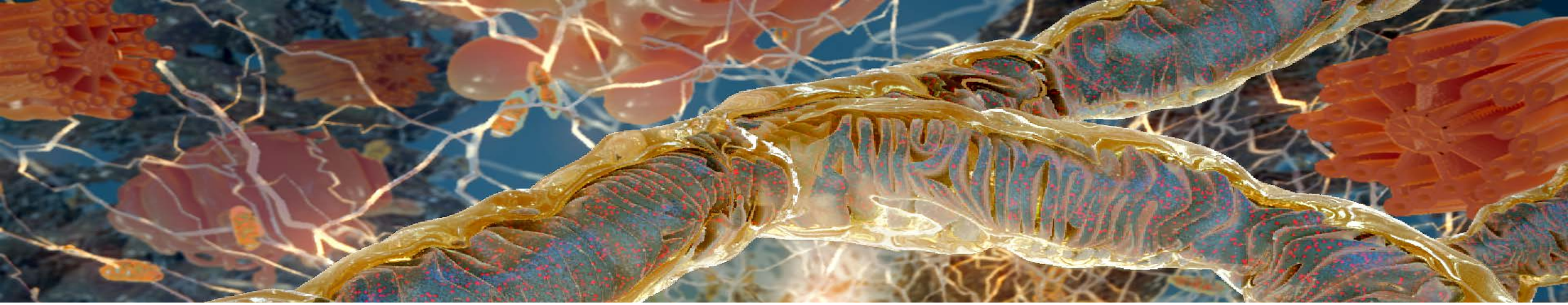
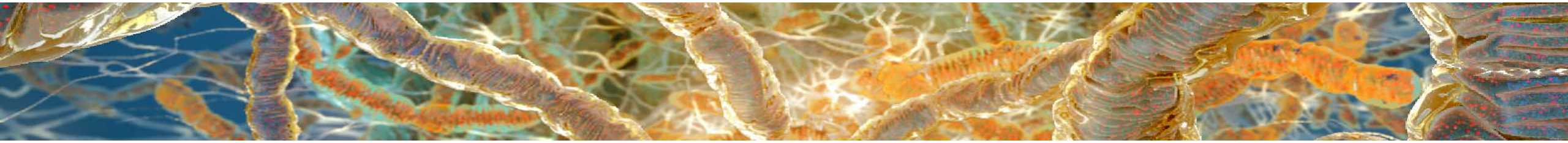


ReCLAIM-2 Study Topline Results

A Phase 2 Study of Elamipretide Safety & Efficacy in Geographic Atrophy



Stealth BIOTHERAPEUTICS

21MAY2022

Disclosures

Consultant

4DMT, Abpro, Adverum, Aerie, Affamed, Aldeyra, Allegro, Allergan, Allgenesis, Annexon, **Apellis**, Aprea, AsclepiX, Aviceda, Bayer, BVT, Chengdu Kanghong, DTx, Eloxx, Galimedix, Genentech, Inc., Graybug, Gyroscope, Hemera, Horizon, Iveric Bio, Janssen, jCyte, Kodiak, Lensgen, NGM, Notal Vision, Novartis, Ocular Therapeutix, Oriole, Oxurion, Palatin, Regeneron, Regenxbio, Roche, Santen, SciFluor, Stealth, Surrozen, Thea, Verseon, Vinci; Grant Support: Apellis, AsclepiX, Bayer, Chengdu Kanghong, Gyroscope, Hemera, Iveric Bio, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, Stealth; Stock/Stock Options: Adverum, Aldeyra, Allegro, Aviceda, DTx, jCyte, Ocular Therapeutix, Vinci

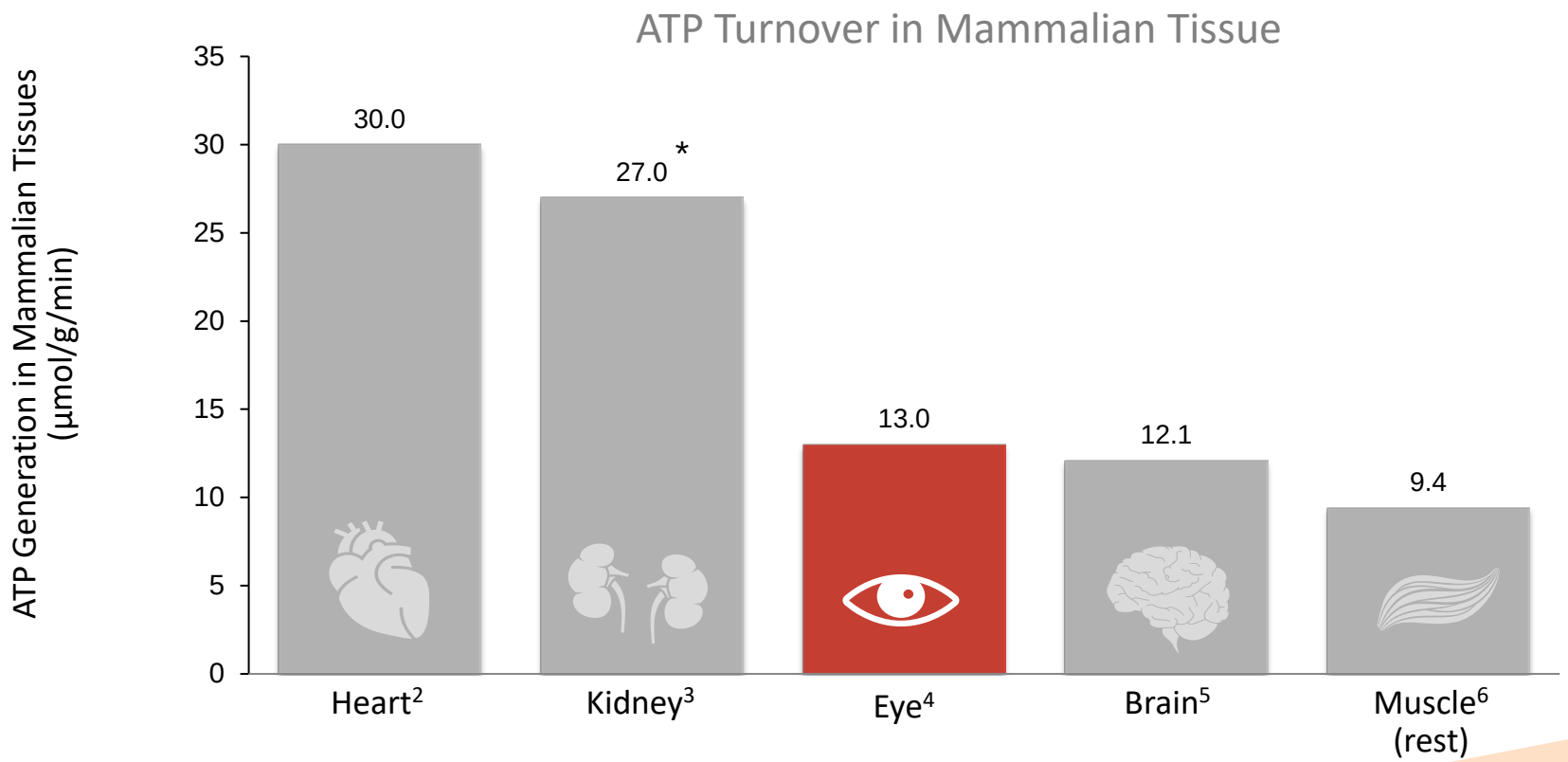
Research funding

- Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric , Kanghong, Kodiak, NGM, Notal Vision, Novartis, Regeneron, Regenxbio, and **Stealth**

- Studies funded by Stealth Biotherapeutics

Rationale for Targeting Mitochondria & Energy Demands in the Eye

The eye is one of the largest energy (ATP) producers and consumers in the human body



Optimal mitochondrial function decreases with age

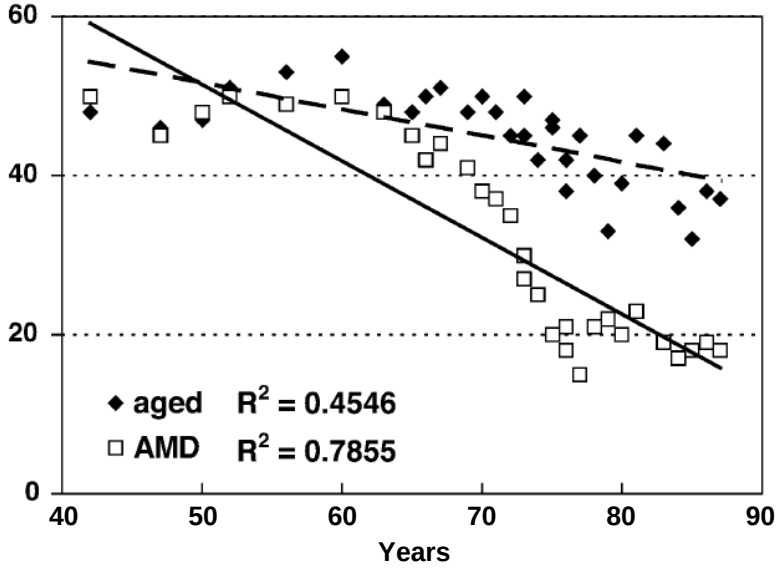
Prevalence of AMD increases with age

Liu et al., Int. J. Mol. Sci. 2021, 22, 3689, 2, Stanley, et al. Physiol Rev. 2005: 3, Soltoff, et al. Ann. Rev. Physiol. 1986: 4, Okawa, et al. Curr Biol. 2008: 5, Lei, et al. PNAS. 2003: 6, Befroy, et al. Diabetes

