

Phase 1/2a Study of OpRegen[®] - Human Allogeneic Retinal Pigment Epithelial (RPE) Cells - in Patients with Geographic Atrophy (GA)

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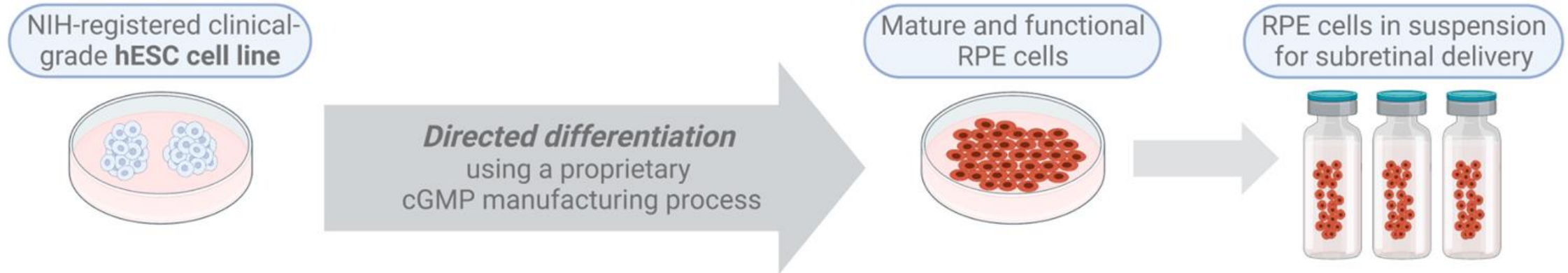
Adiel Barak, David Boyer, Allen C. Ho, Tareq Jaouni, Richard McDonald, Christopher D. Riemann, David G. Telander, Miao Zhang, Simon S. Gao, Henry Wiley, Dolly Chang, Avi Ben-Shabat, Gary S. Hogge, Benjamin Reubinoff

Disclosures

- Financial disclosures
 - EB: Employee of Hadassah-Hebrew University Medical Center, Consultant to CellCure Neurosciences, a subsidiary of Lineage Cell Therapeutics, and Genentech, Inc.

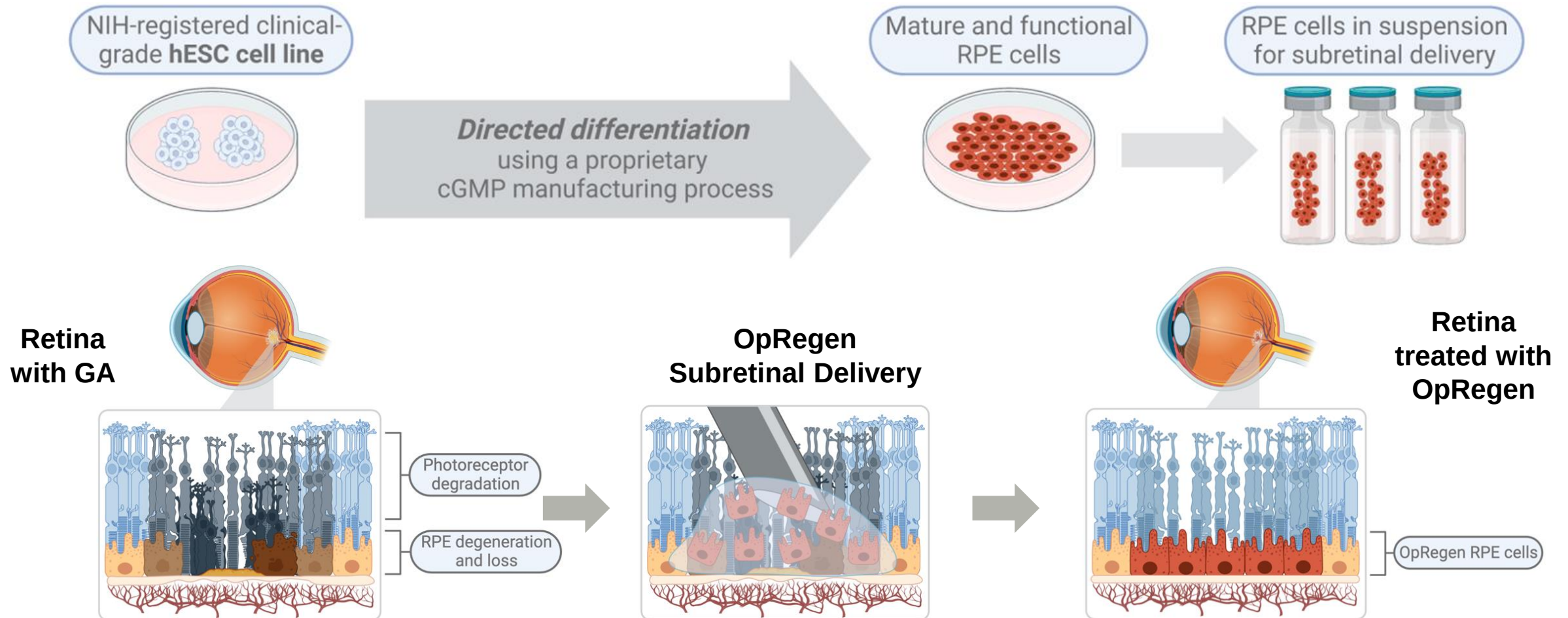
OpRegen – A Suspension of Allogeneic RPE Cells

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

Safety Summary

- All 24 (100%) treated patients reported ≥ 1 AE and ≥ 1 ocular AE
 - Most frequent systemic AE: URTI (n=7)
 - Most frequent ocular AEs: conjunctival hemorrhage/hyperemia (n=17) and ERM (n=16)
- Most AEs were mild (Cohorts 1-3, 87%; Cohort 4, 93%)
- One patient discontinued due to an AE (stage IV lung adenocarcinoma unrelated to treatment)
- No reported cases of:
 - Rejection following OpRegen subretinal delivery
 - Acute or delayed intraocular inflammation
 - Sustained intraocular pressure increase

Ocular AEs Occurring in ≥ 2 Patients, n (%)	Cohorts 1-3 (n=12) Legally Blind Vitrectomy (n=12)	Cohort 4 (n=12) Impaired Vision Vitrectomy (n=5) Orbit SDS (n=7)
Conjunctival hemorrhage / hyperemia	9 (75%)	8 (67%)
ERM (macular fibrosis) ^a	10 (83%)	6 (50%)
Clinically significant ERM ^b	1 (8%)	2 (17%)
Cataract	8 (67%)	1 (8%)
RPE detachment	1 (8%)	5 (42%)
Retinal hemorrhage	1 (8%)	5 (42%)
Subretinal fluid	5 (42%)	2 (17%)
Persistent subretinal fluid (>2 weeks)	0	1 (8%)
Choroidal neovascularization/ neovascular AMD	1 (8%)	3 (25%)
Retinal detachment	1 (8%)	1 (8%)
Retinoschisis	1 (8%)	2 (17%)

^a7/12 (58%) patients in Cohorts 1-3 and 5/12 (42%) in Cohort 4 had ERM at baseline; 6/10 patients with a reported ERM AE in Cohorts 1-3 and 2/6 in Cohort 4 had pre-existing ERM.

