

Exploratory optical coherence tomography (OCT) analysis in patients with geographic atrophy (GA) treated by OpRegen[®]: Results from the Phase 1/2a trial

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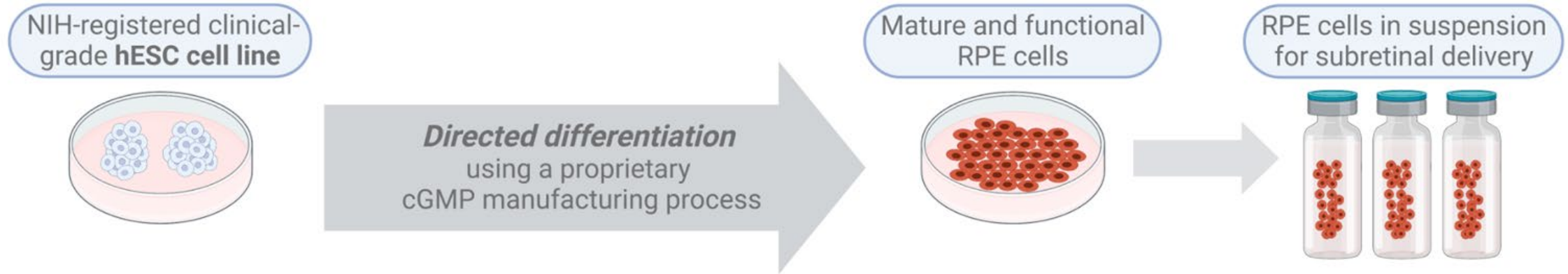
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Disclosures

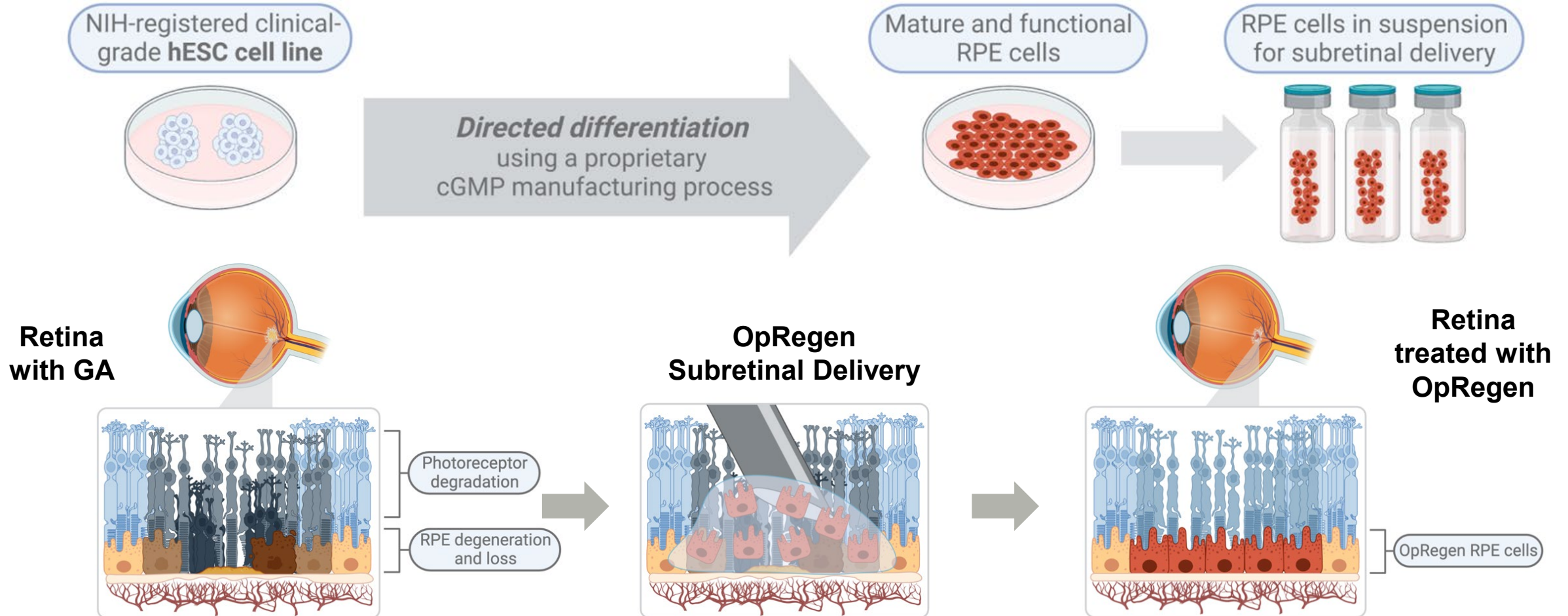
- Financial disclosures
 - EB: Employee of Hadassah Medical Center, Consultant to CellCure Neurosciences, a subsidiary of Lineage Cell Therapeutics

OpRegen – A Suspension of Allogeneic RPE Cells

With the Potential to Counteract RPE Cell Dysfunction & Loss in GA



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cGMP, current Good Manufacturing Practice; hESC, human embryonic stem cell; RPE, retinal pigment epithelium.
NIH registry for hESC cell line HAD-C 102 available at https://grants.nih.gov/stem_cells/registry/current.htm?id=428. Figures created with BioRender.com.

Phase I/IIa Study Design (NCT02286089)

An Open-Label, Single-Arm, Multi-Center, Dose-Escalation Trial

Key Eligibility Criteria

Patients with bilateral GA secondary to AMD

Cohorts 1-3 (n=12):

- Legally blind (BCVA: $\leq 20/200$)
- GA area: 1.25–17 mm²

Cohort 4 (n=12):

- Impaired vision (BCVA: $\geq 20/250$ and $\leq 20/64$)
- GA area: ≥ 4 and ≤ 11 mm²

Single OpRegen Administration

Cohort 1 (n=3)
50,000 cells

Cohort 2 (n=3)
Up to 200,000 cells

Cohort 3 (n=6)
Up to 200,000 cells

Cohort 4 (n=12)
Up to 200,000 cells

Objectives & Follow-up

Primary and secondary objectives assessed at 12 months following OpRegen subretinal delivery; patients followed for up to 5 years

Primary Objective:

- To evaluate the safety and tolerability of OpRegen following subretinal delivery

Secondary Objective:

- To evaluate the potential activity of OpRegen by assessing changes in visual function and retinal structure



Subretinal Delivery Via:

- Vitrectomy/retinotomy (n=17)
- Suprachoroidal cannula using Orbit SDS® (Gyroscope Therapeutics) in Cohort 4 only (n=7)

Perioperative Immunosuppressive Regimen:

- Tacrolimus 0.01 mg/kg daily administered until up to 6 weeks after surgery
- Mycophenolate up to 2.0 g daily administered until at least 3 months after surgery

Baseline Characteristics, Follow-up, & Safety Summary^a

- The most frequent ocular AEs reported in all patients on study were conjunctival hemorrhage/hyperemia (71%) and ERM (67%)^d
- Most AEs reported following OpRegen administration were mild (87%)
- No reported cases of:
 - Rejection following OpRegen delivery
 - Acute or delayed intraocular inflammation
 - Sustained intraocular pressure increase
 - Discontinuation due to a related AE
- No cluster of AEs related to immunosuppressive regimen were reported

Baseline Characteristic	Cohorts 1-3 (n=12) Legally Blind	Cohort 4 (n=12) Impaired Vision
Age, years, mean (SD / min–max)	78.1 (±8.2 / 64.8–92.2)	75.7 (±8.0 / 60.1–87.6)
Sex, female male, n	7 5	6 6
Study Eye BCVA ^b , letters, mean (SD / min–max)	23.5 (±11.7 / 0–39) [24 letters ≈ 20/320]	44.8 (±7.5 / 28–54) [45 letters ≈ 20/125]
Study Eye GA Area ^c , mm ² , mean (SD / min–max)	12.7 (±6.7 / 6–30)	7.4 (±2.9 / 1.6–10.9)
Study Follow-up, months, mean (min–max)	41.4 (9.3–56.8)	18.4 (10.9–35.1)

^aSafety data previously presented (Ho AC et al. ARVO 2022. <https://iovs.arvojournals.org/article.aspx?articleid=2780049>)

^bThe worse eye based on BCVA was selected for OpRegen subretinal delivery. ^cBased on central grading of fundus autofluorescence imaging.

^d6/10 patients with a reported ERM AE in Cohorts 1-3 and 2/6 patients in Cohort 4 had pre-existing ERM; 3 patients had clinically significant ERM requiring surgical intervention. ERM, epiretinal membrane.

