Subcutaneous Elamipretide for Treatment of Noncentral Geographic Atrophy Secondary to AMD

Ongoing Findings From the ReCLAIM Program

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Leading Mitochondrial Medicine

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Disclosures

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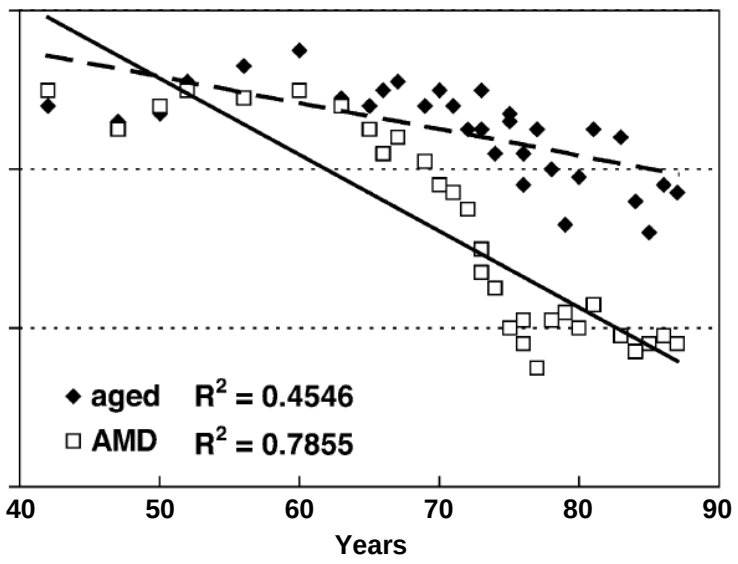
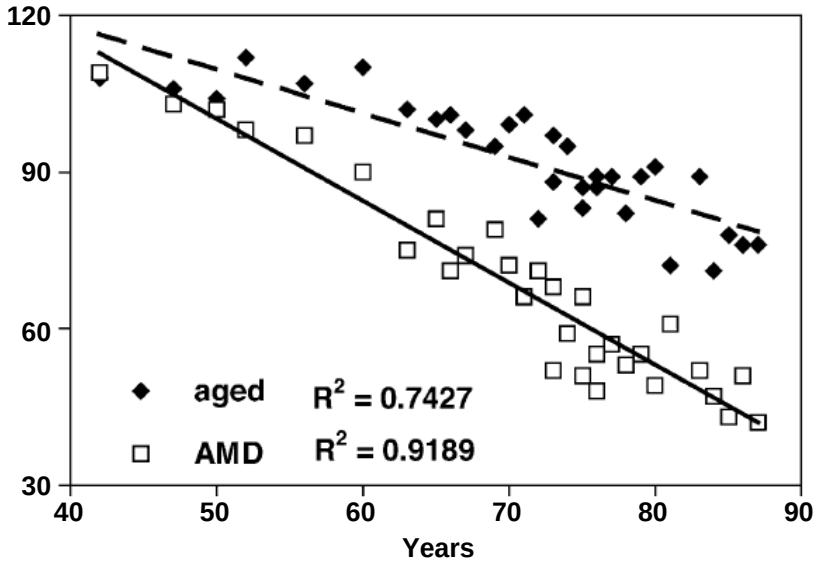
Progressive mitochondrial abnormalities in the RPE contribute to AMD

Changes in RPE mitochondrial properties in aged vs AMD eyes

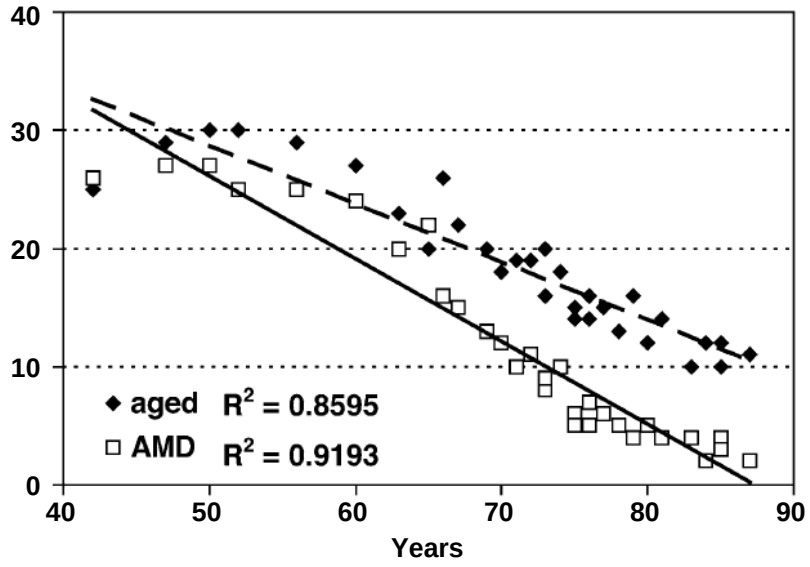
# of mitochondria/cell



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

AMD, age-related macular degeneration; RPE, retinal pigment epithelium.