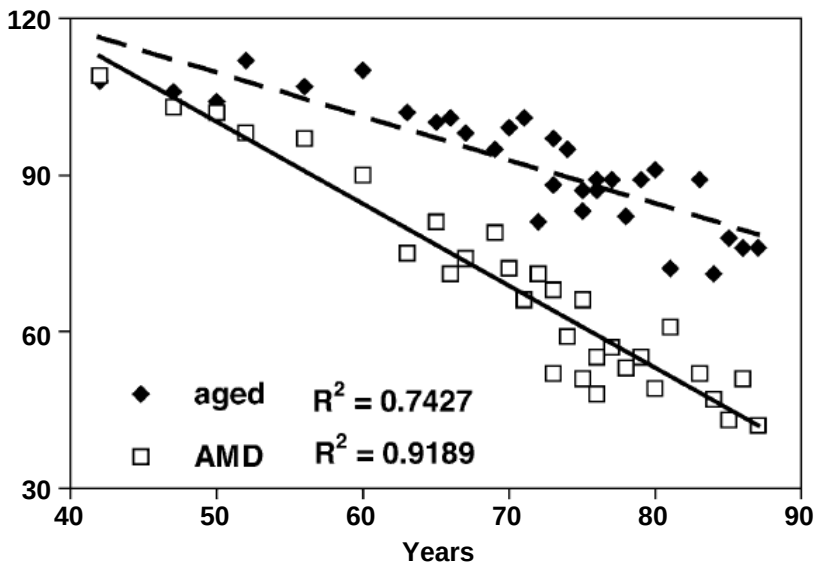
Progressive Mitochondrial Dysfunction Contributes to AMD

Changes in RPE mitochondrial properties in aged vs AMD eyes

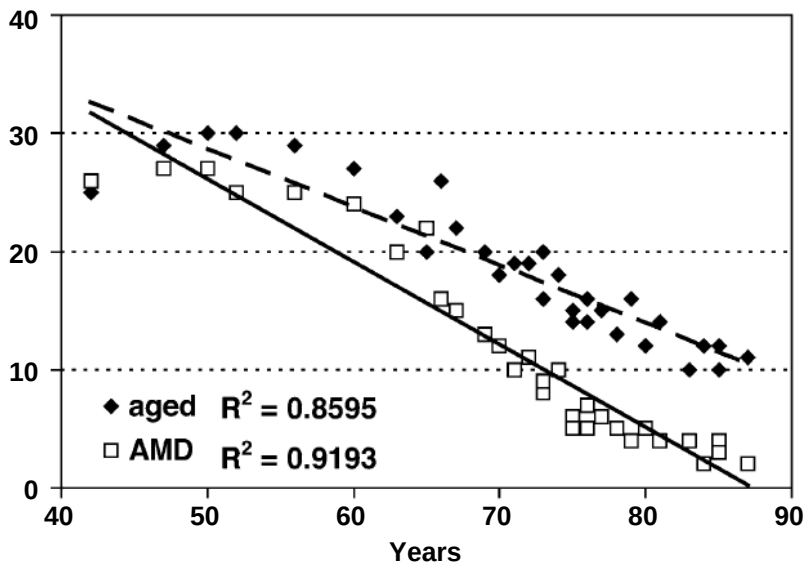
# of mitochondria/cell



Mean mitochondrial area (μm²/cell)



# of cristae/mitochondrion



RPE mitochondria in AMD eyes undergo more pronounced degenerative changes, with lower mitochondrial density, organelle area, and cristae number

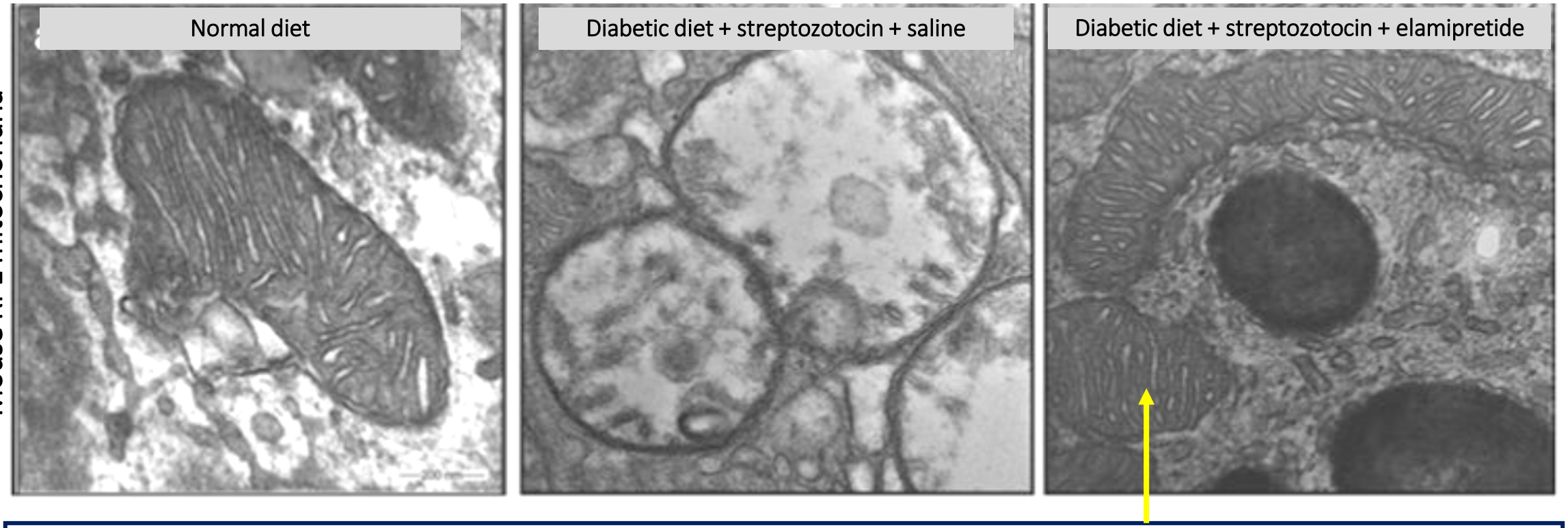
Feher J, Kovacs I, Artico M, et al. *Neurobiol Aging*. 2006;27(7):983-993.

Perkins et al. Molecular Vision 2003; 9:60-73

Elamipretide Protects Mitochondria in Diabetic Mouse Model

Elamipretide: mitochondria-targeted agent that **1**.) improves inner mitochondrial membrane stability, **2**.) enhances ATP synthesis and **3**.) reduces pathogenic reactive oxygen species (ROS)

Mouse RPE mitochondria



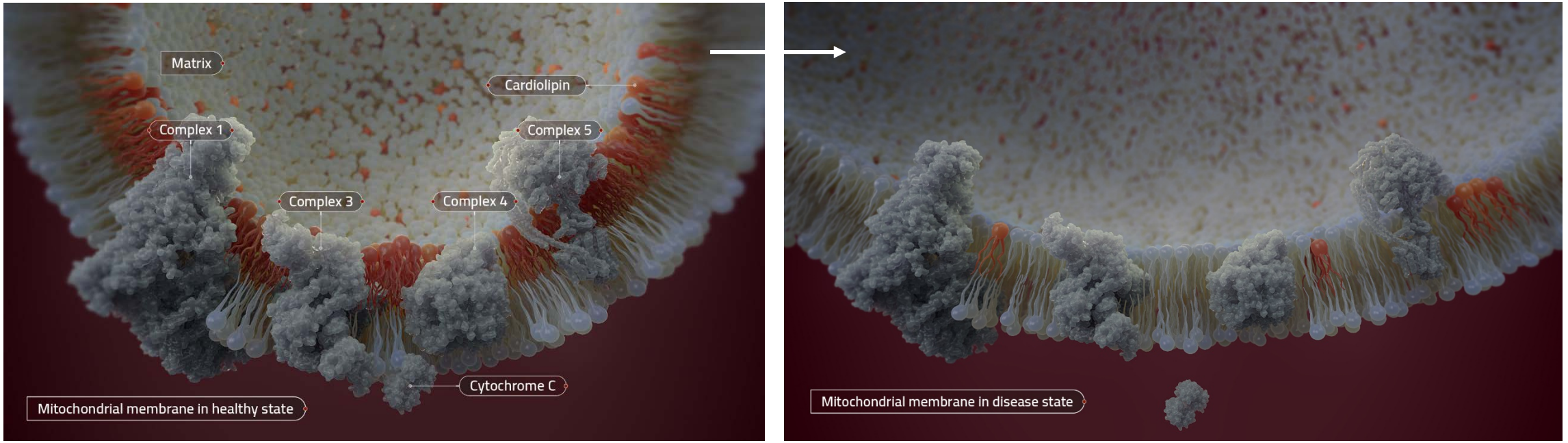
In diabetic mice treated with elamipretide, mitochondria retain normal architecture and cristae structure

