Phase I/IIa Study of the Safety and Activity of OpRegen® in Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

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Abstract #3714956
Presentation #1862

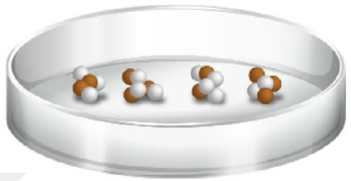
Presented at the Association for Research in Vision and Ophthalmology (ARVO) 2022 Annual Meeting | Denver, CO, USA | May 1-4, 2022

OpRegen – A Suspension of Allogeneic RPE Cells
With the Potential to Counteract RPE Cell Loss in GA

OpRegen

NIH-registered clinical-grade hESC cell line[a]

Neural spheres with pigmented areas



Mature and functional RPE cells

Utilizes a proprietary, large-scale, cGMP manufacturing process

[a]NIH registry for hESC cell line HAD-C 102 available at https://grants.nih.gov/stem_cells/registry/current.htm?id=428.

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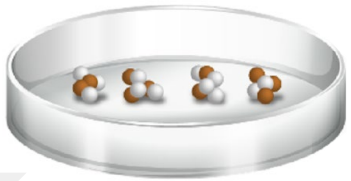

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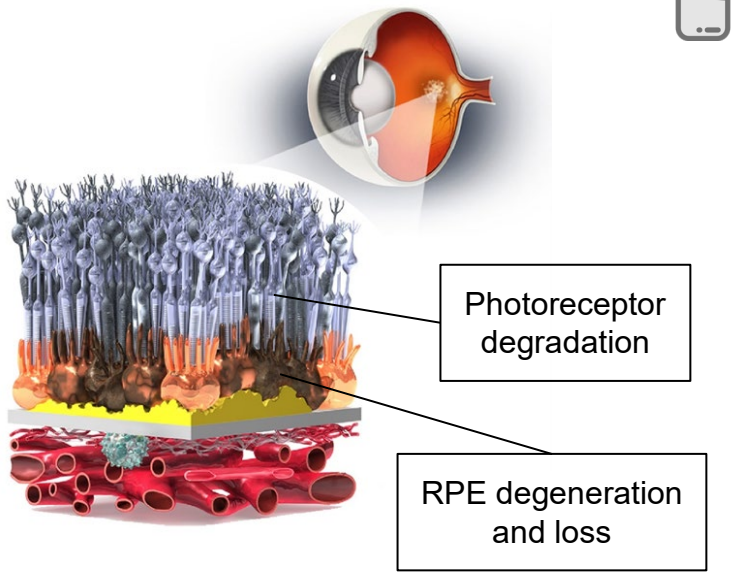
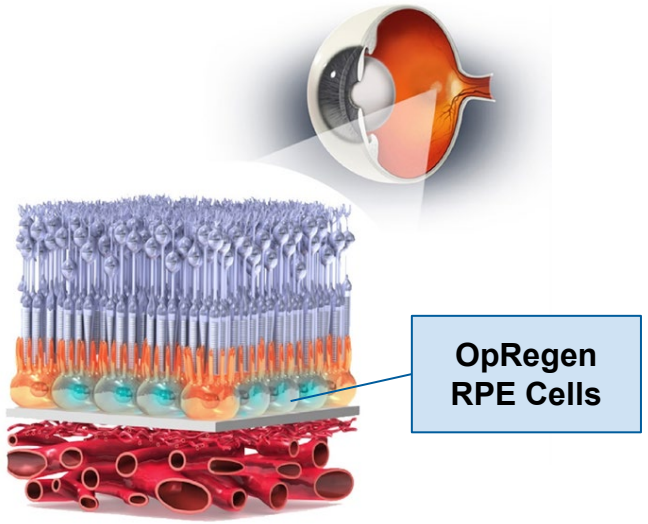
Before OpRegen subretinal delivery



After OpRegen subretinal delivery



OpRegen has the potential to counteract RPE cell loss in areas of GA by supporting retinal structure and function

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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: ≤20/200)
- GA area: 1.25–17 mm^2

Cohort 4 (n=12):

- Impaired vision (BCVA: ≥20/250 and ≤20/64)
- GA area: ≥4 and ≤11 mm^2

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

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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 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)

[a]The worse eye based on BCVA was selected for OpRegen subretinal delivery. [b]Based on central grading of fundus autofluorescence imaging.
Data cutoff: 18 Jan 2022.