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

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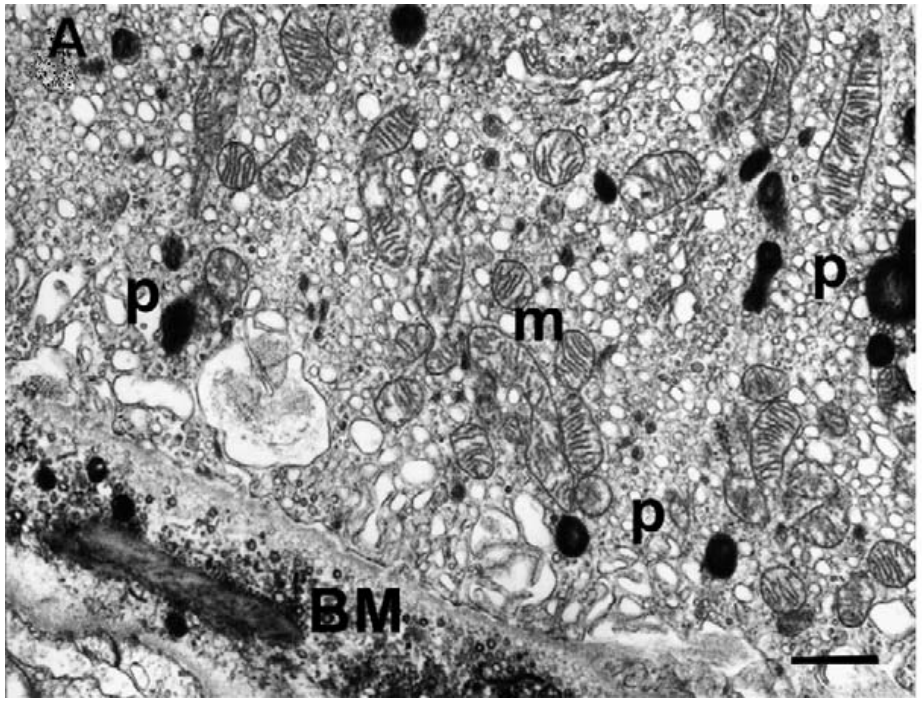
Normal aging and AMD are characterized by differences in mitochondrial morphology

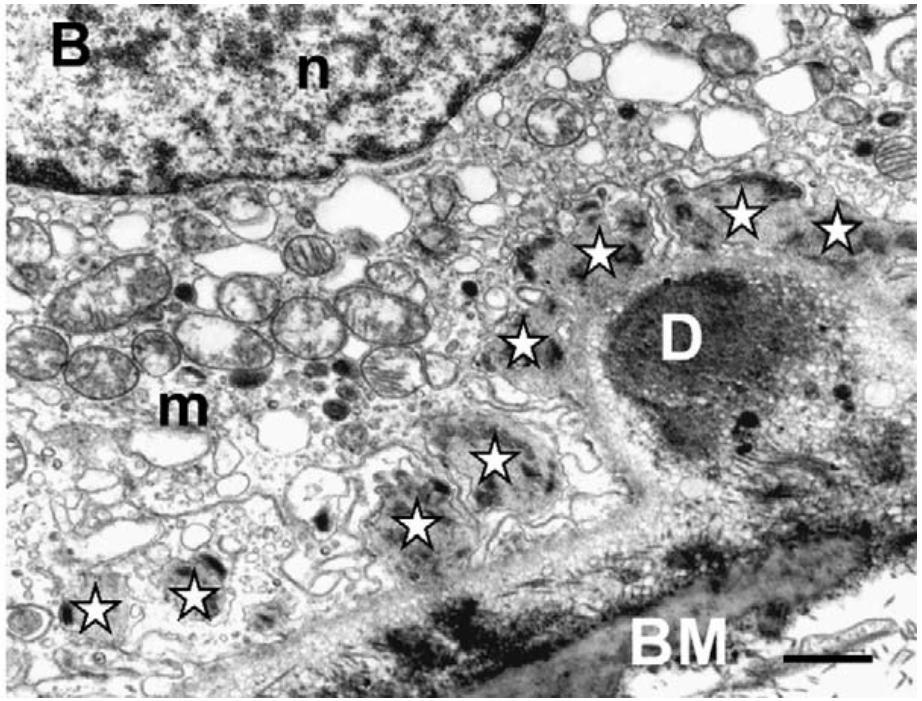
Electron microscopy of RPE mitochondria

Normal aging (83-year-old female)



Typical mitochondrial morphology

AMD (84-year-old female)