Mitochondrial Inner Membrane is Disrupted in Disease

Mechanism of disease

In healthy states, cardiolipin promotes inner mitochondrial membrane curvature to organize respiratory complexes

ROS-mediated damage of cardiolipin disrupts cristae curvature and organization of respiratory complexes



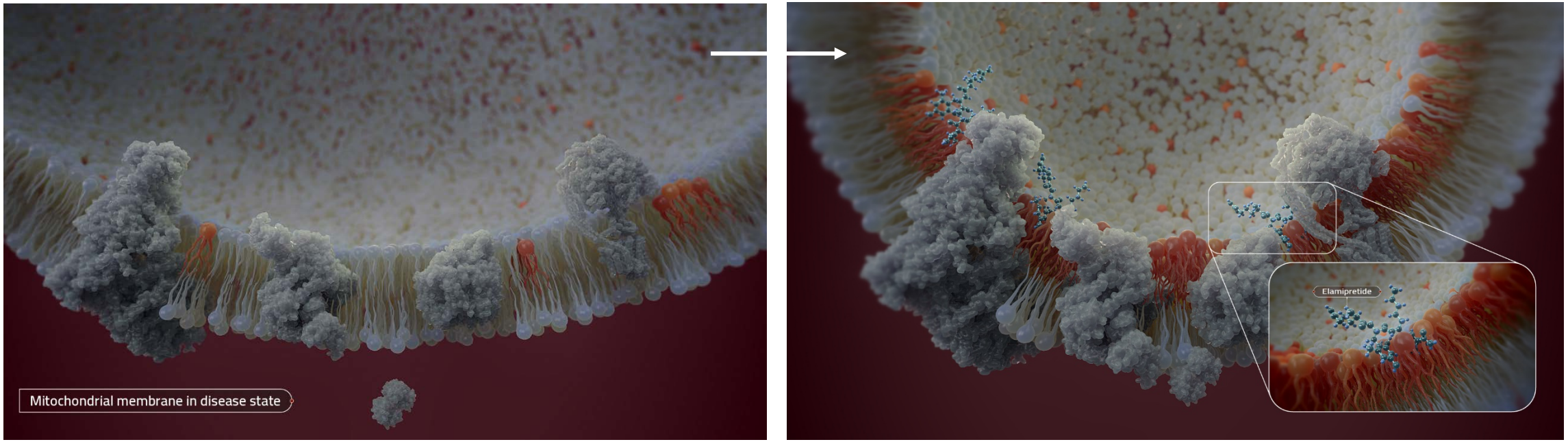
ROS, Reactive oxygen species

Elamipretide Binding to Cardiolipin Stabilizes the Inner Mitochondrial Membrane Structure

Mechanism of action

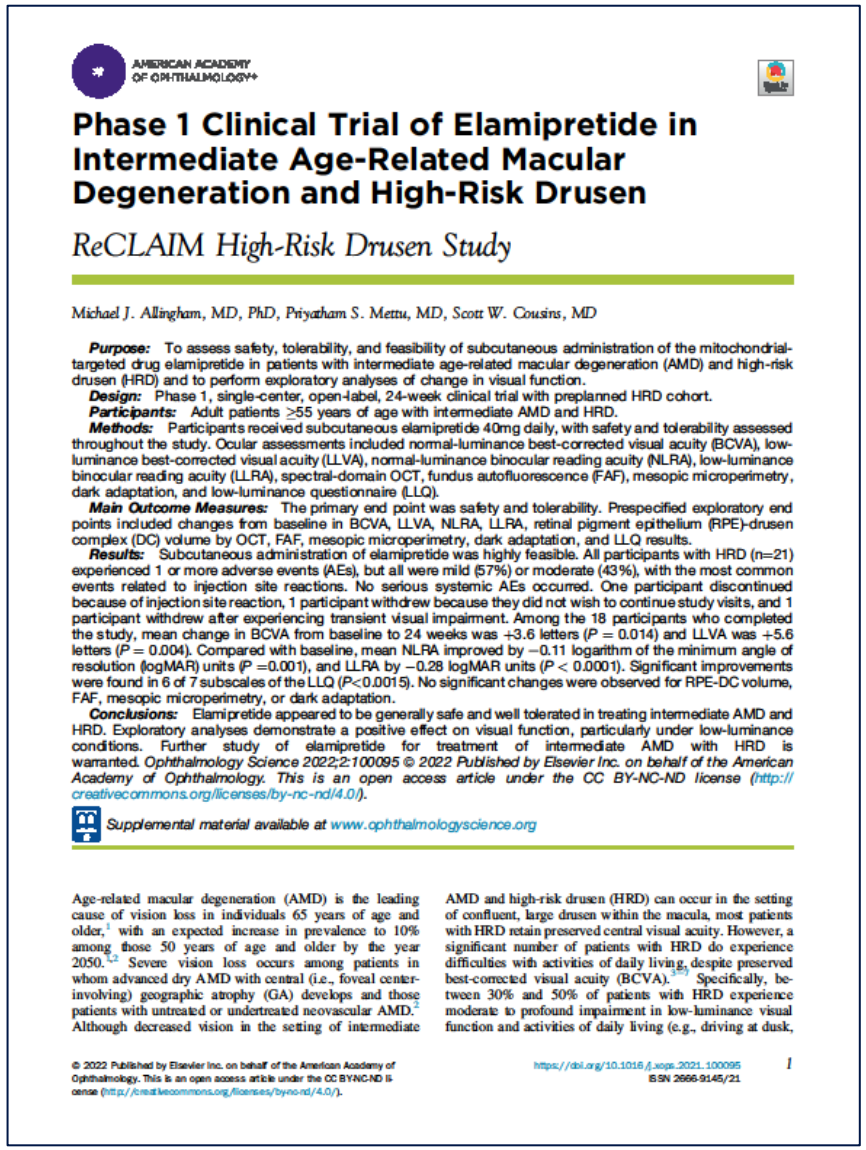
ROS-mediated damage of cardiolipin disrupts cristae curvature and organization of respiratory complexes

Elamipretide binds to cardiolipin and restores mitochondrial structure and function



ROS, Reactive oxygen species

ReCLAIM Trial: Proof of Concept in AMD (HRD and NCGA)



AMERICAN ACADEMY OF OPHTHALMOLOGY+

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 40mg 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.

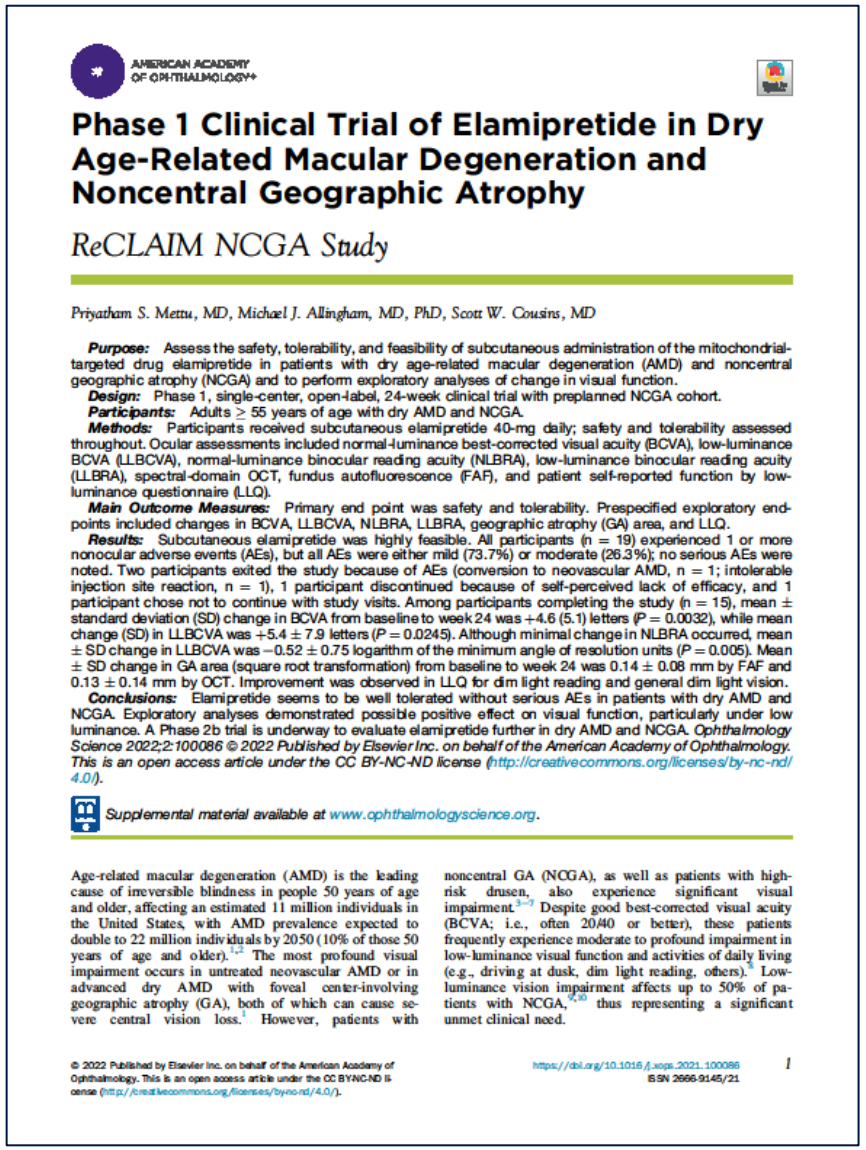
Results: Subcutaneous administration of elamipretide was highly feasible. All participants with HRD (n=21) experienced 1 or more adverse events (AEs), but all were mild (57%) or moderate (43%), with the most common events related to injection site reactions. No serious systemic AEs occurred. One participant 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.

