Phase 1/2a Clinical Trial of Transplanted Allogeneic Retinal Pigmented Epithelium (RPE, OpRegen) Cells in Advanced Dry Age-Related Macular Degeneration (AMD): Interim Results

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Cincinnati Eye Institute &
University of Cincinnati

Retinal Society
54th Annual Scientific Meeting
29 Sep - 2 Oct, 2021
Chicago, IL, USA

Financial Disclosures (CDR)

Alcon – Consultant, Speaker
Alimera – Consultant, Speaker
Alimera Deutschland GmBH – Consultant, Speaker
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Animal Eye Institute – Consultant
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Bausch & Lomb/Valeant – Speaker, Consultant
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VEO – Owner/Cofounder
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Monies for research: AGTC, Alcon, Alimera, Allergan, Arepio, BioTime / Lineage, Chengdu Kanghong, Clearside, Genentech/Roche, Gyroscope, Janssen / Johnson & Johnson, Lowry-MacTel Registry, Neurotech, Nightstar/Biogen, NotalVision, Novartis, Ophthotec/Iveric, Regeneron, RegenxBio, Spark

Avastin, Kenalog and GoreTex are not FDA approved for intraocular use

Financial Disclosures *(related to this presentation)*

Christopher D. Riemann: Consultant (C), Investigator

Eyal Banin: Lineage Cell Therapeutics (Cell Cure Neurosciences); Patent (P), Consultant (C)

Adiel Barak: None, Investigator

David Boyer: Consultant (C), Investigator

Rita Ehrlich: None, Investigator

Allen C. Ho: Consultant (C), Investigator

Tareq Jaouni: None, Investigator

Richard McDonald: None, Investigator

David G. Telander: None, Investigator

Avi Ben Shabat: Lineage Cell Therapeutics (Cell Cure Neurosciences); Employment (E)

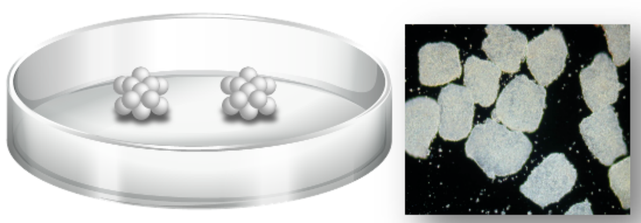
Jordi M. Monés: Lineage Cell Therapeutics (Cell Cure Neurosciences); Consultant (C)

Joyce Velez: Lineage Cell Therapeutics; Employment (E)

Gary S. Hogge: Lineage Cell Therapeutics; Employment (E)

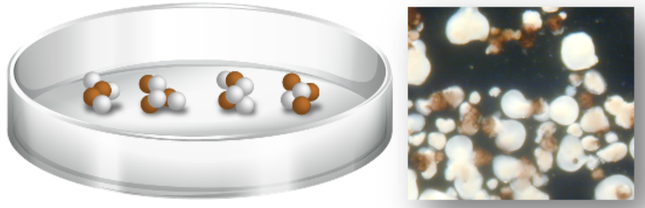
Benjamin Reubinoff: Lineage Cell Therapeutics (Cell Cure Neurosciences); Patent (P), Consultant (C)

Large-Scale cGMP Differentiation and Transplant of hESC-Derived Retinal Pigmented Epithelial (RPE) Cells

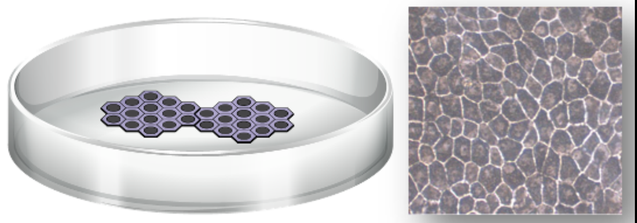


Clinical-grade cell clusters from established cell line

Source of original hESC (HAD C-102) was a single supernumerary IVF blastocyst frozen >5 years. Ethically obtained, HPI maintained, informed consent granted, and without compensation. HAD-C102 is eligible for use in NIH funded research. (https://grants.nih.gov/stem_cells/registry/current.htm?id=428)