Severe mitochondrial disorganization

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

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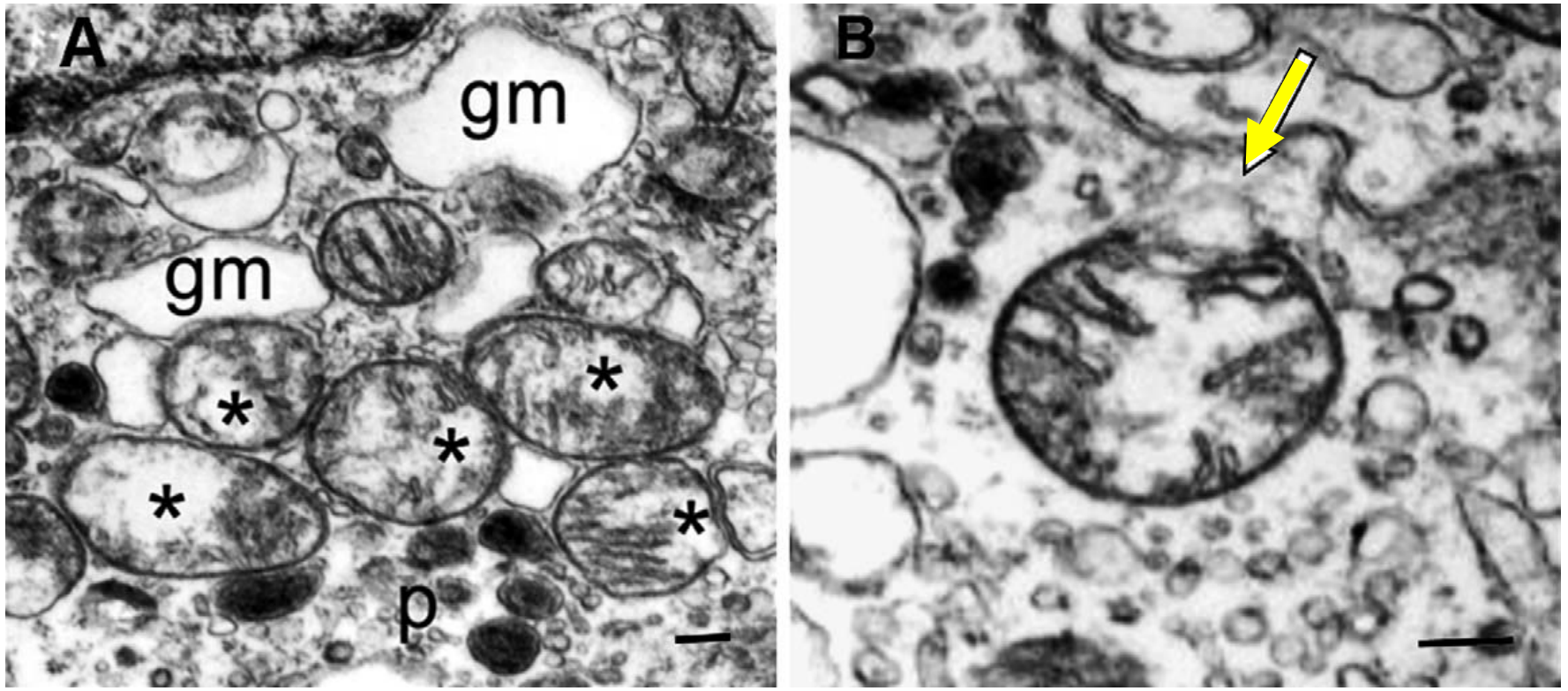
AMD is characterized by marked morphological defects in mitochondria

Electron microscopy of mitochondrial abnormalities in AMD (84-year-old female)

"Ghost" mitochondria (gm)

Extensive loss of cristae and matrix density (*)