Supplemental material available at www.ophthalmologyscience.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).[3–5] 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,

https://doi.org/10.1016/j.xops.2021.100095
ISSN 2666-9145/21



AMERICAN ACADEMY OF OPHTHALMOLOGY+

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

ReCLAIM NCGA Study

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

Purpose: Assess the safety, tolerability, and feasibility of subcutaneous administration of the 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: Adults ≥ 55 years of age with dry AMD and NCGA.

Methods: Participants received subcutaneous elamipretide 40-mg daily; safety and tolerability assessed throughout. Ocular assessments included normal-luminance best-corrected visual acuity (BCVA), low-luminance BCVA (LLBCVA), normal-luminance binocular reading acuity (NLBRA), low-luminance binocular reading acuity (LLBRA), spectral-domain OCT, fundus autofluorescence (FAF), and patient self-reported function by low-luminance questionnaire (LLQ).

Main Outcome Measures: Primary end point was safety and tolerability. Prespecified exploratory end-points included changes in BCVA, LLBCVA, NLBRA, LLBRA, geographic atrophy (GA) area, and LLQ.

Results: Subcutaneous elamipretide was highly feasible. All participants (n = 19) experienced 1 or more nonocular 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 because of AEs (conversion to neovascular AMD, n = 1; intolerable injection site reaction, n = 1), 1 participant discontinued because of self-perceived lack of efficacy, and 1 participant chose not to continue with study visits. Among participants completing the study (n = 15), mean ± standard deviation (SD) change in BCVA from baseline to week 24 was +4.6 (5.1) letters ($P = 0.0032$), while mean change (SD) in LLBCVA was +5.4 ± 7.9 letters ($P = 0.0245$). Although minimal change in NLBRA occurred, mean ± SD change in LLBCVA was −0.52 ± 0.75 logarithm of the minimum angle of resolution units ($P = 0.005$). Mean ± SD change in GA area (square root transformation) 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 seems to be well tolerated without serious AEs in patients with dry AMD and NCGA. Exploratory analyses demonstrated possible positive effect on visual function, particularly under low luminance. A Phase 2b trial is underway to evaluate elamipretide further in dry AMD and NCGA.

Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people 50 years of age 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 of age 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 noncentral GA (NCGA), as well as patients with high-risk drusen, also experience significant visual impairment.[3–7] Despite good best-corrected visual acuity (BCVA; 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 patients with NCGA,[9,10] thus representing a significant unmet clinical need.

https://doi.org/10.1016/j.xops.2021.100086
ISSN 2666-9145/21

ReCLAIM-2 Trial Design

Screening	BL	W4	W8	W12	W24	W36	W48	W52: Washout

NCGA area ≥0.05mm^2/ <10.16 mm^2

≥150 µm from foveal center

BCVA ≥ 55 letters

LLVA ≥ 10 letters

>5 letters low luminance deficit

ELAMIPRETIDE
n=117

PLACEBO
n=59

FOLLOW-UP

PRIMARY ENDPOINT FAMILY

- Mean change in low luminance best-corrected visual acuity (LLVA)
- Change in geographic atrophy (GA) area by optical coherence tomography (OCT)

SECONDARY/EXPLORATORY ENDPOINTS

- Categorical change in LLVA
- Ellipsoid zone (EZ) attenuation and associated biomarkers of retinal and mitochondrial health
- Conversion to choroidal neovascularization (wet AMD)

* ClinicalTrials.gov Identifier: NCT03891875 for additional trial details

ReCLAIM-2 Patient Disposition and Baseline Characteristics

	Elamipretide	Placebo
Treated	117	59
mITT Population (%)	114 (97.4)	58 (98.3)
Early Discontinuation from Study (%)	34 (29.1)	8 (13.6)
Age (SD)	76.0 (8.4)	75.8 (8.8)
LL BCVA (SD)	53.4 (16.17)	58.8 (10.70)
BCVA (SD)	75.8 (9.10)	76.6 (7.90)
LL Deficit (SD)	22.4 (12.34)	17.8 (8.07)
Sqrt GA Area (mm) by OCT (SD)	1.47 (0.76)	1.38 (0.68)
GA Area (mm^2) by OCT (SD)	2.73 (2.42)	2.37 (2.17)
OCT GA Distance to Fovea (SD)	0.49 (0.37)	0.45 (0.35)
Extrafoveal (%)/Foveal (%)	96 (84)/18 (16)	49 (84)/9 (16)
Multi (%)/Unifocal (%)	85 (73)/32 (27)	43 (74)/15 (26)
% Total EZ Attenuation (SD)	16.01 (12.46)	12.20 (8.75)
% Partial EZ Attenuation (SD)	25.94 (19.58)	20.82 (15.29)
Central 1mm Mean EZ-RPE Thickness (SD)	16.97 (12.66)	18.85 (12.11)

ReCLAIM-2: Safety Profile Consistent with Previous Clinical Experience

	Elamipretide 40 mg N=117 (%)	**Placebo N=59 (%)**
Adverse Events	101 (86%)	42 (71)
Injection Site adverse events	70 (60%)	16 (27)
Serious adverse events Drug related Deemed unrelated to drug	 0 18 (15%)	 0 6 (10%)
Deaths	2 COVID-19 Respiratory Failure	0
Study eye converted to Wet AMD/CNV	6 (5%)	4 (7%)

