

# Association of Ellipsoid Zone Integrity and Treatment Response in Non-Neovascular AMD Treated With Subcutaneous Elamipretide

*Post Hoc Analysis of the Phase 1 ReCLAIM Study*

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# Disclosures

- Justis P. Ehlers: Stealth (Consultant); Aerpio (Financial Support, Consultant); Alcon (Financial Support, Consultant); Thrombogenics/Oxurion (Financial Support, Consultant); Regeneron (Financial Support, Consultant); Genentech (Financial Support); Boehringer Ingelheim (Financial Support); Genentech/Roche (Consultant); Novartis (Financial Support, Consultant); Zeiss (Consultant); Adverum (Consultant); Leica (Patent, Consultant); Allergan (Financial Support, Consultant); Allegro (Consultant); Santen (Consultant).
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The background of the slide is a microscopic image. It features several elongated, rod-shaped cells, possibly bacteria or protozoa, which are semi-transparent and show internal structures. Scattered throughout the field of view are numerous small, bright purple spherical particles. The overall color palette is dark, with deep blues and purples.

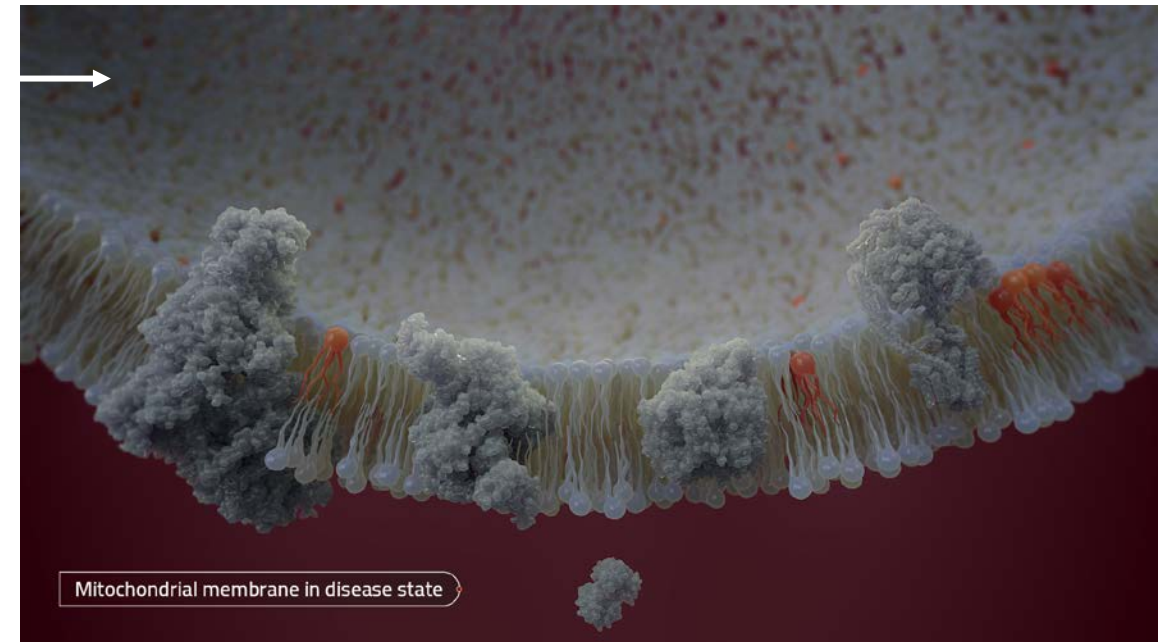
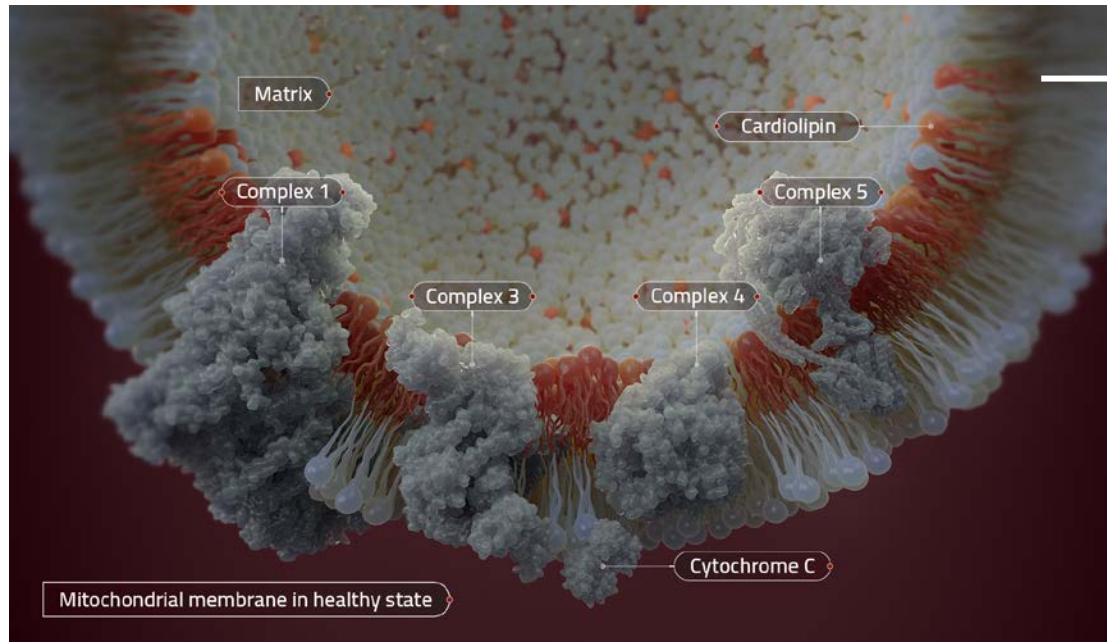
# Scientific Background

# 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



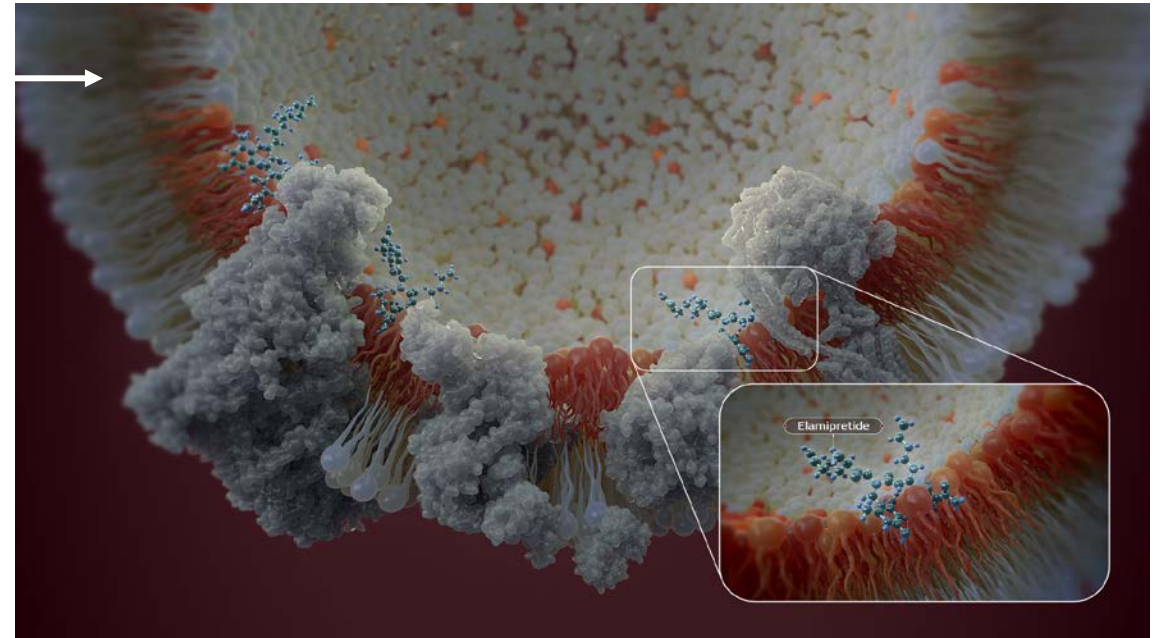
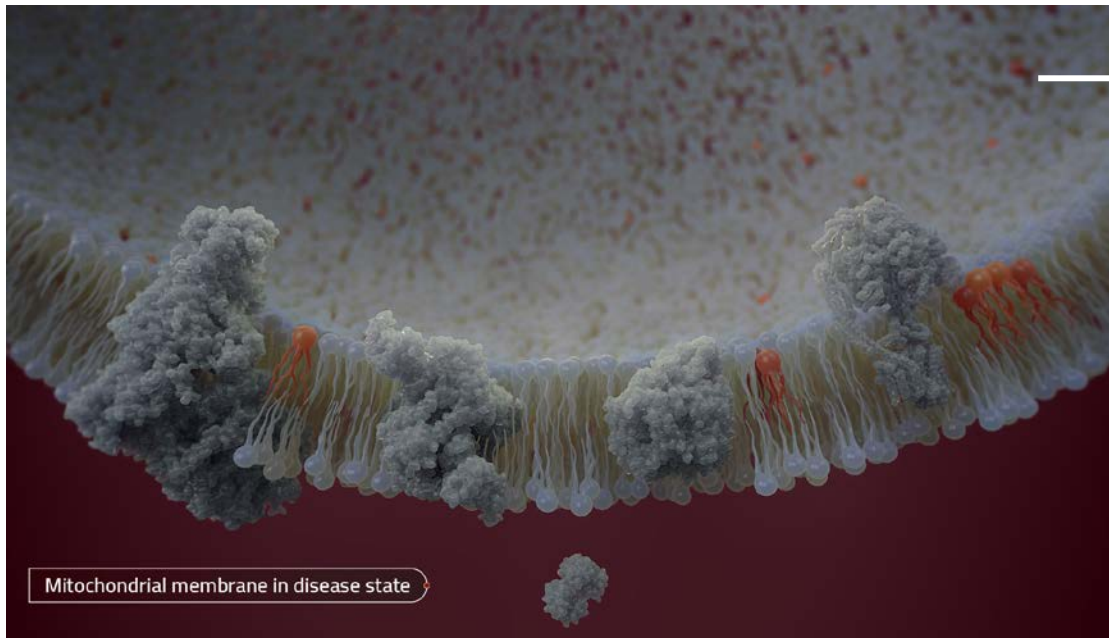


