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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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

**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.
Elamipretide Protects RPE Mitochondria in a Diabetic Mouse Model

Transmission electron micrographs of mouse RPE mitochondria

<table>
<thead>
<tr>
<th>Normal diet</th>
<th>Diabetic diet + streptozotocin + saline</th>
<th>Diabetic diet + streptozotocin + elamipretide</th>
</tr>
</thead>
</table>

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

ReCLAIM Study Design and Results
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 ≥1.27 mm² (~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
## Baseline Subject Demographics

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

**Best-corrected visual acuity (BCVA)**

<table>
<thead>
<tr>
<th>Mean ETDRS letters</th>
<th>Baseline</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.7</td>
<td>78.3</td>
</tr>
</tbody>
</table>

Increase of 4.6±5.1 letters ($P=0.003$)

**Low-luminance visual acuity (LLVA)**

<table>
<thead>
<tr>
<th>Mean ETDRS letters</th>
<th>Baseline</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.9</td>
<td>49.3</td>
</tr>
</tbody>
</table>

Increase of 5.4±7.9 letters ($P=0.019$)
ReCLAIM
Visual Acuity Outcomes in the High-Risk Drusen Subgroup (N=21)

Best-corrected visual acuity (BCVA)

- Mean ETDRS letters: Baseline 79.4, Week 24 82
- Increase of 3.6±6.4 letters (P=0.025)

Low-luminance visual acuity (LLVA)

- Mean ETDRS letters: Baseline 63.7, Week 24 68.4
- Increase of 5.6±7.8 letters (P=0.005)
Quantitative OCT and Compartmental Mapping Biomarker Characterization
ML-Enhanced Multi-Layer Segmentation and Compartmental Mapping

Layer Segmentation

a) ILM

b) Between OPL/ONL

c) EZ

d) RPE

\[
\text{ONL/HFL-EZ} \quad \text{EZ-RPE}
\]

6 × 6 mm

Loading macular cube into OCT Mapping software

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.
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**

**Normal**
- Total Attenuation: 0.0%
- EZ-RPE Volume: 1.27 mm³

**Abnormal**
- Total Attenuation: 3.3%
- EZ-RPE Volume: 1.23 mm³
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
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
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)
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)
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 µm vs 117 µm; $P = 0.006$)
- 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)
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)
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
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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