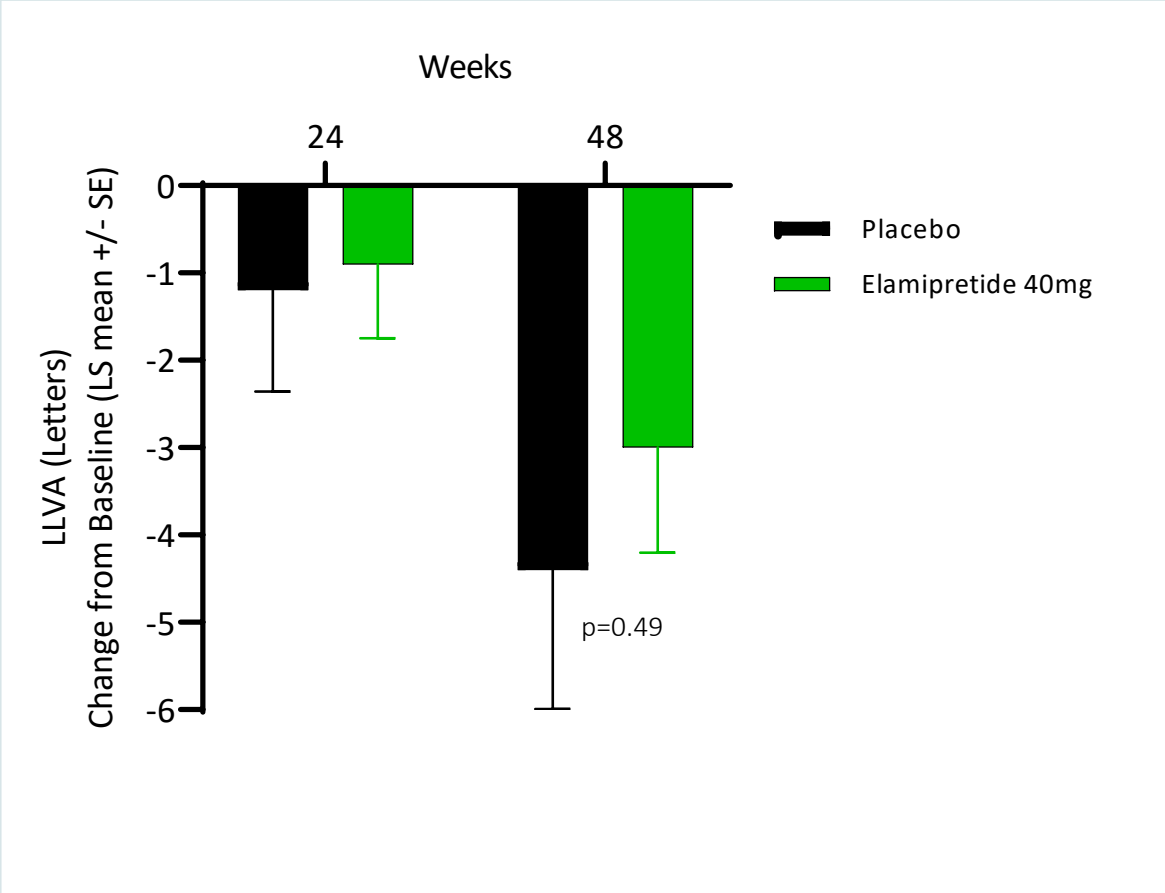
Adverse Events Occurring >5%

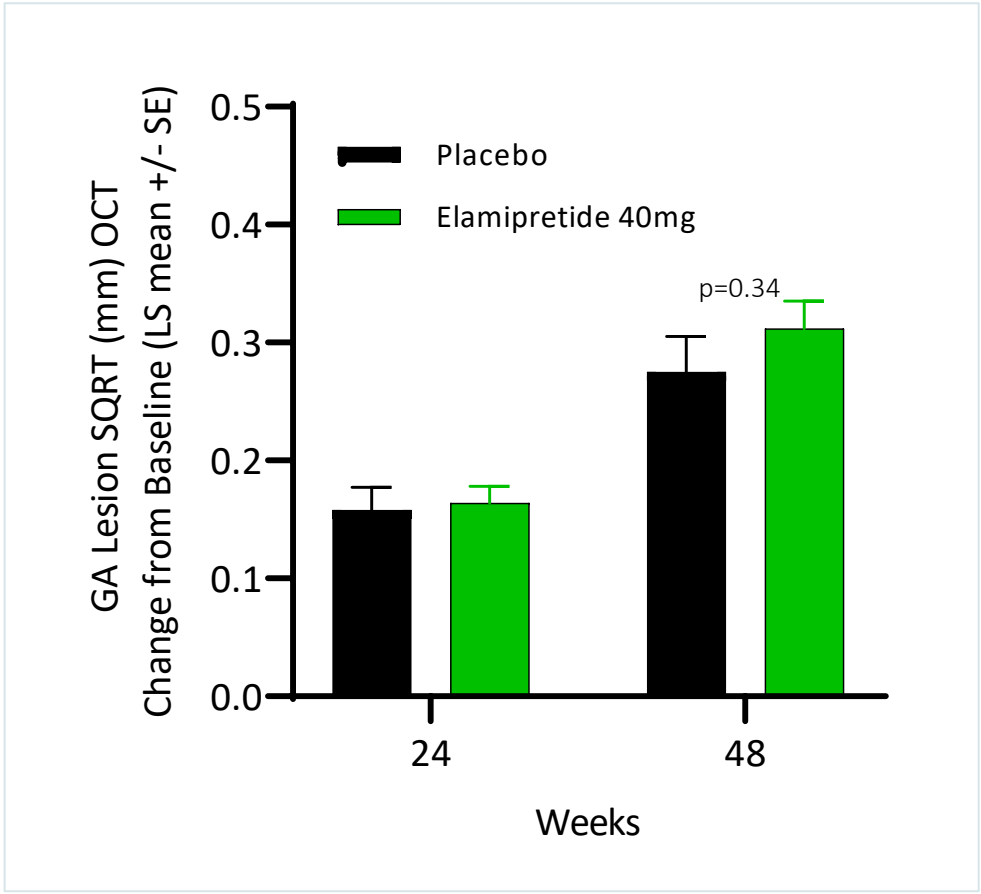
SOC Preferred Term	Elamipretide 40 mg N=117 (%)	Placebo N=59 (%)
General disorders and administration site conditions		
Injection site pruritus	46 (39.3)	0
Injection site pain	33 (28.2)	6 (10.2)
Injection site bruising	15 (12.8)	11 (18.6)
Injection site erythema	22 (18.8)	0
Injection site hemorrhage	17 (14.5)	4 (6.8)
Injection site induration	16 (13.7)	3 (5.1)
Injection site hypertrophy	10 (8.5)	4 (6.8)
Injection site mass	13 (11.1)	0
Injection site swelling	11 (9.4)	0
Infections and infestations		
Urinary tract infection	4 (3.4)	7 (11.9)
Pneumonia	6 (5.1)	1 (1.7)
Investigations		
Eosinophil count increased	7 (6.0)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.9)	3 (5.1)

*Preferred terms for events occurred in >5% of subjects in either group are displayed

ReCLAIM-2 Primary Endpoint Family

Primary endpoints of mean change in LLVA and GA progression measured by OCT were not significant

