Exploratory analysis of visual acuity gain with mfERG and OCT biomarkers in a non-exudative AMD trial

Vlad Diaconita, MD, Daniel Russakoff PhD,
Jonathan Oakley PhD, Meredith Mundy,
Hanna R. Coleman MD, Jason Slakter MD, Scott E. Brodie, MD, PhD

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BACKGROUND:

- Correlation between function and structure in patients with macular degeneration is of great clinical interest, and the focus of novel clinical trials.
- Improvement in best-corrected visual acuity (BCVA) is a key endpoint in non-exudative age-related macular degeneration (dAMD) trials.
- Functional biomarkers from multifocal electroretinogram (mfERG) and structural ones from Optical Coherence Tomography (OCT) may provide insight into treatment response, especially in early and intermediate dAMD disease states.
- This exploratory analysis aimed to identify a minimal feature set that classifies strong responders in a sham-controlled trial evaluating the i-Lumen AMD transpalpebral microcurrent stimulation (MCS) therapy.

METHODS:

- Eleven participants from a double-masked, multicenter, randomized, sham-controlled trial of non-exudative AMD were analyzed over 12 months (Figure 1). Participants received 7 days of either active MCS therapy (i-Lumen AMD) or sham treatment over the initial 2 months. Assessments included BCVA, mfERG implicit times and amplitudes, and OCT segmented layer thickness in central and parafoveal regions. Responders were categorized as:
  - 1. Strong Responders (BCVA increase ≥9 letters, N1 latency decrease): N = 5
  - 2. Weak Responders (BCVA increase <9 letters, N1 latency decrease): N = 1
  - 3. Atypical Responders (BCVA increase ≥9 letters, N1 latency increase): N = 1
- Analysis of variance compared treatment and sham groups. Predictive features were ranked using Mahalanobis distance—a multivariate metric accounting for feature correlation and scale—to maximize class separation.

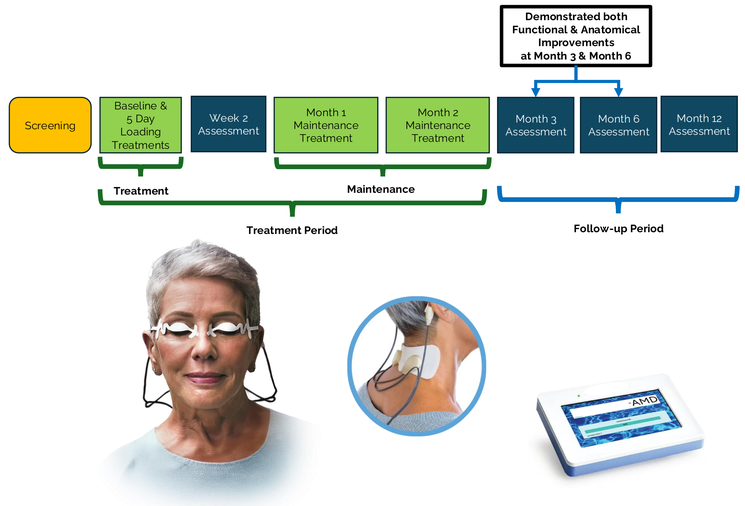

Figure 1 – Trial Schedule and Illustration of trial MCS therapy administration (i-Lumen AMD)

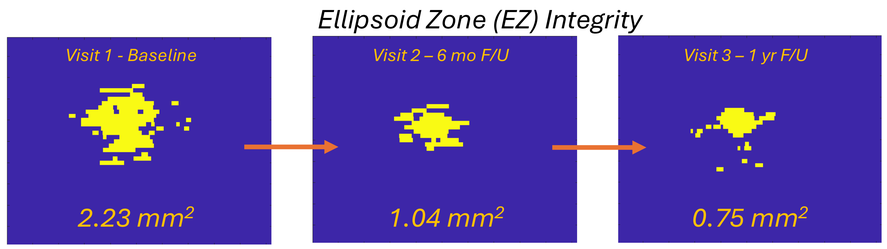

Figure 2 – Ellipsoid Zone (EZ) Integrity measured (Orion Software, Voiant LLC[1]) optically shows improvement in this example participant. This was associated with RPE complex collapse and may be an early indicator of stabilization of disease progression.