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Subretinal Delivery Via:

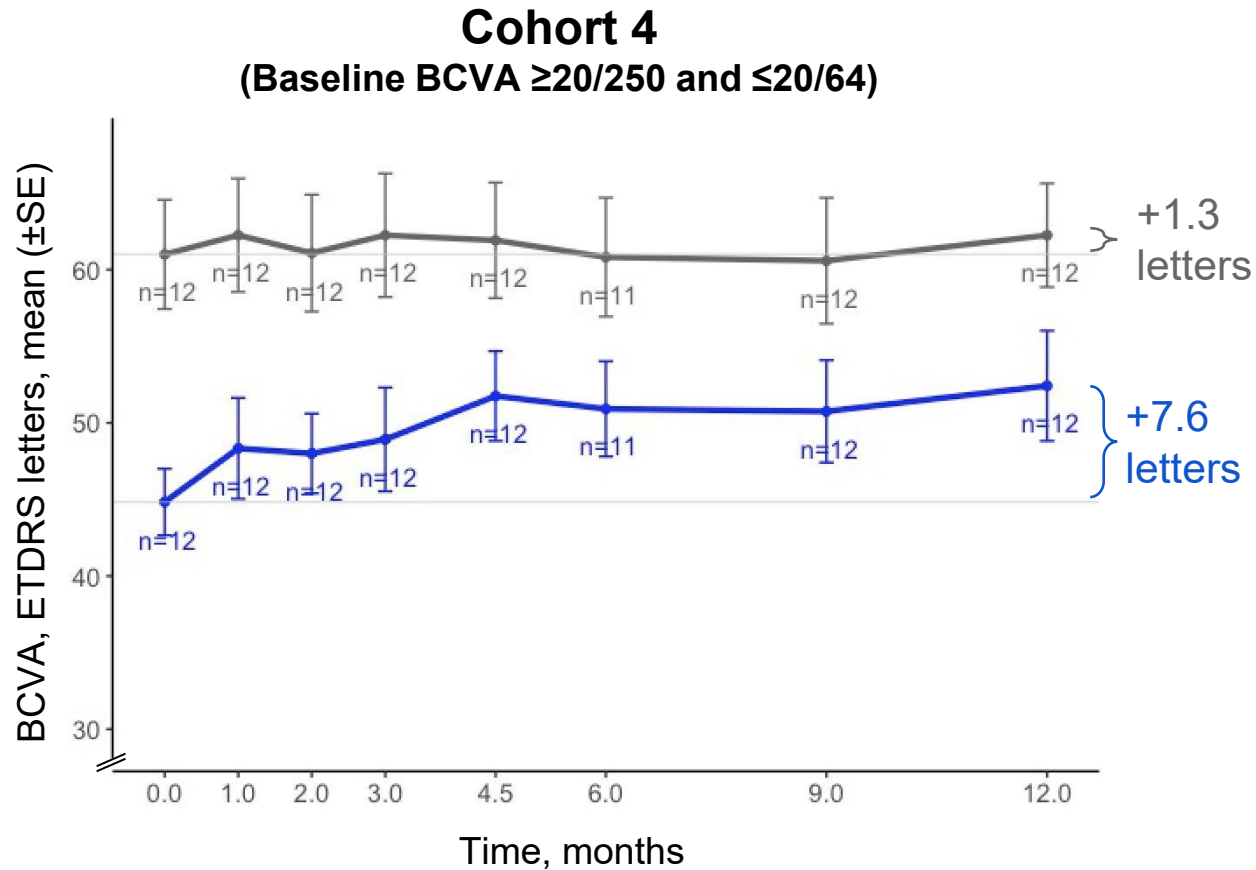
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Preliminary Evidence of Visual Function Improvements

Average 7.6 Letter Gain and 25% of Patients With ≥ 15 Letter Gain in Cohort 4



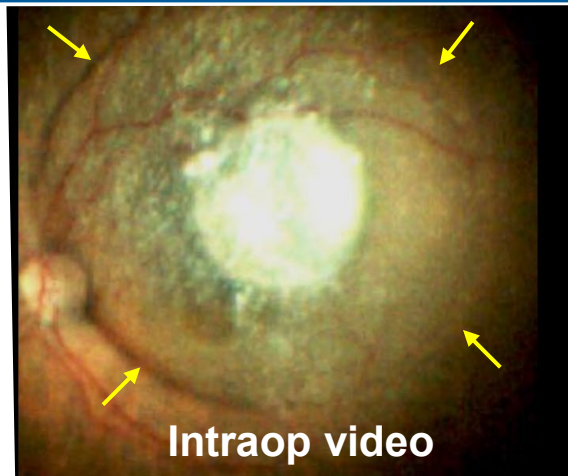
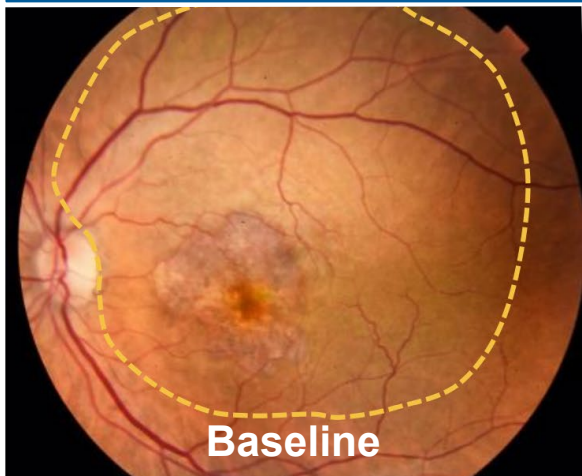
	≥ 15 Letter Gain at Month 12, n/N (%)
Fellow Eye	0/12 (0%)
Study Eye ^a	3/12 (25%)

^aPatients had bilateral GA, and the worse eye based on BCVA was selected for OpRegen subretinal delivery.
Data cutoff: 18 Jan 2022.

OpRegen Bleb Coverage Determined by Surgical Video

Extensive bleb coverage (n=5)

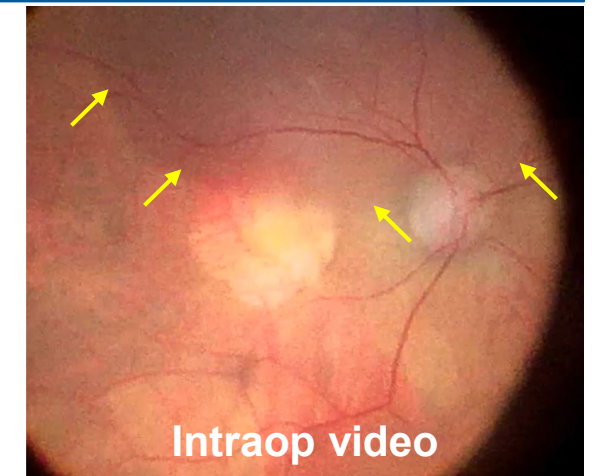
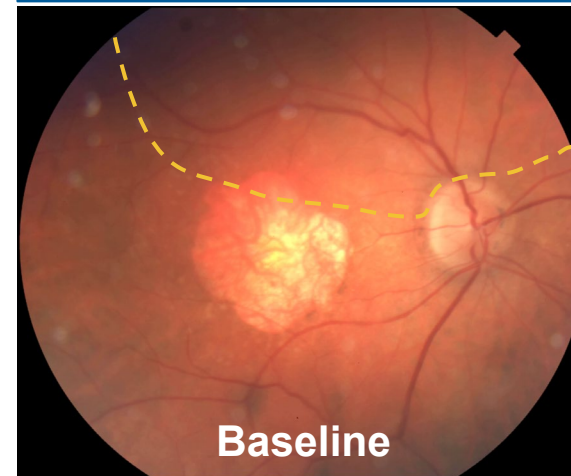
Extensive bleb coverage of GA (including fovea)



Case #18

Limited bleb coverage (n=7)