^bClinically significant indicates ERM requiring surgical intervention.

Data cutoff: 18 Jan 2022.

Baseline Characteristics and Study Follow-up

Greater Disease Severity in Cohorts 1-3 Versus Cohort 4

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 (±8.1 / 60.0–87.7)
Sex, female male, n	7 5	6 6
Study Eye BCVA ^a , 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 ^b , mm ² , mean (SD / min–max)	12.7 (±6.7 / 6–30)	7.4 (±2.9 / 1.4–11)
Study Follow-up, months, mean (min–max)	41.4 (9.3–56.8)	18.9 (11.5–35.1)

^aThe worse eye based on BCVA was selected for OpRegen subretinal delivery. ^bBased on central grading of fundus autofluorescence imaging.
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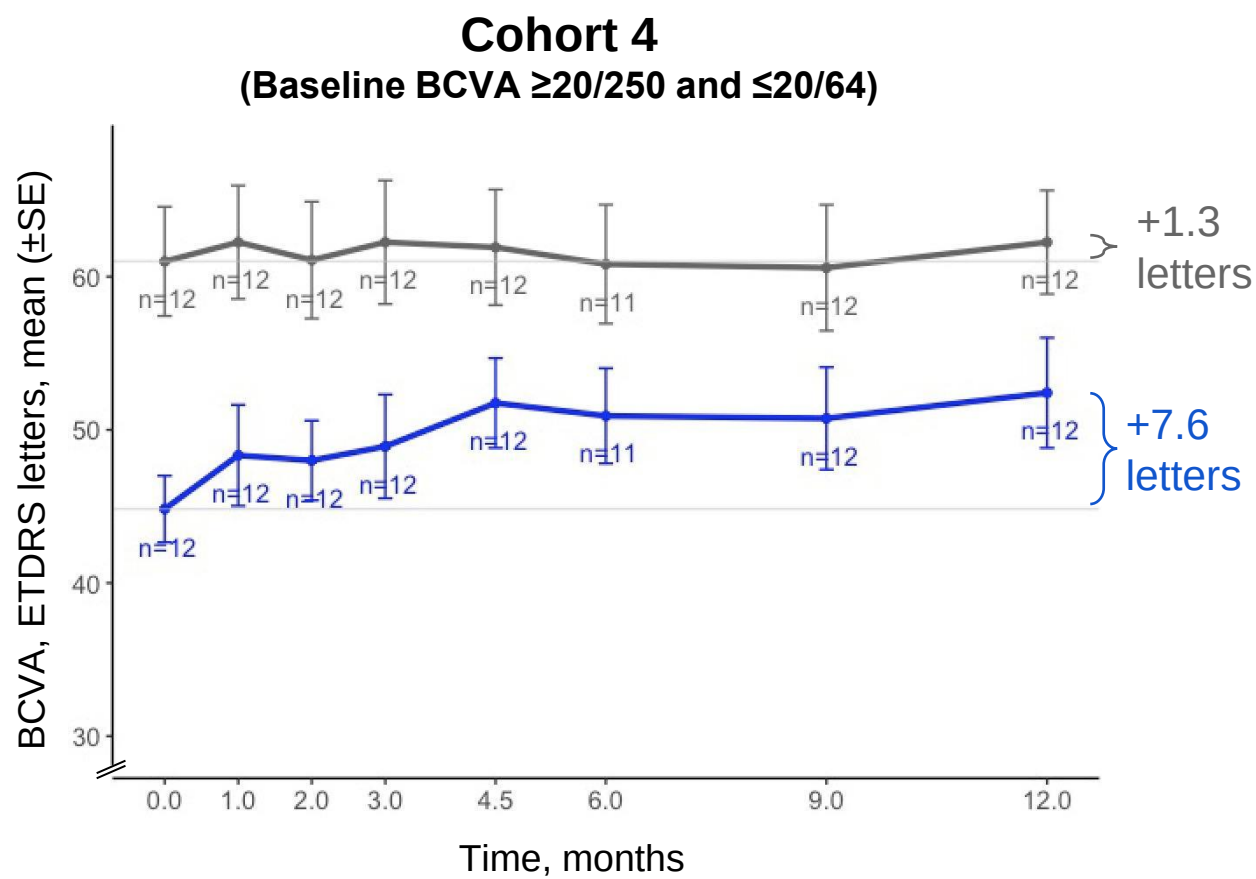
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Preliminary Evidence of Visual Function Improvements

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

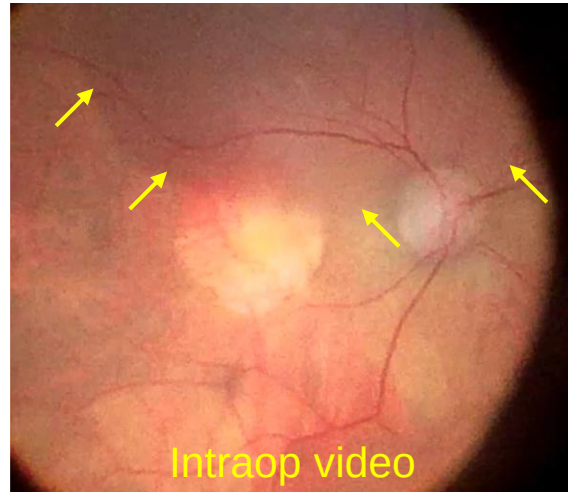
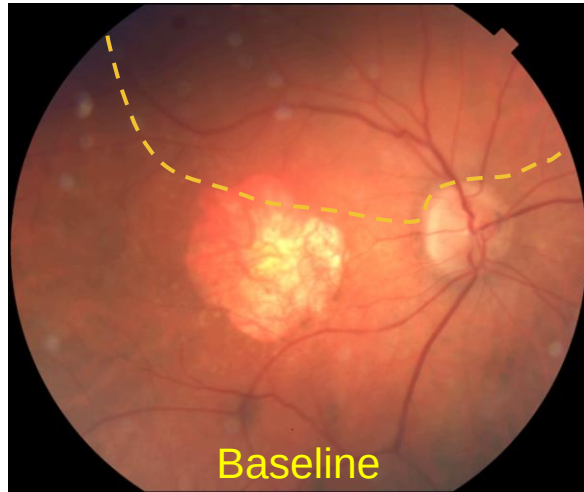


