

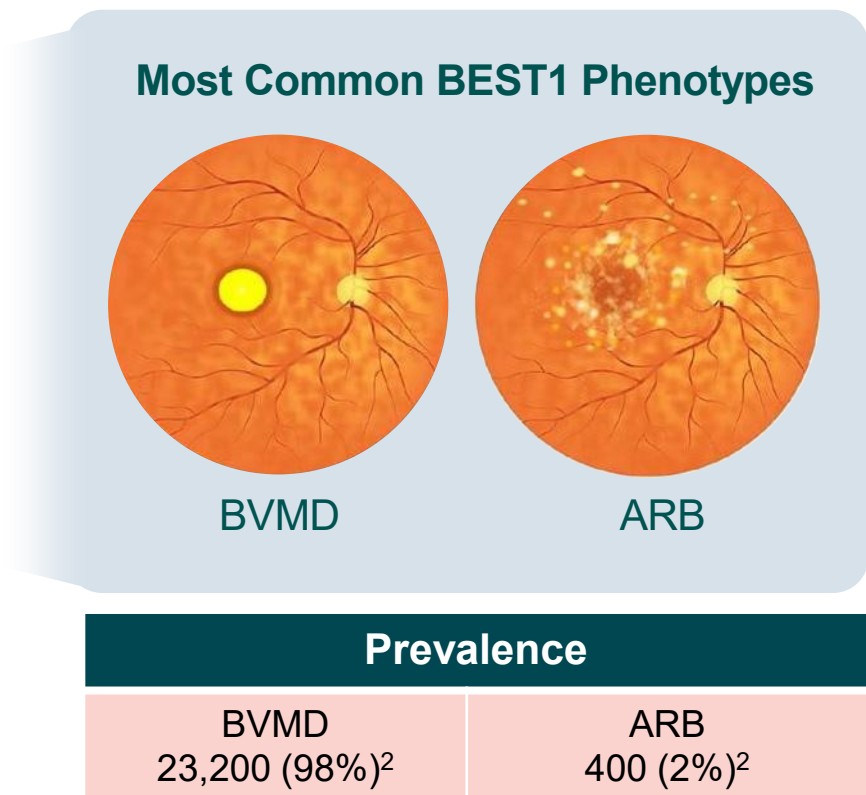
Prediction of Retinal Sensitivity Changes Following Treatment in BEST Disease

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Retina in Rio 2026



BEST1: Group of Inherited Retinal Diseases with a Range of Onset and Slow Rate of Progression and no Approved Treatment Options

Overview & Prevalence	- Mutations in <i>BEST1</i> have been associated with at least five clinically distinct retinal degenerative diseases, with onset from childhood to adulthood¹ - Accounts for ~3.5% of all IRDs¹ Global prevalence*: ~45,400 patients² U.S. prevalence: 23,600 patients (~23,200 BVMD and ~400 ARB)²
Clinical Features ^{1,3}	- Serous retinal detachment - BVMD (most common) is characterized by vitelliform (“egg-yolk”) lesion beneath the macula¹ - Macular atrophy - CNV
Symptoms ^{3,4}	- Loss of central vision - Metamorphopsia (distorted vision) - Scotoma (blind spot) - Photophobia⁴



*Global prevalence estimate includes United States, EU4 (France, Spain, Germany, & Italy), UK, Middle East/North Africa, and China.

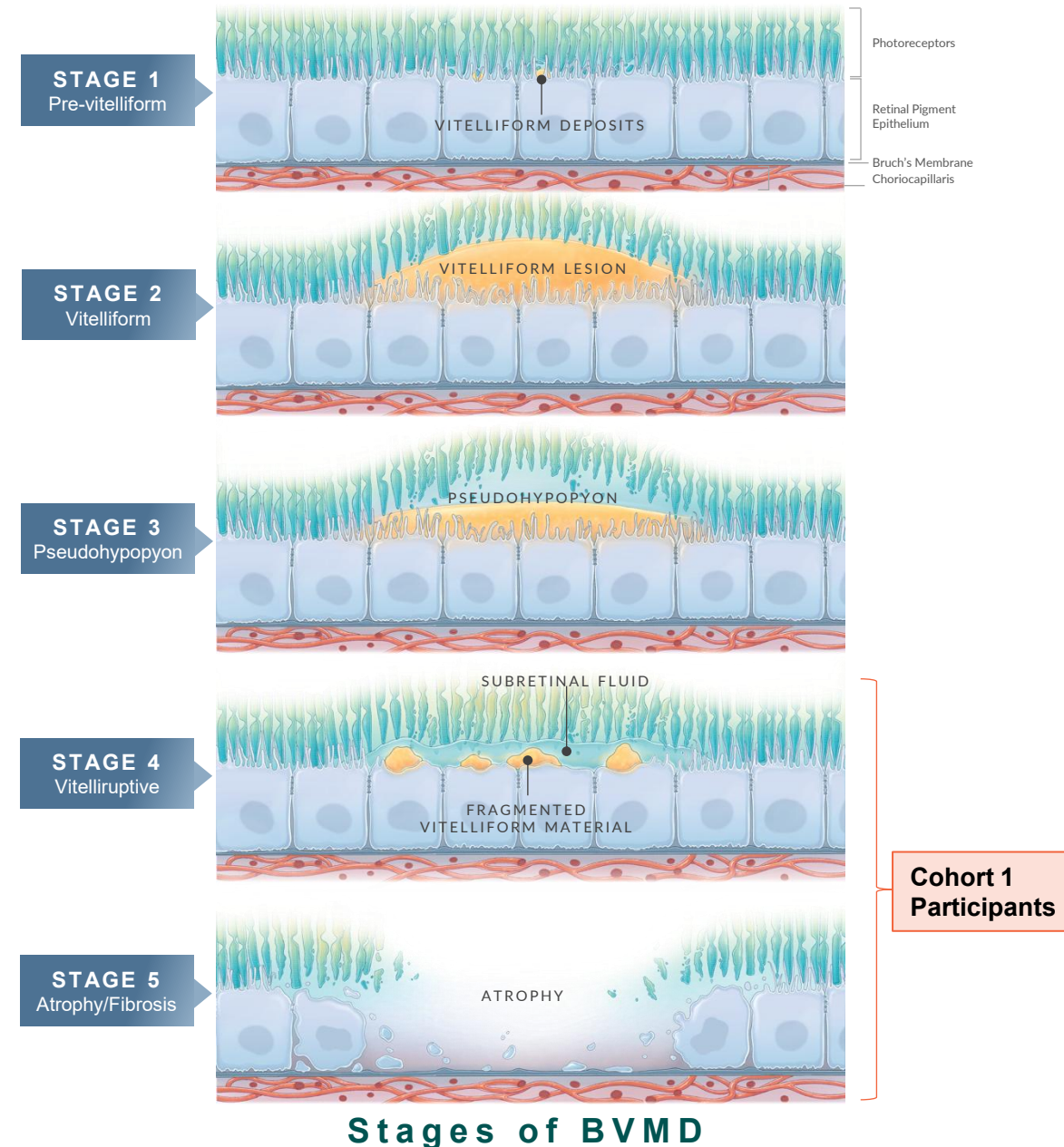
ARB, autosomal recessive bestrophinopathy; BEST1, bestrophin 1; BVMD, best vitelliform macular dystrophy; CNV, choroidal neovascularization; IRD, inherited retinal disease.