Minimal to no bleb coverage of GA



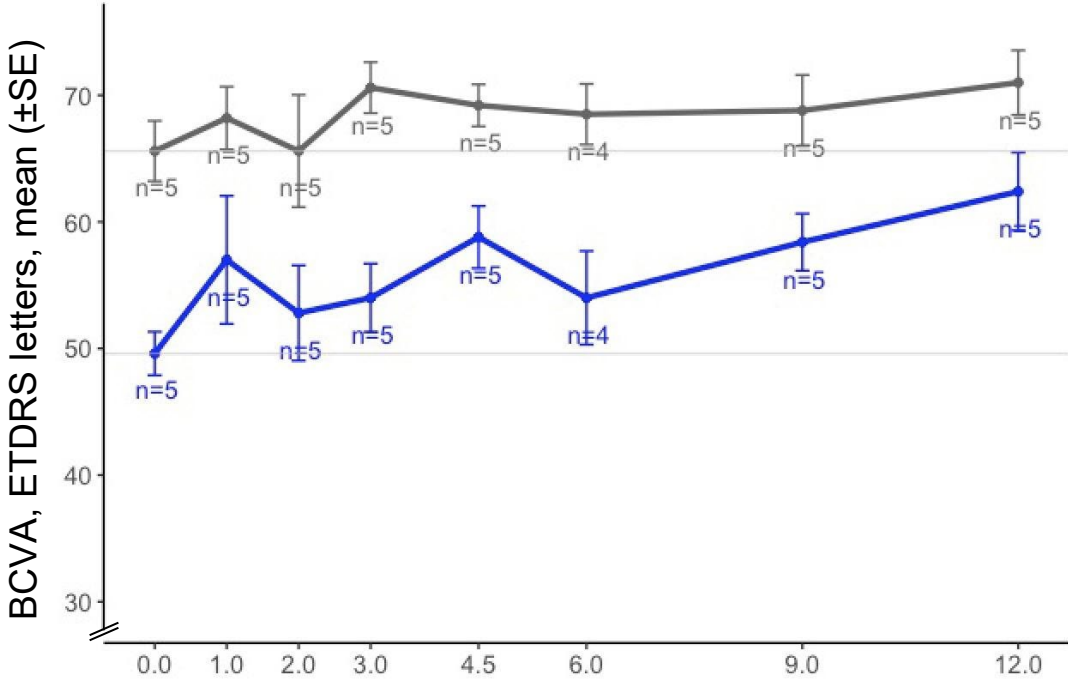
Case #14

BCVA Change by Extent of OpRegen Bleb Coverage

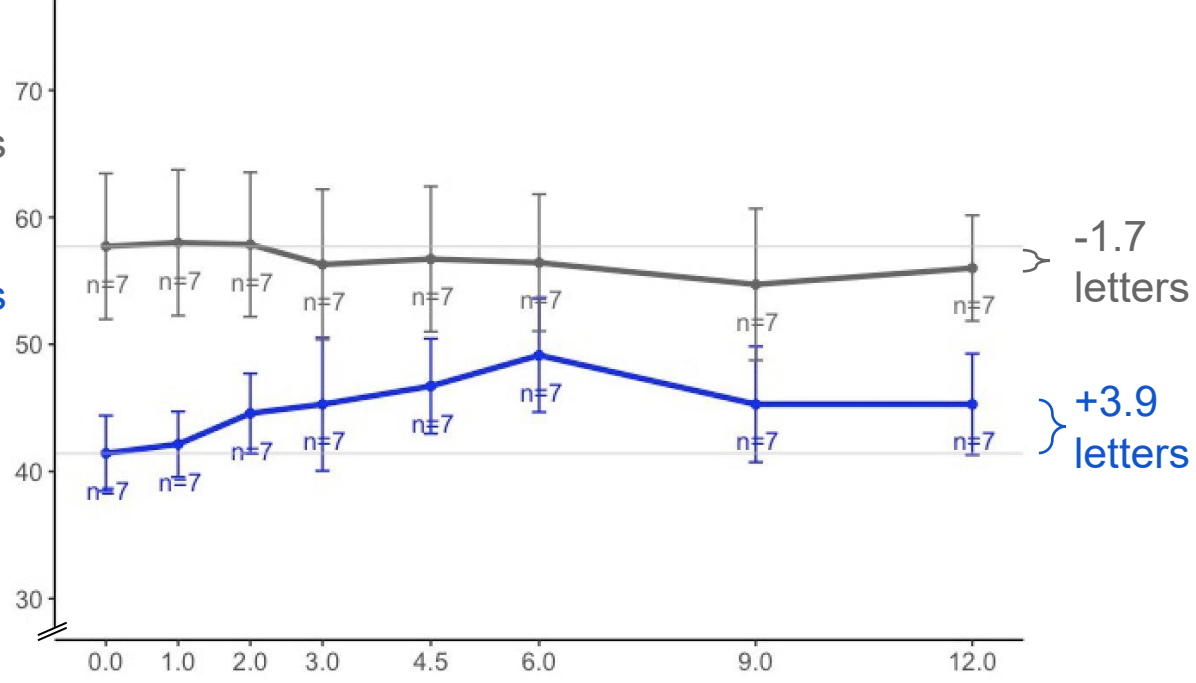
Average 12.8 Letter Gain in Study Eye with Extensive Bleb Coverage

Eyes with **extensive** bleb coverage (n=5)

Eyes with **limited** bleb coverage (n=7)



+5.4 letters
+12.8 letters



-1.7 letters
+3.9 letters

Time, months

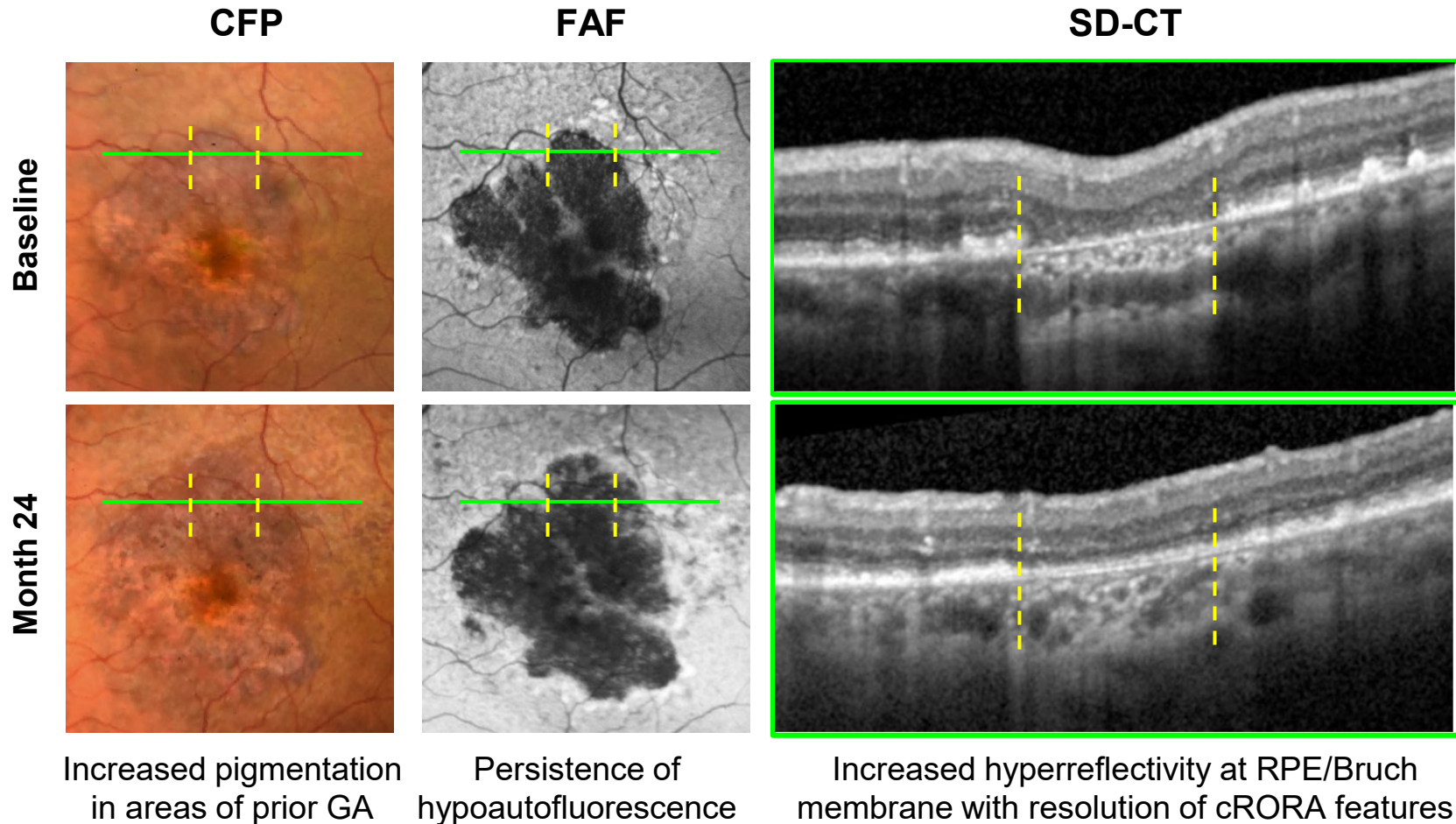
Time, months

— Study Eye — Fellow Eye

Data cutoff: 18 Jan 2022.