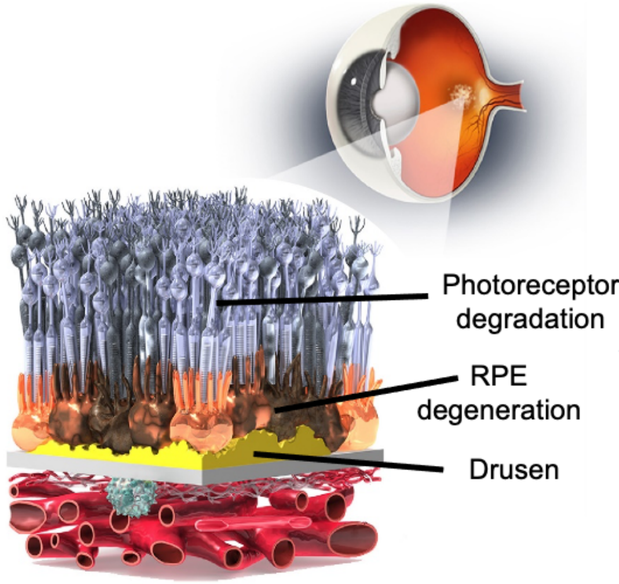


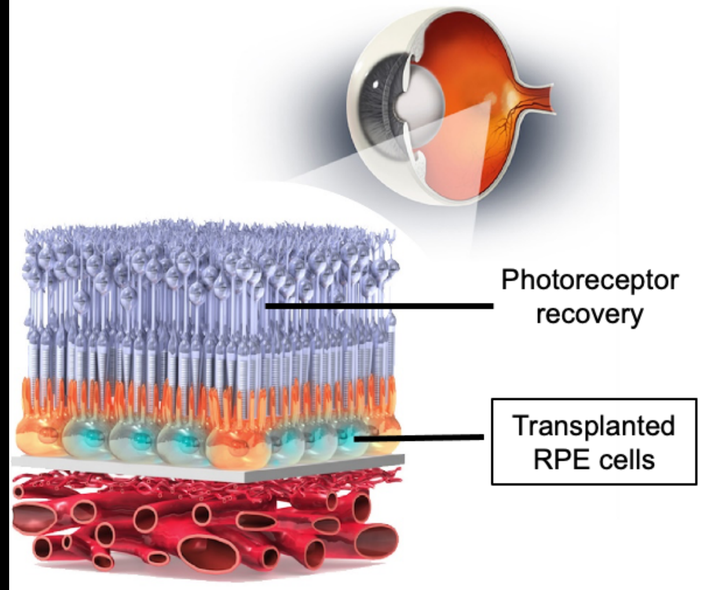
Neural Spheres with pigmented areas



>99% pure RPE cells

Scale up to 5 billion cells per 3-liter bioreactor





M. Idelson et al., Cell Stem Cell 2009

Retinal images adapted from www.scienceofamd.org

Study Objectives

Phase 1/2a Clinical Trial (NCT02286089)

Primary Objective:

To evaluate the ***safety and tolerability*** of subretinally transplanted hESC - derived RPE cells (OpRegen) in patients with advanced dry age-related macular degeneration (AMD) and geographic atrophy (GA)

Secondary Objective:

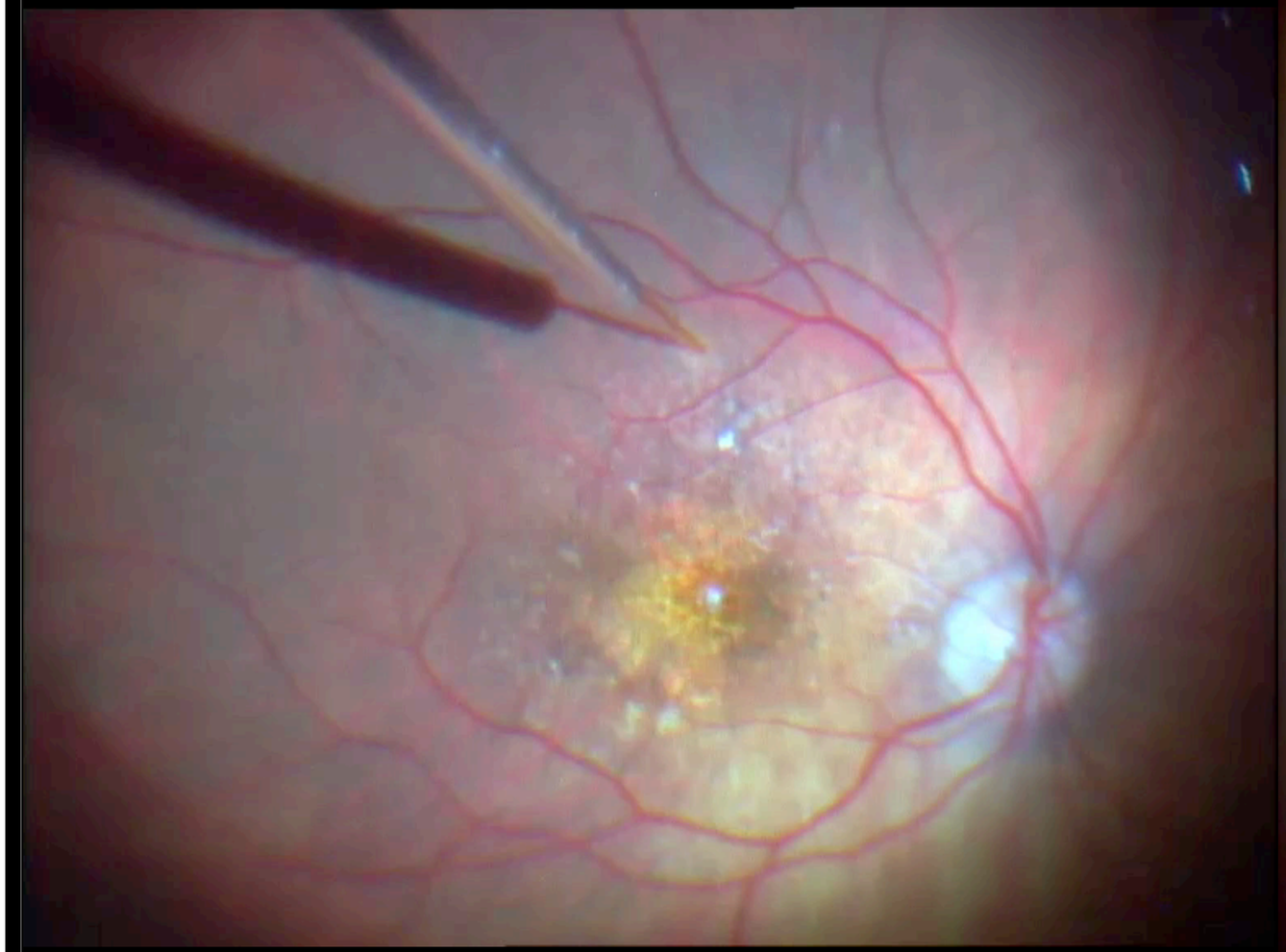
To evaluate ***survival and possible effects*** of OpRegen treatment by assessing changes in retinal structure and function

Exploratory Objective:

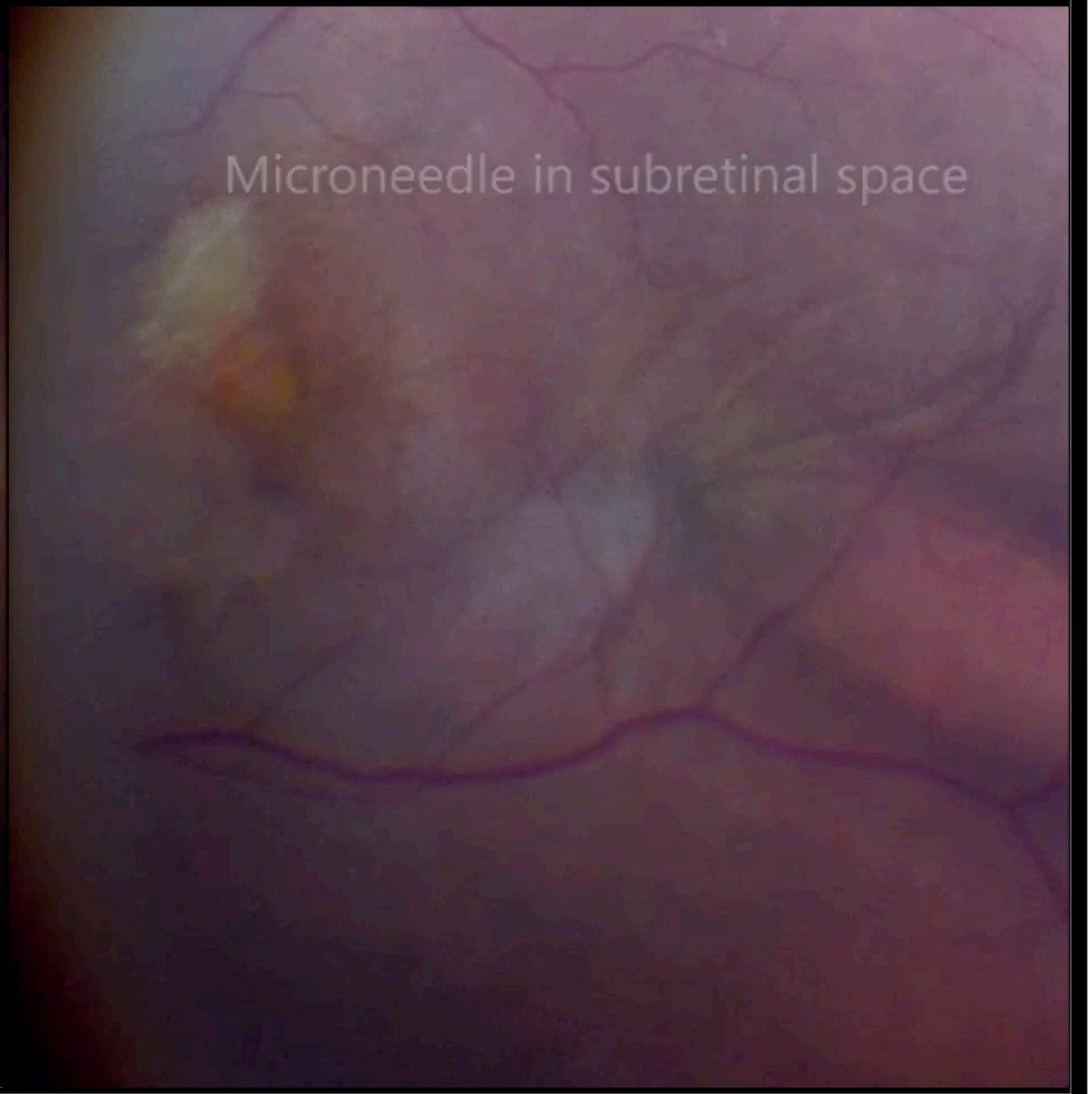
Evaluate safety in Cohort 4 participants who receive a subretinal injection of OpRegen ***"thaw and inject"*** (TAI) preparation using the ***Orbit™ Subretinal Delivery System*** (Orbit SDS)*

* Orbit and Orbit SDS are trademarks of Gyroscope Therapeutics Limited (Gyroscope)

PPV / Retinotomy



Orbit SDS



Study Design, Population, Management

Parameter	Cohorts 1-3 (legally blind) n = 12 of 12 planned (*complete*)	Cohort 4 (better BCVA) n = 12 of 12 planned *(complete)*
Phase / design	Phase I-IIa; staggered design; IND (NCT02286089)	
Duration	Screening up to 8 Weeks; short term F/U – 1 year; long term F/U – 4 years	
Management	Central reading/central labs/Independent DSMB/Advisory Committees	
Treated disease	Advanced Dry AMD and GA	
Subretinal Dose (delivered via PPV and retinotomy {n = 17} or SDS {n = 7})	Cohort 1: 50K cells Cohorts 2-3: up to 200K cells	Up to 200K cells
BCVA	≤ 20/200	≤ 20/64 and ≥ 20/250
GA size – Central Reading assessment	≥ 1.25mm^2 and ≤ 17 mm^2	≥ 4 mm^2 and ≤ 11 mm^2
Historical Growth of GA	N/A	SQRT per year of > 0.25 mm
Cataract status	Not defined	Pseudophakic or phakic w/ Orbit SDS
Significant concomitant diseases exclusion (systemic / ocular)	Defined *a priori*	
Immunosuppression	PO tacrolimus from 1 week prior to Sx until 6 weeks post-op PO mycophenolate from 1 week prior to Sx to at least 3 months post-op	