# Elamipretide Binding to Cardiolipin Stabilizes the Inner Mitochondrial Membrane Structure

## 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**



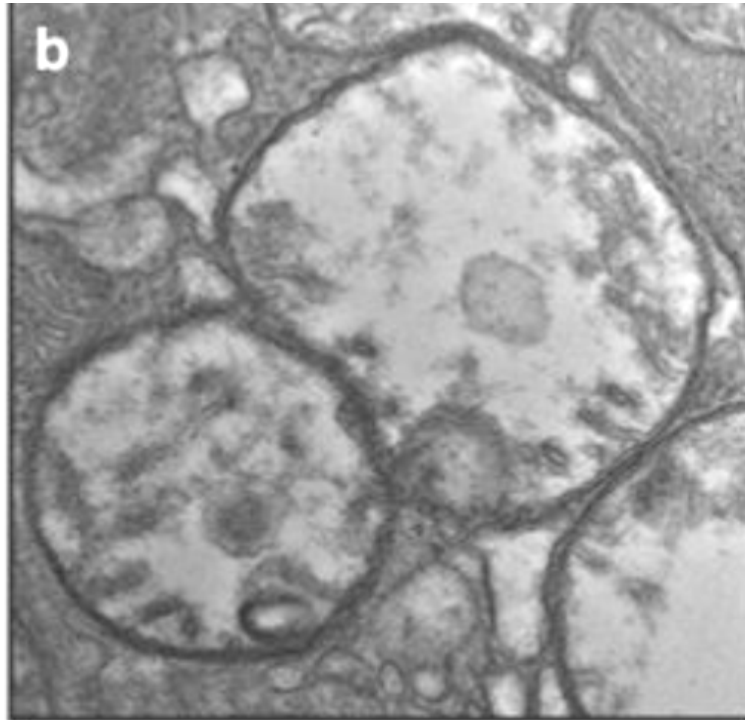
# Elamipretide Protects RPE Mitochondria in a Diabetic Mouse Model

## Transmission electron micrographs of mouse RPE mitochondria

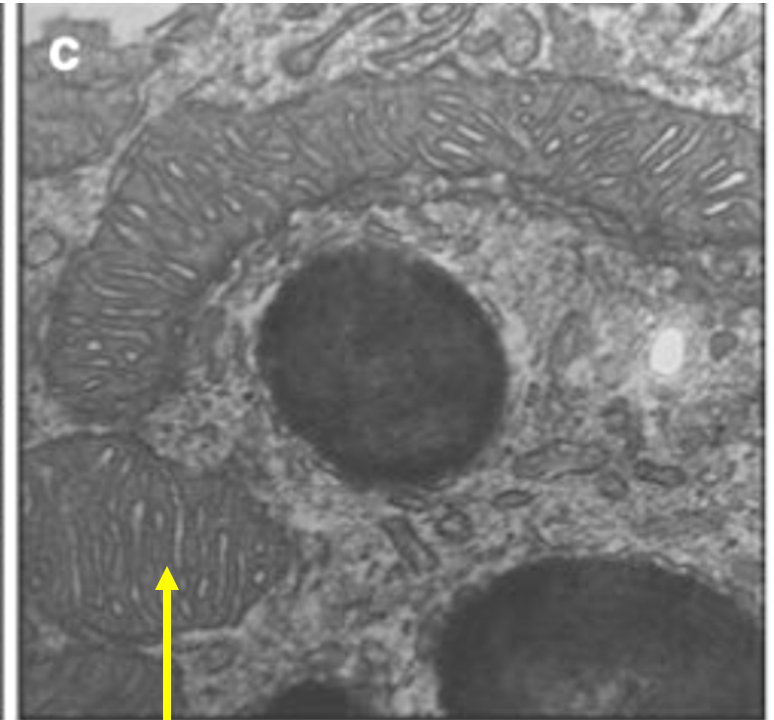
Normal diet



Diabetic diet + streptozotocin + saline



Diabetic diet + streptozotocin + elamipretide



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



The background of the slide is a microscopic image showing several elongated, rod-shaped cells. These cells have a translucent blue outer membrane and contain numerous small, dark purple or black granules. The cells are scattered across the frame, with some appearing more prominent than others. The overall color palette is dominated by deep blues and purples, creating a scientific and high-tech atmosphere.

# ReCLAIM Study Design and Results

# ReCLAIM

## *Study Design and Enrollment Criteria*

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

Subjects with intermediate AMD (N=40)

**Elamipretide 40 mg subQ QD**

**Week 24: Primary endpoint**

### Endpoints

**Primary endpoint: Safety**

**Efficacy Primary endpoint:**

- Change in low-luminance visual acuity (LLVA)

**Efficacy exploratory endpoints, included:**

- Change in best-corrected visual acuity (BCVA)

### Noncentral GA subgroup

- Noncentral GA
  - Cumulative lesion area  $\geq 1.27 \text{ mm}^2$  (~0.5 disc areas)
- No choroidal neovascularization
- BCVA  $\geq 55$  letters
- Low-luminance deficit  $> 5$  letters

### High-risk drusen subgroup

- High-risk drusen
  - $\geq 1$  large ( $\geq 125 \text{ }\mu\text{m}$ ) druse or multiple medium-size (63-124  $\mu\text{m}$ ) drusen
- No choroidal neovascularization
- BCVA  $\geq 55$  letters
- Low-luminance deficit  $> 5$  letters



# ReCLAIM

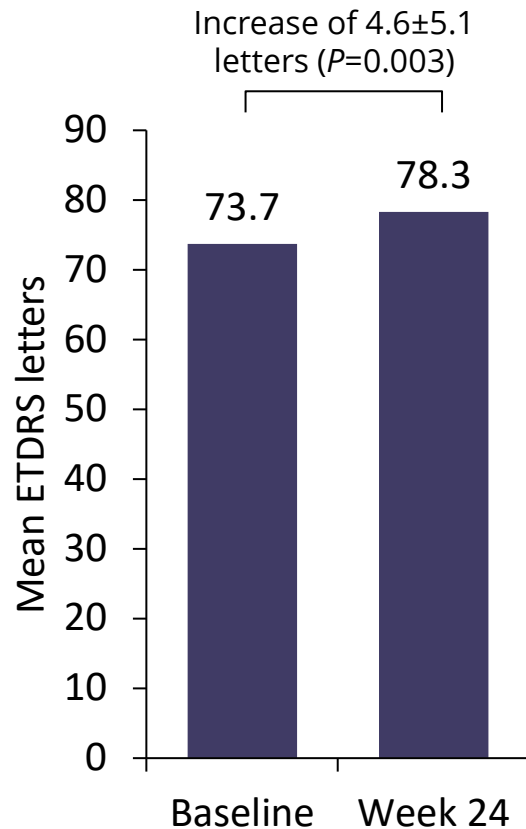
## *Baseline Subject Demographics*

	Noncentral GA (N=19)	High-risk drusen (N=21)	Total (N=40)
<b>Age, years</b>			
• 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
<b>Sex, n (%)</b>			
• Male	8 (42.1%)	8 (38.1%)	16 (40.0%)
• Female	11 (57.9%)	13 (61.9%)	24 (60.0%)
<b>Ethnicity, n (%)</b>			
• 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%)
<b>White, n (%)</b>	19 (100.0%)	21 (100.0%)	40 (100.0%)
<b>Smoking status, n (%)</b>			
• 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