Mitochondrial dissolution with bleb formation on internal and external membranes

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

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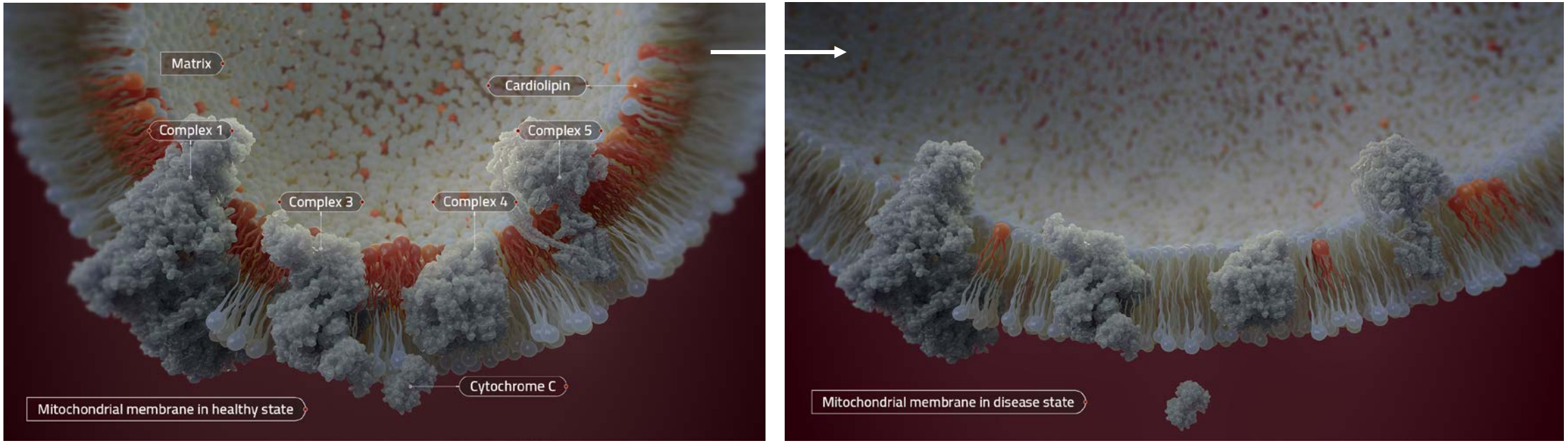
Mitochondrial inner membrane is disrupted in disease

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



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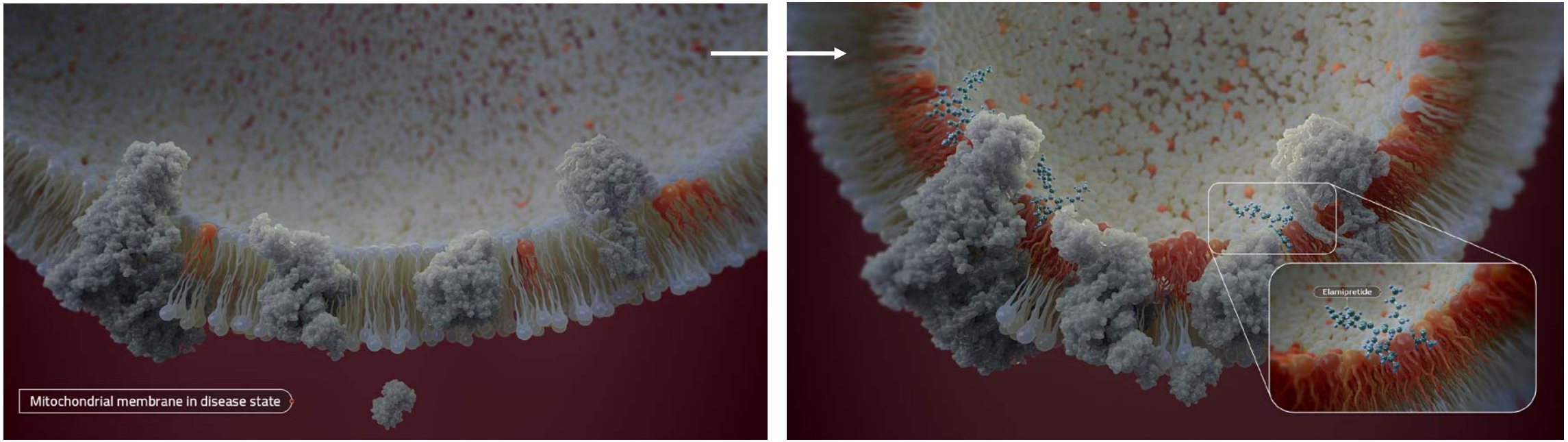
Elamipretide binding to cardiolipin stabilizes the inner mitochondrial membrane structure