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Safety Summary
OpRegen Was Well Tolerated With an Acceptable Safety Profile

- 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)
- The majority of AEs reported (Cohorts 1-3, 87%; Cohort 4, 93%) were mild
- No cluster of AEs related to immunosuppressive regimen were reported
- One patient discontinued due to an AE (stage IV lung adenocarcinoma unrelated to treatment)
- No cases of rejection following OpRegen subretinal delivery have been reported
- No acute or delayed intraocular inflammation, or sustained intraocular pressure increase observed
- Interpretations of the data are limited by the small dataset and the single-arm nature of this study

ERM, epiretinal membrane; URTI, upper respiratory tract infection.
Data cutoff: 18 Jan 2022.

Ocular AEs With OpRegen
Mainly Related to the Surgical Procedures for Subretinal Delivery

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 (CNV) / neovascular AMD	1 (8%)	3 (25%)
Retinal detachment	1 (8%)	1 (8%)
Retinoschisis	1 (8%)	2 (17%)

[a]7/12 (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. [b]Clinically significant indicates ERM requiring surgical intervention.

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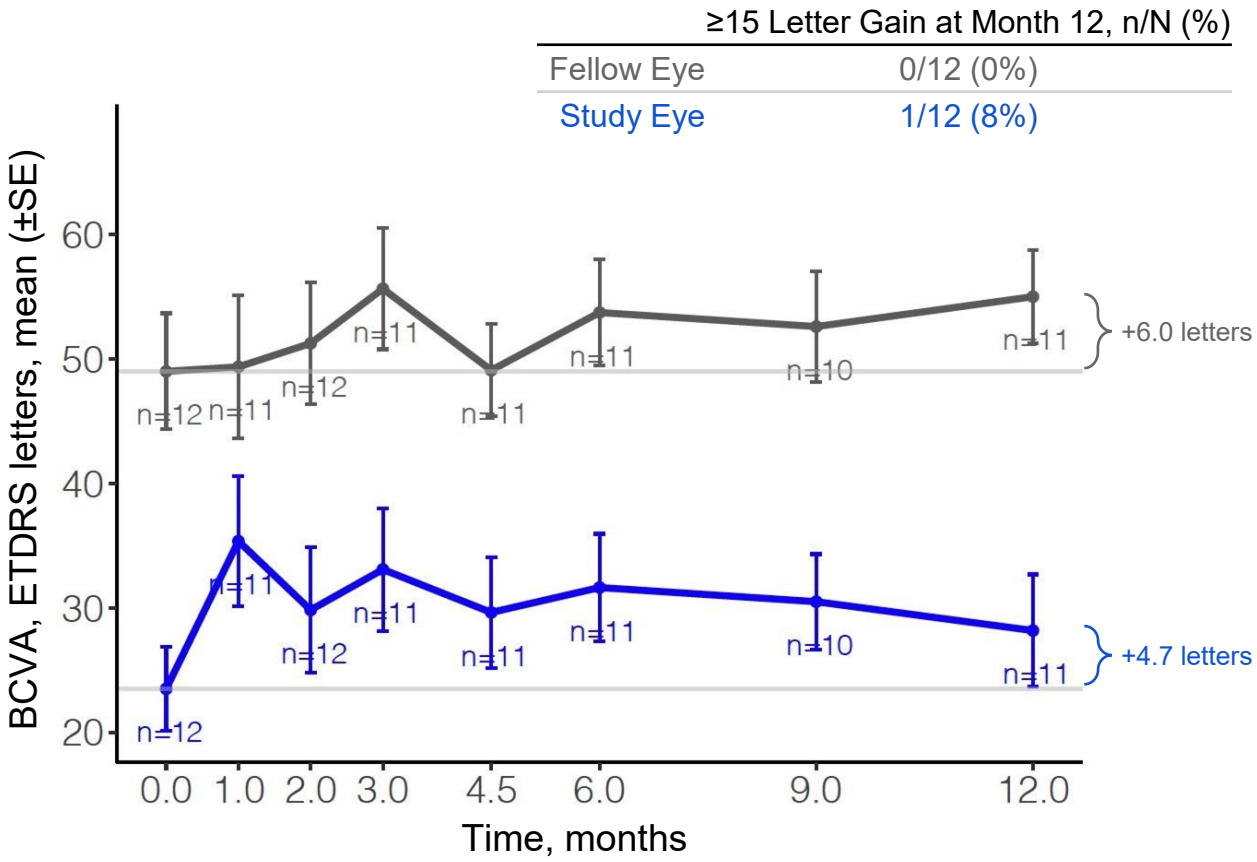
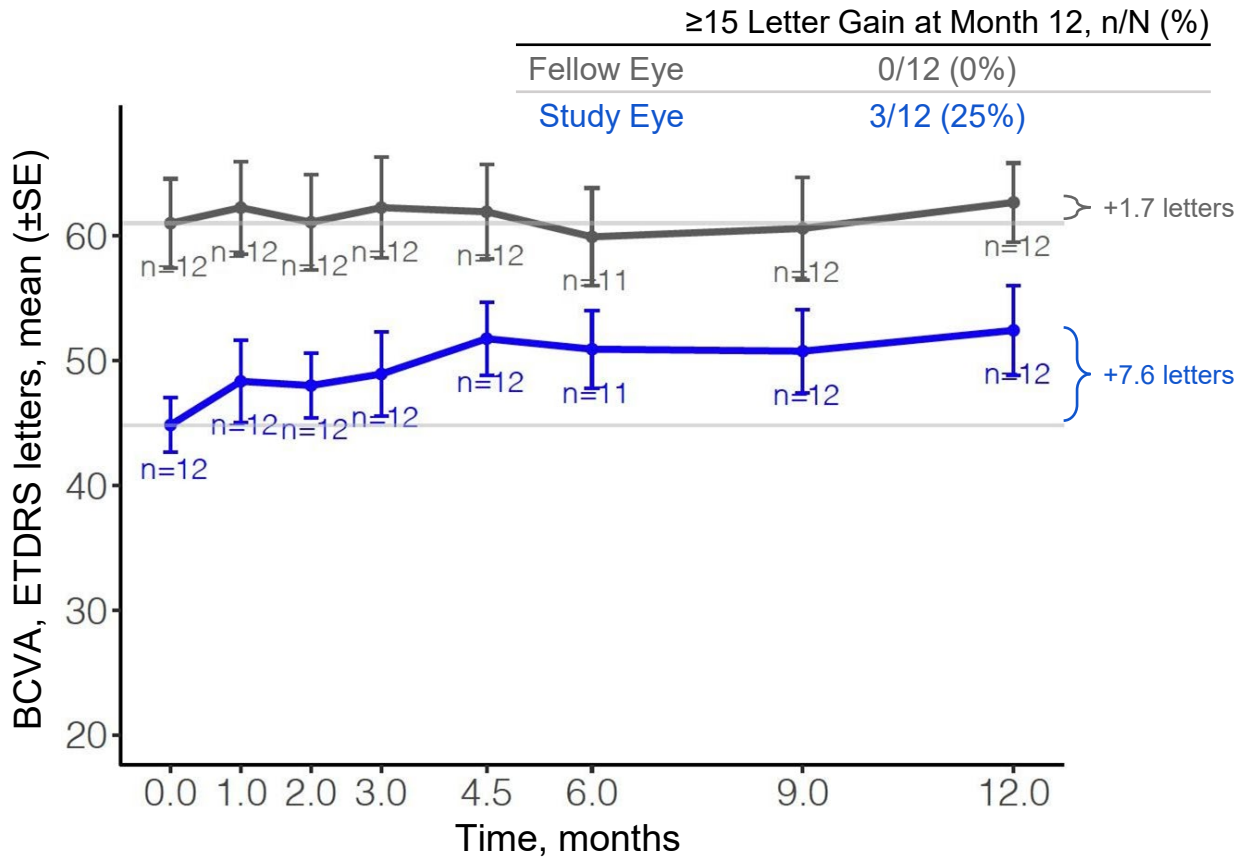
Preliminary Evidence of Visual Function Improvements

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

Cohorts 1-3
(Baseline BCVA ≤20/200)



Cohort 4
(Baseline BCVA ≥20/250 and ≤20/64)