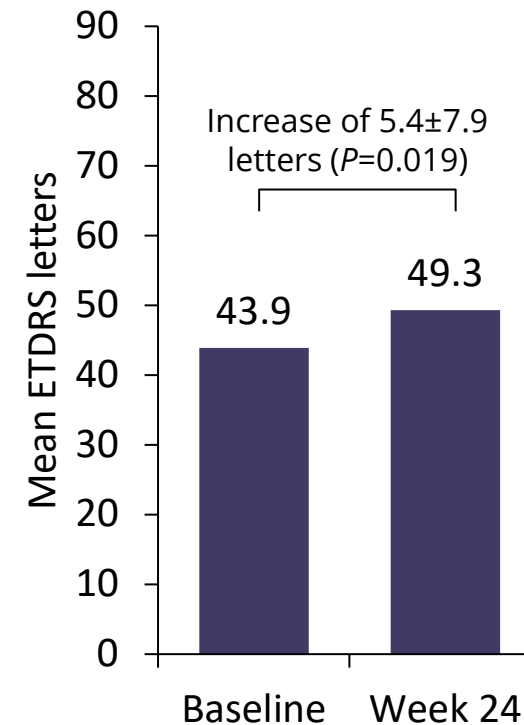
# ReCLAIM

## *Visual Acuity Outcomes in the Noncentral GA Subgroup (N=19)*

### Best-corrected visual acuity (BCVA)



### Low-luminance visual acuity (LLVA)

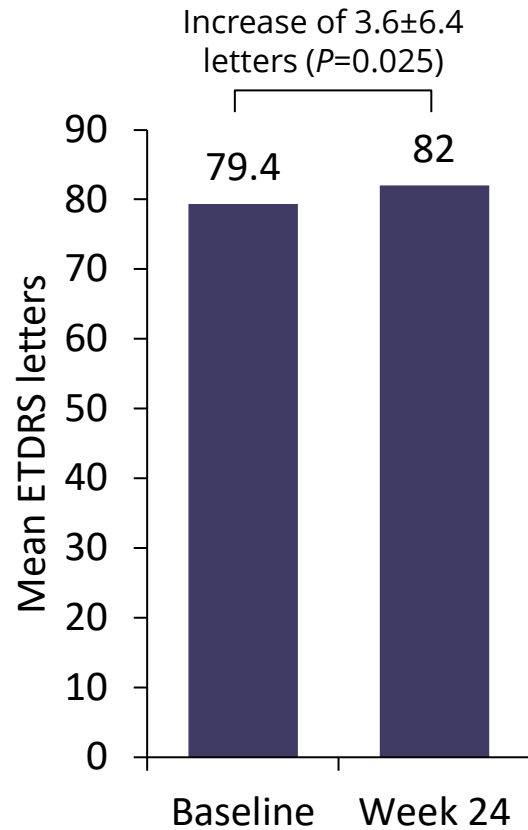




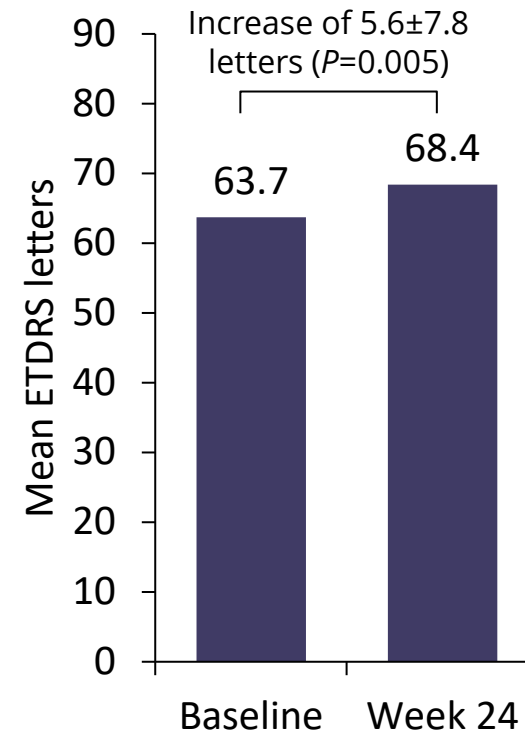
# ReCLAIM

## *Visual Acuity Outcomes in the High-Risk Drusen Subgroup (N=21)*

### Best-corrected visual acuity (BCVA)



### Low-luminance visual acuity (LLVA)



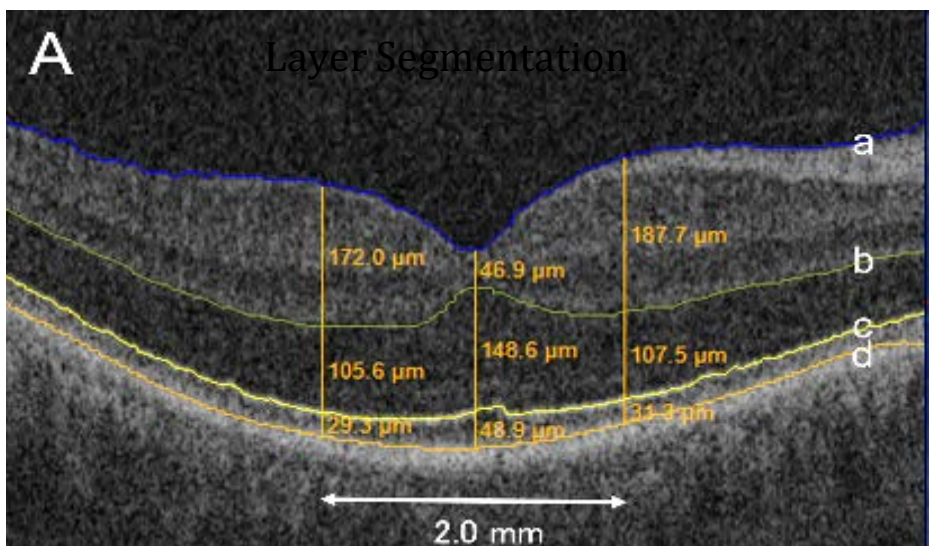
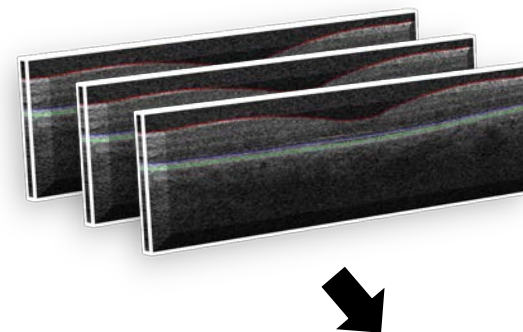
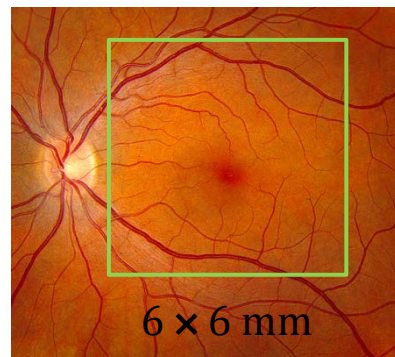
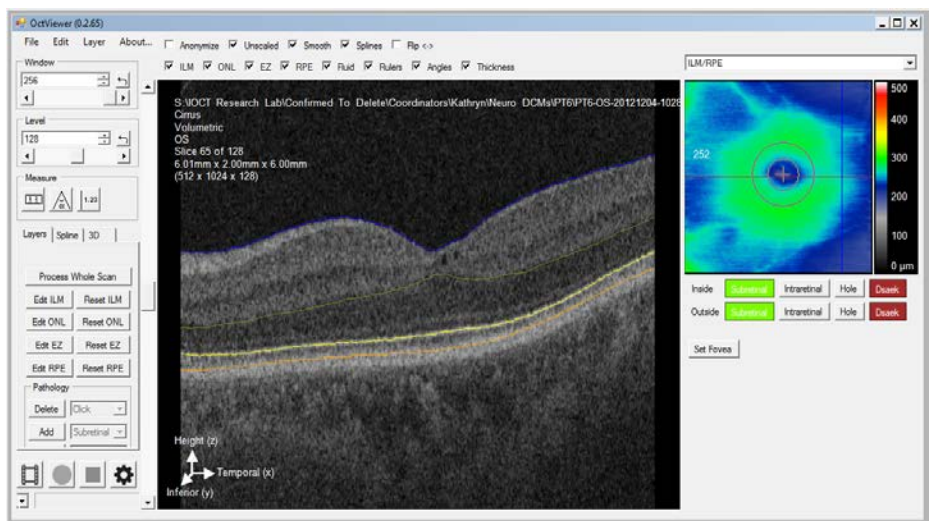