Assessment of GA Following OpRegen Delivery

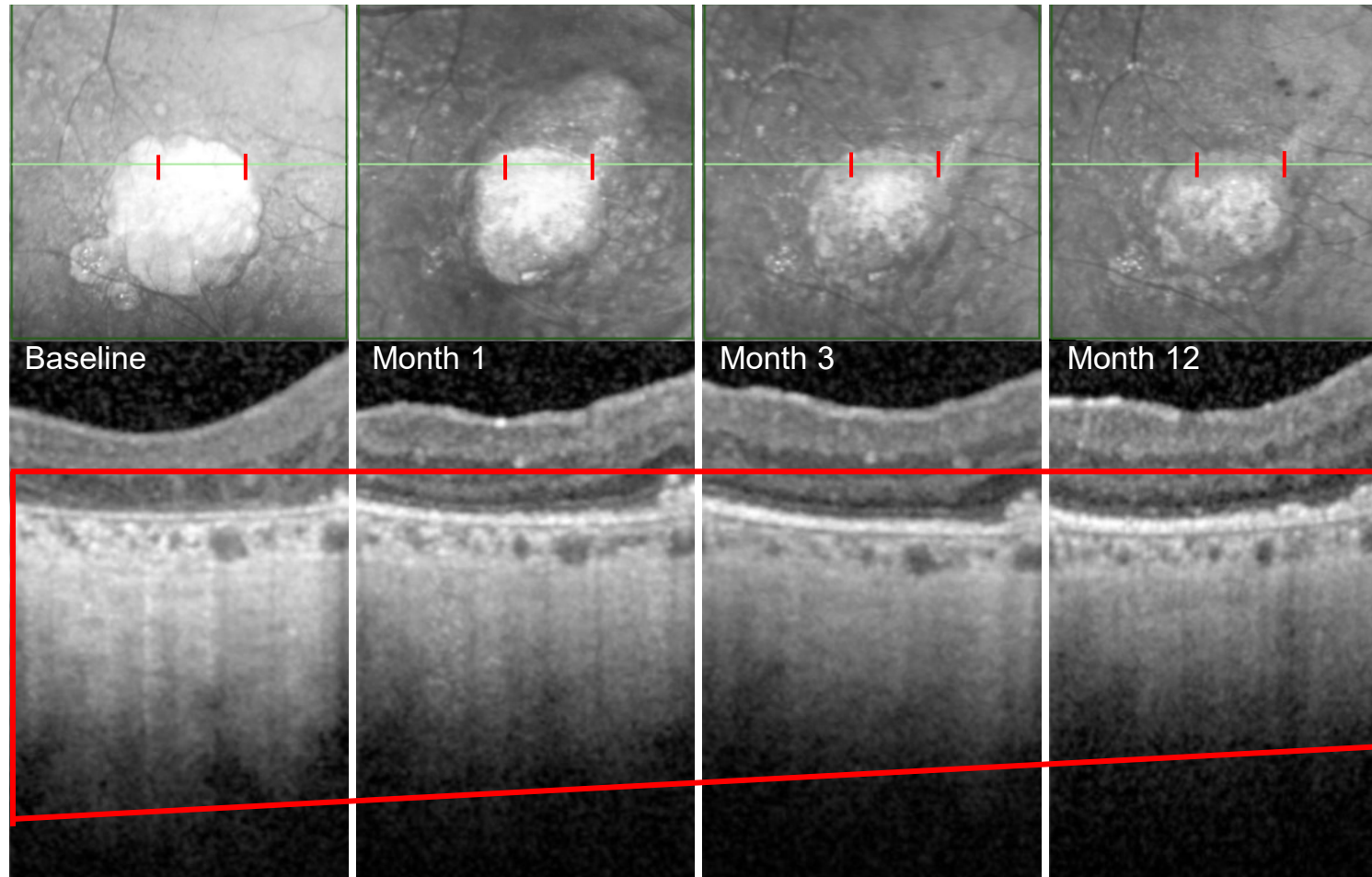
Advantages of SD-OCT versus Fundus Autofluorescence (FAF) Imaging



- The allogeneic hESC-derived RPE cells in OpRegen are young and have low lipofuscin content
- Therefore, OpRegen RPE cells are not expected to be readily detectable by standard FAF following subretinal delivery and are actually hypo-AF
- OCT imaging may thus be better suited to study retinal structure and define atrophy following transplantation

SD-OCT Imaging Suggests OpRegen Presence in Areas of Former GA

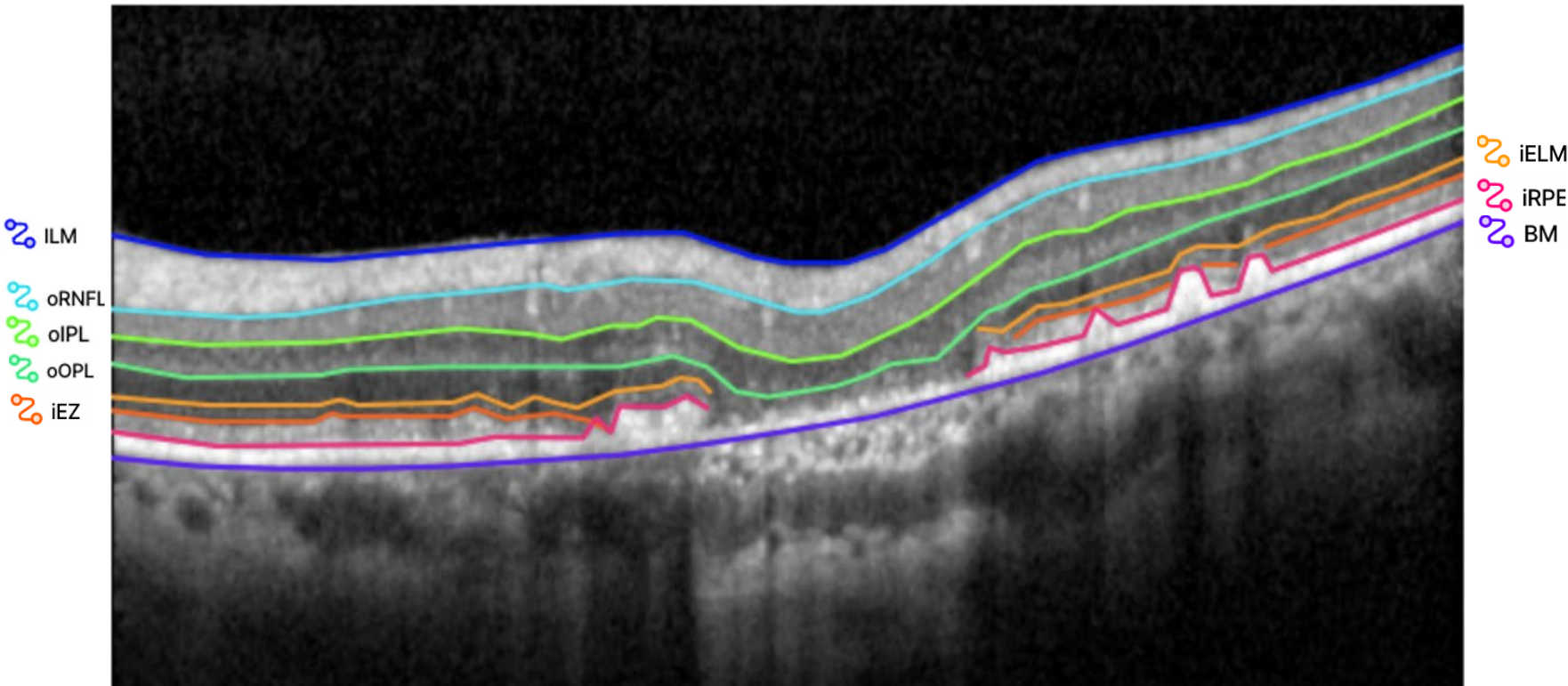
Greater Hyperreflectivity Visible at RPE/BM & Weaker Choroidal Hypertransmission



- ← Reappearance of ONL and ELM
- ← Greater hyperreflectivity visible at RPE/BM
- ← Weaker choroidal hypertransmission

OCT Segmentation and Quantification Process

OCT Provides Greater Resolution to Assess Changes in RPE and ELM



ELM (external limiting membrane):

Absence or presence of the hyper-reflective band representing ELM (orange line).

RPEDC (retinal pigment epithelium drusen complex):