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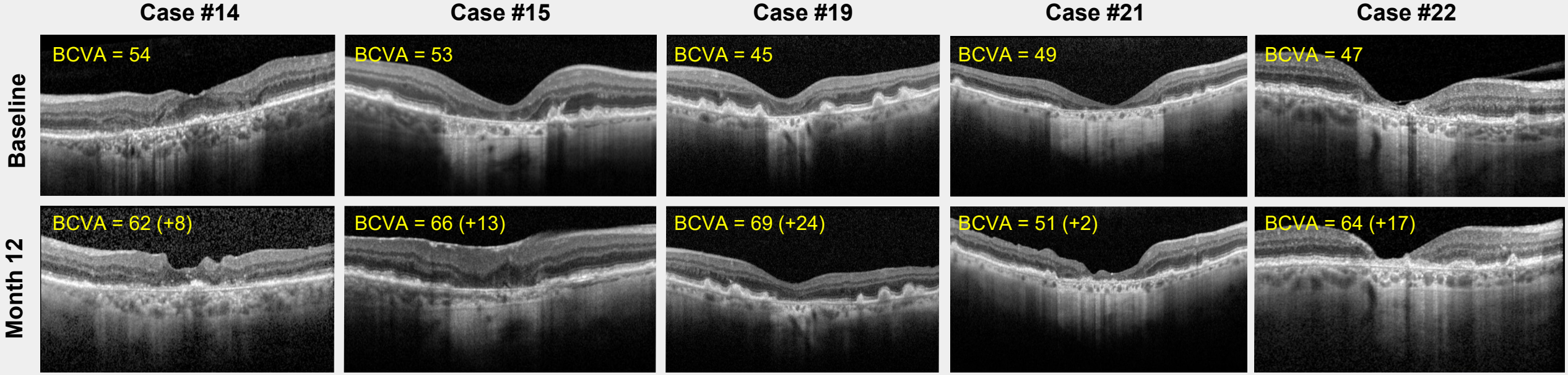
Subretinal Delivery of OpRegen to GA Area and Fovea

Greater Visual Function Gains With Areas of Outer Retinal Structure Improvement

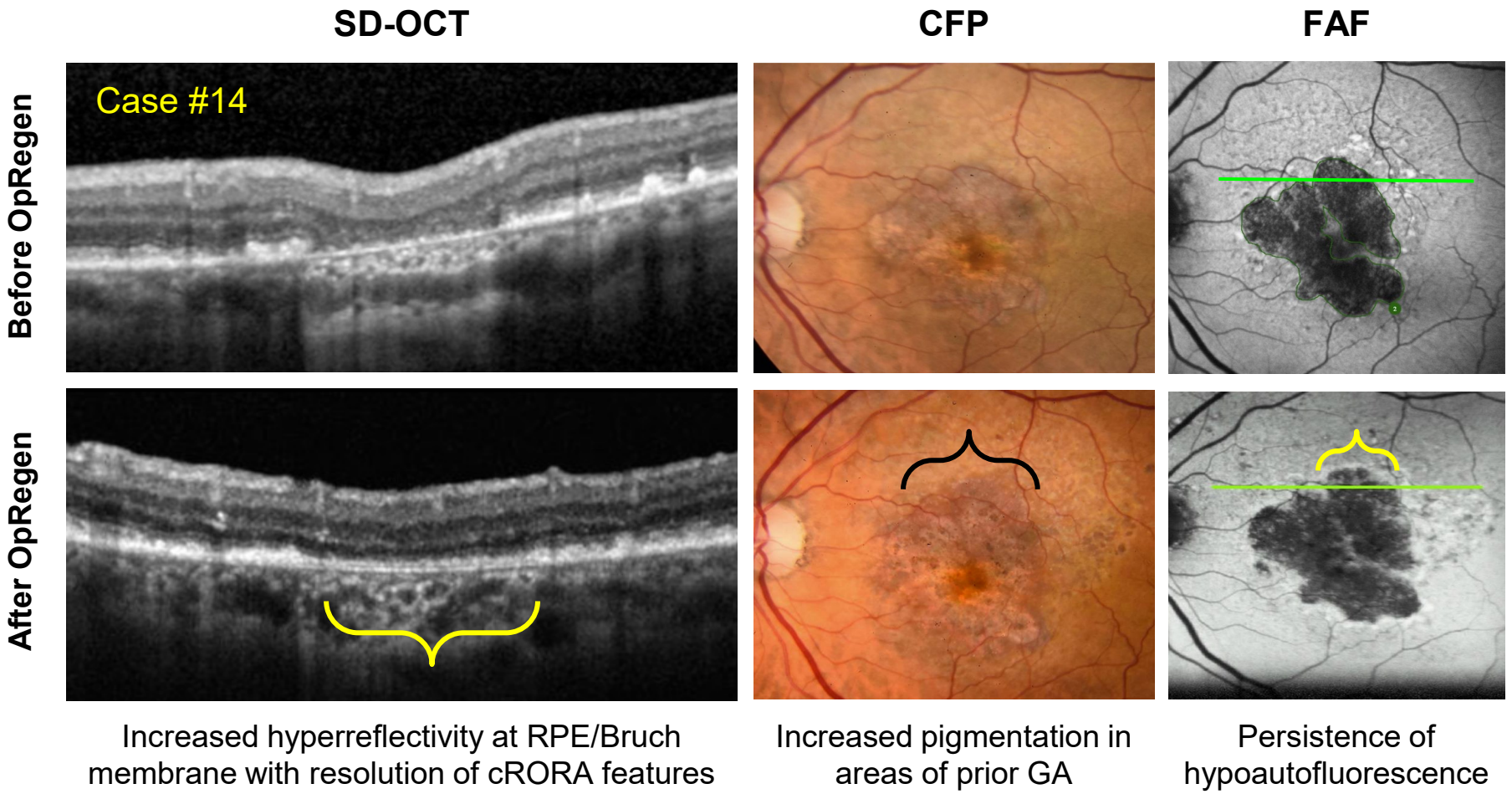
- Five patients in Cohort 4 had OpRegen delivered to most or all of the GA area, including the fovea
  - These 5 patients had greater gains in visual function (average 12.8 letter gain), with evidence for regions of apparent improvement of outer retinal structure as assessed by SD-OCT