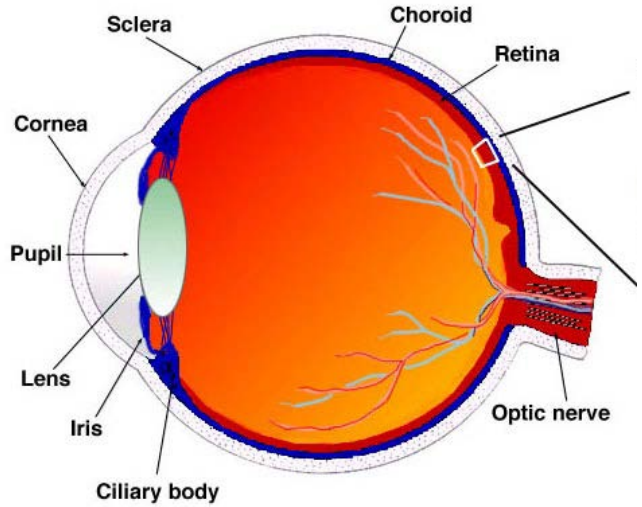


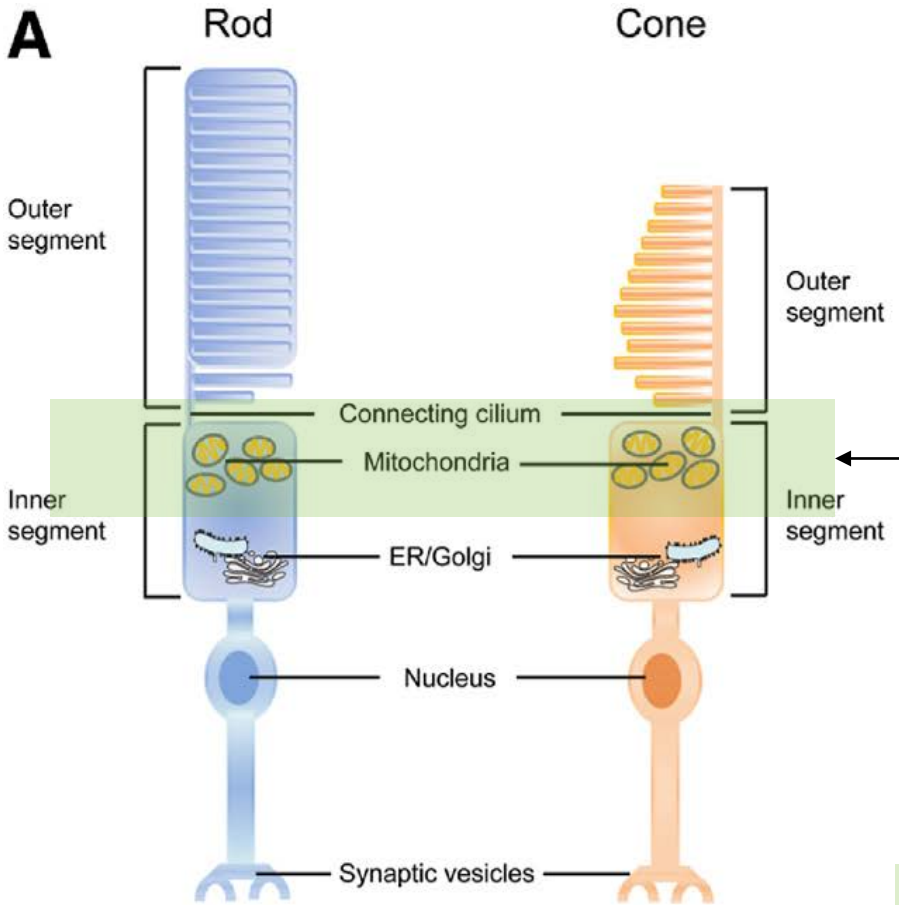


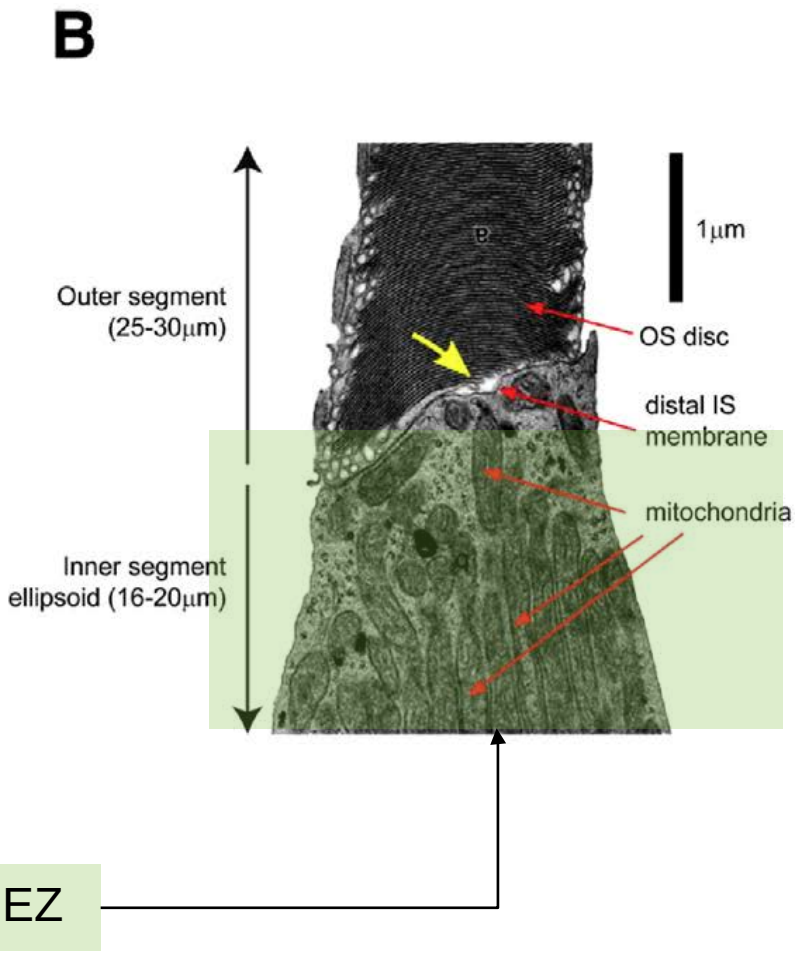
Least Square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, for LLVA, placebo n=52 and 48 for 24 and 48 weeks, respectively while elamipretide n=93 and 82, respectively. From GA assessment, placebo n=48 and 45, for 24 and 48 weeks, respectively while elamipretide n=89 and 76, respectively.

Retinal Anatomy: Focus on the Mitochondria-Rich Ellipsoid Zone

The EZ suffers progressive damage that precedes vision loss and GA in dry AMD

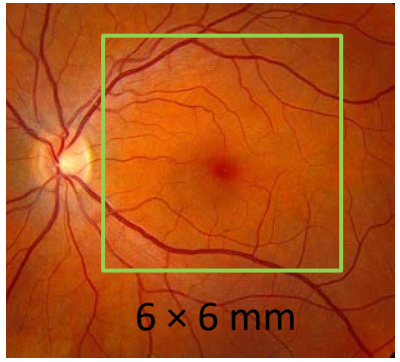




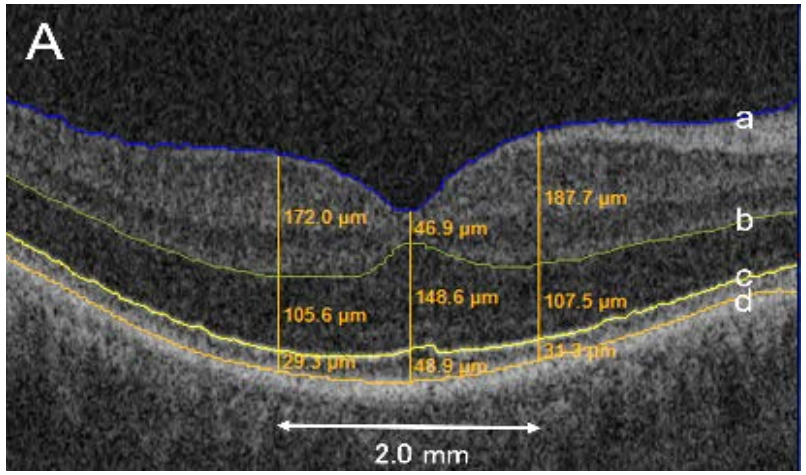


Analysis of the Mitochondria-Rich Ellipsoid Zone (EZ)

EZ attenuation as a clinical trial endpoint (e.g. ReCLAIM-2, MacTel, Stargardt)