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



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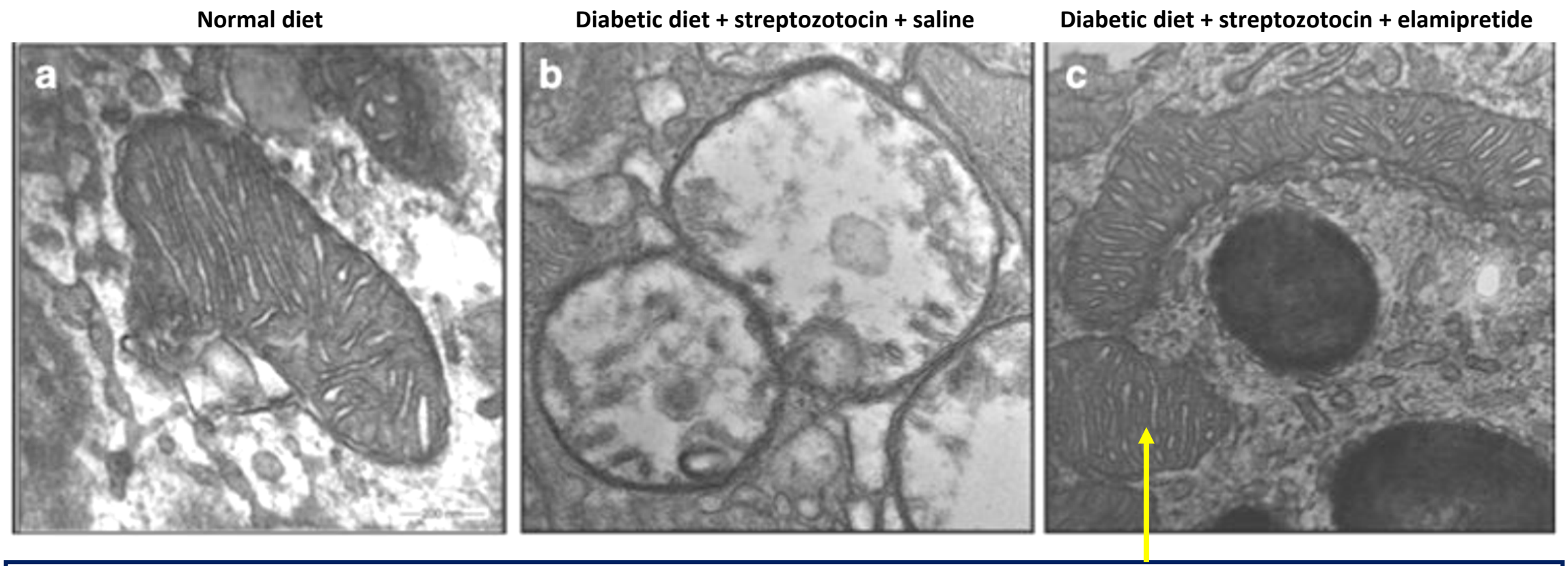
Elamipretide protects RPE mitochondria in a diabetic mouse model

Transmission electron micrographs of mouse RPE mitochondria



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

Szeto HH, Birk AV. *Clin Pharmacol Ther*. 2014;96(6):672-683.

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ReCLAIM
Study attributes and enrollment criteria

An open-label, phase 1 trial of subcutaneous elamipretide for treatment of intermediate AMD

Noncentral GA subgroup

- Noncentral GA
  - Cumulative lesion area ≥1.27 mm^2 (~0.5 disc areas)
- No choroidal neovascularization
- BCVA ≥55 letters
- Low-luminance deficit >5 letters

High-risk drusen subgroup

- High-risk drusen
  - ≥1 large (≥125 µm) druse or multiple medium-size (63-124 µm) drusen
- No choroidal neovascularization
- BCVA ≥55 letters
- Low-luminance deficit >5 letters

BCVA, best corrected visual acuity; GA, geographic atrophy.

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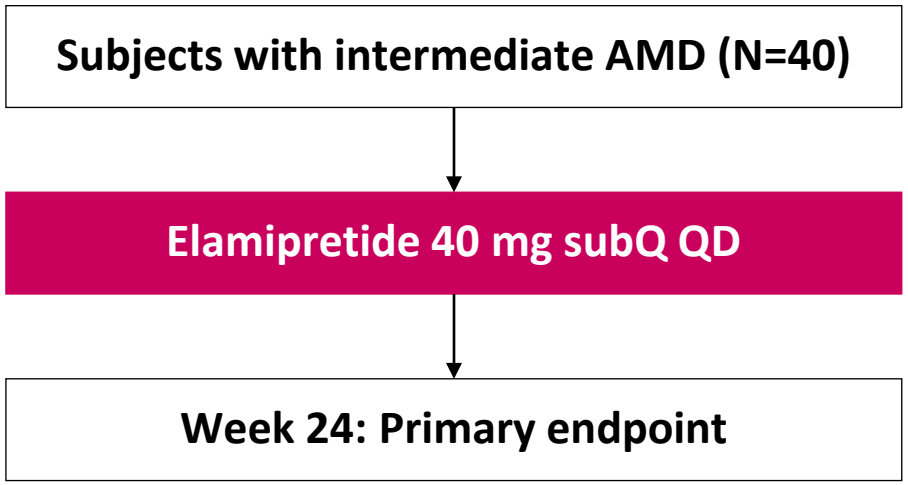
ReCLAIM
Study design



Endpoints

Primary endpoint: Safety

Exploratory endpoints: Efficacy

- Best-corrected visual acuity (BCVA)
- Low-luminance visual acuity (LLVA)
- Best-corrected reading acuity (BCRA)
- Low-luminance reading acuity (LLRA)

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Baseline subject demographics