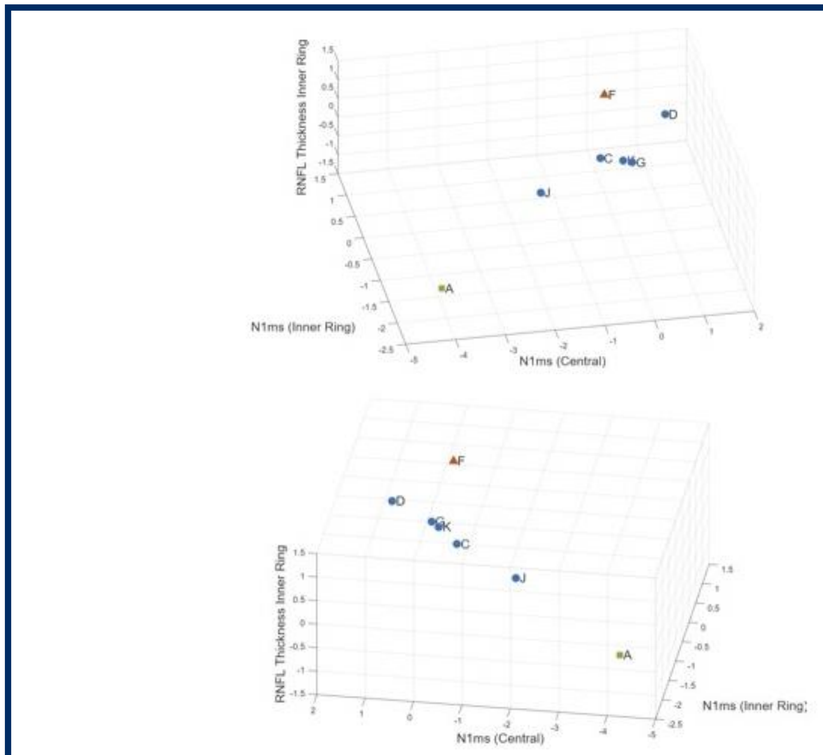

Figure 3 – Two views of a 3D Mahalanobis distance plot showing responder class separation based on N1 latency (central, inner ring) and RNFL thickness (inner ring). Blue = strong responders (C,D,G,K, J), green = weak responders (A), red = atypical (F).

RESULTS:

- Active treatment was significantly associated with BCVA improvement over 12 months ($p = 0.0050$).
- Although EZ integrity showed improvement, this was associated with Retinal Pigment Epithelial Detachment (RPED) collapse and may in fact be an early indicator of stabilization of disease (Figure 2).
- Strong responders showed the largest BCVA gains. The best-performing feature triplet included N1 latency in the central region, N1 latency in the inner ring, and RNFL thickness in the inner ring. This combination yielded Mahalanobis distances of 13.34 and 65.7 for outliers, with strong responders clustering within 0.82–1.79 (Figure 3).

FUTURE DIRECTIONS:

- Re-assessment of biomarkers and progression at study conclusion for the entire cohort.
- Multimodal assessment of mfERG and OCT biomarkers, including EZ-RPE Thickness and EZ Integrity.

CONCLUSIONS:

- Combining mfERG and OCT segmentation features can improve classification of strong responders in non-exudative AMD treatment trials.
- This proof-of-concept suggests N1 implicit time may serve as an early predictor of BCVA improvement.
- Larger datasets are needed to validate these findings and refine predictive models.

REFERENCES

1. Diaconita V, et al. *Accurate Machine-Learning (ML) Ellipsoid Zone (EZ) Measurements of Volume and EZ Total Loss of Optical Coherence Tomography (OCT) Scans in Non-exudative Macular Degeneration Eyes.* AMD Imaging II, Session #417. SAIVO Annual Meeting, October 2025

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