	≥15 Letter Gain at Month 12, n/N (%)
Fellow Eye	0/12 (0%)
Study Eye ^a	3/12 (25%)

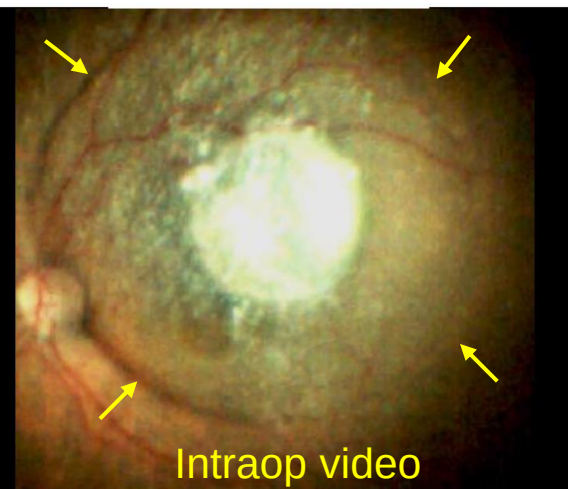
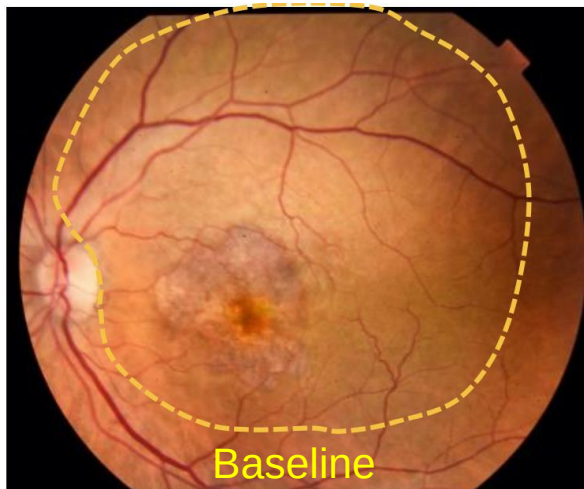
^aPatients had bilateral GA and the worse eye based on BCVA was selected for OpRegen subretinal delivery.
Data cutoff: 18 Jan 2022.

OpRegen Bleb Coverage Determined by Surgical Video

Cohort 4: Extensive Bleb Coverage of GA (Including Fovea) in 5/12 Cases
Minimal to No Bleb Coverage of GA in 7/12 Cases



Case #18
Bleb mostly superior to macula
Only superior pole of GA has coverage

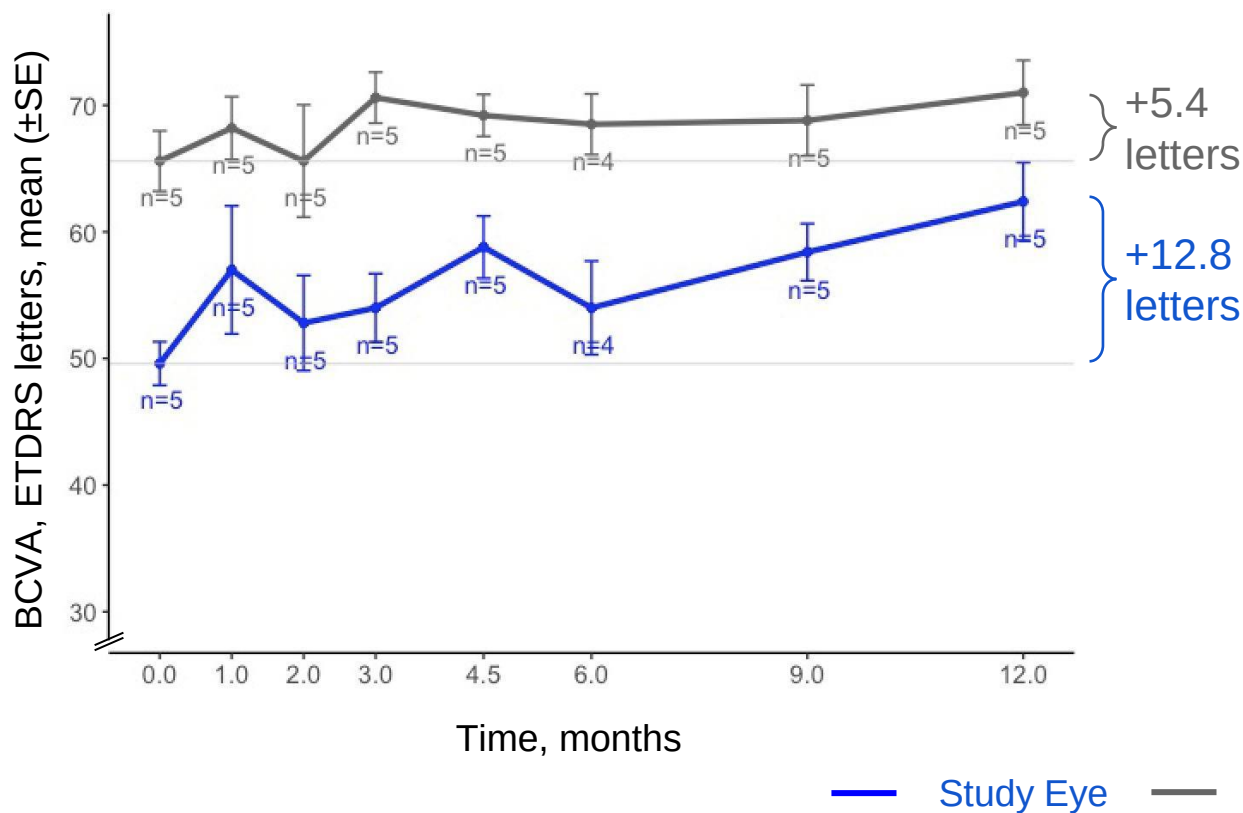


Case #14
Bleb occupies most of macula
Complete coverage of GA
Note: White area at center is a subretinal air bubble,
explored for its utility in some PPV cases