OCT



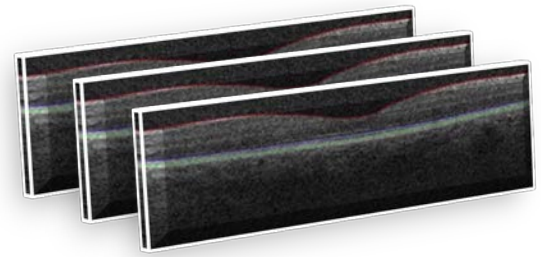
a) ILM

b) Between OPL/ONL

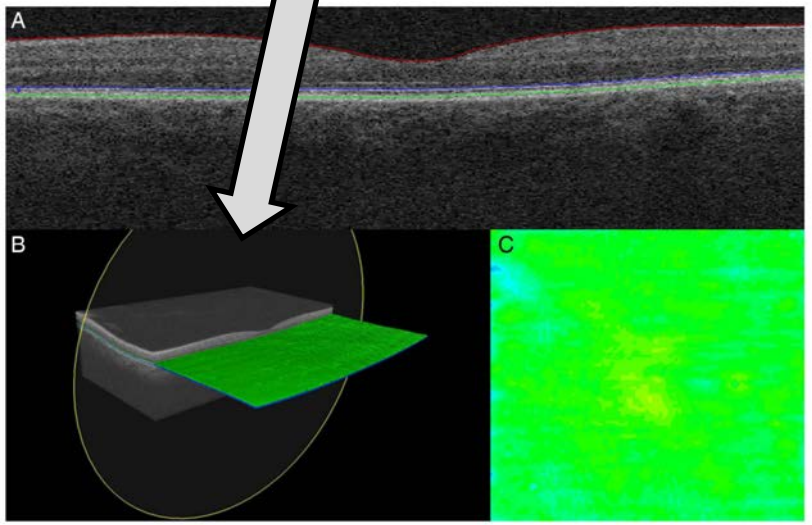
c) EZ

d) RPE

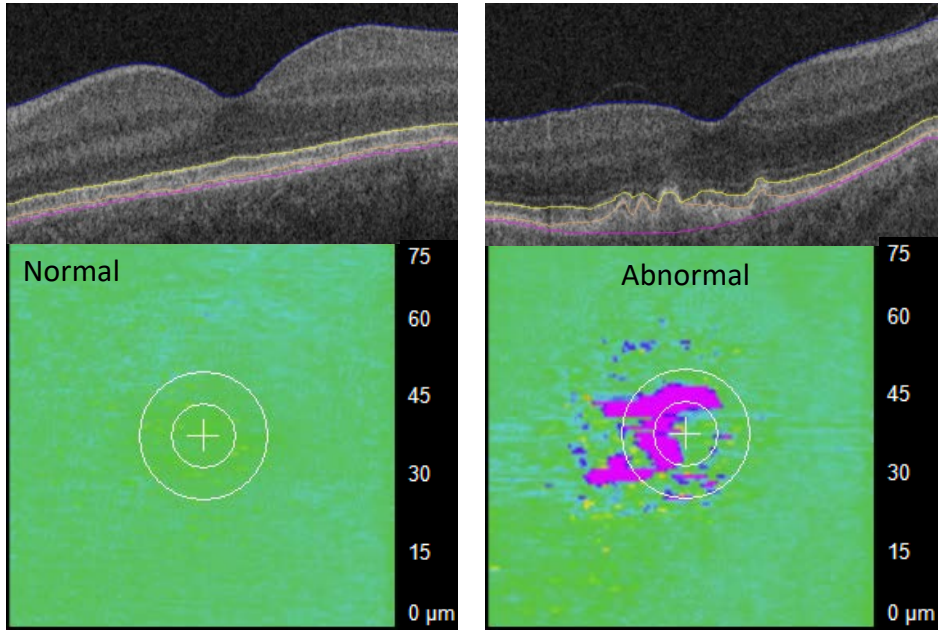
} EZ-RPE



3D reconstruction of macular cube



En face view of normative EZ mapping



= normal

= partial attenuation

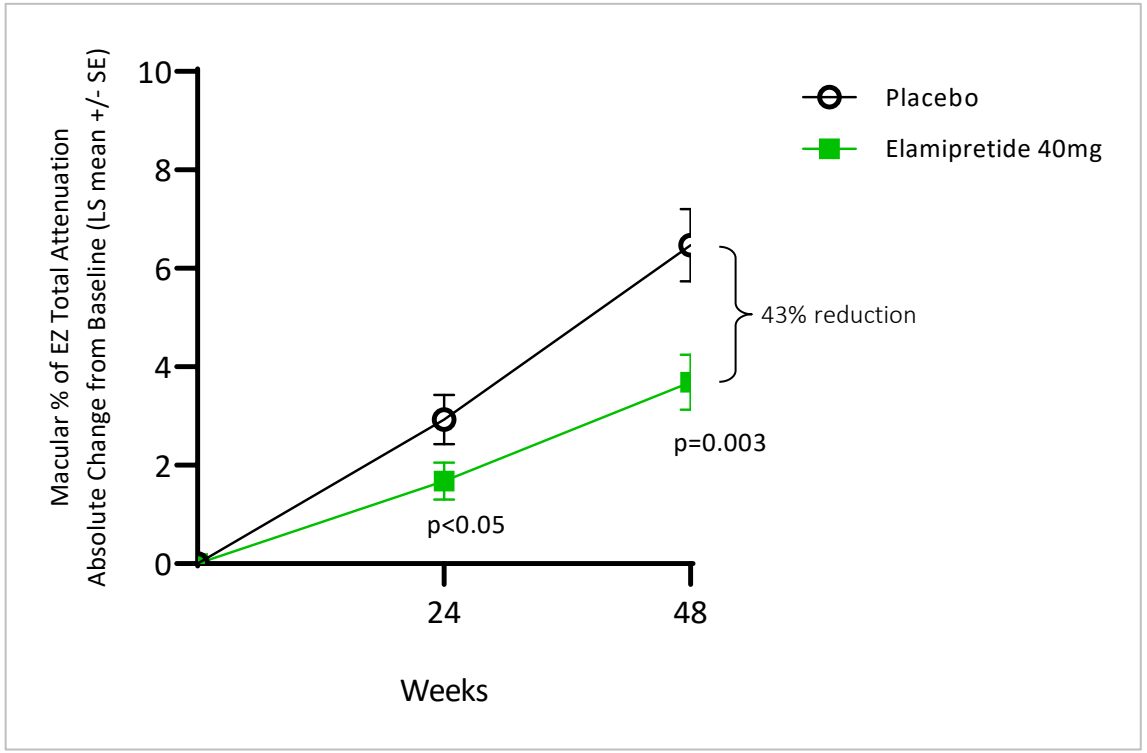
= total attenuation

Ito et al. BJO 2016

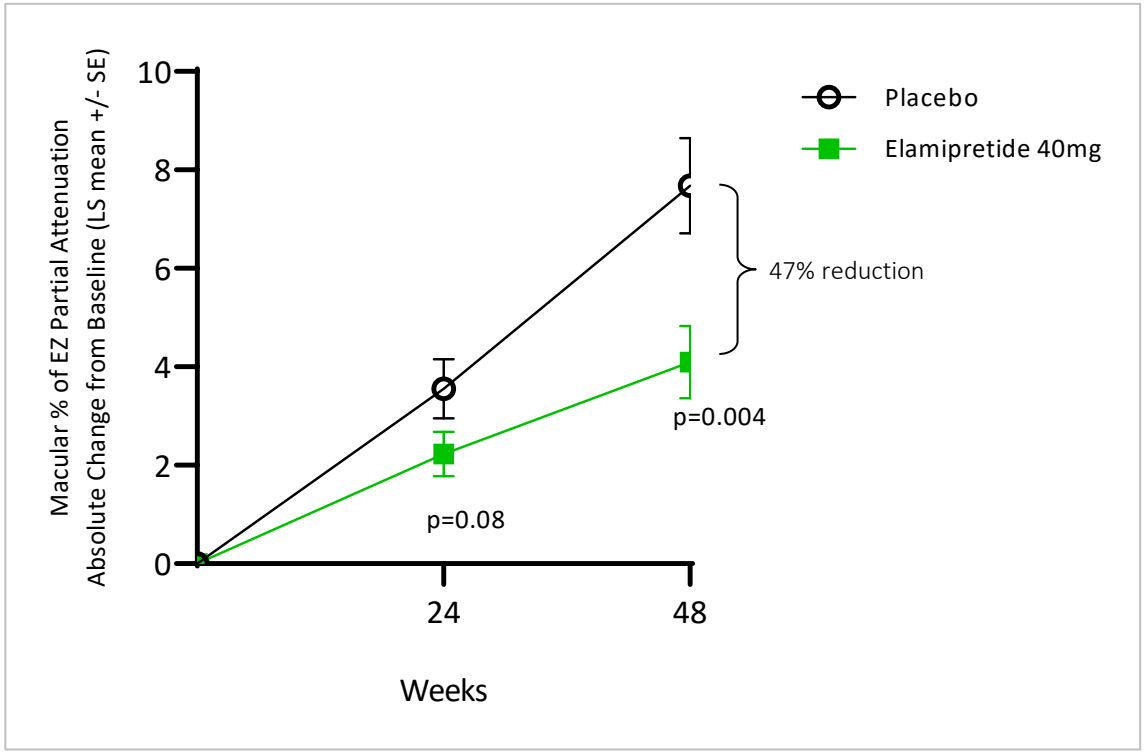
Elamipretide Reduced Attenuation of the Mitochondria-Rich EZ

Prespecified analysis provides proof of mechanism and elamipretide target engagement

Total EZ Attenuation: thickness of 0 µm on *en face map*



Partial EZ Attenuation: thickness of <20 µm on *en face map*



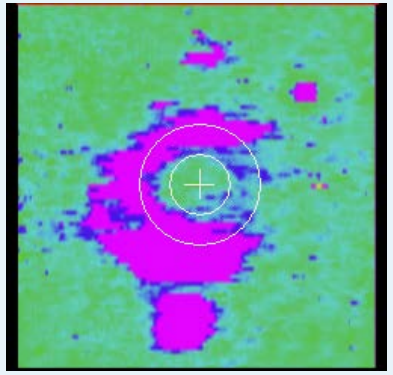
Least Square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The mITT population was used for the analysis, for Total Attenuation, placebo n=50 and 42 for 24 and 48 weeks, respectively while elamipretide n=89 and 71, respectively. From Partial Attenuation, placebo n=50 and 42, for 24 and 48 weeks, respectively while elamipretide n=89 and 71, respectively. Statistical analysis showing nominal “p values”

Retinal Mitochondrial Health Predicts Potential Response to Therapy

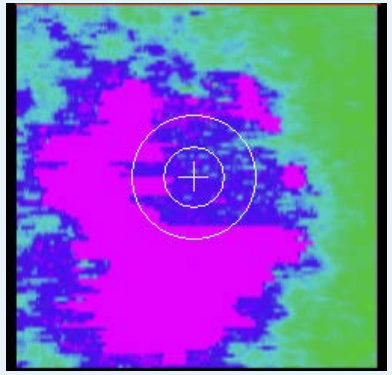
Low Luminance Visual Acuity Correlates With Ellipsoid Zone Health

ReCLAIM

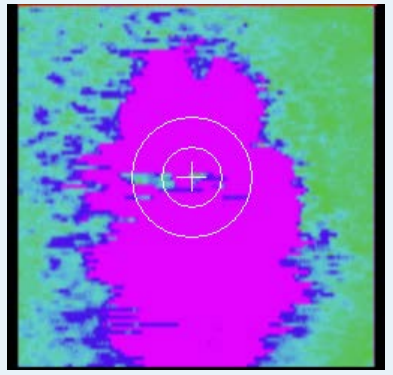
18-letter gain
Patient C: NCGA cohort



4-letter gain
Patient B: NCGA cohort



2-letter gain
Patient A: NCGA cohort



LLVA change inversely correlated with the baseline % macular EZ attenuation (p=0.002)

ReCLAIM-2

LLVA change correlated with **baseline** …

- ✓ macular % of total EZ attenuation (p<0.01)
- ✓ macular % of partial EZ attenuation (p<0.01)

LLVA change correlated with **change** in…

- ✓ macular % total EZ attenuation (p < 0.01)

ReCLAIM-2 provides evidence that slowing EZ attenuation has a positive effect on visual function