1. Amato A, et al. *Saudi J Ophthalmol.* 2023;37(4):287-295. 2. BEST1 Market Landscape Quantitative Market Research, Triangle Insights Group, Q3 2026. 3. Johnson AA, et al. *Prog Retin Eye Res.* 2017;58:45-69.

4. Tripathy K, et al. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

BEST1 Disease Biology

- **BEST1 gene encodes for bestrophin-1**, a homopentameric (i.e., 5 identical monomers) Ca^{2+} -activated chloride channel required for RPE maintenance and retinal physiology
 - **BEST1 mutations in BVMD disrupt cellular ion and fluid homeostasis** resulting in electrophysiological abnormalities, RPE dysfunction, and retinal degeneration via:
 - Defective **clearance of toxic waste** products (e.g., lipid deposits)
 - **Impaired RPE-photoreceptor interactions** (e.g., defective phagocytosis)
 - **Build-up of vitelliform material** (toxic waste products) and fluid under the retina
- Vitelliform material occurs early and is the hallmark of BVMD
 - Subretinal fluid occurs late in disease and pools in atrophic areas



OPGx-BEST1 Gene Therapy is Designed to Target RPE and Restore Bestrophin Function

- Designed to restore retinal ion homeostasis in bestrophinopathies, ameliorating retinal structural and functional deficits
- *BEST1* is targeted using the AAV2 capsid employed in LUXTURNA® and an RPE-specific promoter
- Most bestrophinopathies exhibit a slow rate of decline and central photoreceptors usually remain viable for decades, providing a wide therapeutic window
- BIRD-1: Phase 1/2 Study of OPGx-BEST1 Subretinal Gene Therapy in adult (≥ 18 years old) participants with BVMD or ARB
 - Cohort 1: low dose - 1.5E9 vg/eye
 - Cohort 2: high dose - 4.5E9 vg/eye

OPGx-BEST1 Gene Therapy

Vector	AAV2
Delivery	Single subretinal injection

Participant Demographics: Low-Dose Cohort 1

	101-101	101-104	102-101	102-102	101-106
Age	63	59	50	45	31
Sex	Female	Female	Male	Male	Male
BEST phenotype	ARB	ARB	BVMD	BVMD	BVMD
Baseline VA* (study eye†)	1	50	49	61	47
Baseline VA* (fellow eye)	43	65	68	72	56
Follow-up duration	6 months	6 months	3 months	3 months	3 months
Severity of disease	End-stage with significant atrophy	End-stage with significant atrophy	End-stage with sub-foveal, sub-RPE scar	Advanced stage vitello-eruptive with some scarring	Earlier stage without significant atrophy or scarring

*ETDRS letters equivalent calculated from logMAR.

†Worse eye deemed study eye.

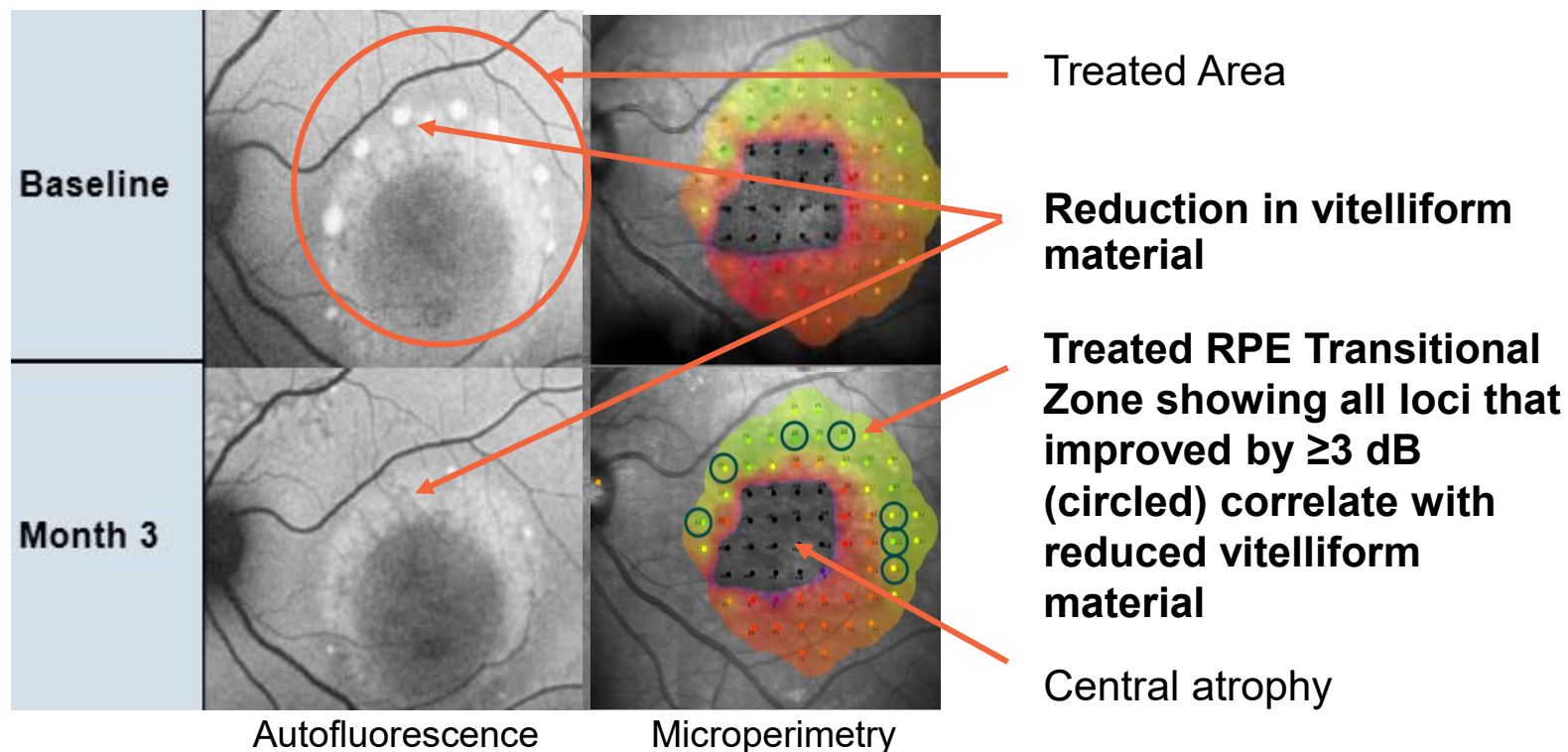
ARB, autosomal recessive bestrophinopathy; BEST, bestrophin; BVMD, best vitelliform macular dystrophy; ETDRS, Early Treatment Diabetic Retinopathy Study; RPE, retinal pigment epithelium; VA, visual acuity.

