## 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

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# 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



ROS, Reactive oxygen species.

## Elamipretide Binding to Cardiolipin Stabilizes the Inner Mitochondrial Membrane Structure



ROS, Reactive oxygen species.

### Elamipretide Protects RPE Mitochondria in a Diabetic Mouse Model



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

## **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



#### Noncentral GA subgroup

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

#### 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)

#### 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

## ReCLAIM Baseline Subject Demographics

	Noncentral GA (N=19)	High-risk drusen (N=21)	Total (N=40)
Age, years			
<ul> <li>Mean (SD)</li> </ul>	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 <i>,</i> 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

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



## Low-luminance visual acuity (LLVA)



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





## Low-luminance visual acuity (LLVA)



## Quantitative OCT and Compartmental Mapping Biomarker Characterization

## ML-Enhanced Multi-Layer Segmentation and Compartmental Mapping







Layer Segmentation





3D reconstruction of macular cube

*En face* view of normative EZ mapping

ML, Machine learning; ILM, Inner limiting membrane; EZ, Ellipsoid-zone; RPE, Retinal pigment epithelium; ONL, Outer nuclear layer; OPL, Outer plexiform layer; HFL, Henle's fiber layer.

## 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 μm) and partial attenuation (i.e.,< 20 μm) on *en face map*)
- RPE total attenuation (i.e., GA)
- Sub-RPE Volume
- ONL/HFL-EZ thickness
- ONL/HFL-EZ volume

## EZ Integrity Maps



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)

# *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:

 $\geq$  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)



B-Scan at Fovea

**RPE-BM Map** 

(Pink = GA)





EZ-RPE Map (Pink – Total EZ Attenuation)

**NIR Fundus Image** 

## ReCLAIM- Quantitative Compartmental OCT Analysis Non-central GA Patient Case Example (4 letters gain)



**NIR Fundus Image** 

**EZ-RPE** Map

**B-Scan at Fovea** 





**RPE-BM Map** (Pink = GA)

(Pink – Total EZ Attenuation)

### ReCLAIM- Quantitative Compartmental OCT Analysis Non-central GA Patient Case Example (18 letters gain)



NIR Fundus Image

EZ-RPE Map (Pink – Total EZ Attenuation) B-Scan at Fovea





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  $\mu$ m vs 117  $\mu$ 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)

B-Scan at Fovea

**RPE-BM Map** 

(Pink = GA)

NIR Fundus Image





EZ-RPE Map (Pink – Total EZ Attenuation)



## ReCLAIM- Quantitative Compartmental OCT Analysis High Risk Drusen Patient Case Example (10 letters gain)

**B-Scan at Fovea** 

**RPE-BM Map** 

(Pink = GA)



NIR Fundus Image





## 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

# 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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