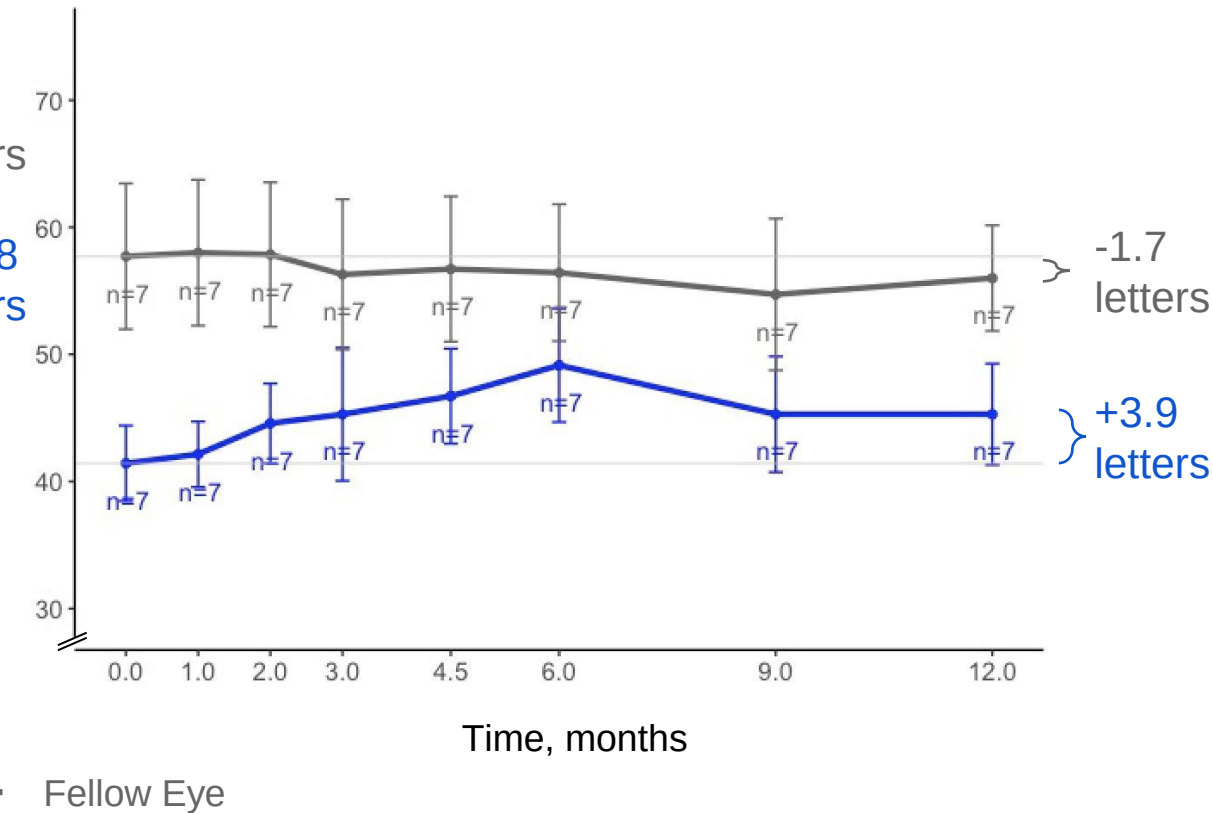
BCVA Change by Extent of OpRegen Bleb Coverage

Average 12.8 Letter Gain in Study Eye with Extensive Bleb Coverage

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



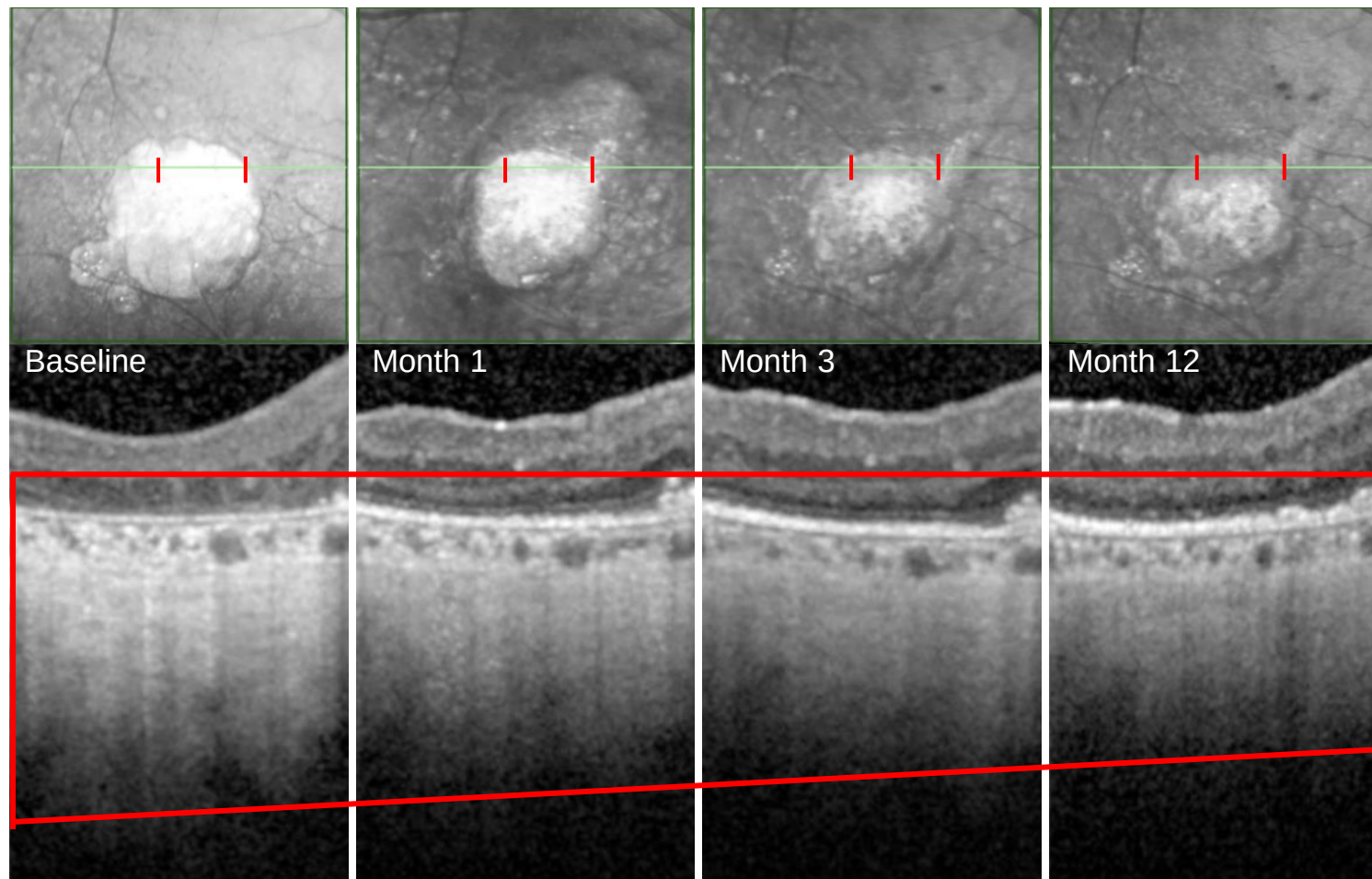
Eyes with **limited** bleb coverage (n=7)



Data cutoff: 18 Jan 2022.