Microperimetry Showed BVMD Improvement in the Treated RPE Transitional Zone

Defining the Transitional Zone

- Border area surrounding the atrophic lesion with RPE and photoreceptors that are structurally intact but functionally compromised or at risk of imminent atrophic progression
- Highest potential to be rescued with OPGx-BEST1
- **Treated RPE Transitional Zone** is the area of rescuable photoreceptors around the atrophic lesion where OPGx-BEST1 treatment is administered
- **New natural history data¹:** Untreated BVMD sensitivity only declines with highest rate detected in the transition zone – No untreated eye met the 3 dB improvement threshold, consistent with fellow eyes in Cohort 1

75% 3/4 evaluable participants* demonstrated **retinal sensitivity improvement[†]** in the Transitional Zone



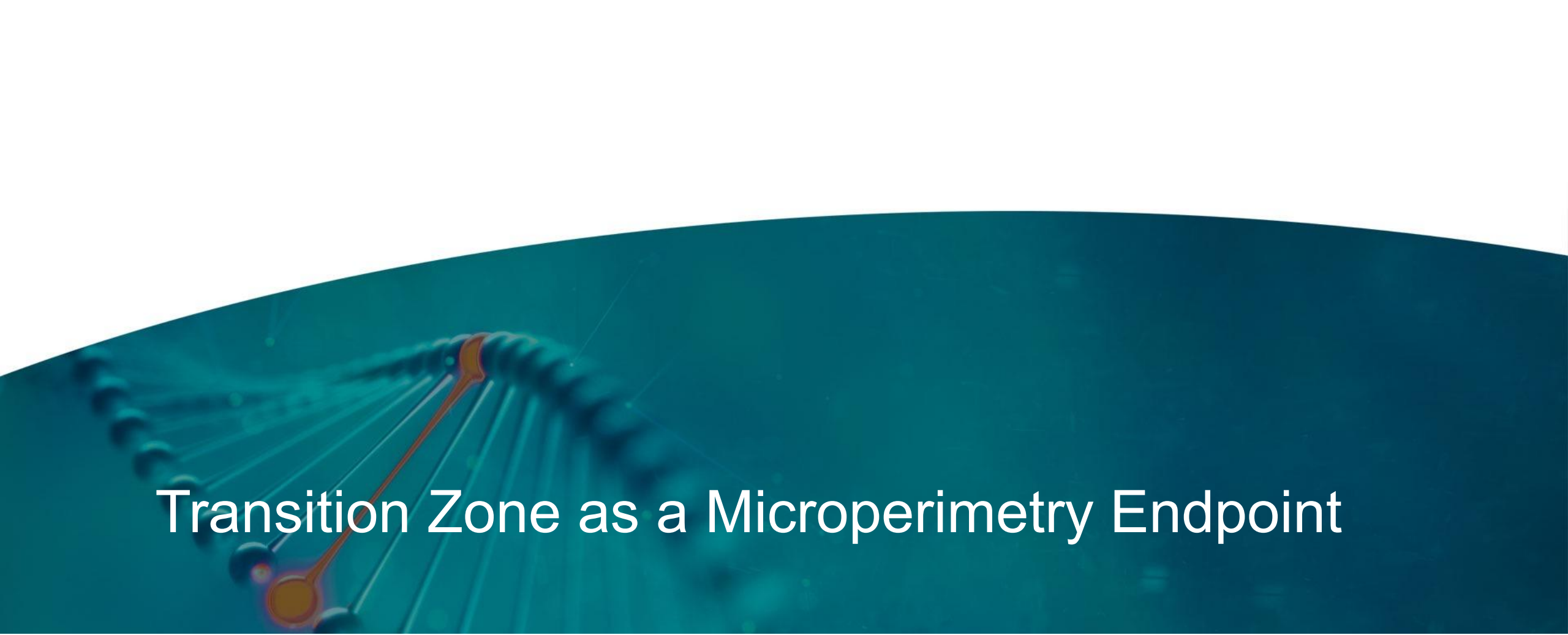
FDA aligned on ≥ 3 dB change from baseline in ≥ 5 loci in treated RPE Transitional Zone anchored to a patient reported outcome

*All eyes includes all evaluable patients (n=4); 101-101 could not complete microperimetry due to low vision.

[†]Improvement is defined as ≥ 5 loci area within the treated transitional zone improving by ≥ 3 dB from baseline.

BVMD, best vitelliform macular dystrophy; dB, decibel; FDA, Food and Drug Administration; RPE, retinal pigment epithelium.

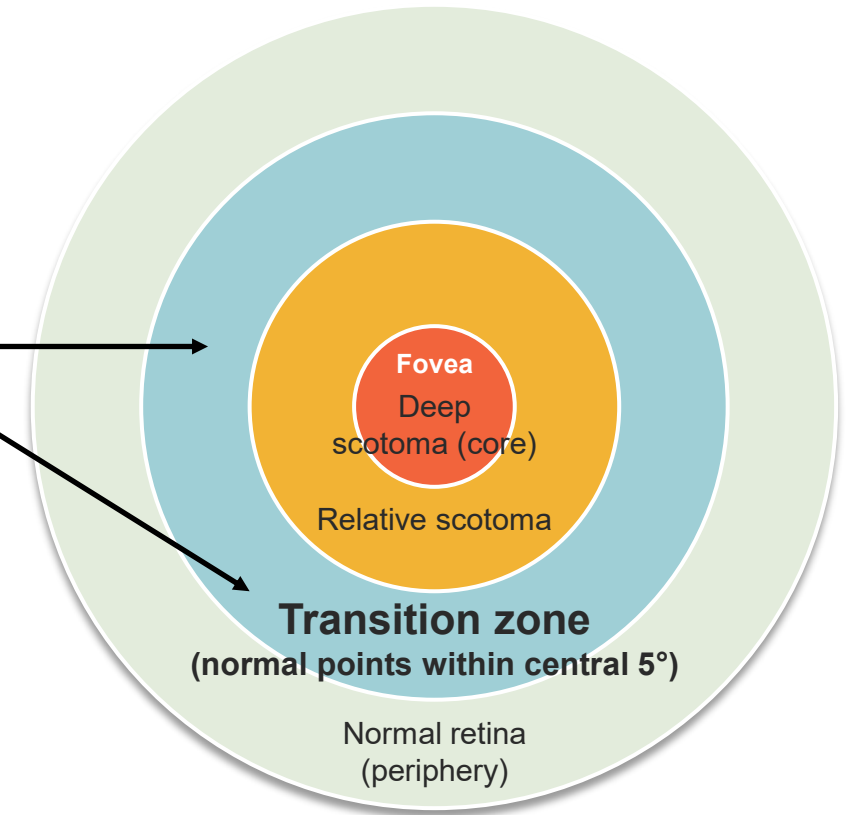
1. Bianco L, et al. *Invest Ophthalmol Vis Sci.* 2026;67(11):1.

A Newton's cradle with five spheres is shown in a dark teal, semi-transparent background. The spheres are arranged in a slight arc, and the central sphere is slightly offset, creating a sense of motion. The background has a subtle gradient and some faint, glowing lines.