SD-OCT, spectral domain optical coherence tomography. BCVA measured by ETDRS letter score.

Assessment of GA Following OpRegen Delivery

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



Increased hyperreflectivity at RPE/Bruch membrane with resolution of cRORA features

Increased pigmentation in areas of prior GA

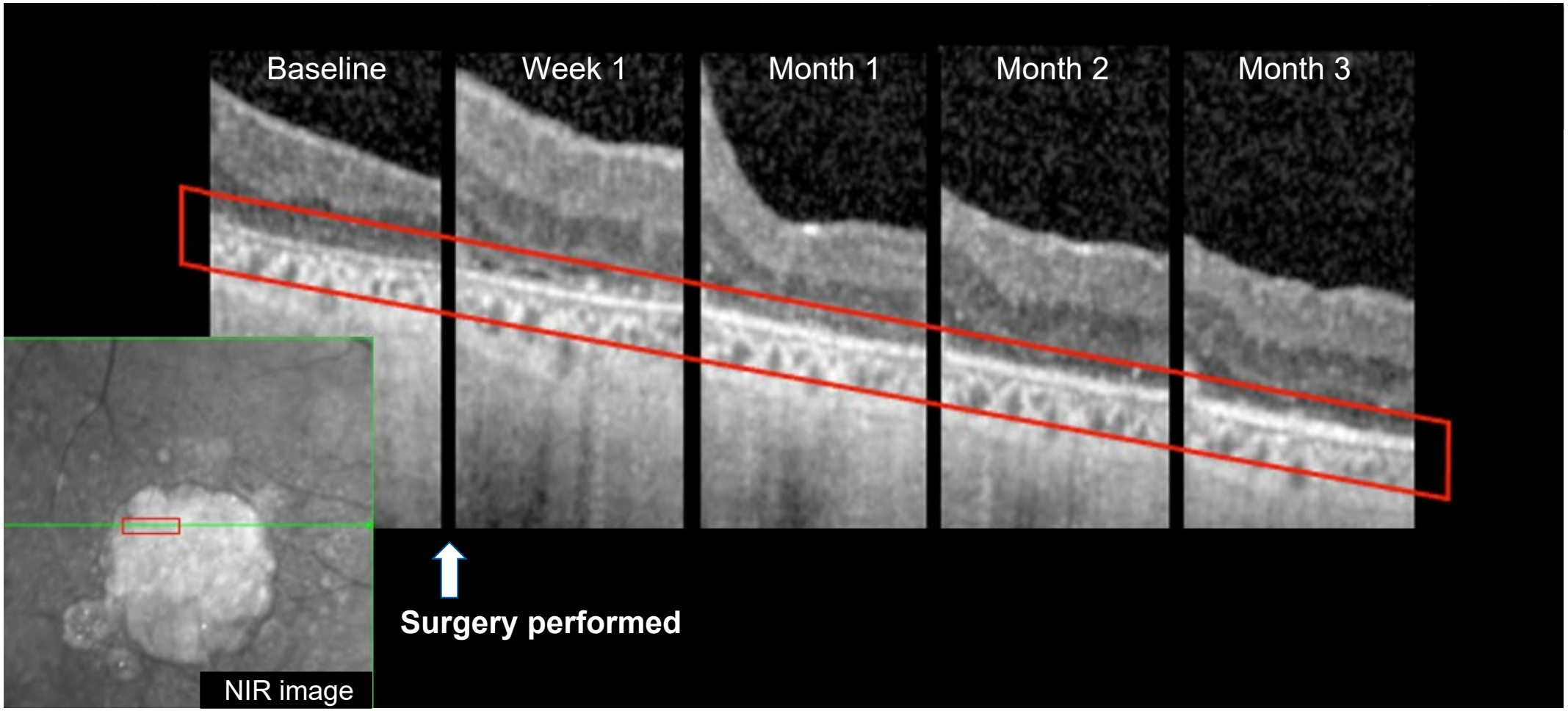
Persistence of hypoautofluorescence

- 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

CFP, color fundus photography; cRORA, complete RPE and outer retinal atrophy.