Study Status and Baseline Characteristics

	Cohorts 1 - 3 (legally blind) Recruitment complete (n = 12)	**Cohort 4 (better VA)** Recruitment complete (n = 12)	
	Via pars plana vitrectomy (PPV) and retinotomy	**Via PPV and retinotomy** (n = 5)	**Via Orbit SDS** (n = 7)
n (%) subjects dropout	2 (17%) (2 medical illness)	1 (12.5%) (Withdrawal of consent/COVID)	0
Age: mean (SD / min - max), yrs	78.1 (± 8.2 / 64.8 – 92.2)	78.1 (± 2.8 / 74.6 – 81.0)	73.9 (± 10.3 / 60.0 – 87.7)
ETDRS BCVA: mean (SD / min - max)	23.7 (± 11.7 / 0 – 39) letters [24 letters ≈ 20/400]	49.6 (± 3.8 / 45 – 54) letters [50 letters ≈ 20/100]	41.4 (± 8.9 / 28 – 55) letters [41 letters ≈ 20/160]
GA area: mean (SD / min - max)	12.7 (± 6.7 / 6 – 30) mm^2	6.2 (± 2.8 / 1.4 – 8) mm^2	8.2 (± 2.9 / 4 – 11) mm^2
Mean F/U (min - max)	45.7 (11 - 72) months	22.6 (10 - 38) months	16.1 (10 - 27) months

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Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability

- No unexpected adverse events (AEs) or serious adverse events (SAEs), appears well tolerated to date with some patients > 5 years post-treatment
- All patients (N = 24) reported at least one AE
  - The majority of AEs were mild (331/380, 87%)
- AEs in Eye Related Disorders System (n = 172 events)
  - n = 137 in patients treated via PPV (n = 17 patients; 56.0 years F/U)
  - n = 35 in patients treated via Orbit SDS (n = 7 patients; 9.8 years F/U)
- *No acute or delayed inflammation, no sustained increased IOP*

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*cont*)

AE Term	Via PPV / Retinotomy (n = 17)	Via Orbit SDS (n = 7)
Conjunctival Hemorrhage	9 / 17	6 / 7
Limited Subretinal Hemorrhage	1 / 17 (asymptomatic & auto resolved)	4 / 7 (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	15 / 17	1 / 7
Subretinal Pigmentation	10 / 17 (potentially a positive finding)	3 / 7 (potentially a positive finding)
Subretinal Fluid, persisting >24h	4 / 17 (all resorbed within 72h)	4 / 7 (2 of 4 resorbed <72h) One (1) patient had persistent SRF for 3 months until complete resorption without treatment
CNV	1 / 17 (began >2 yrs post-procedure) – continues to undergo regular anti-VEGF therapy and is responsive	3 / 7 - One (1) Type 2 CNV – 6M post-op at choroidal puncture site, successfully treated with single administration of an anti-VEGF; 2 others at area of GA occurred <6M post-op, both responding to treat and extend anti-VEGF
Lamellar or macular hole	2 / 17 (associated with ERM)	1 / 7 (resolved without treatment or sequelae)
Retinoschisis	2 / 17 (associated with ERM)	1 / 7
Retinal tear	2 / 17	0 / 7

Ocular SAEs	Via PPV (n = 17) - *5 events in 4 patients*	Via Orbit SDS (n = 7)
ERM	3/17, clinically significant, severe ERM requiring surgical peel, all successful	0 / 7
Retinal Detachment	2/17 (2 weeks post-procedure; not related to the study medication/RPE cells; considered to be related to surgical procedure/PPV and/or due to peripheral retinal tear/hole, 1 RD was successfully repaired, 1 failed to recover)	0 / 7