Transition Zone as a Microperimetry Endpoint

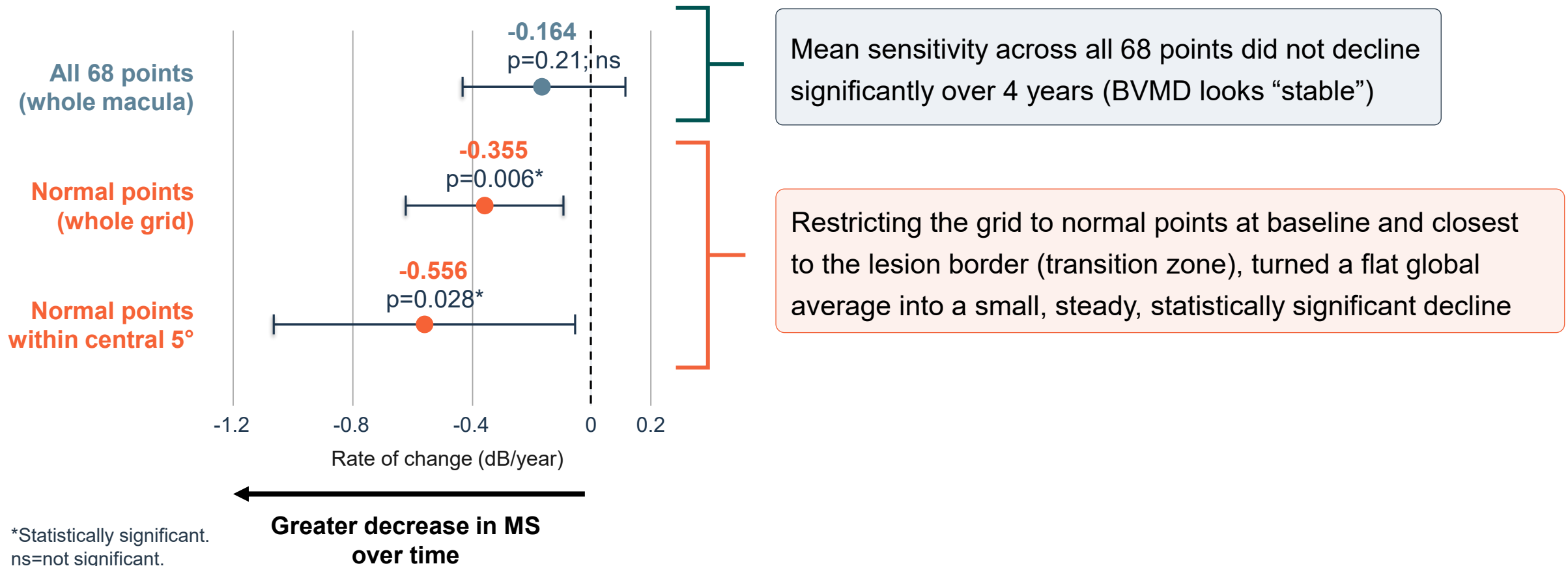
Natural history of macular sensitivity in BVMD: Microperimetry-derived outcome measures in preparation for clinical trials

- BVMD lesions have a core that is already scotomatous, and normal retina farther out
- Between them sits the transitional border zone: Points that still test normal today, immediately next to degenerating retina
 - This zone is concentrated within the central 5° around the fovea
- **Study objective:**
 - Natural history cohort study of 23 eyes from 13 patients with confirmed BVMD over 4.4 years
 - Tested sensitivity at 68 points (central 10°) at each visit, then tracked how much that sensitivity declined per year



No meaningful changes in the whole macula, but transition zone had a significant decline in mean sensitivity over time

Annual mean sensitivity rate of change (dB/year), by subset of test points - per-eye regression, N = 23 eyes



Why this matters for trial design

1

Whole-macula averages hide real progression

- Global mean sensitivity across all 68 points was statistically unchanged over 4 years; an averaging artifact, not evidence of a stable retina
- Averages are misleading; mixes healthy-looking spots with already-damaged spots, which can't decline much further

2

Transition zone reveals a real and significant decrease in sensitivity over time

- Restricting analysis to points normal at baseline, especially those within the central 5°, closest to the lesion border, uncovers a small but statistically significant, steady annual sensitivity decline (−0.36 to −0.56 dB/year)

3

Transition zone as a candidate microperimetry endpoint

- BVMD is characterized by a slow and progressive functional decline, and whole-macula averages aren't sensitive enough to measure progression within a realistic trial timeframe
- But if you specifically track the transition points near the edge of the lesion (between preserved and degenerated outer retina), you can detect a measurable decline and determine whether a treatment is slowing disease progression