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

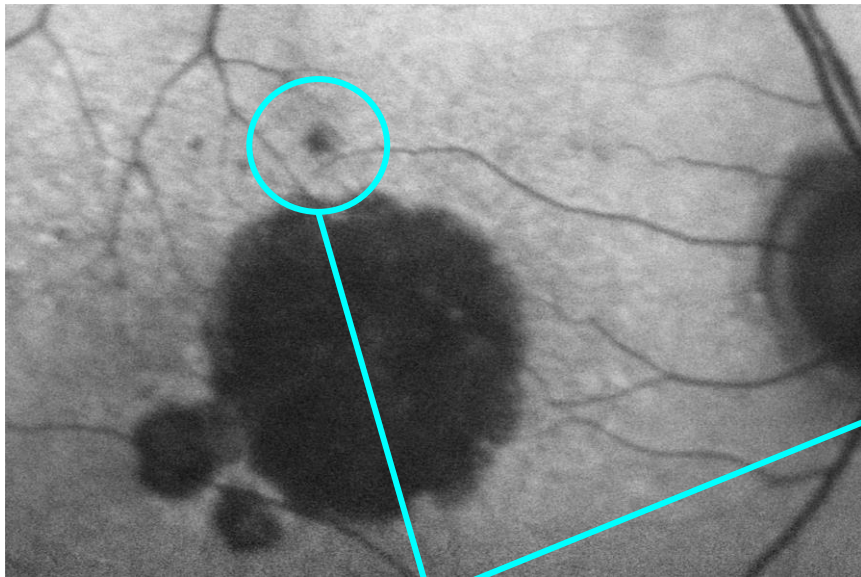
Greater Hyperreflectivity Visible at RPE/BM & Weaker Choroidal Hypertransmission



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

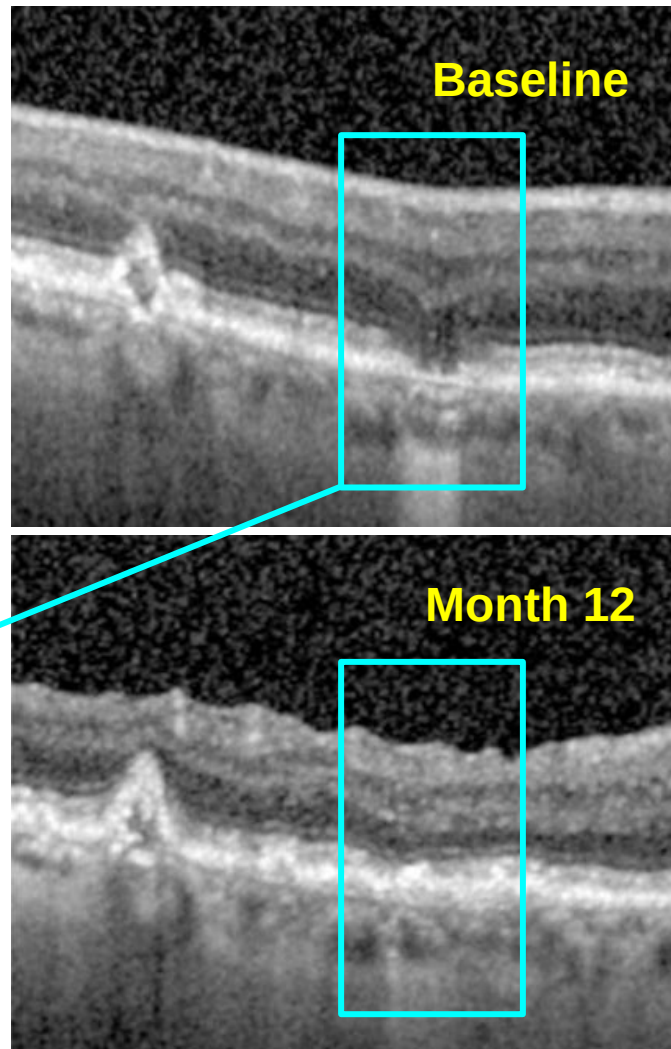
Resolution of iRORA after OpRegen treatment

In Cases With Extensive OpRegen Bleb Coverage of Area of GA



Area of hypoautofluorescence on FAF at baseline with features of iRORA on SD-OCT

iRORA, incomplete RPE and outer retinal atrophy.



- Focal disruption of the RPE layer, choroidal hypertransmission, and outer retinal subsidence at baseline are no longer present at month 12
- Registration of scans is confirmed by presence of a prominent druse and by choroidal vascular markings

Case #21

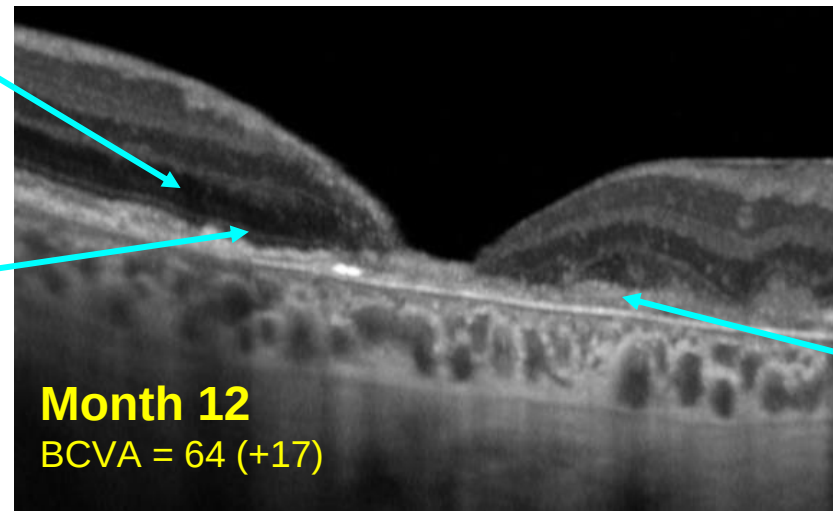
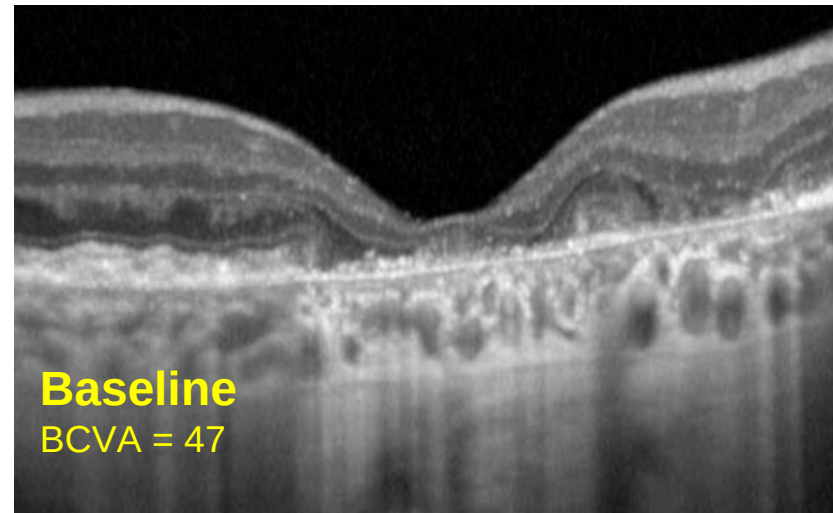
Examples of Improvements in Outer Retinal Structure by SD-OCT