Greater Hyperreflectivity Visible at RPE/Bruch Membrane

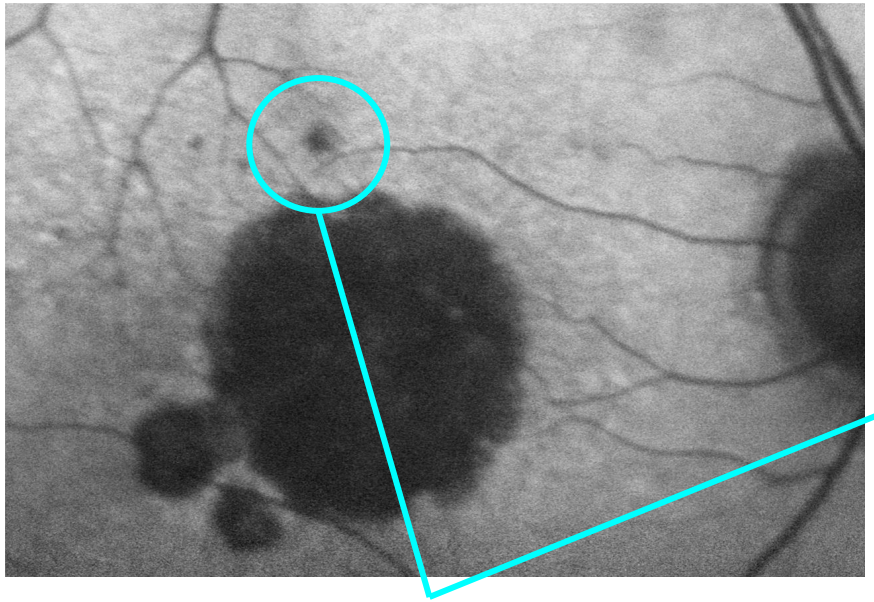
SD-OCT Imaging Suggests OpRegen Presence in Areas of Former GA



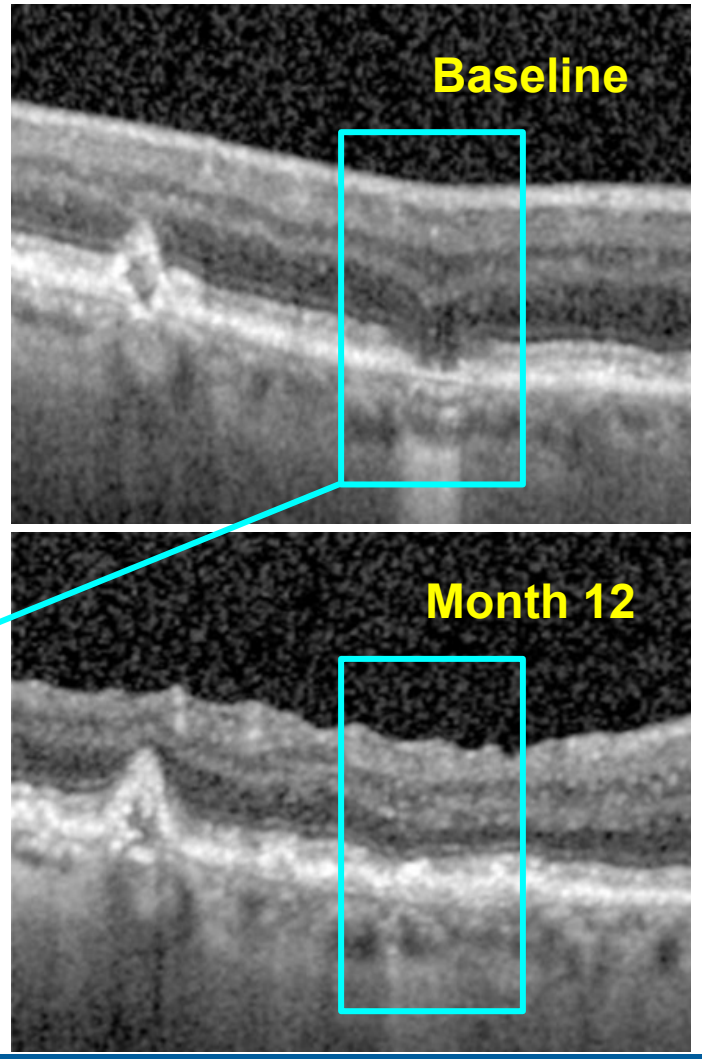
Adapted from slide courtesy of Brandon Lujan, MD.