# Quantitative OCT and Compartmental Mapping Biomarker Characterization



# ML-Enhanced Multi-Layer Segmentation and Compartmental Mapping

Loading macular cube into OCT Mapping software



a) ILM

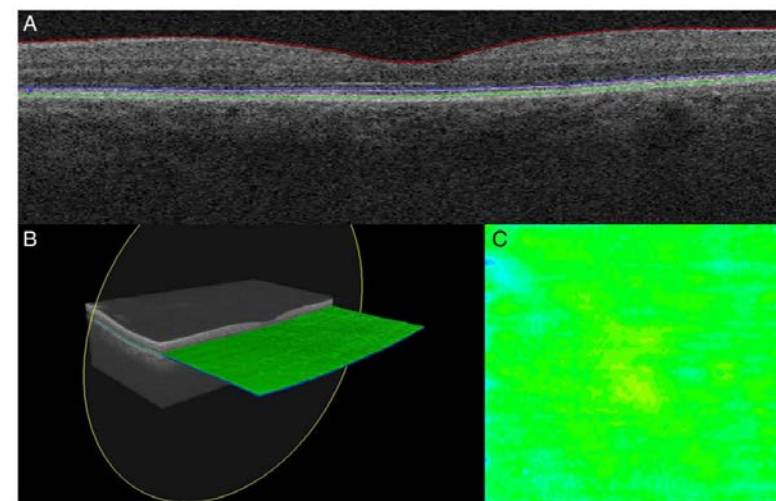
b) Between OPL/ONL

c) EZ

d) RPE

ONL/HFL-EZ

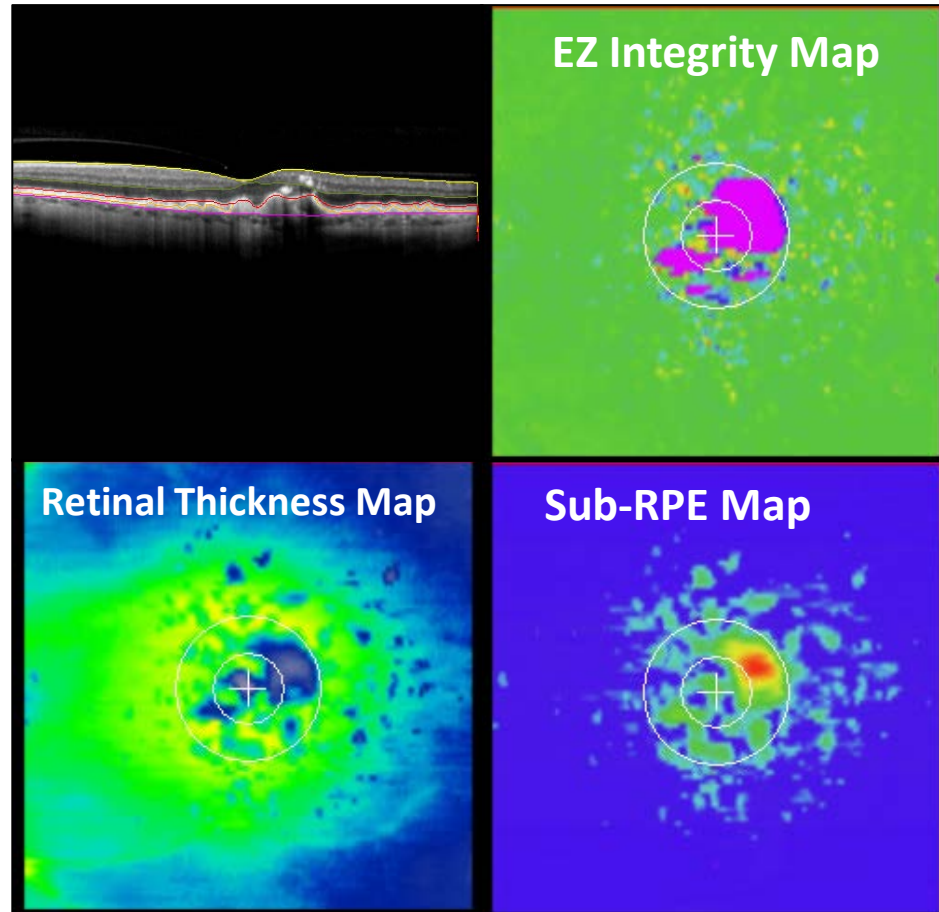
EZ-RPE



3D reconstruction of  
macular cube

En face view of  
normative EZ mapping

# Outer Retinal and Sub-RPE Mapping Outputs



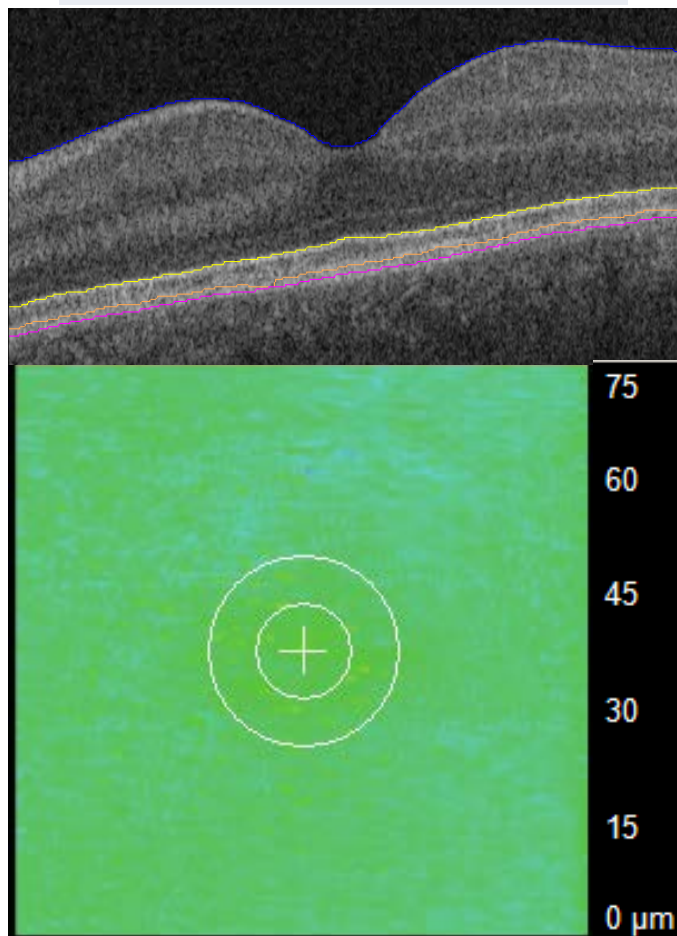
Quantitative retinal parameters include:

- EZ-RPE CST
- EZ-RPE volume
- Percentage of EZ-RPE total attenuation (i.e., thickness of 0  $\mu\text{m}$ ) and partial attenuation (i.e.,  $< 20 \mu\text{m}$ ) on *en face map*
- RPE total attenuation (i.e., GA)
- Sub-RPE Volume
- ONL/HFL-EZ thickness
- ONL/HFL-EZ volume