Learnings from the Ongoing Phase 1/2 Study of OPGx-BEST1

Transition Zone Could be Optimized for Greater Specificity

Current Study

- TTZ loci selected
- Averages of **3.125** and **3.5 dB**

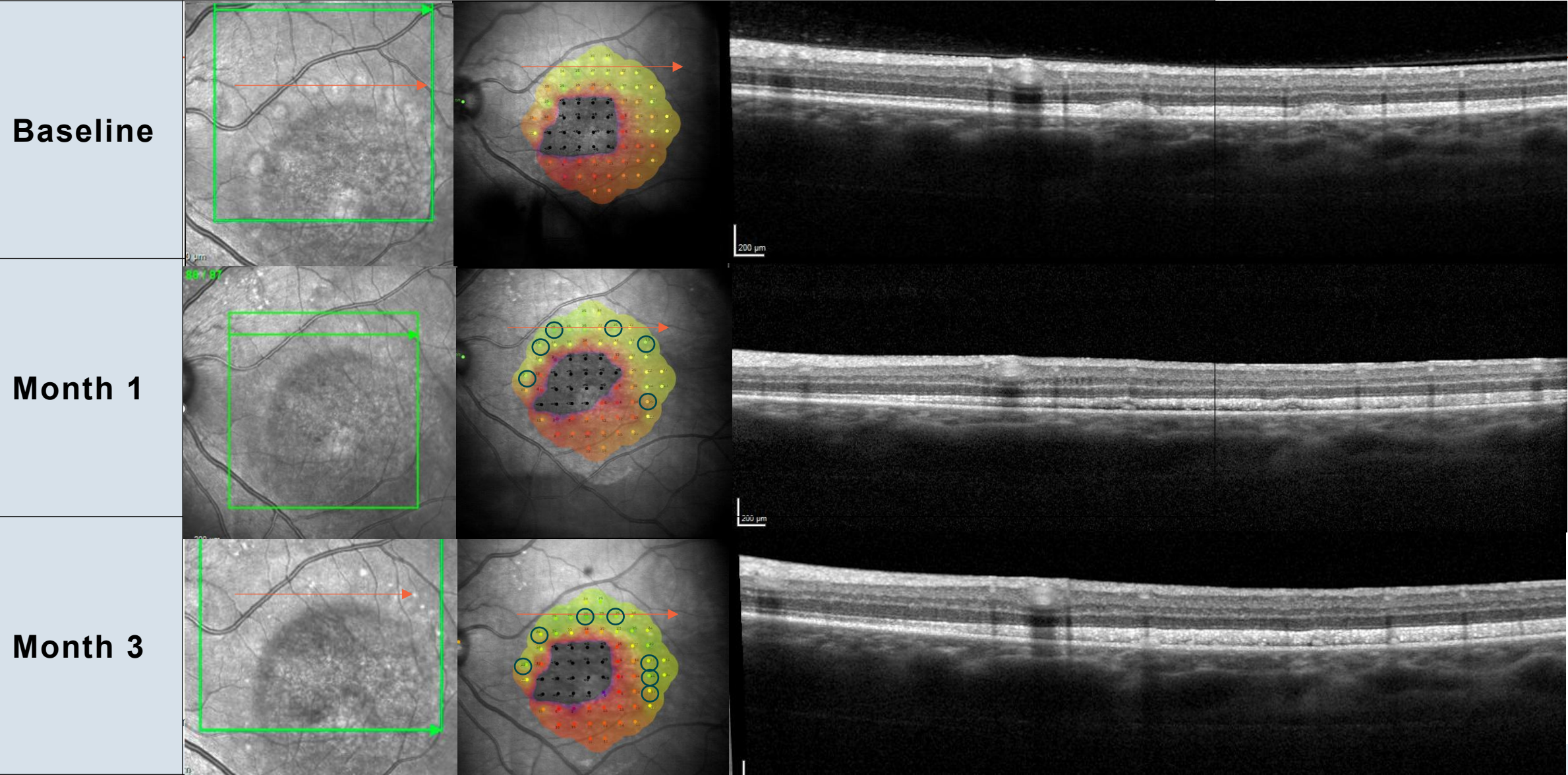
What We Learned

- Averages could have been higher with more selective loci
- Hyperautofluorescent spots alone would have averaged **4-5 dB**

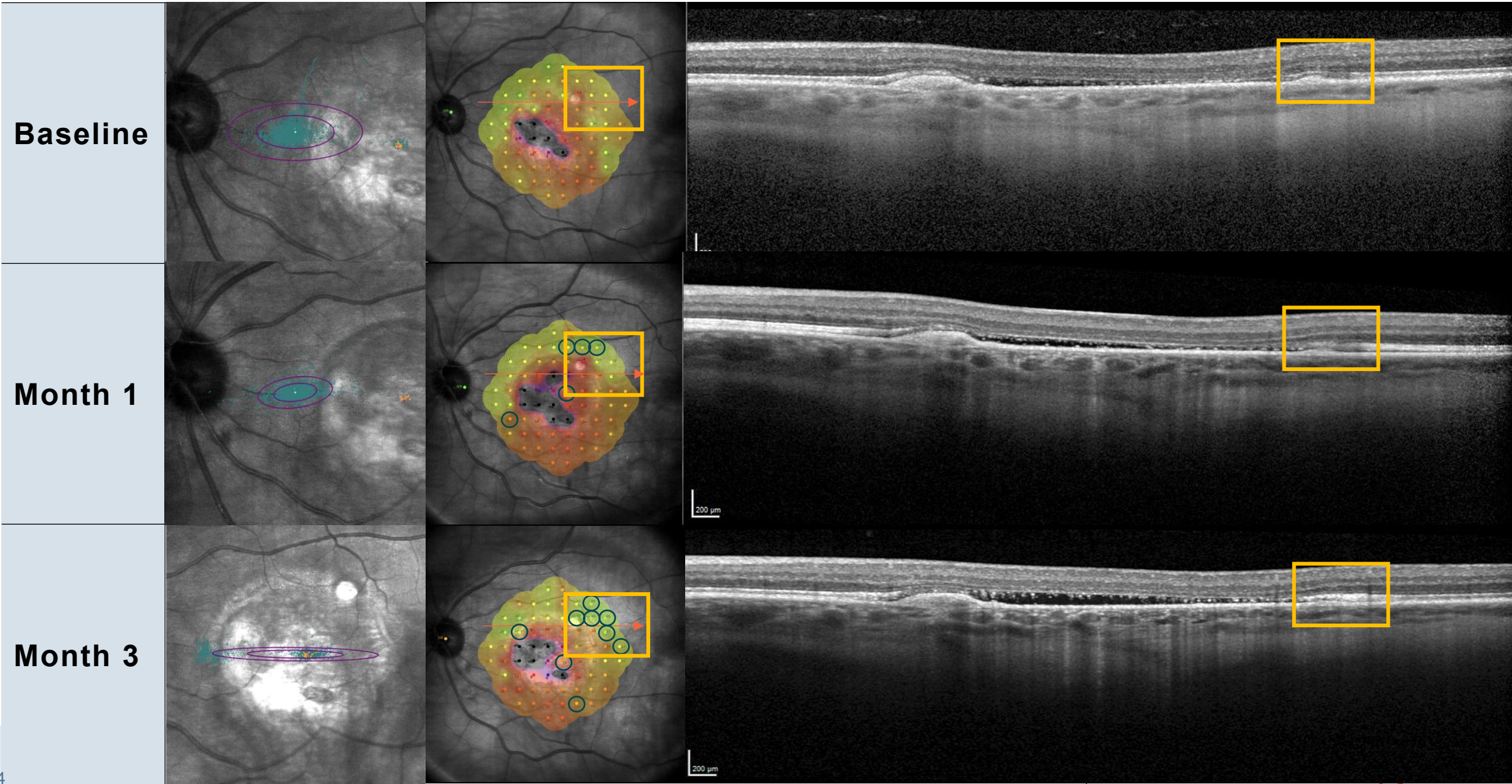
Future Study

- **Increase specificity for loci** likely to improve using:
 - Multimodal imaging (FAF, OCT)
 - Baseline demographics
 - Treatment areas

Microperimetry Improved within the Transitional Zone and Translated to Reduction in Vitelliform Lesions



Microperimetry Improved in the Transitional Zone and Correlated with Decreased Vitelliform Material