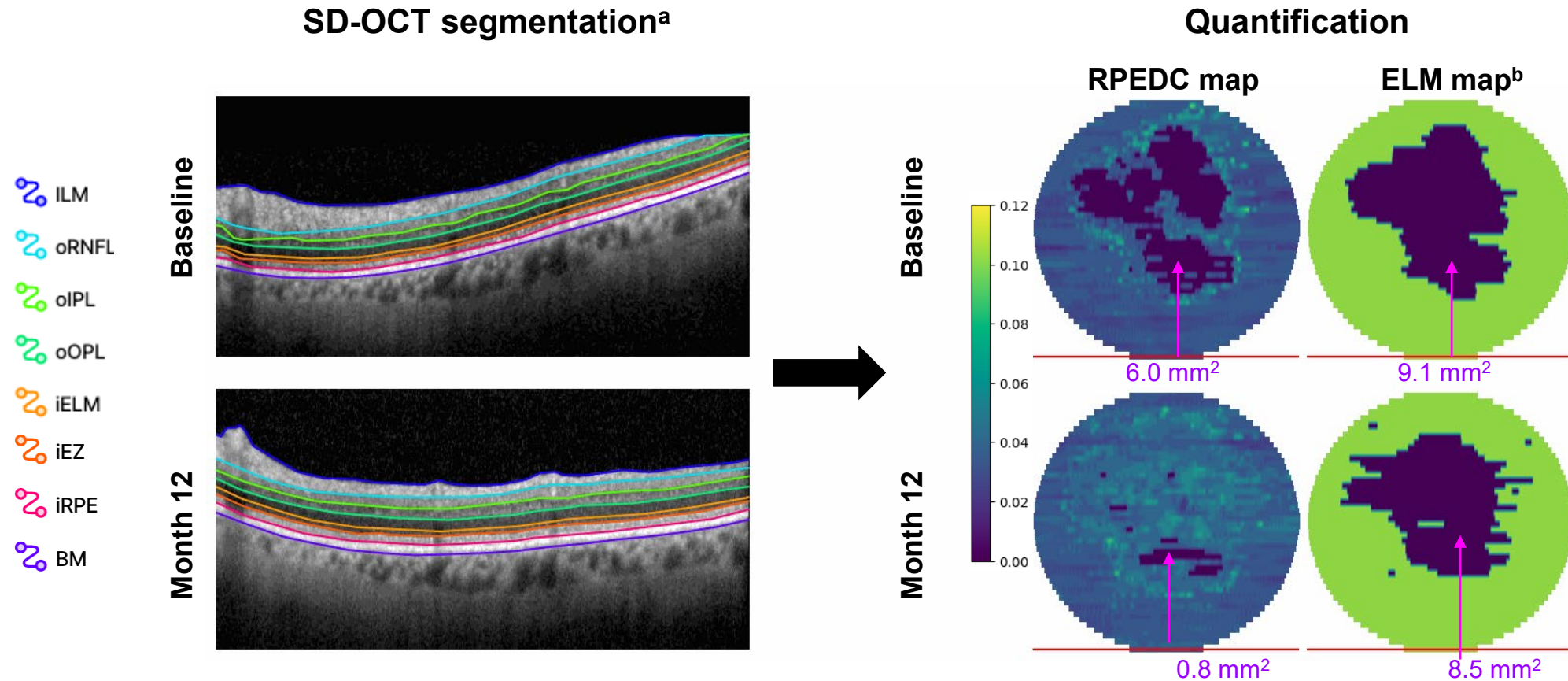
The thickness between the hyper-reflective bands representing inner border of RPE (red line) and **BM (purple line)** when RPE is present. RPEDC thickness is 0 when RPE band is absent.

Segmentation result generated by Genentech EyeNotate OCT segmentation algorithm, reviewed and corrected by a single masked expert grader.

BM, Bruch's membrane; EZ, ellipsoid zone; i-, inner boundary of layer; ILM, internal limiting membrane; IPL, inner plexiform layer; o-, outer boundary of layer; OPL, outer plexiform layer; RNFL, retinal nerve fiber layer.

OCT Segmentation and Quantification Process

RPEDC and ELM Maps Constructed by Each Segmentation Scan



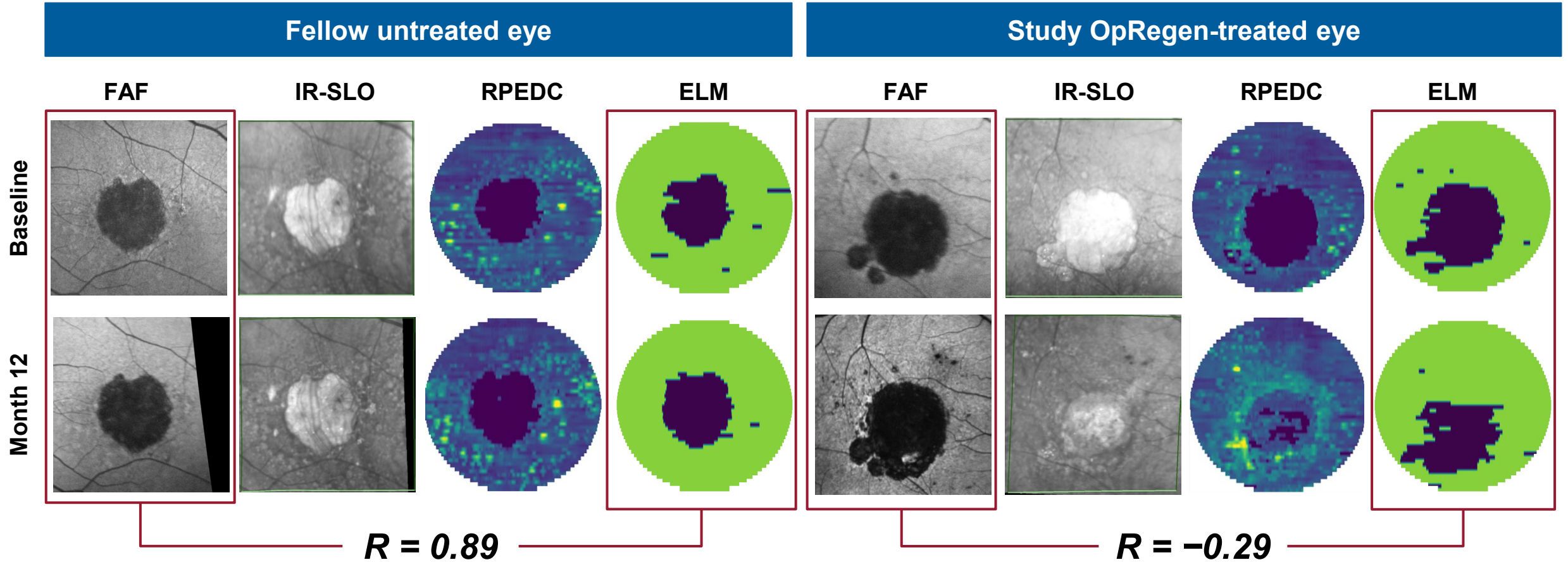
ELM, external limiting membrane; RPEDC, retinal pigment epithelium drusen complex.

^aSegmentation result is generated by Genentech EyeNotate OCT segmentation algorithm, reviewed and corrected by a single masked expert grader.

^bELM map, binary external limiting membrane presence/absence map, green when ELM is present, dark blue when ELM is absent.

FAF-Measured GA Area & OCT-Measured ELM Loss

Loss of Correlation Between Change in FAF- and OCT-Measured GA Area in OpRegen-Treated Eye



IR-SLO, infrared scanning laser ophthalmoscopy.

Segmentation result is generated by Genentech EyeNotate OCT segmentation algorithm, reviewed and corrected by a single masked expert grader.

Case #21

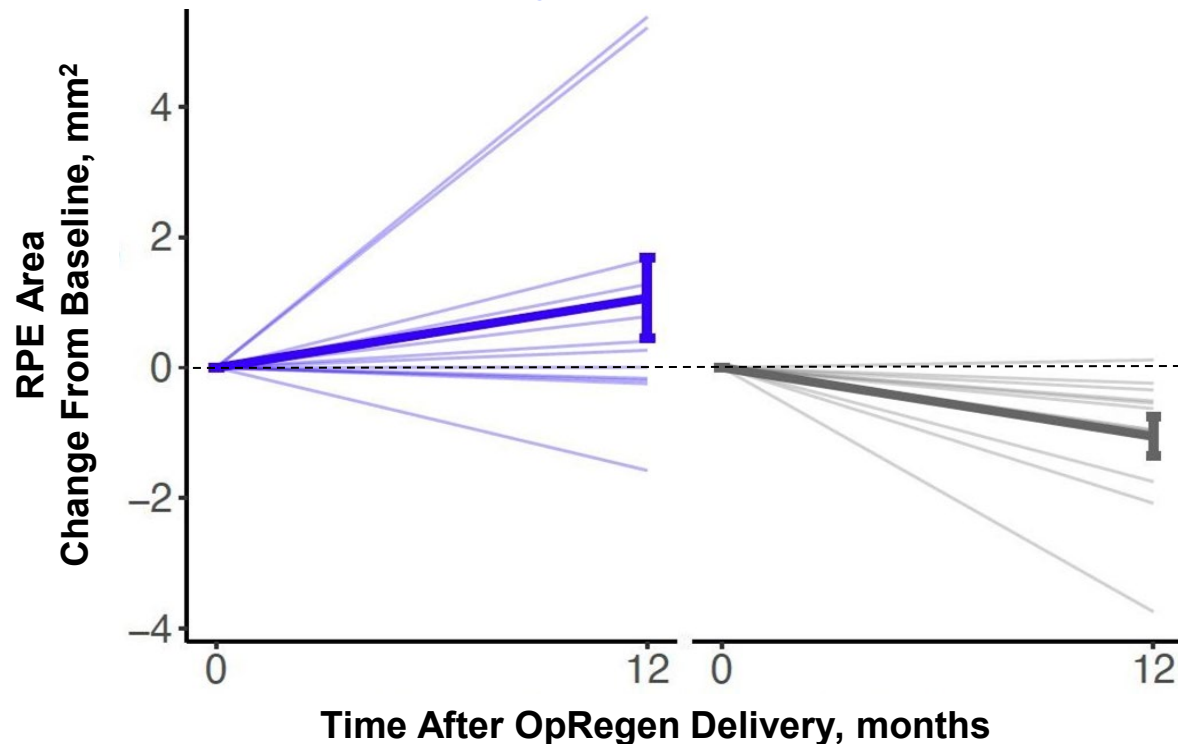
Changes in Retinal Structure After OpRegen Treatment in Cohort 4