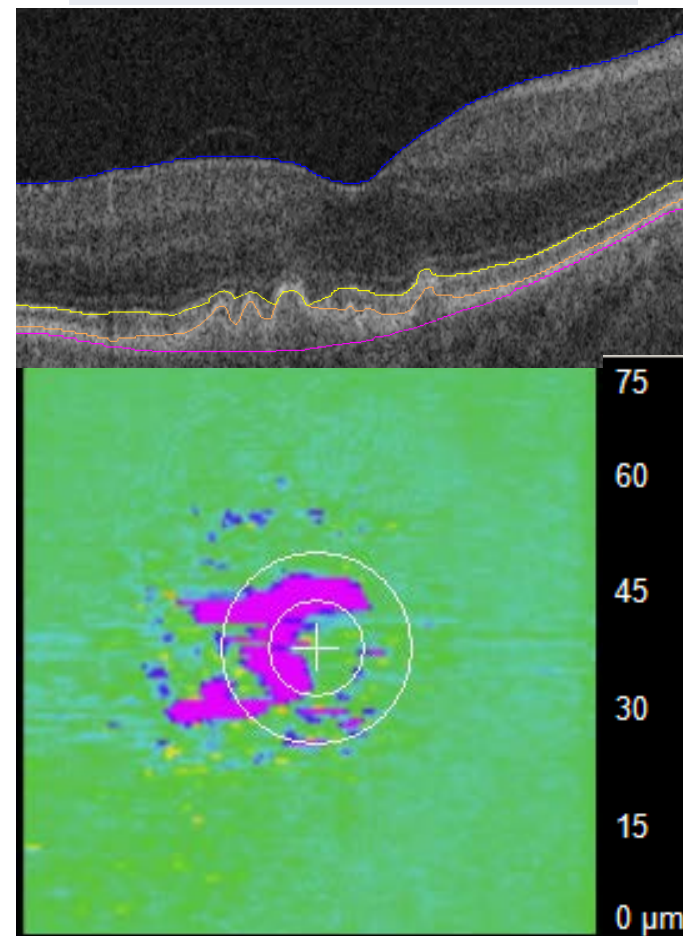
# *EZ Integrity Maps*

**Normal**



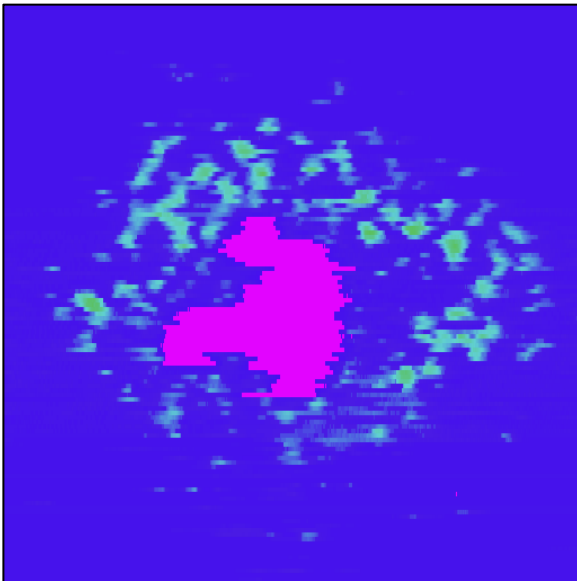
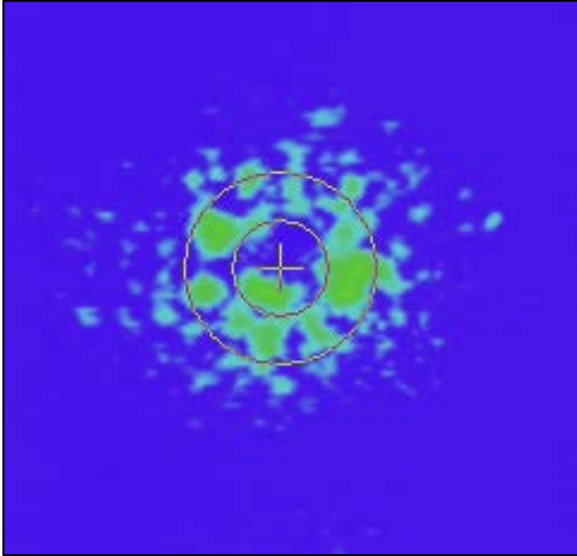
Total Attenuation: 0.0%  
EZ-RPE Volume: 1.27 mm<sup>3</sup>

**Abnormal**



Total Attenuation: 3.3%  
EZ-RPE Volume: 1.23 mm<sup>3</sup>

## *Sub-RPE Compartment Maps*



### **RPE-Bruch's membrane maps**

- In normal eyes, these maps would be completely blue, representing the close apposition of the RPE and Bruch's membrane.
- Green represents elevation of the RPE (i.e., drusen).
- Pink represents RPE atrophy (i.e., GA)



The background of the slide is a microscopic image showing several elongated, rod-shaped cells. These cells are stained with a blue/purple dye, revealing internal structures such as nuclei and possibly flagella. The cells are scattered across the frame, with some appearing more prominent than others. The overall color palette is dominated by deep blues and purples, creating a scientific and somewhat abstract atmosphere.

# *Post Hoc* Analysis Methods and Results

# ReCLAIM- *Quantitative Compartmental OCT Analysis Methods*

Higher-order OCT features evaluated via automated machine-learning augmented multilayer retinal segmentation with expert reader manual verification to quantify:

- Outer retinal integrity [e.g., EZ-RPE thickness, percent EZ attenuation, outer retinal parameters (i.e., ONL to RPE thickness)].
- Sub-RPE compartment metrics.

*Post hoc* analysis assessed correlation between baseline higher order OCT features and change in LLVA from baseline to Week 24

# ReCLAIM- *Quantitative Compartmental OCT Analysis*

## *Results in Non-Central GA Patients*

In the non-central GA subgroup ( $n = 19$ ), changes from baseline to week 24 in LLVA were significantly correlated to:

- Baseline macular percentage of total EZ attenuation ( $r = -0.72$ ;  $P = 0.002$ )
- Baseline pan-macular EZ-RPE volume ( $r = 0.62$ ;  $P = 0.01$ )

Eyes gaining 2 lines or more had:

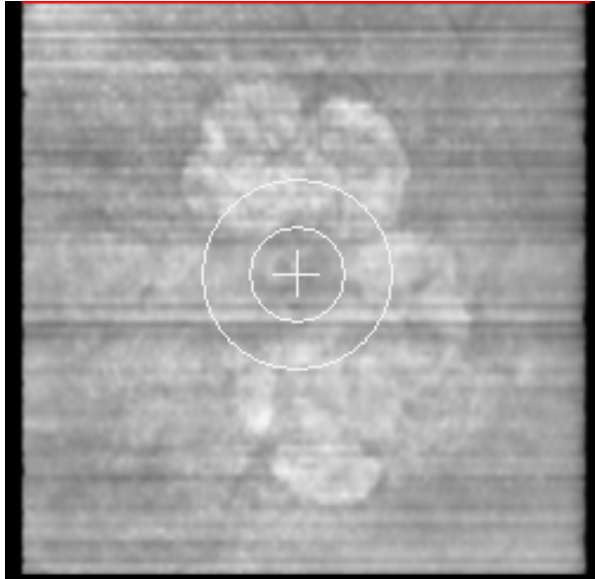
- Significantly less macular total EZ attenuation at baseline (9.0% vs 27%;  $P = 0.03$ )
- Significantly less percentage area of macular GA (4.7% vs 15.6%;  $P = 0.004$ )



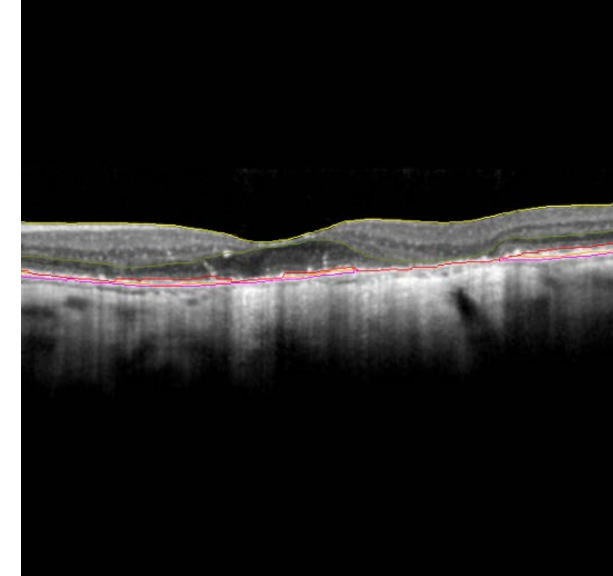
# ReCLAIM- Quantitative Compartmental OCT Analysis