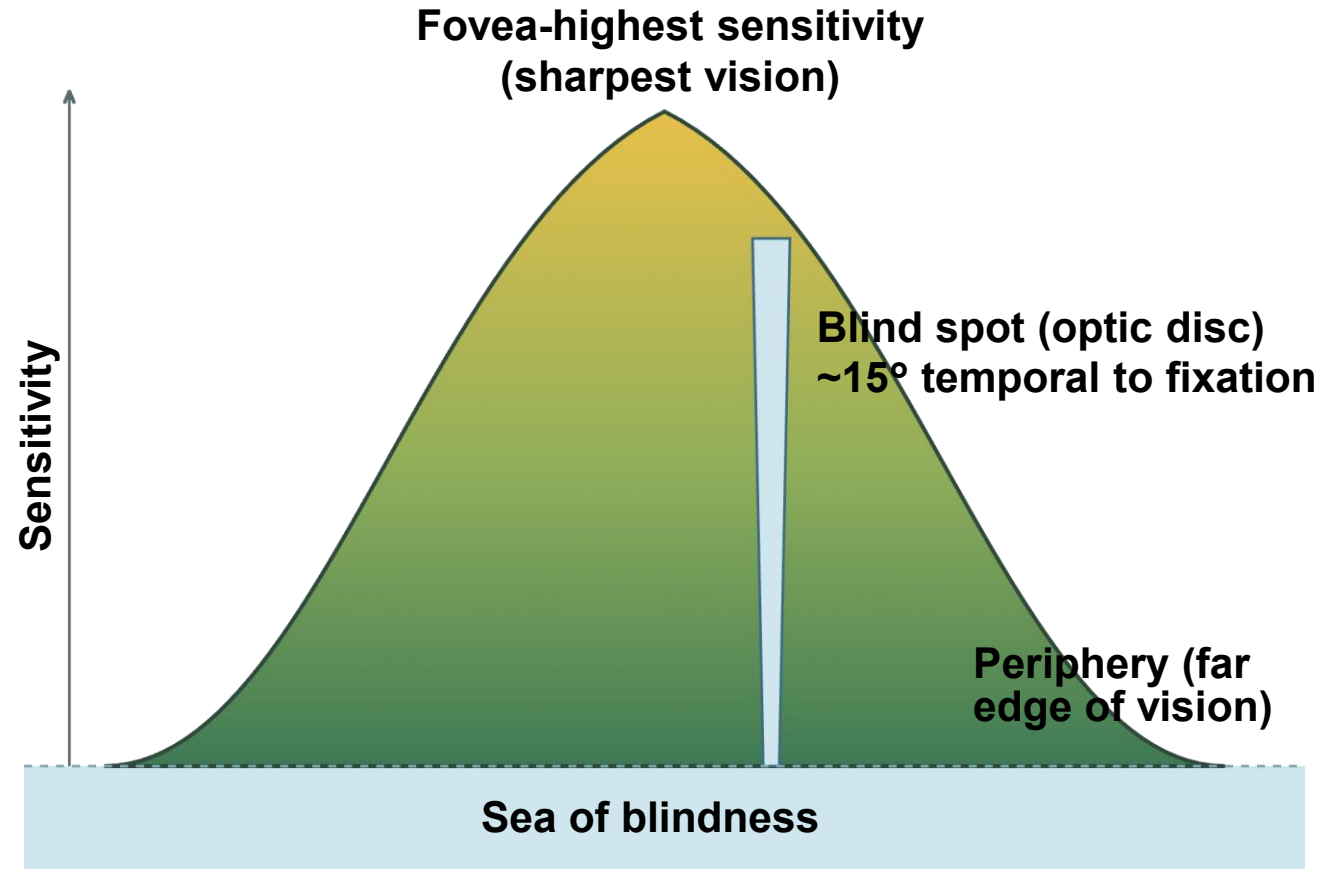




OCT-derived EZ-to-RPE Thickness as a Structural Endpoint

The Hill of Vision: Volumetric Visual Fields Predict Treatment Effect

- Also known as the Island of Vision in a Sea of Blindness
- Classic 3-D model of the visual field introduced by Harry Traquair in the 1920s
- Sensitivity peaks at the fovea and fades toward the periphery
- Used to interpret kinetic and static/automated perimetry (each tested point is a height on the hill)
- In retinal diseases, volume under the hill can serve as an endpoint that is less affected by floor effects than simple mean sensitivity





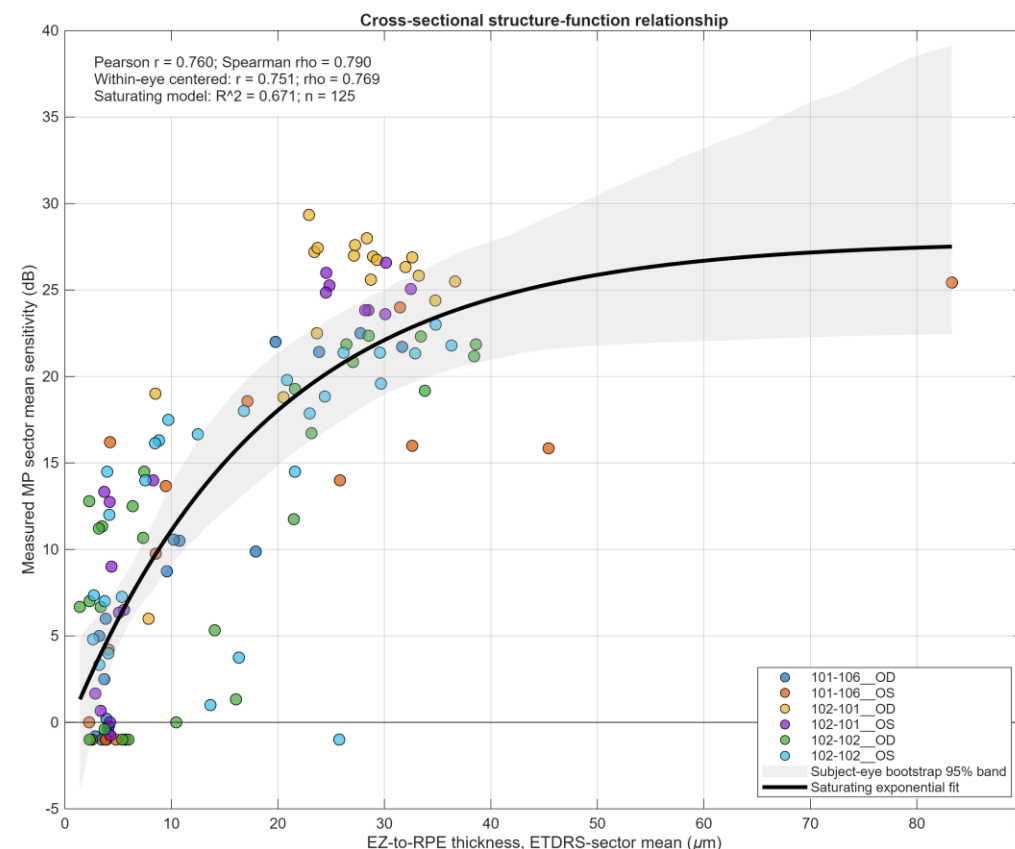
Learnings from the Ongoing Phase 1/2 Study of OPGx-BEST1

Analysis 1: Characterization of spatial relationship between EZ-to-RPE thickness and retinal sensitivity

OCT-derived EZ-to-RPE thickness was compared, sector by sector, against retinal sensitivity measured with MAIA microperimetry - testing whether retinal structure predicts retinal function in 3 participants (N=6 eyes; 161 sector comparisons)

Comparison	Pearson	Spearman
Measured microperimetry	0.760	0.784
HOV sensitivity	0.749	0.788
Measured, within-eye (subject-eye centered)	0.760	0.784
HOV, within-eye (subject-eye centered)	0.761	0.772

- **EZ-to-RPE thickness was strongly associated with both microperimetry and HOV sensitivities;** Associations were unchanged after subject-eye centering, demonstrating strong within-eye spatial relationship
- **Non-linear models significantly outperformed linear regression,** with 68% (microperimetry) and 69% (HOV) variances explained
- **Data supports EZ-to-RPE thickness as a spatial structural correlate** of retinal function



Analysis 2: Evaluation of treatment on EZ-to-RPE thickness

Evaluate whether treatment is associated with changes in EZ-to-RPE thickness (using the fellow untreated eye as control) in 3 participants (N=6 eyes)

- **Treated eyes demonstrated a consistent improvement in EZ-to-RPE thickness, with no change in fellow eyes**
 - By Day 90, the treated-minus-fellow difference was positive in all 3 participants despite heterogeneous early (Day 30) responses
- **Largest responder (101-106) showed a confirmed structural gain**
 - Mean EZ-to-RPE thickness increased by ~11.1 μm in treated eye vs 1.5 μm in fellow eye by Day 90

Treated-minus-fellow change in mean EZ-to-RPE thickness

Participant	Day 30 (OS – OD)	Day 90 (OS – OD)
101-106	+8.69 μm	+9.59 μm
102-101	+2.94 μm	+1.21 μm
102-102	-7.62 μm	+1.40 μm
Cohort mean	+1.34 μm	+4.07 μm