Correlation analyses were performed post-hoc, statistical analysis showing nominal “p values”

Relationship between EZ and Visual Acuity has been established in multiple diseases

Ellipsoid Zone Integrity and Visual Acuity Changes during Diabetic Macular Edema Therapy: A Longitudinal Study

Lucy J. Kessler,[1,2] Gerd U. Auffarth,[1] Dmitrii Bagautdinov,[1] and Ramin Khoramnia[1,2]

Quantification of residual ellipsoid zone and its correlation with visual functions in patients with cone-rod dystrophy

Takumi Hara, Han Peng Zhou, Marie Kitano, more... Show all autl

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https://doi.org/10.1177/1120672121990561

Visual Acuity Is Correlated with the Area of the Foveal Avascular Zone in Diabetic Retinopathy and Retinal Vein Occlusion

Chandrakumar Balaratnasingam, MD, PhD • Maiko Inoue, MD • Seungjun Ahn, MS • ...
Elona Dhrami-Gavazi, MD • Lawrence A. Yannuzzi, MD • K. Bailey Freund, MD • Show all authors

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Original Article

Visual Acuity in Retinal Vein Occlusion Diabetic, and Uveitic Macular Edema: Central Subfield Thickness and Ellipsoid Zone Analysis

Thomas A. Ciulla MD, MBA [1], Barry Kapik MS [1], Dilraj S. Grewal MD [2], Michael S. Ip MD [3]

Progression characteristics of ellipsoid zone loss in macular telangiectasia type 2

Daniel Pauleikhoff, Roberto Bonelli, Adam M Dubis, Frederic Gunnemann, Kai Rothaus, Peter Charbel Issa, Tjebo FC Heeren, Tunde Peto, Traci E Clemons ... See all authors

Article

Ellipsoid Zone Defects in Retinal Vein Occlusion Correlates With Visual Acuity Prognosis: SCORE2 Report 14

Tyler Etheridge[1], Ellen T. A. Dobson[2], Marcel Wiedenmann[3], Neal Oden[4], Paul VanVeldhuisen[4], Ingrid U. Scott[5], Michael S. Ip[6], Kevin W. Eliceiri[2,7,8], Barbara A. Blodi[1,7], and Amitha Domalpally[1,7]

[1] Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
[2] Laboratory for Optical and Computational Instrumentation, Center for Quantitative Cell Imaging, University of Wisconsin-Madison, Madison, WI, USA
[3] KNIME GmbH, Konstanz, Germany
[4] The Emmes Company, LLC, Rockville, MD, USA
[5] Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA
[6] Doheny Eye Institute, University of California Los Angeles Stein Eye Institute, Los Angeles, CA, USA
[7] McPherson Eye Research Institute, University of Wisconsin-Madison, Madison, WI, USA
[8] Department of Medical Physics, University of Wisconsin-Madison, Madison, WI, USA

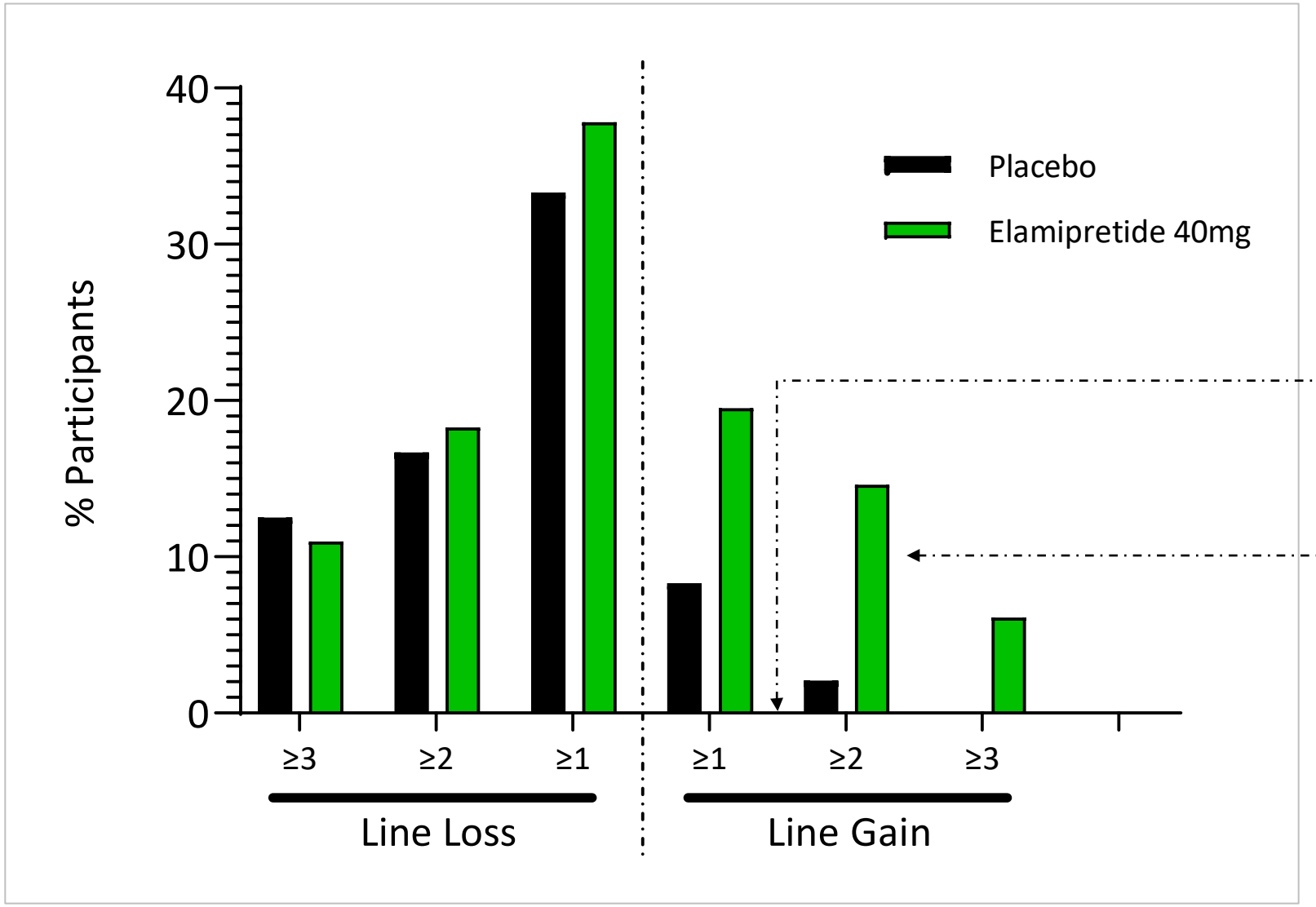
OPTICAL COHERENCE TOMOGRAPHY BASELINE PREDICTORS FOR INITIAL BEST-CORRECTED VISUAL ACUITY RESPONSE TO INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT IN EYES WITH DIABETIC MACULAR EDEMA

The CHARTRES Study

Santos, Ana R. MSc*,†; Costa, Miguel Â. MSc*; Schwartz, Christian*; Alves, Dalila MSc*; Figueira, João MD, PhD*,‡,§; Silva, Rufino MD, PhD*,‡,§; Cunha-Vaz, Jose G. MD, PhD*,§

ReCLAIM-2 Demonstrated Categorical 2+ Line LLVA Improvement

No other investigational product has demonstrated the potential to improve LLVA in patients with GA secondary to dry AMD



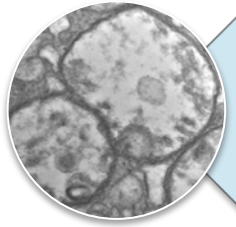
8+ Letter Gain:
Elam: 17% (n=14)
Placebo: 4% (n=2)
P<0.05

≥2 Line Gain:
Elam: n=12 @ 2 lines
Elam: n=5 @ 3 lines
P=0.04

The mITT population was used for the analysis, placebo n=48 and elamipretide n=82. Statistical analysis showing nominal significance levels

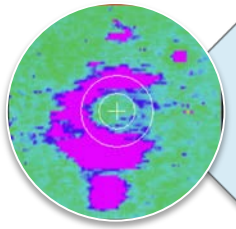
ReCLAIM-2 Data: Key Take-away Topics

Confirmed Proof of Mechanism, Informs Phase 3 Endpoints and Enrichment Strategies



Retinal mitochondrial dysfunction leading to ellipsoid zone (EZ) attenuation precedes and predicts pathologic changes associated with dry AMD progression

Changes in low luminance visual acuity (LLVA) correlated with baseline EZ attenuation, consistent with other diseases



Elamipretide-mediated reduction of progressive EZ attenuation correlates with visual function improvements

On-going clinical trial development and enrichment will be informed by ReCLAIM-2 results:

EZ attenuation as a surrogate endpoint for visual function

elamipretide potential to improve visual function