## Non-central GA Patient Case Example (2 letters gain)

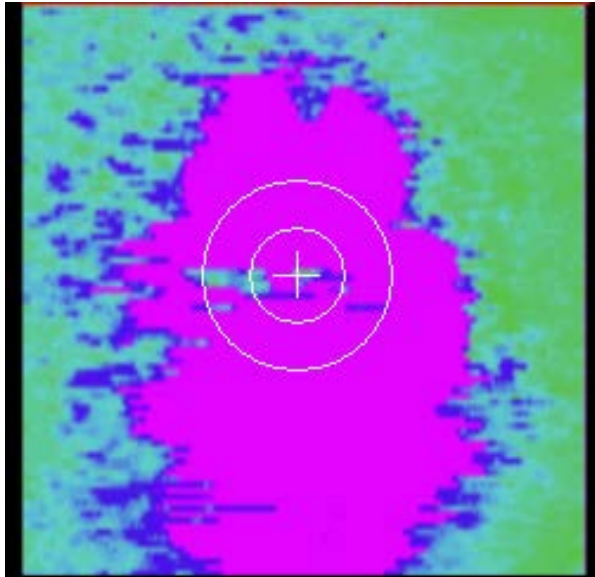
NIR Fundus Image



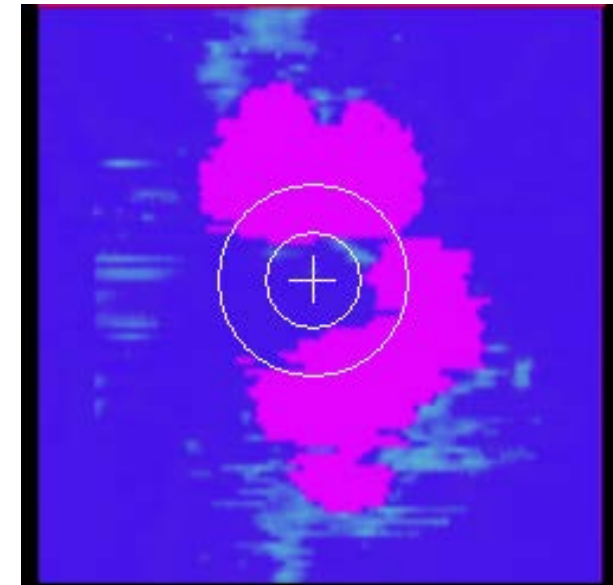
B-Scan at Fovea



EZ-RPE Map  
(Pink – Total EZ Attenuation)



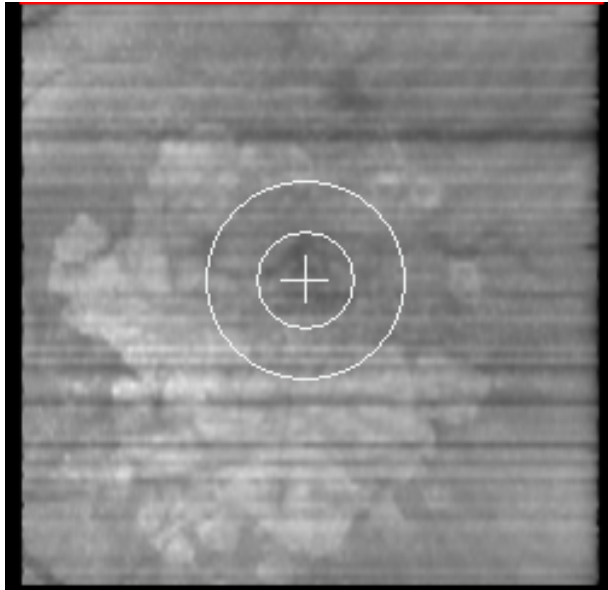
RPE-BM Map  
(Pink = GA)



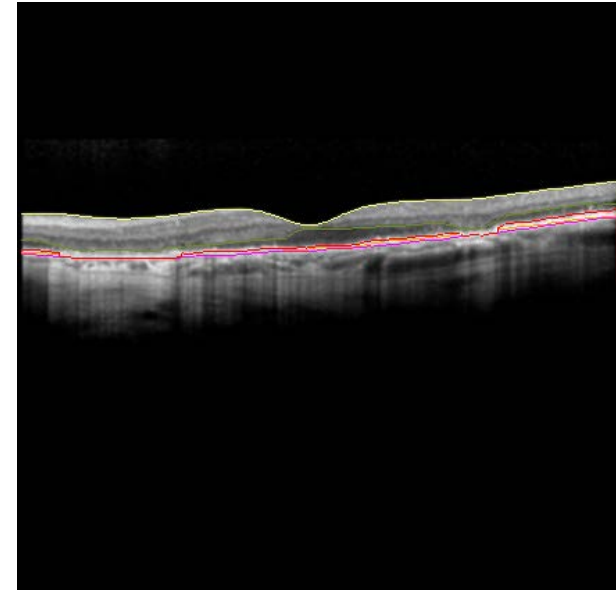
# ReCLAIM- Quantitative Compartmental OCT Analysis

## Non-central GA Patient Case Example (4 letters gain)

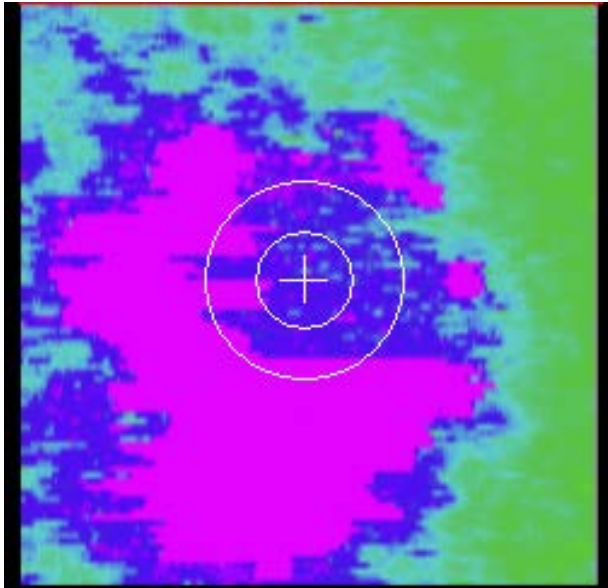
NIR Fundus Image



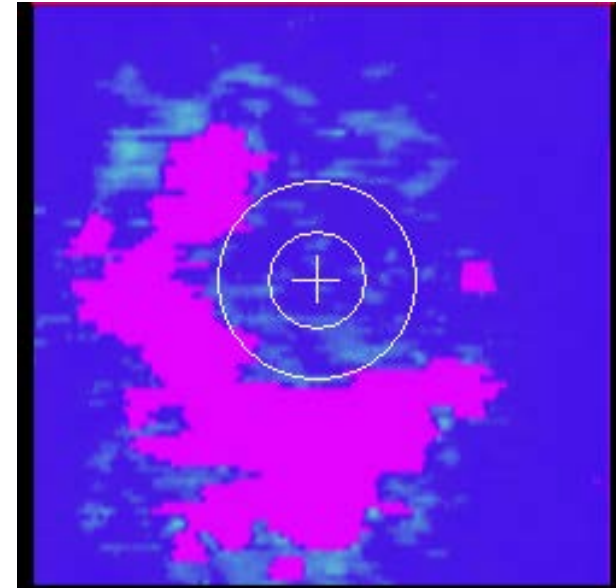
B-Scan at Fovea



EZ-RPE Map  
(Pink – Total EZ Attenuation)



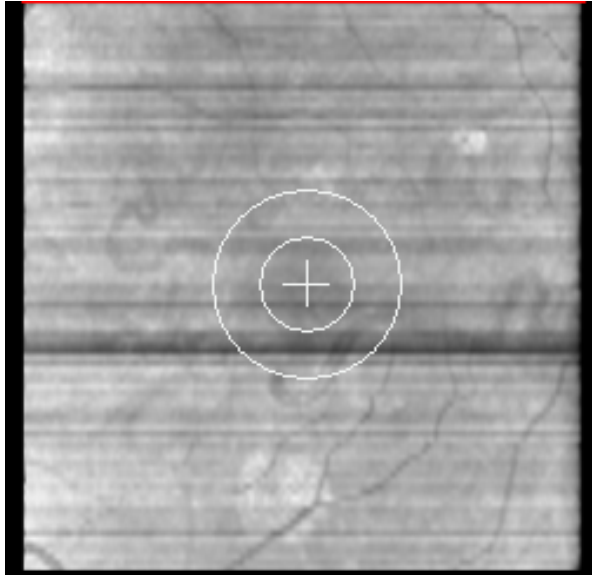
RPE-BM Map  
(Pink = GA)