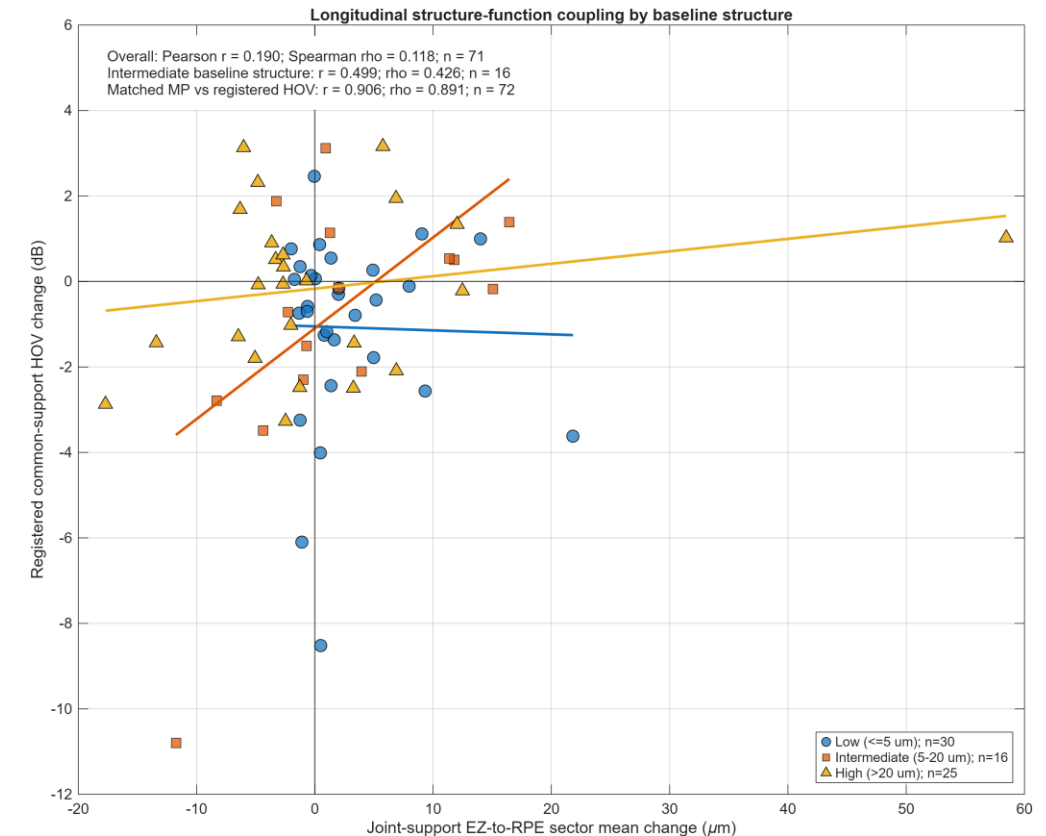
EZ-to-RPE thickness may provide a more sensitive structural endpoint than microperimetric sensitivity; Thickness improvement from baseline occurred between Month 1 and Month 3, suggesting a treatment effect

Analysis 3: Longitudinal structure-function association over time

Compared longitudinal change in EZ-to-RPE thickness with change in retinal sensitivity using microperimetry and HOV mapping in 3 participants (N=6 eyes; 106 sector comparisons)

Comparison	Pearson	Spearman
Measured microperimetry change	0.050	0.044
Registered HOV change	0.200	0.167
HOV change, within-eye	0.133	0.145
HOV vs. matched-location sensitivity	0.918	0.916

- **HOV revealed a modest, but more consistent positive structure-function relationship compared to microperimetry**
- **Longitudinal change was coupled with baseline intermediate EZ-to-RPE thickness**
 - Strongest coupling was observed in EZ-to-RPE thickness of 5-20 μm
 - Little coupling seen in low ($\leq 5 \mu\text{m}$) or high ($>20 \mu\text{m}$) EZ-to-RPE thickness





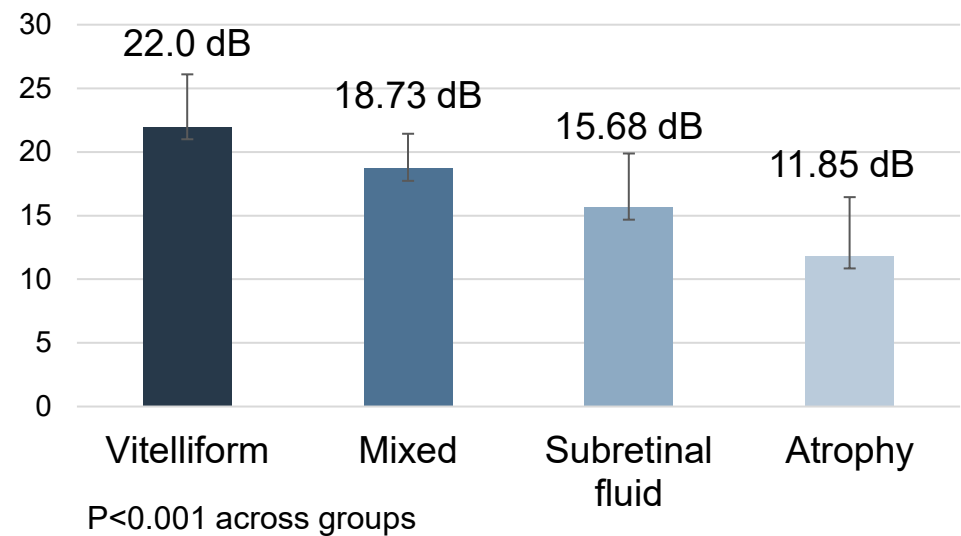
OCT Biomarkers and Retinal Sensitivity in BVMD

BVMD, best vitelliform macular dystrophy; OCT, optical coherence tomography.

Clinical Correlation Between OCT Biomarkers and Retinal Sensitivity in BVMD

Cross-sectional study of 57 eyes of 30 patients with BVMD (84% / n=48 eyes were in a clinical stage) to determine whether lesion composition and other OCT/OCTA biomarkers predict microperimetric sensitivity