In Cases With Extensive OpRegen Bleb Coverage of Area of GA

Outer retinal layer improvement near the foveal center

Hyporeflective layer continuous with **outer nuclear layer** at scan margins extends more centrally

Hyperreflective layer continuous with **external limiting membrane** also extends more centrally

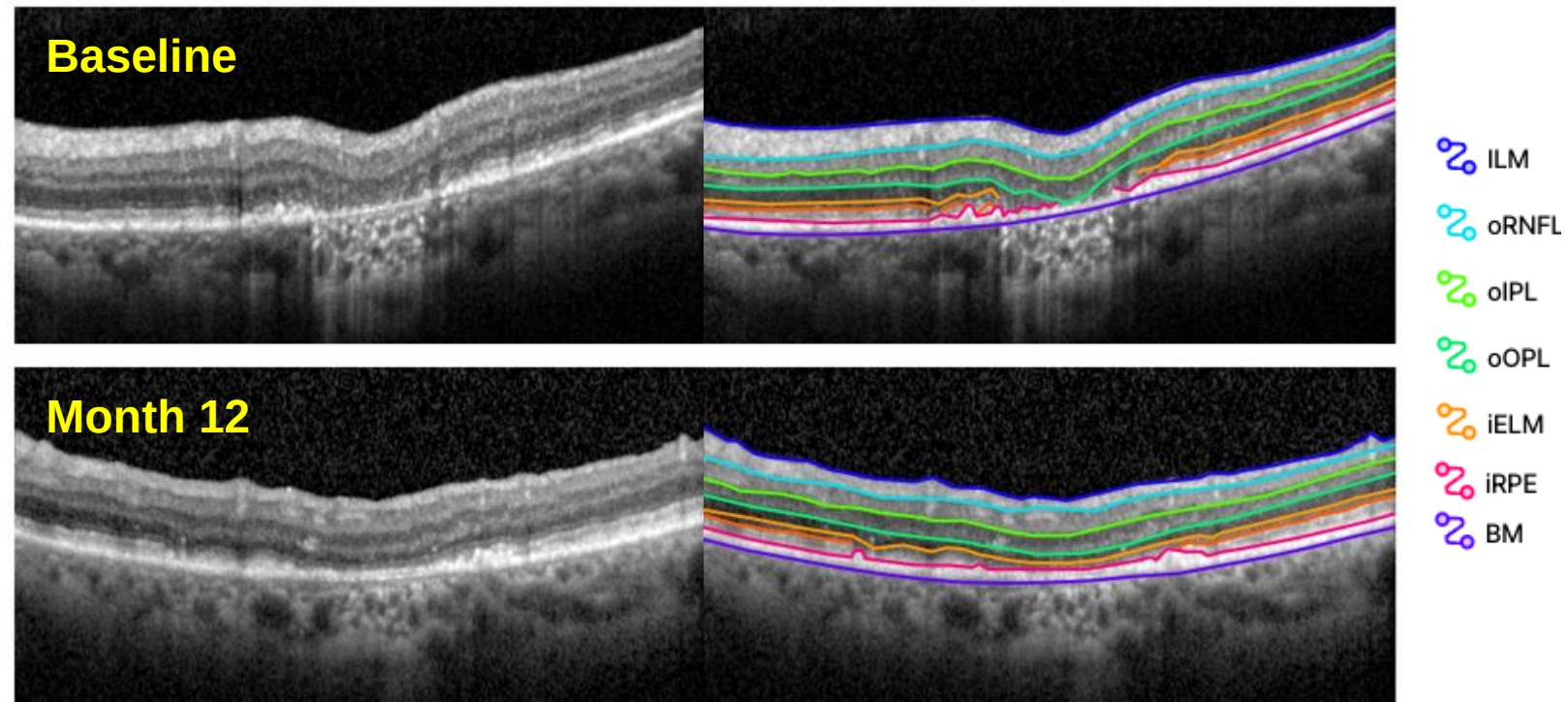
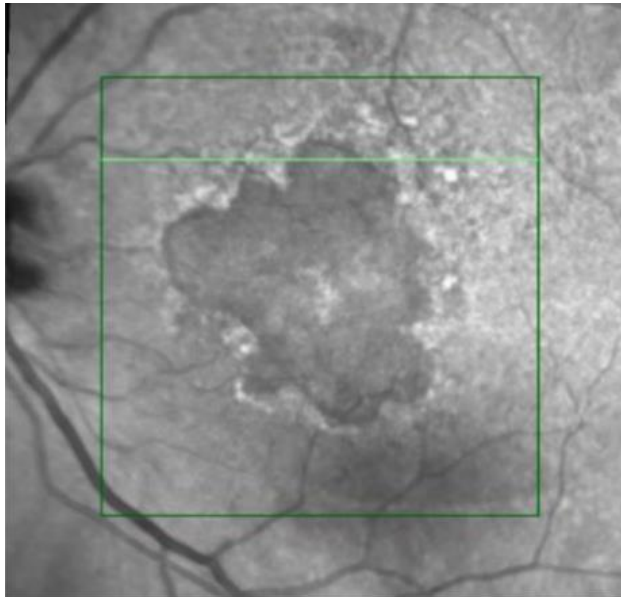