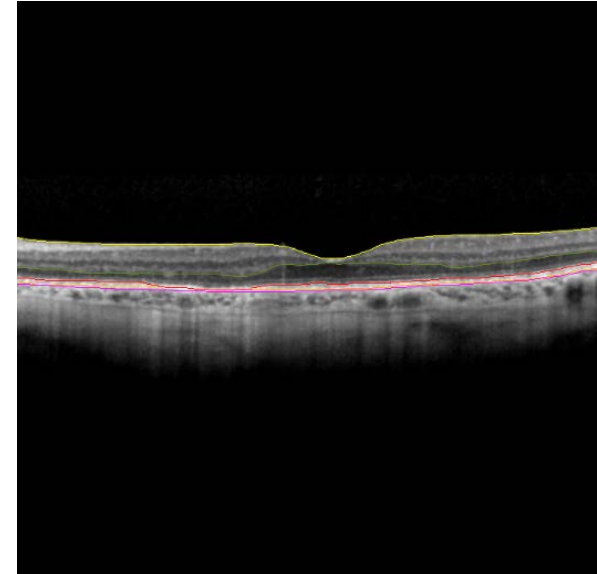
# ReCLAIM- Quantitative Compartmental OCT Analysis

## Non-central GA Patient Case Example (18 letters gain)

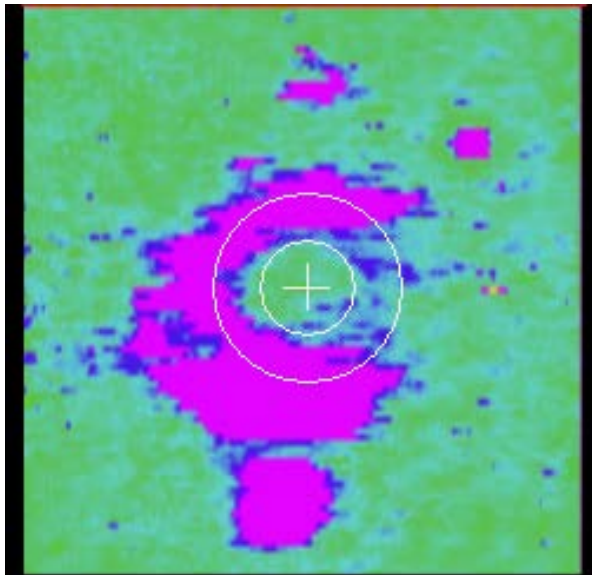
NIR Fundus Image



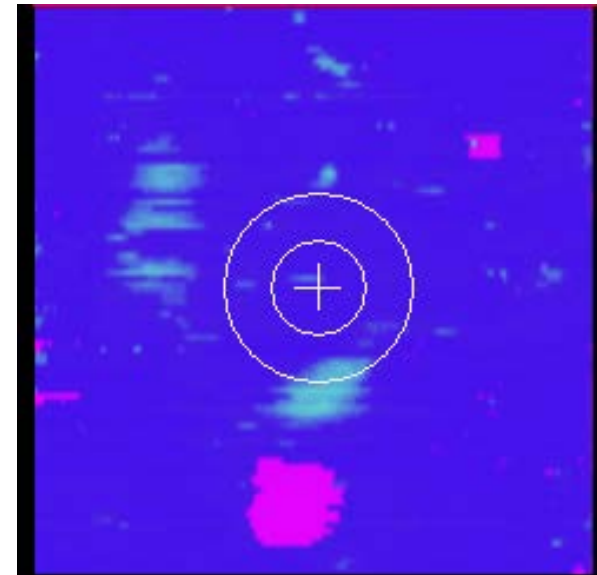
B-Scan at Fovea



EZ-RPE Map  
(Pink – Total EZ Attenuation)



RPE-BM Map  
(Pink = GA)





# ReCLAIM- *Quantitative Compartmental OCT Analysis* *Results (High Risk Drusen)*

In high risk drusen subgroup ( $n = 21$ ), changes from baseline to week 24 in LLVA correlated to:

- Mean central macular (e.g., central 2 mm) retinal thickness ( $r = 0.58$ ;  $P = 0.009$ )

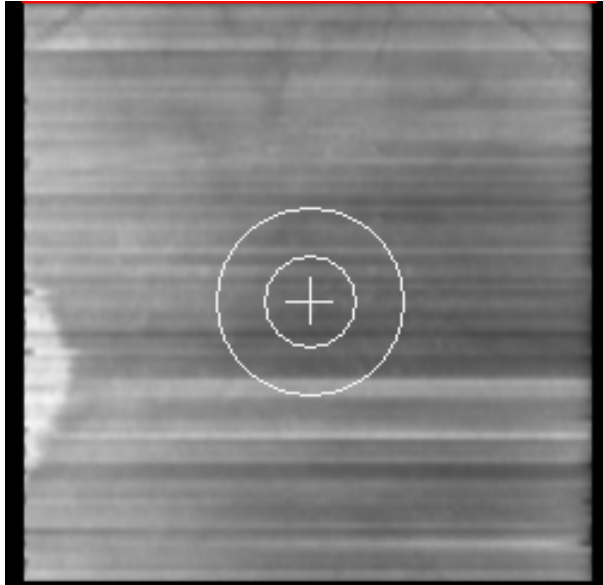
Eyes gaining 2 lines or more had:

- Significantly greater baseline preservation of the central macular outer retina (ONL-RPE thickness,  $137\ \mu\text{m}$  vs  $117\ \mu\text{m}$ ;  $P = 0.006$ )
- Trend towards less baseline macular partial EZ attenuation ( $1.1\%$  vs  $5.0\%$ ;  $P = 0.06$ )

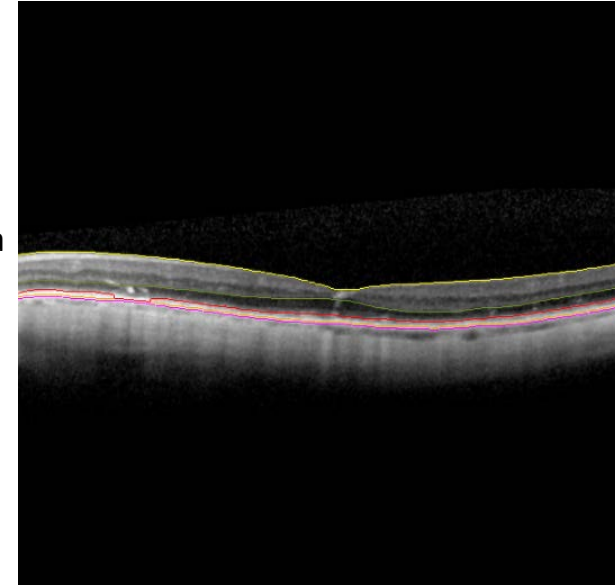
# ReCLAIM- Quantitative Compartmental OCT Analysis

## High Risk Drusen Patient Case Example (2 letters loss)

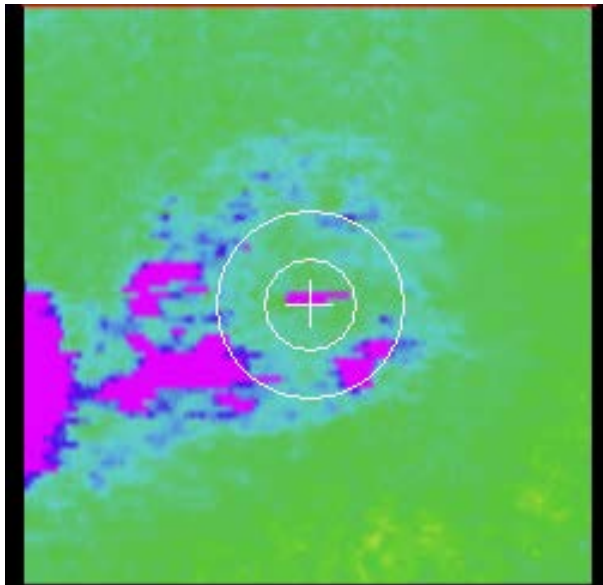
NIR Fundus Image



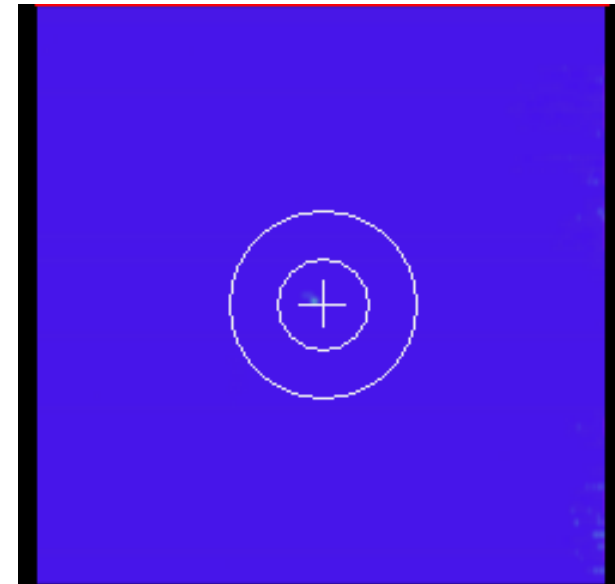
B-Scan at Fovea



EZ-RPE Map  
(Pink – Total EZ Attenuation)