Mean MAIA Retinal Sensitivity by OCT Lesion Type



Sensitivity declined as lesions progressed toward atrophy

Analysis of Clinical Imaging Factors on Retinal Sensitivity

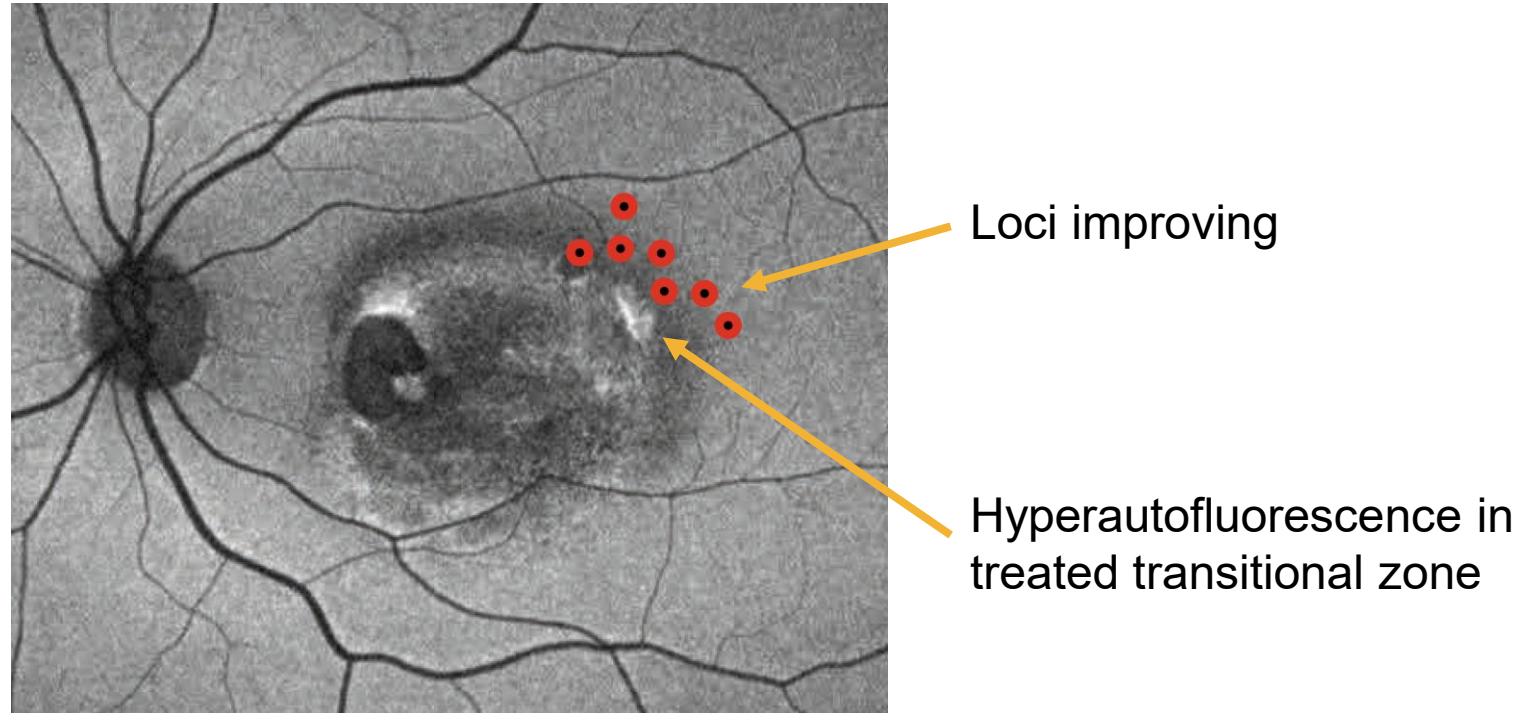
Variable	Beta coefficient (dB)
Hyperautofluorescent (NIR-FAF pattern)*	+7.4
Vitelliform lesion (vs atrophy)	+7.6
Mixed lesion (vs atrophy)	+6.2
Subretinal fluid lesion (vs atrophy)	+4.7
ONL thickness, per µm	+0.2

All P<0.05

R²=0.641 | OCT lesion type and ONL thickness

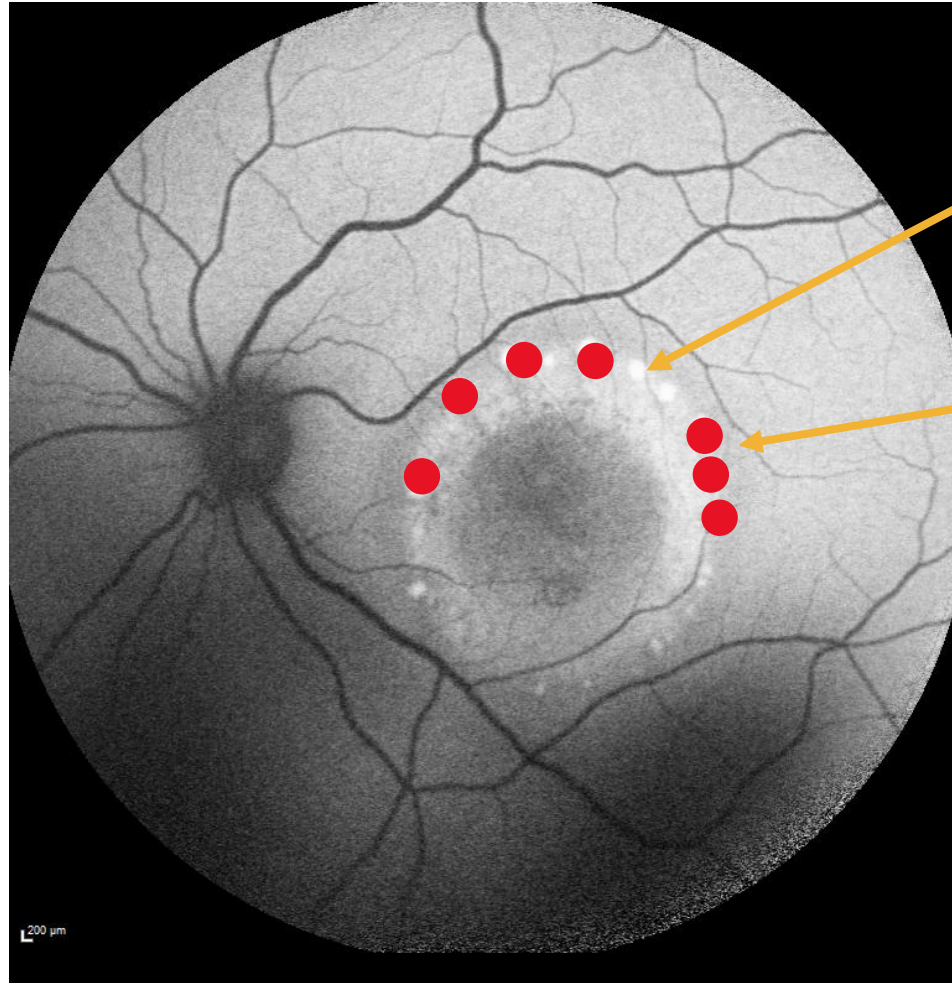
Hyperautofluorescence, OCT lesion type, and ONL thickness best correlated with mean retinal sensitivity

Hyperautofluorescence Correlates with Microperimetry Changes in Participant 102-102



Hyperautofluorescence in the treated transitional zone was strongly associated with improvement in mean retinal sensitivity

Hyperautofluorescence Correlates with Microperimetry Changes in Participant 101-106



Hyperautofluorescence in treated transitional zone

Loci improving

Hyperautofluorescence in the treated transitional zone was strongly associated with improvement in mean retinal sensitivity

Application to the Opus Clinical Trials

PH 1/2 - COHORT 2 DESIGN

- Microperimetry loci will be prespecified
- **Target:** Treated transitional zone, enriched by:
 - Baseline EZ-RPE thickness
 - Hyperautofluorescence
 - Vitelliform material on OCT
- **Clinical rationale:** Earlier stage patients have higher magnitude of improvement

PATH TO PIVOTAL TRIAL

- Cohort 2 will further inform pivotal trial
- Longitudinal data from Cohort 1 will also further inform pivotal trial

ULTIMATE GOAL:
Create a linear regression model to describe loci likely to improve