Greater hyperreflectivity at the level of **RPE/Bruch membrane**

Case #22

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

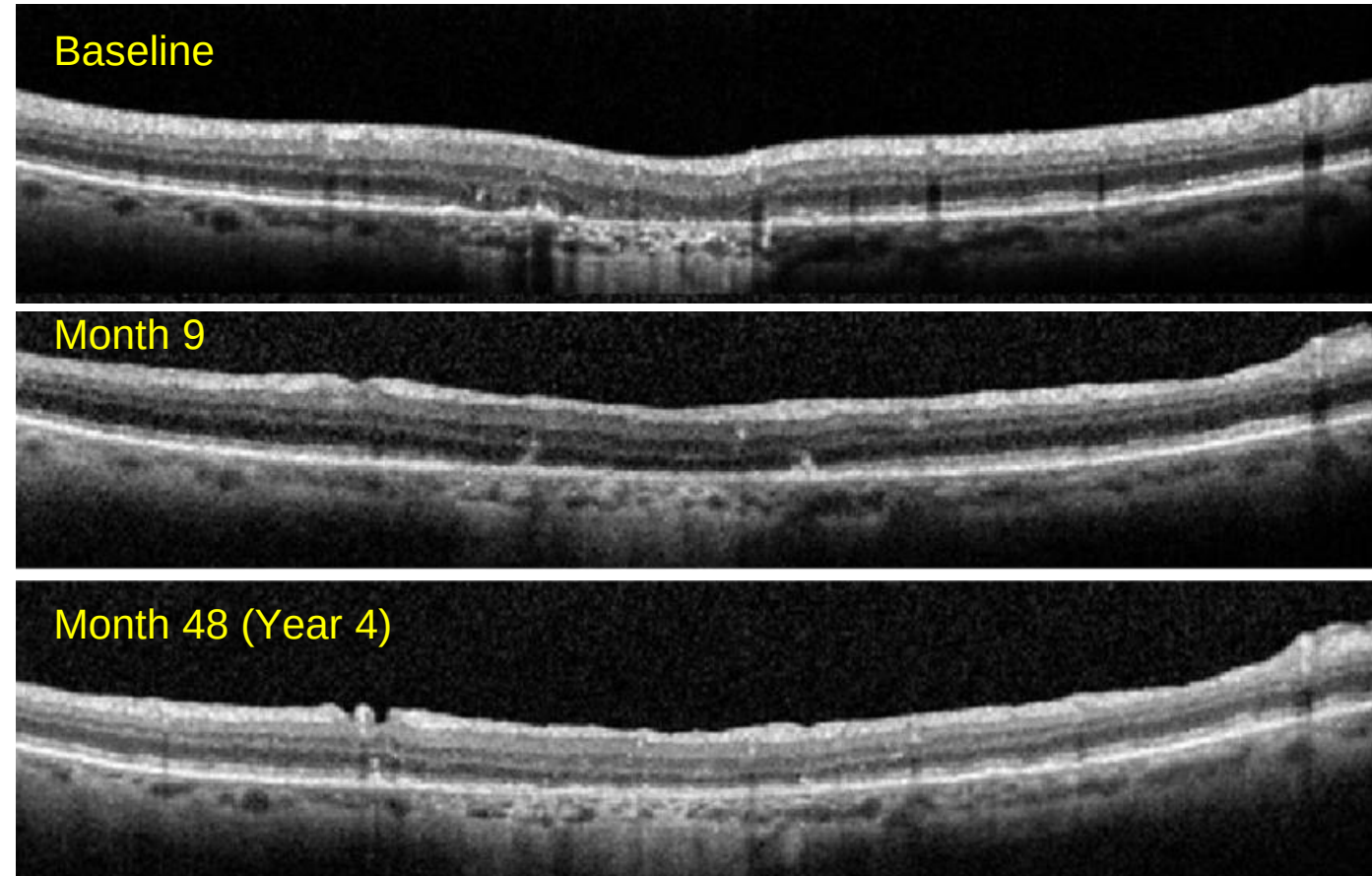
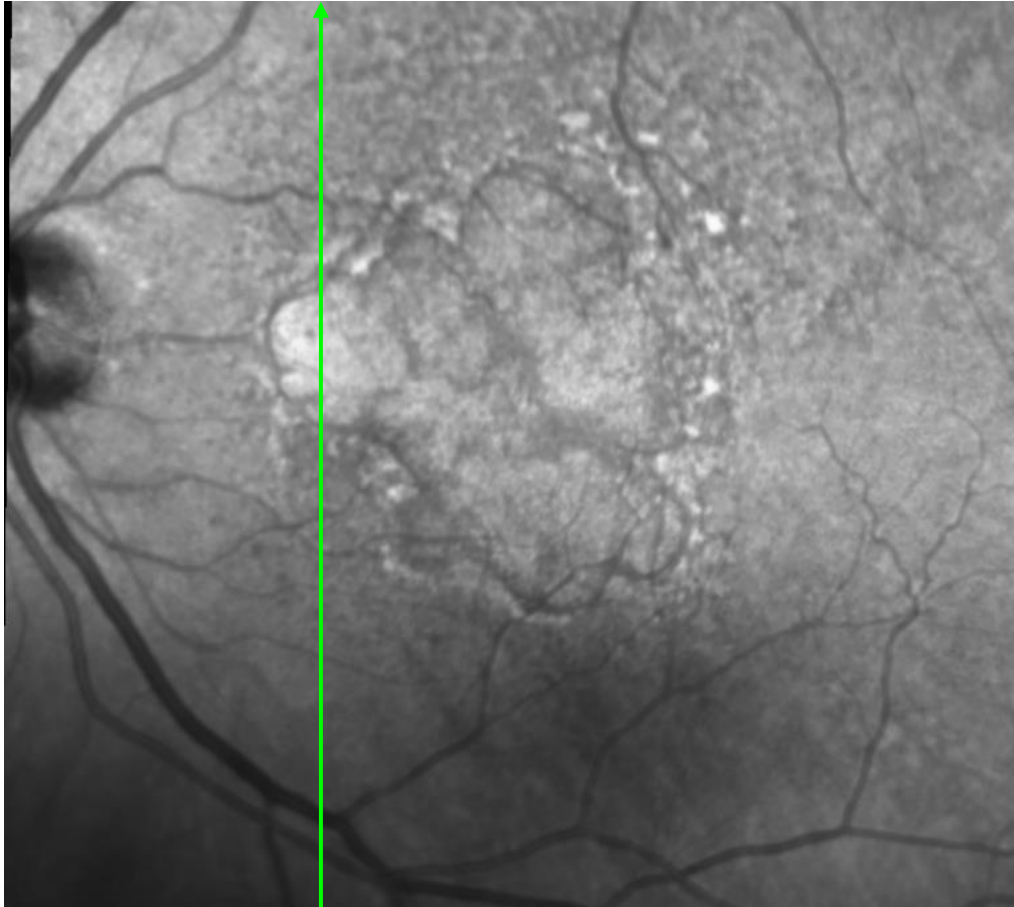
- Resolution of retinal subsidence, with greater continuity of outer retinal layers
- Similar features also seen at nasal, superior, and inferior borders of GA

cRORA, complete RPE and outer retinal atrophy; 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.