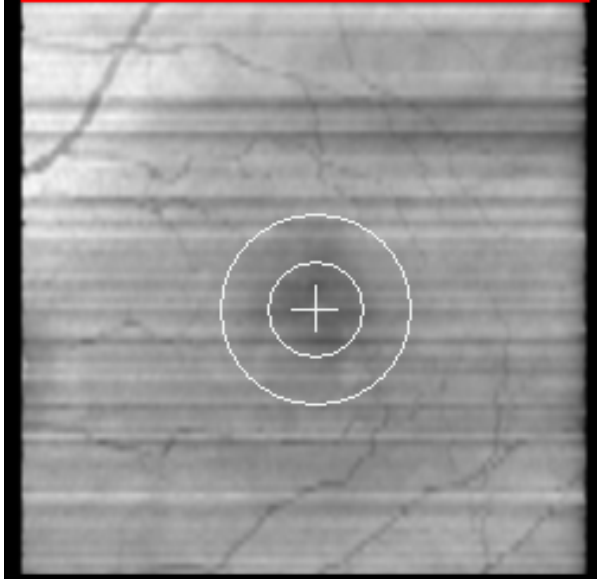
RPE-BM Map  
(Pink = GA)



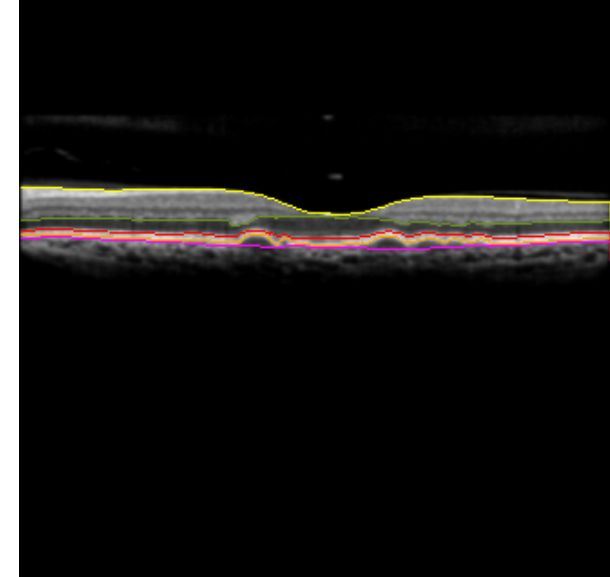
# ReCLAIM- Quantitative Compartmental OCT Analysis

## High Risk Drusen Patient Case Example (10 letters gain)

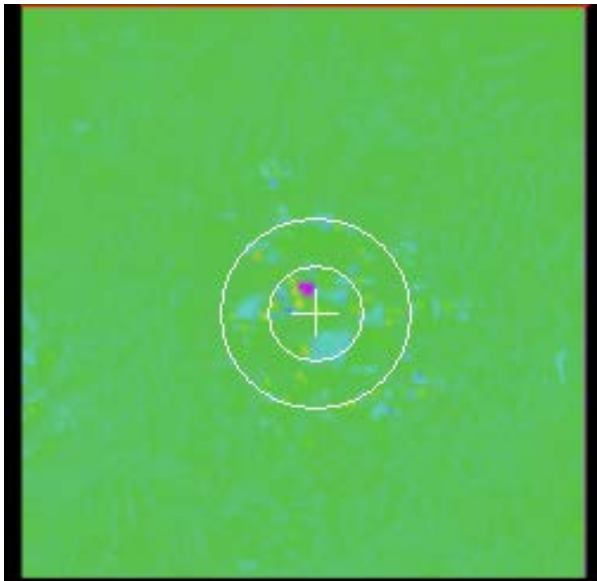
NIR Fundus Image



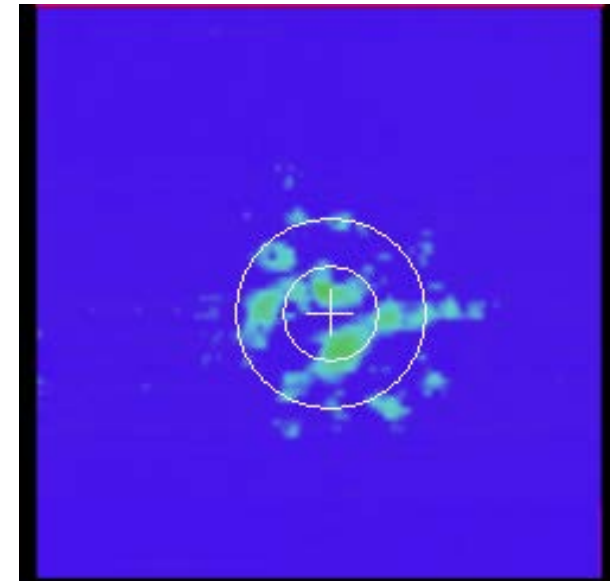
B-Scan at Fovea



EZ-RPE Map  
(Pink – Total EZ Attenuation)



RPE-BM Map  
(Pink = GA)





The background of the slide is a microscopic image showing several elongated, rod-shaped cells. These cells have a translucent, light blue outer membrane and a darker, more textured interior. Inside the cells, there are numerous small, dark blue or purple granules, possibly representing internal organelles or inclusions. The cells are scattered across the frame, with some appearing more clearly than others. The overall color palette is dominated by shades of purple and blue, creating a scientific and somewhat ethereal atmosphere.

# Limitations

# ReCLAIM – *Quantitative Compartmental OCT Analysis*

## *Limitations*

**Small sample size**

**No placebo control group for comparison**

**Post-hoc assessment for hypothesis generation and exploratory evaluation**

**Assessments performed without multiple comparison correction due to exploratory nature of analysis**



The background of the slide is a microscopic image showing several elongated, rod-shaped cells. These cells have a translucent, light blue outer membrane and a darker, more granular interior. Inside the cells, there are numerous small, dark blue or purple spherical structures, possibly representing internal organelles or genetic material. The overall color palette is dominated by deep purples and blues, creating a scientific and somewhat ethereal atmosphere. The word "Conclusions" is centered in the upper half of the image in a clean, white, sans-serif font.

# Conclusions



# ReCLAIM – *Quantitative Compartmental OCT Analysis*

## *Conclusions*

**Exploratory assessment of baseline higher order OCT parameters, such as EZ integrity and the sub-RPE compartment, demonstrated correlation of select parameters with functional response to elamipretide treatment**

**Disruption of outer retinal features may be an important biomarker for potential treatment response to elamipretide**

**Further research is needed to better characterize these potential imaging biomarkers and evaluate their potential role for clinical trial enrichment and prediction of treatment response**



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- Jordan Bell
- Nicole Cardwell
- Sydney Sterben
- CJ Bell
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- Hasan Cetin, MD
- Carmen Calabrise
- Alison Martin
- Christopher Mugnaini
- Alex Halasi
- Natalie Coughlin
- Katherine Wise



The background of the slide is a microscopic image. It features a dense field of small, purple, spherical cells, likely bacteria or yeast, which are out of focus. Overlaid on this are several rod-shaped organisms, possibly protozoa or larger bacteria, which are in sharper focus. These organisms have a translucent, light blue-green body and contain numerous small, dark blue or black granules. Some of these granules are arranged in a spiral pattern within the organisms. The overall lighting is dim, with the purple cells providing a vibrant, textured backdrop for the more detailed rod-shaped structures.

Thank you!