Slower Rates of RPE and ELM Band Loss in OpRegen-Treated Eye

Area of RPE change (n=12)

Study eye
 $+1.1 \pm 2.1$ RPE gain

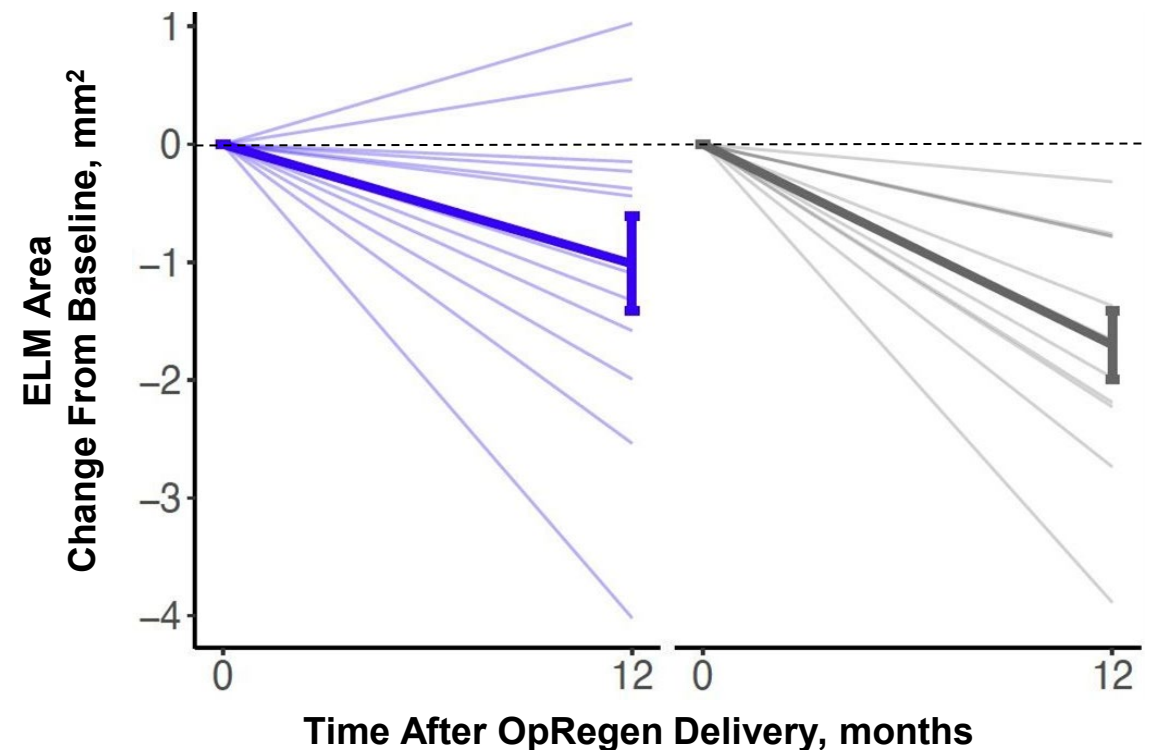
Fellow eye
 -1.1 ± 1.1 RPE loss



Area of ELM change (n=12)

Study eye
 -1.0 ± 1.4 ELM loss

Fellow eye
 -1.7 ± 1.0 ELM loss



Thick lines represent the mean and error bars represent standard error.
Data cutoff: 18 Jan 2022.

RPE and ELM Change by Extent of OpRegen Bleb Coverage

Improvement in Outer Retinal Layers Correlates with Extent of Coverage

Area of RPE change

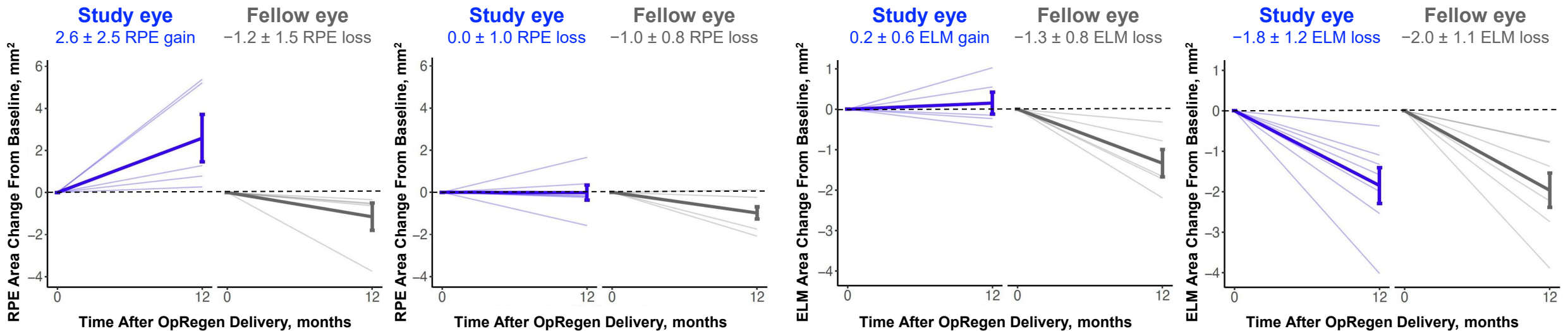
Extensive Bleb Coverage (n=5)

Limited Bleb Coverage (n=7)

Area of ELM change

Extensive Bleb Coverage (n=5)

Limited Bleb Coverage (n=7)

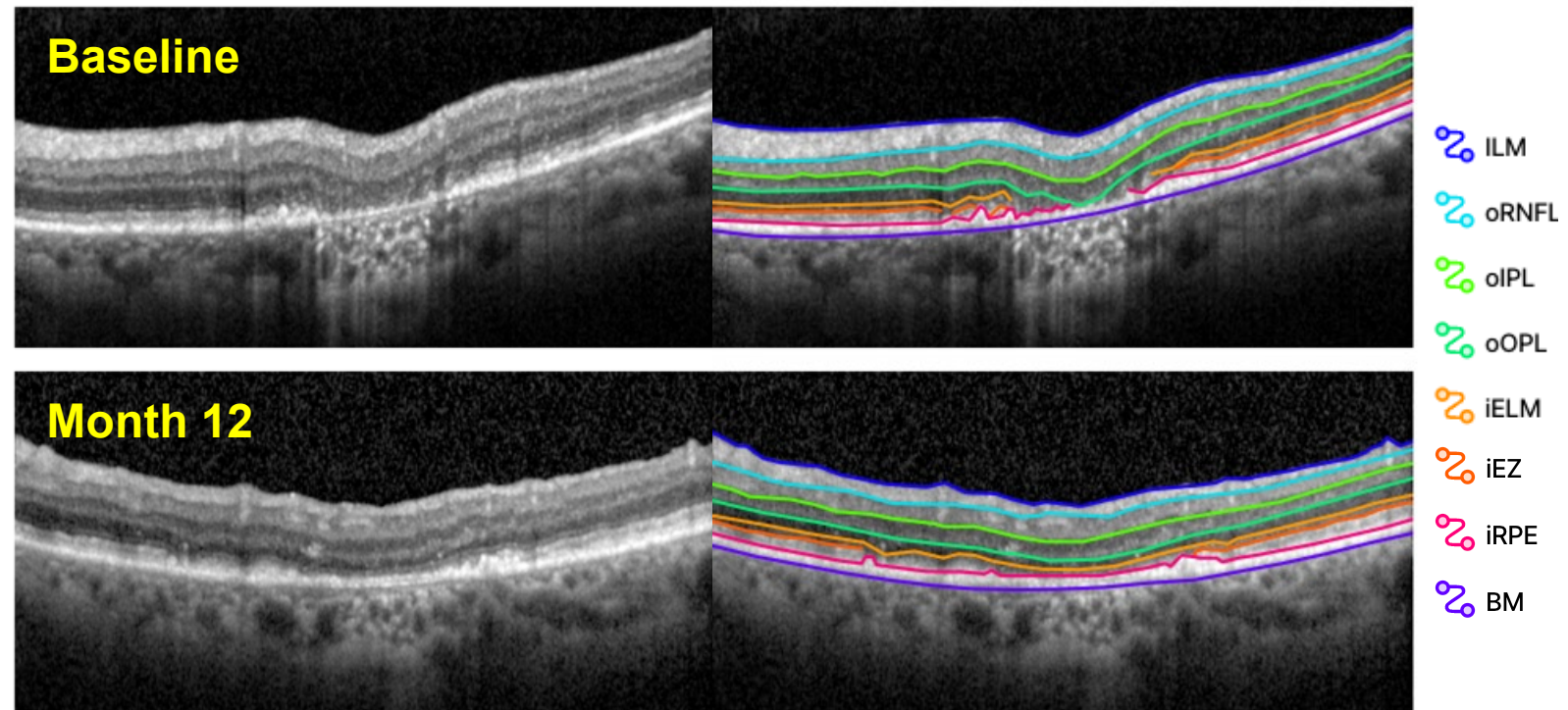
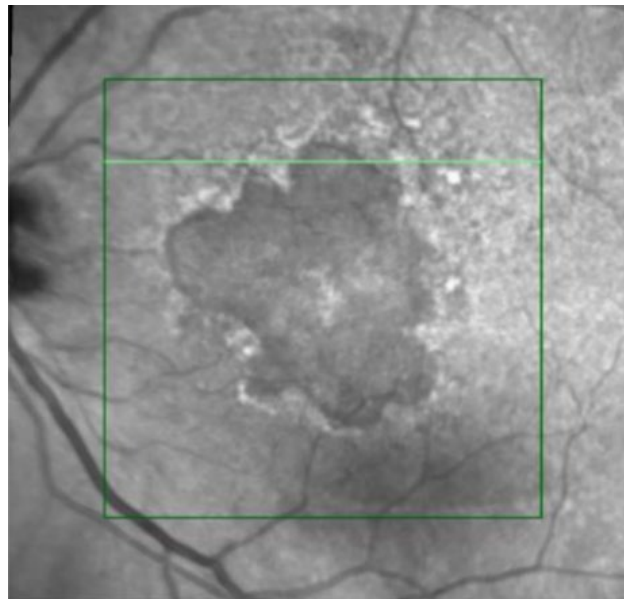