Examples of Improvements in Outer Retinal Structure by SD-OCT
In Cases With OpRegen Delivery to the Area of GA

Resolution of iRORA
Case #21



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

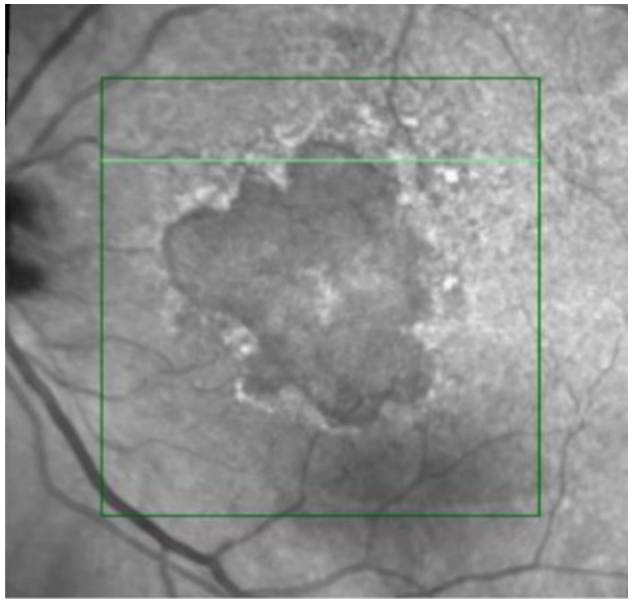


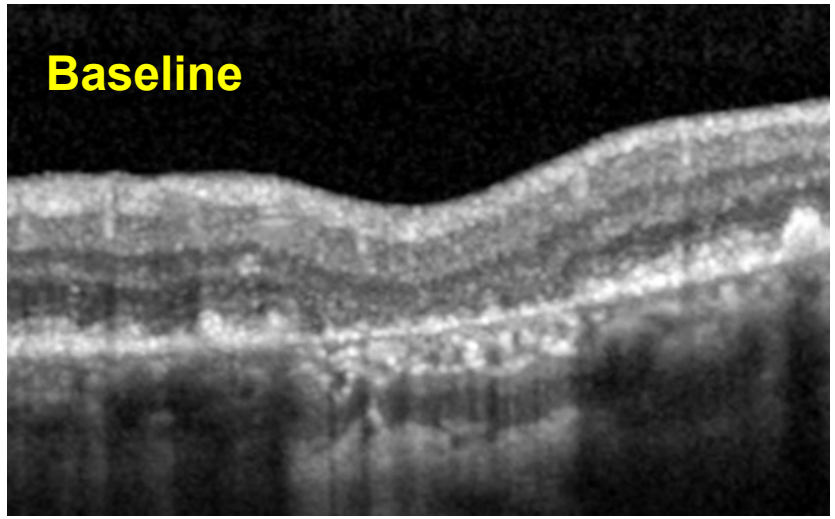
- Focal disruption of the RPE layer, choroidal hypertransmission, and outer retinal subsidence at baseline are no longer present at month 12
- Registration of scans is confirmed by presence of a prominent druse and by choroidal vascular markings

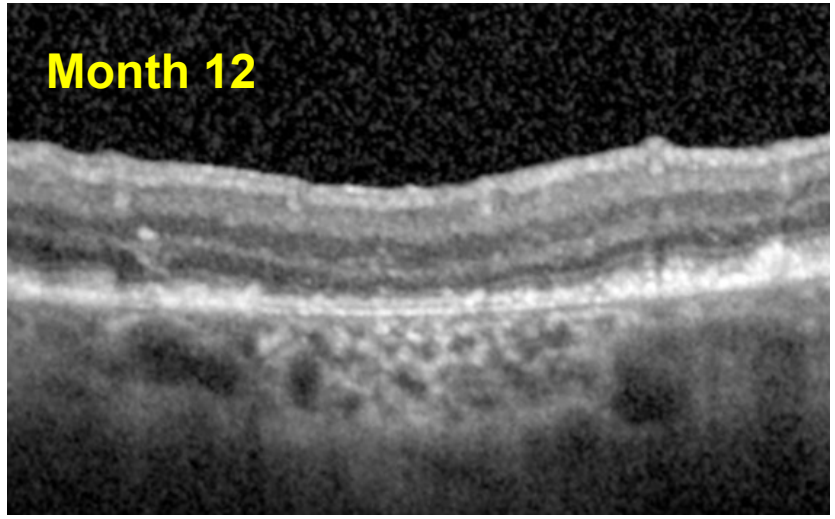
iRORA, incomplete RPE and outer retinal atrophy.