	Noncentral GA (N=19)	High-risk drusen (N=21)	Total (N=40)
Age, years			
• Mean (SD)	76.0 (8.22)	70.9 (8.54)	73.3 (8.67)
• Median	74.7	69.3	72.8
• Min, max	64, 96	59, 87	59, 96
Sex, n (%)			
• Male	8 (42.1%)	8 (38.1%)	16 (40.0%)
• Female	11 (57.9%)	13 (61.9%)	24 (60.0%)
Ethnicity, n (%)			
• Hispanic or Latino	1 (5.3%)	1 (4.8%)	2 (5.0%)
• Not Hispanic or Latino	18 (94.7%)	20 (95.2%)	38 (95.0%)
White, n (%)	19 (100.0%)	21 (100.0%)	40 (100.0%)
Smoking status, n (%)			
• Never smoker	8 (42.1%)	13 (61.9%)	21 (52.5%)
• Former smoker	11 (57.9%)	8 (38.1%)	19 (47.5%)
• Current smoker	0	0	0

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ReCLAIM
Safety outcomes

	Noncentral GA (N=19)	High-risk drusen (N=21)	Total (N=40)
Injection site reactions			
• Pruritus	21 (100.0%)	17 (89.5%)	38 (95.0%)
• Bruising	16 (76.2%)	13 (68.4%)	29 (72.5%)
• Erythema	16 (76.2%)	14 (73.7%)	30 (75.0%)
• Induration	16 (76.2%)	14 (73.7%)	30 (75.0%)
• Pain	9 (42.9%)	6 (31.6%)	15 (37.5%)
• Hemorrhage	6 (28.6%)	7 (36.8%)	13 (32.5%)
• Urticaria	5 (23.8%)	4 (21.1%)	9 (22.5%)
Completed study, n (%)	15 (78.9%)	18 (85.7%)	33 (82.5%)
Withdrawn early, n (%)	4 (21.1%)	3 (14.3%)	7 (17.5%)
Reason for early withdrawal, n (%)			
• Injection site reaction	2 (10.5%)	1 (4.8%)	3 (7.5%)
• Conversion to nAMD	1 (5.3%)	0	1 (2.5%)
• Withdrawal by subject	1 (5.3%)	1 (4.8%)	2 (5.0%)
• Other	0	1 (4.8%)	1 (2.5%)

Subcutaneous elamipretide was generally well tolerated, but injection site reactions were commonplace

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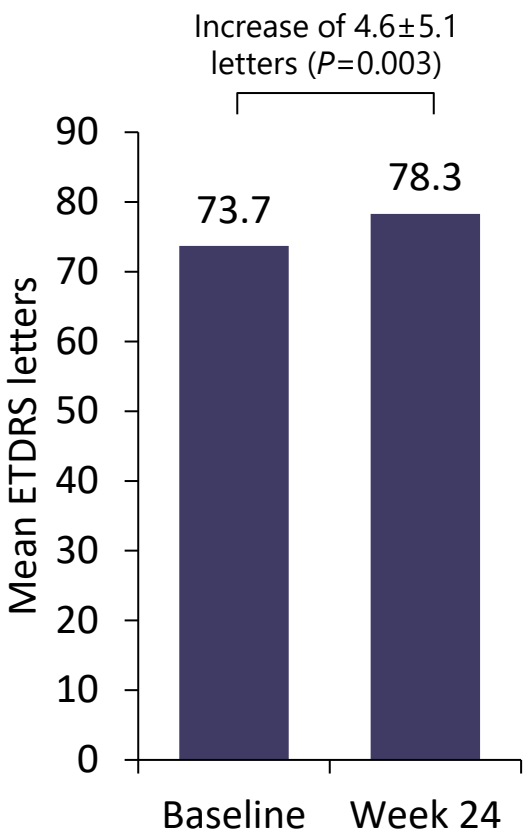
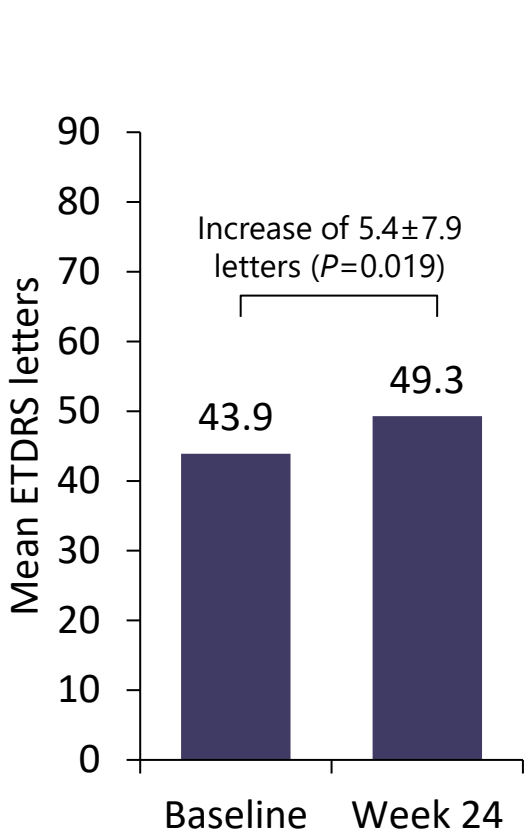
Efficacy outcomes in the noncentral GA subgroup (N=19)