Case #14

Long-Term Assessment of Outer Retina Structure

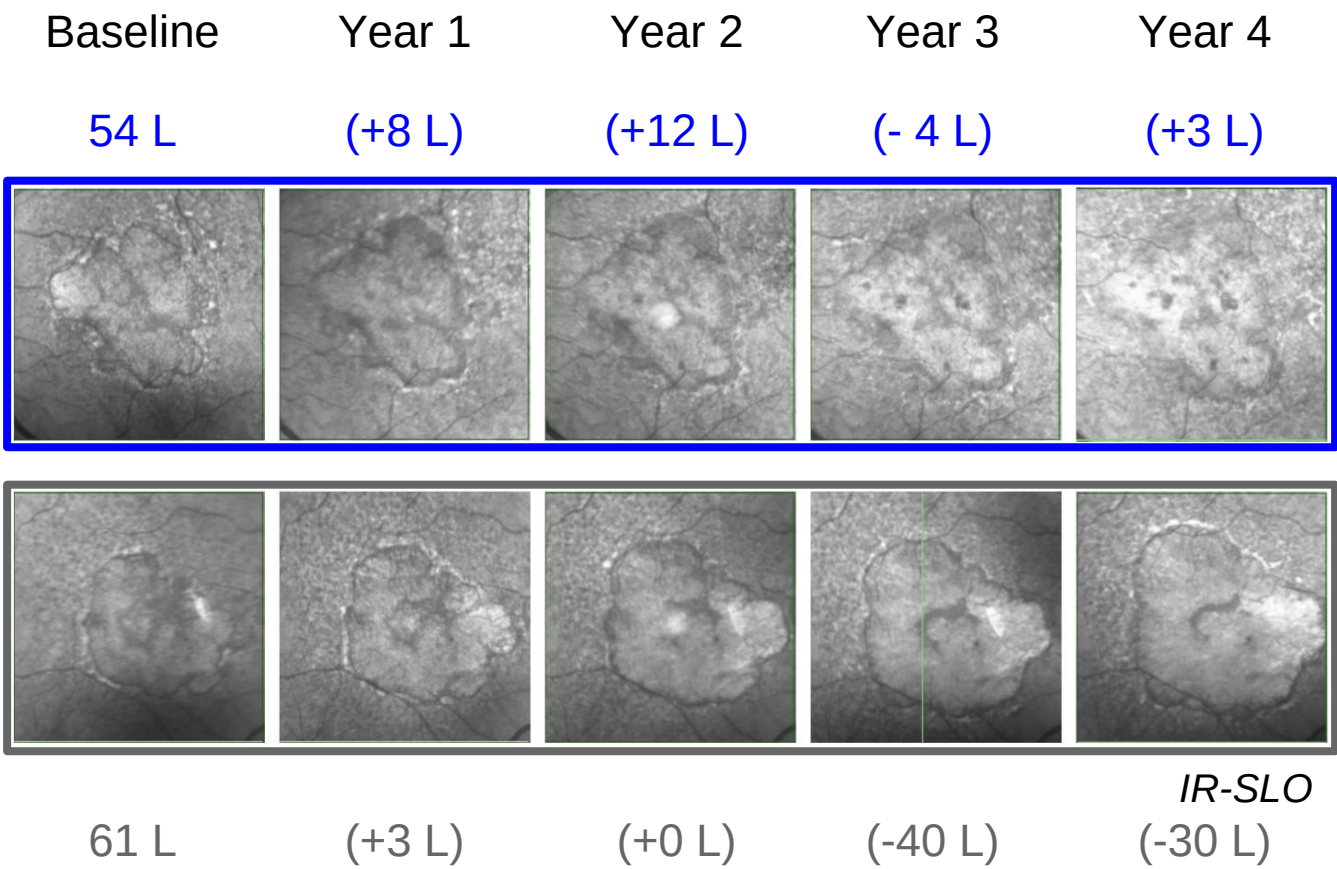
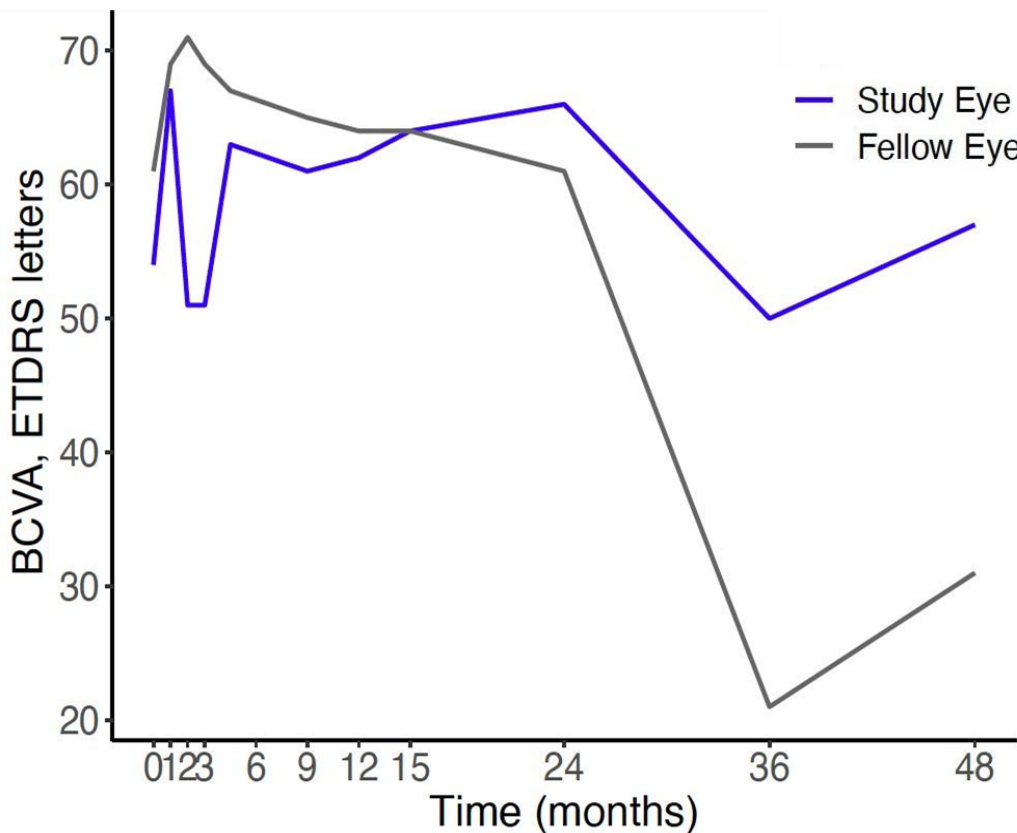
Outer Retinal Improvement Persisted Over 4 years in Study Eye



Case #14

Long-Term Vision Preservation in Study Eye

Vision Loss from GA Progression Over Time in Fellow Untreated Eye



IR-SLO, infrared scanning laser ophthalmoscopy; L, letters.

Summary and Future Directions

- 12-month primary endpoint data from this Phase I/IIa study suggest that OpRegen is well tolerated with an acceptable safety profile and mostly mild AEs
- Preliminary evidence of outer retinal structure improvements with OpRegen was observed, particularly in Cohort 4 patients with extensive OpRegen bleb coverage
 - These improvements are maintained in some patients for up to 4 years, with follow-up continuing
- 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, surgical procedure for subretinal delivery, 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
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- Diana Angelini, Lineage Therapeutics, Inc., Carlsbad, CA, USA
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Imaging Analysis

- Central Reading Center: Merit CRO (EyeKor), Madison, WI, USA
- 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,