In patients with extensive OpRegen bleb coverage, maintenance or improvement of outer retina structure was observed in treated eyes vs worsening in fellow eyes

Thick lines represent the mean and error bars represent standard error.
Data cutoff: 18 Jan 2022.

Resolution of cRORA Near Borders of Baseline GA

In Cases With Extensive OpRegen Bleb Coverage of Area of GA



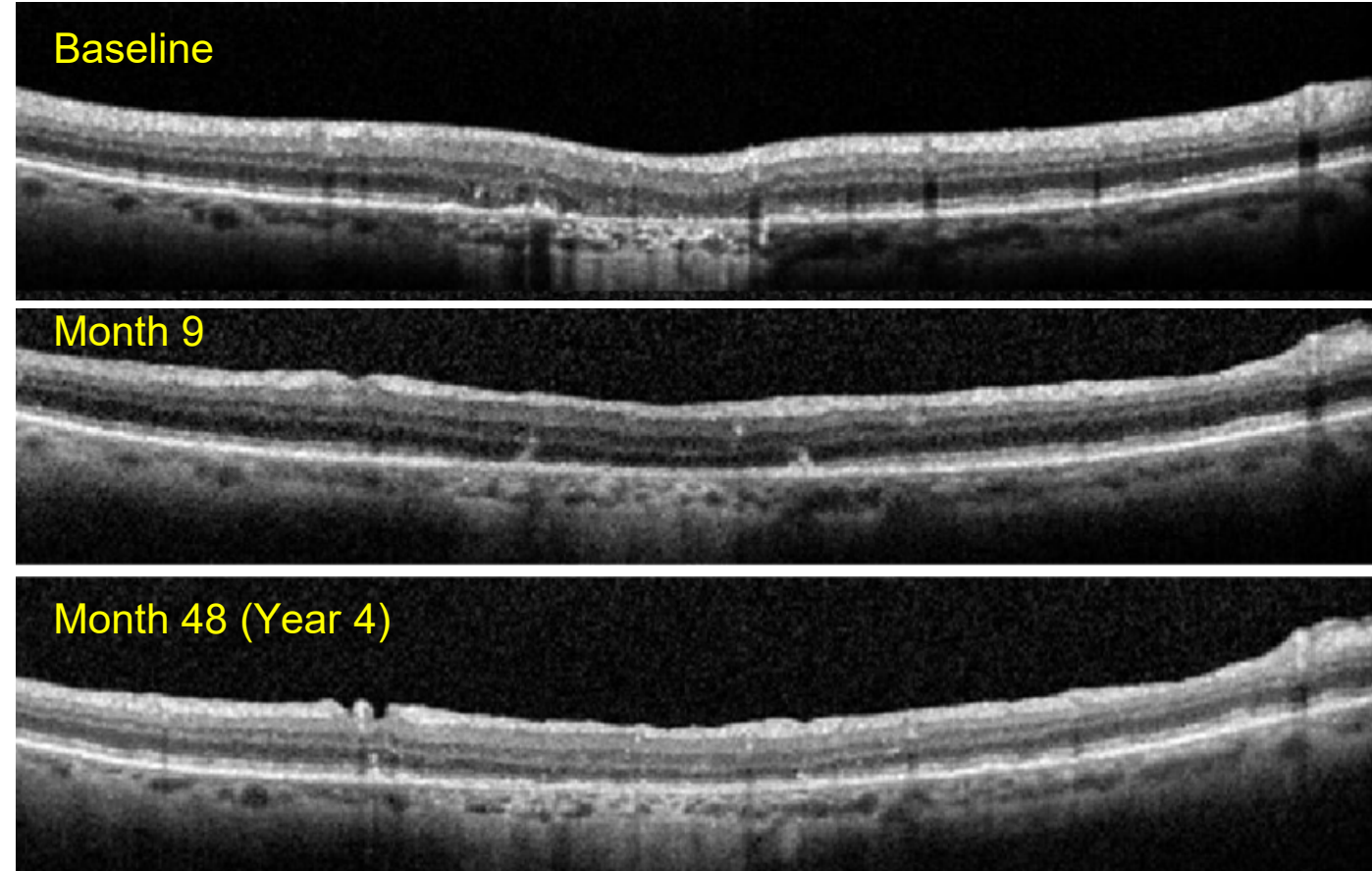
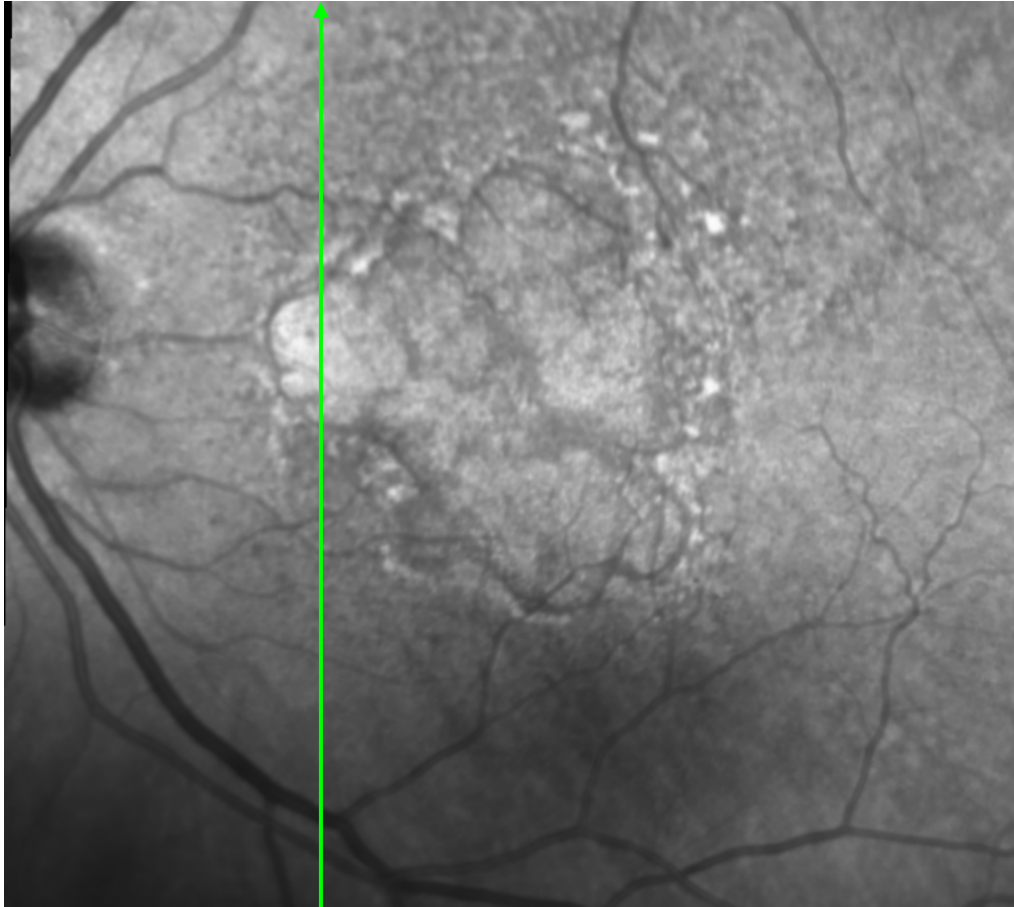
- Features of cRORA no longer present
- Greater hyperreflectivity at the level of RPE/BM
- Less choroidal hypertransmission

- Resolution of retinal subsidence, with greater continuity of outer retinal layers
- Similar features seen at nasal, superior, and inferior borders of GA

BM, Bruch's membrane; cRORA, complete RPE and outer retinal atrophy; EZ, ellipsoid zone; i-, inner boundary of layer; ILM, internal limiting membrane; IPL, inner plexiform layer; o-, outer boundary of layer; OPL, outer plexiform layer; RNFL, retinal nerve fiber layer.