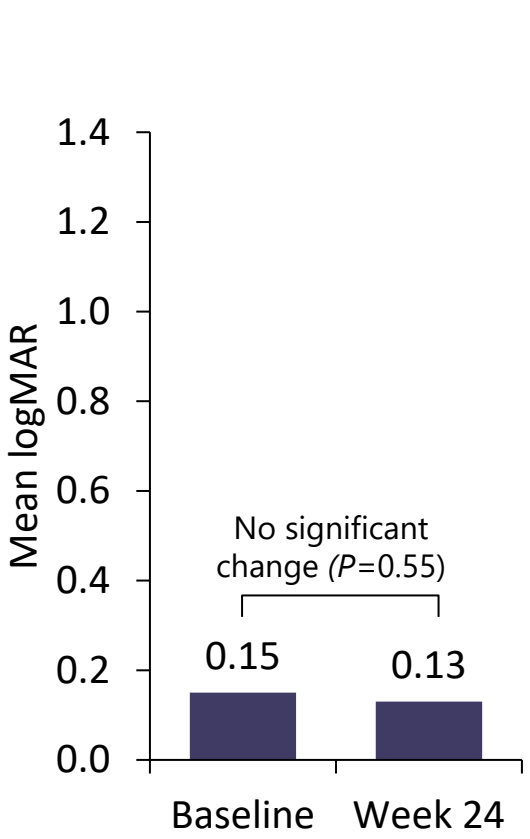
Best-corrected visual acuity (BCVA)



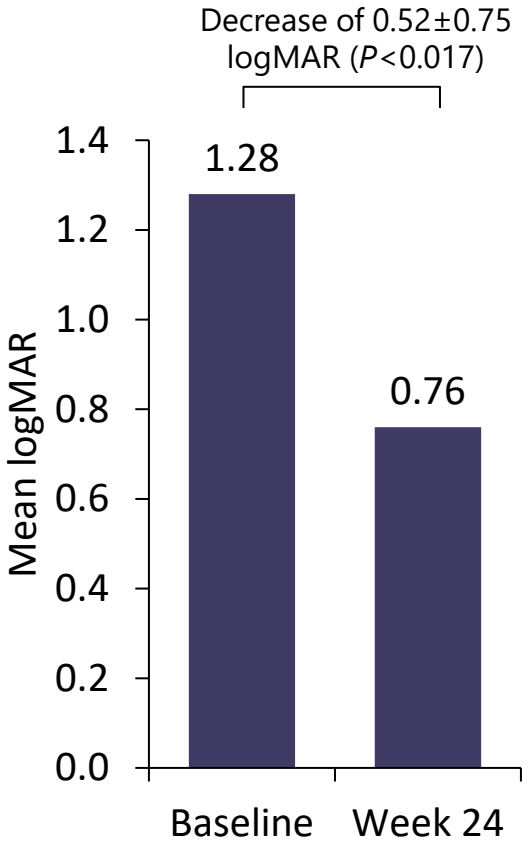
Low-luminance visual acuity (LLVA)



Best-corrected reading acuity (BCRA)



Low-luminance reading acuity (LLRA)



ETDRS, Early Treatment Diabetic Retinopathy Study.

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ReCLAIM-2
Enrollment criteria

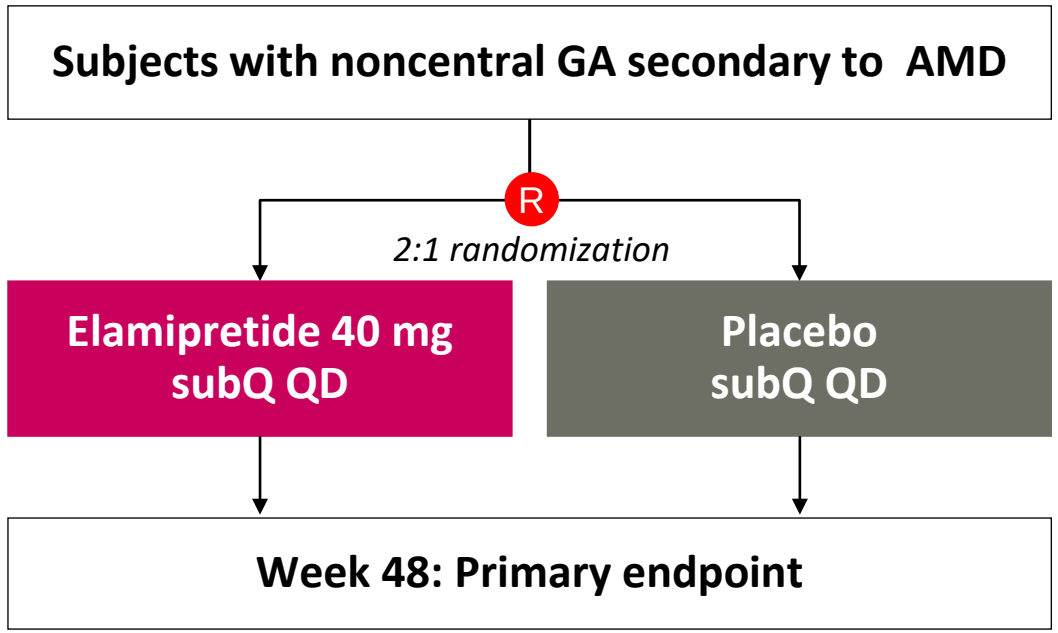
A randomized, placebo-controlled phase 2 trial of subcutaneous elamipretide for treatment of noncentral GA secondary to AMD