Examples of Improvements in Outer Retinal Structure by SD-OCT
In Cases With OpRegen Delivery to the Area of GA

Resolution of cRORA near borders of baseline GA
Case #14







At month 12, compared with baseline:

- Features of cRORA no longer present
- Greater hyperreflectivity at the level of RPE/Bruch membrane
- 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 in this case

cRORA, complete RPE and outer retinal atrophy.

Examples of Improvements in Outer Retinal Structure by SD-OCT

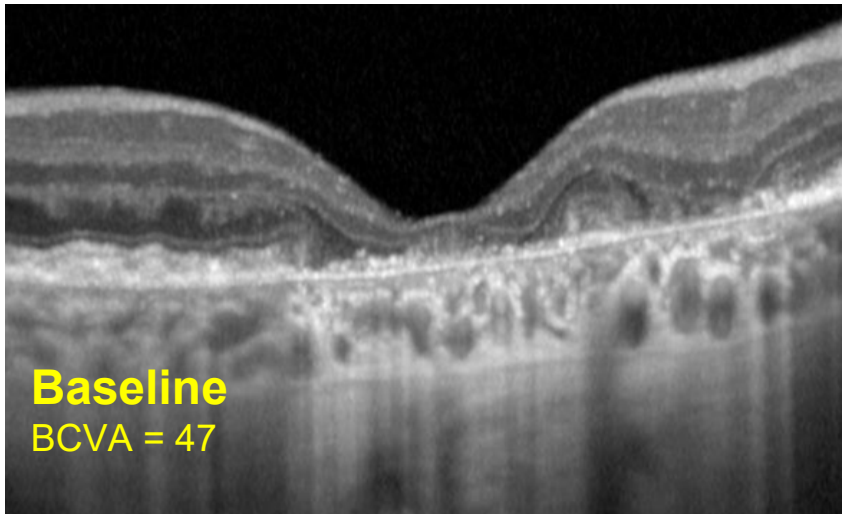
In Cases With OpRegen Delivery to the Area of GA

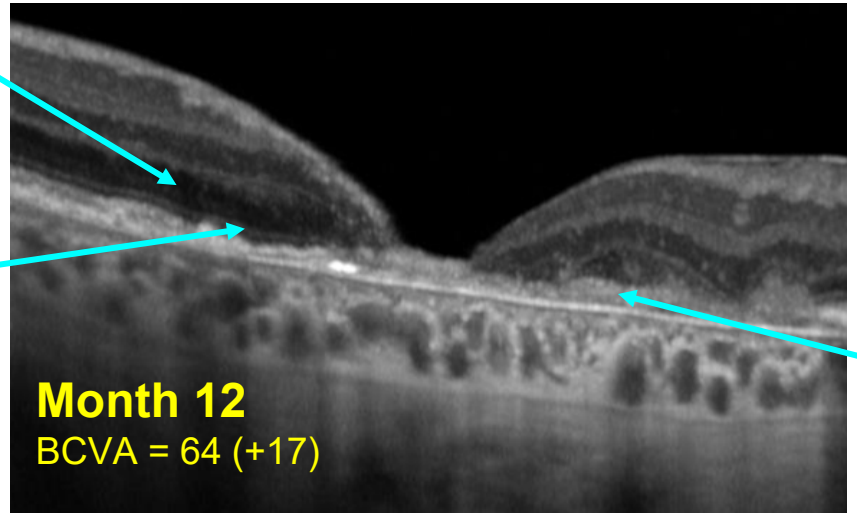
Outer retinal layer improvement near the foveal center

Case #22

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**

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
- The ocular AEs observed with OpRegen were mainly related to the surgical procedures used for subretinal delivery
- 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])
  - SD-OCT imaging analysis is ongoing
- These data support the potential for OpRegen to slow, stop, or reverse disease progression in GA
- 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

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
- 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)

Additional Review and Data Analysis

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