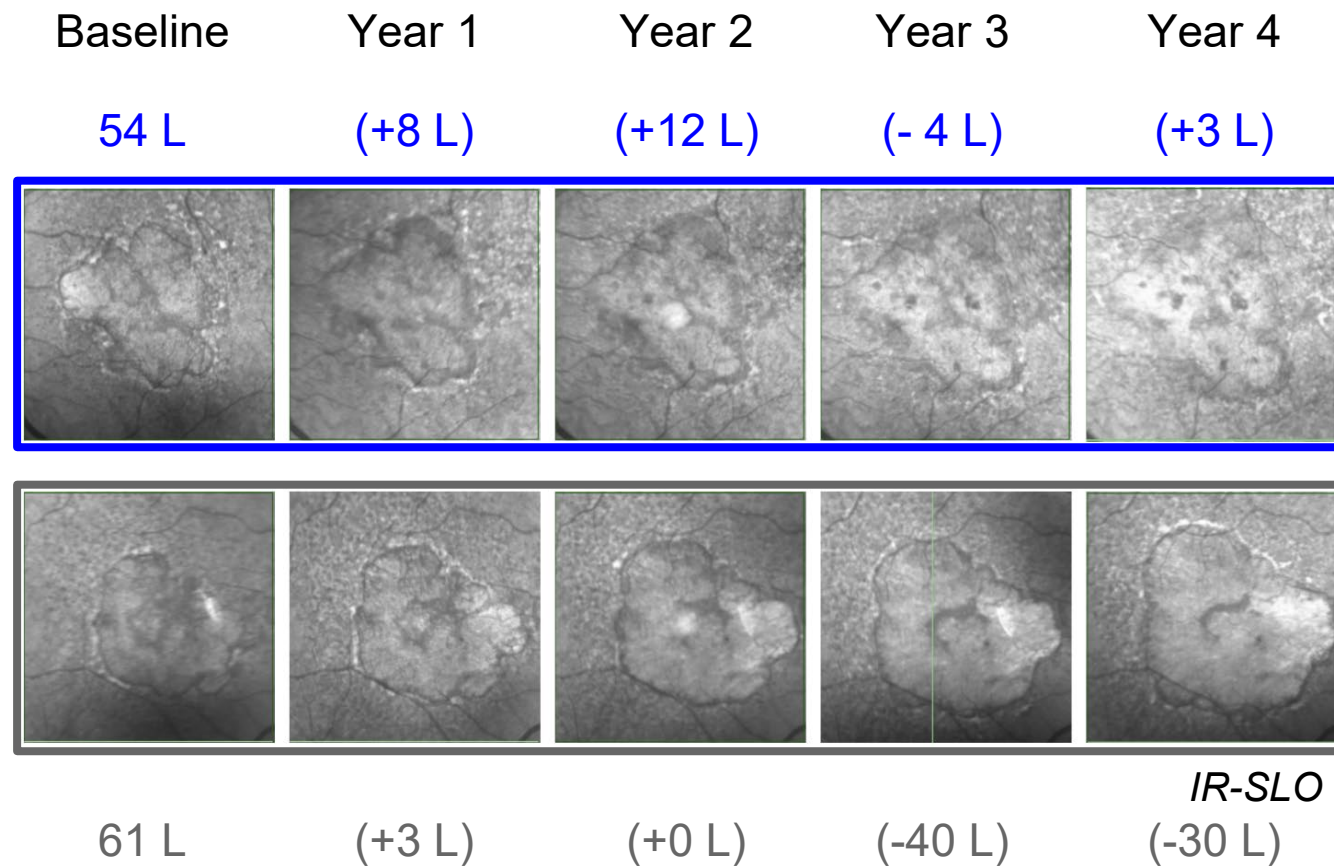
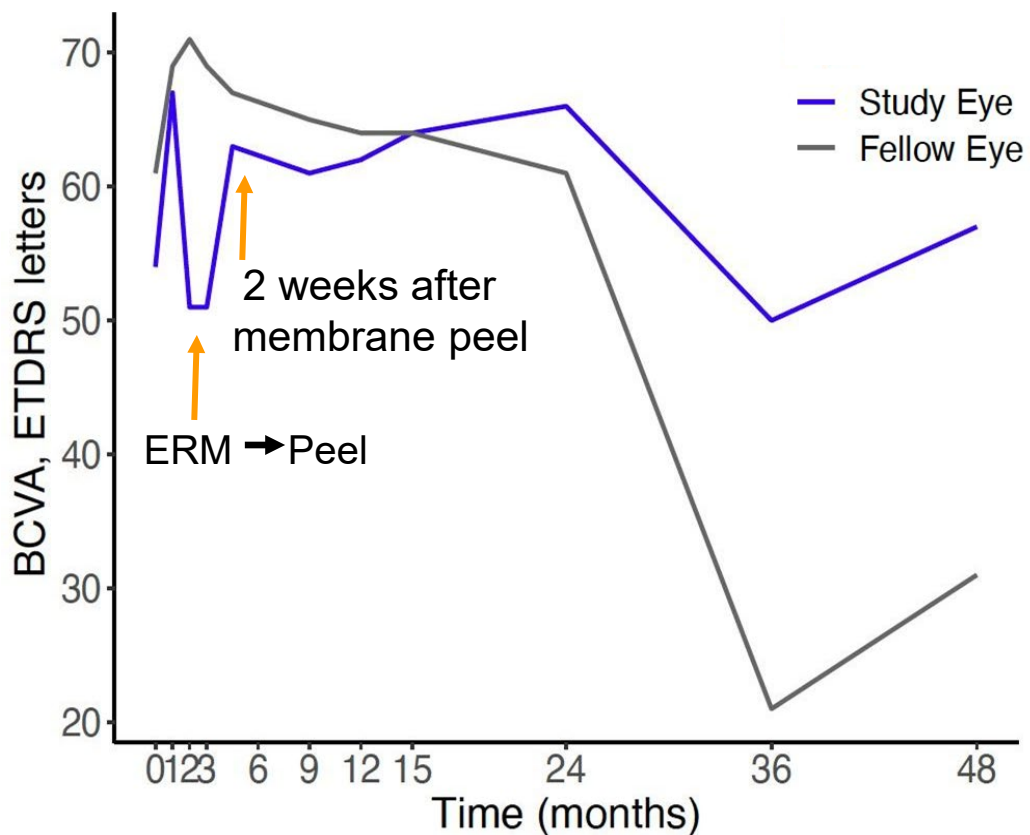
Long-Term Assessment of Outer Retina Structure

Outer Retinal Improvement Persisted Over 4 Years in Study Eye



Long-Term Vision Preservation in Study Eye

Vision Loss from GA Progression Over Time in Fellow Untreated Eye



Summary and Future Directions

- Preliminary evidence of outer retinal structure and visual function improvements with OpRegen was observed in patients with GA and impaired vision (Cohort 4 [n=12])
 - The extent of OpRegen bleb coverage may be important to optimize patient outcomes
 - OCT may be more suitable than FAF to assess retinal integrity post-treatment
- These data suggest that OpRegen RPE cells may provide support to the remaining retinal cells within atrophic areas by counteracting RPE cell dysfunction and loss
- Further assessment of the optimal disease stage for intervention and target delivery location of OpRegen in a larger, controlled clinical study is needed to confirm these preliminary findings
 - A Phase 2a study evaluating the success of OpRegen delivery to target areas of GA is currently enrolling patients (ClinicalTrials.gov: NCT05626114)

Thank You to All Participating Study Sites, Investigators, and Patients!

Investigators

- Adiel Barak, Sourasky Medical Center, Tel Aviv, Israel
- David Boyer, Retina Vitreous Associates Medical Group Los Angeles, CA, USA
- Rita Ehrlich, Rabin Medical Center, Petah Tikva, Israel
- Allen C. Ho, Wills/MidAtlantic, Philadelphia, PA, USA
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- Avi Ben-Shabat, Lineage Cell Therapeutics, Inc. (Cell Cure Neurosciences, Ltd.), Jerusalem, Israel

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- Jessica Hallinan, Lineage Therapeutics, Inc., Carlsbad, CA, USA
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- Diana Angelini, Lineage Therapeutics, Inc., Carlsbad, CA, USA
- Yana Aisen, Lineage Therapeutics, Inc., Carlsbad, CA, USA

Imaging Analysis

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- OCT and GA progression analyses: Jordi M. Monés, Institut de la Màcula, Barcelona, Spain
- Supplemental OCT Analyses: Brandon Lujan, Lujan Imaging LLC, Portland, OR, USA
- Doheny Image Reading and Research Lab (DIRRL)
- OCT Segmentation and Quantification of Lesions: AI Ophthalmology team, Early Clinical Development, Genentech Inc., South San Francisco, CA, USA,