Inclusion criteria	Exclusion criteria

• Adults ≥55 years of age
• Noncentral GA in study eye (FAF-confirmed)
  • Lesion size ≥0.05 mm^2 and ≤10.16 mm^2
  • ≥150 µm from foveal center
• BCVA ≥55 letters
• LLVA ≥10 letters
• Low-luminance deficit >5 letters
	• CNV or other retinal pathology in study eye
	• Concurrent ocular or systemic disease

CNV, choroidal neovascularization; FAF, fundus autofluorescence.

ReCLAIM-2
Study design



Endpoints

Primary endpoint

- Low-luminance visual acuity (LLVA)

Secondary endpoints

- Best-corrected visual acuity (BCVA)
- Low-luminance reading acuity (LLRA)
- Change in GA area (FAF & OCT)

OCT, optical coherence tomography.

ReCLAIM-2
Rationale for LLVA as the primary endpoint

Research Opportunities

Report From the NEI/FDA Endpoints Workshop on Age-Related Macular Degeneration and Inherited Retinal Diseases

Karl Csaky,[1] Frederick Ferris III,[2] Emily Y. Chew,[2] Prashant Nair,[3] Janet K. Cheetham,[4] and Jacque L. Duncan[5]

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[2]National Eye Institute, National Institutes of Health, Bethesda, Maryland, United States
[3]Washington, District of Columbia, United States
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Invited speakers and discussants are listed on page 3457.

Submitted: June 1, 2017
Accepted: June 2, 2017

Citation: Csaky K, Ferris F III, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA Endpoints Workshop on age-related macular degeneration and inherited retinal diseases. *Invest Ophthalmol Vis Sci*. 2017;58:3456–3463. DOI:10.1167/iovs.17-22339

"Area of GA could be acceptable as a primary efficacy variable in principle, but… the challenge is to show that the apparent difference in anatomic progression translates into a functional benefit that can be weighed against safety issues"

"Previous studies have found that loss of visual acuity under low luminance can predict visual acuity loss from GA over a 2-year period in AMD patients"

 Csaky K, Ferris F 3rd, Chew EY, et al. *Invest Ophthalmol Vis Sci*. 2017;58(9):3456-3463.

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ReCLAIM-2
Interim baseline subject demographics

	All subjects	N
Age, years • Mean (SD) • Median • Min, max	 77.0 (8.5) 76.5 56, 99	165
Sex, n (%) • Male • Female	 64 (38.8%) 101 (61.2%)	165
Best-corrected visual acuity (letters), mean (SD)	76.0 (8.7)	165
Low-luminance visual acuity (letters), mean (SD)	55.0 (14.6)	165
Low-luminance deficit (letters), mean (SD)	-21.0 (11.1)	165
Best-corrected reading acuity (logMAR), mean (SD)	0.30 (0.33)	165
Low-luminance reading acuity (logMAR), mean (SD)	0.90 (0.42)	165
Geographic atrophy area on FAF (mm^2), mean (SD)	2.7 (2.5)	152
Geographic atrophy distance to fovea on FAF (mm), mean (SD)	0.49 (0.36)	151
Geographic atrophy area on OCT (mm^2), mean (SD)	2.6 (2.4)	146
Geographic atrophy distance to fovea on OCT (mm), mean (SD)	0.50 (0.63)	153

ReCLAIM-2 is currently ongoing

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Summary

Elamipretide's therapeutic effect occurs via restoration of mitochondrial bioenergetics

The open-label, phase 1 ReCLAIM trial demonstrated that subcutaneous elamipretide has acceptable safety and may improve visual function in subjects with noncentral GA secondary to AMD

The placebo-controlled, phase 2 ReCLAIM-2 trial is currently underway to further evaluate subcutaneous elamipretide for treatment of noncentral GA secondary to AMD

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