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Conjunctival Hemorrhage	9 / 17	6 / 7
Limited Subretinal Hemorrhage	1 / 17 (p=0.0145 PPV vs Orbit SDS - Fisher's exact)	4 / 7 (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	15 / 17	1 / 7
Subretinal Pigmentation	10 / 17 (potentially a positive finding)	3 / 7 (potentially a positive finding)
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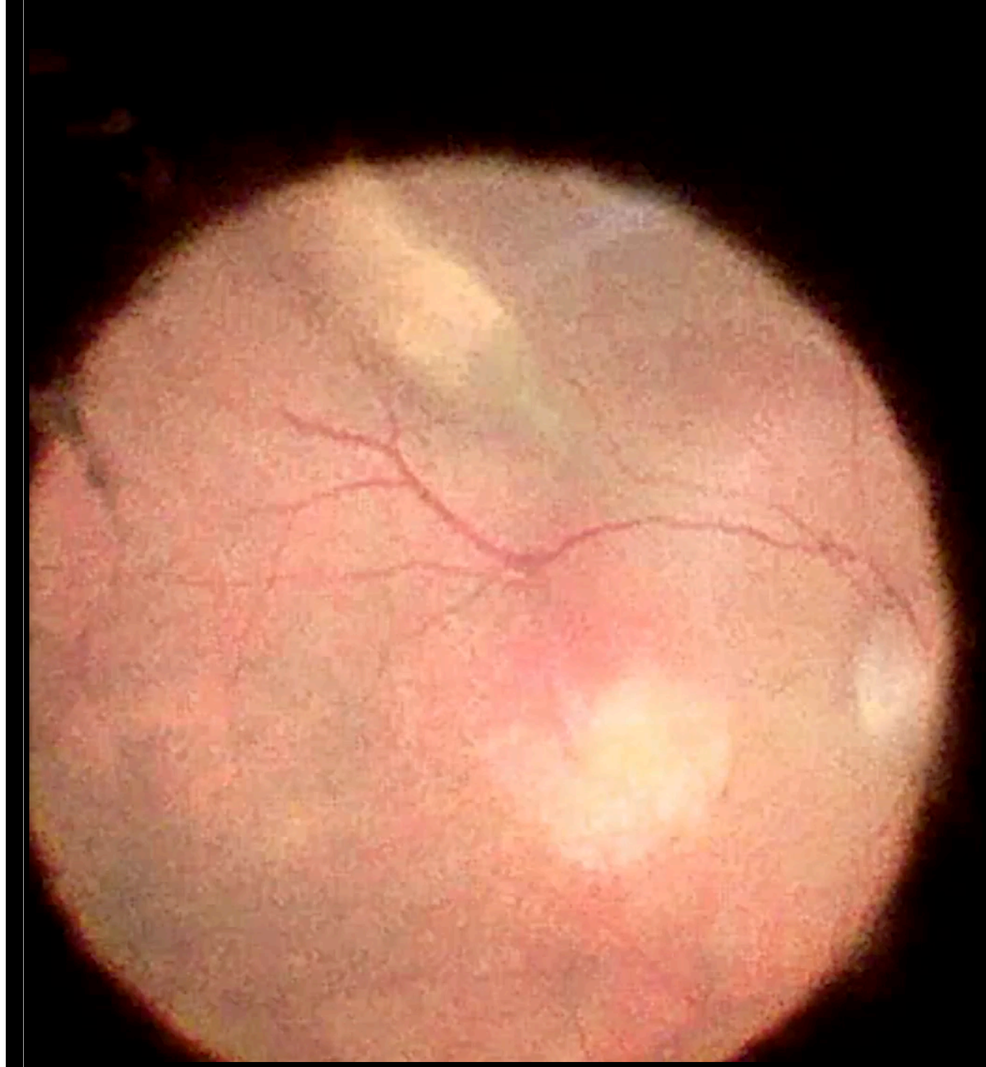
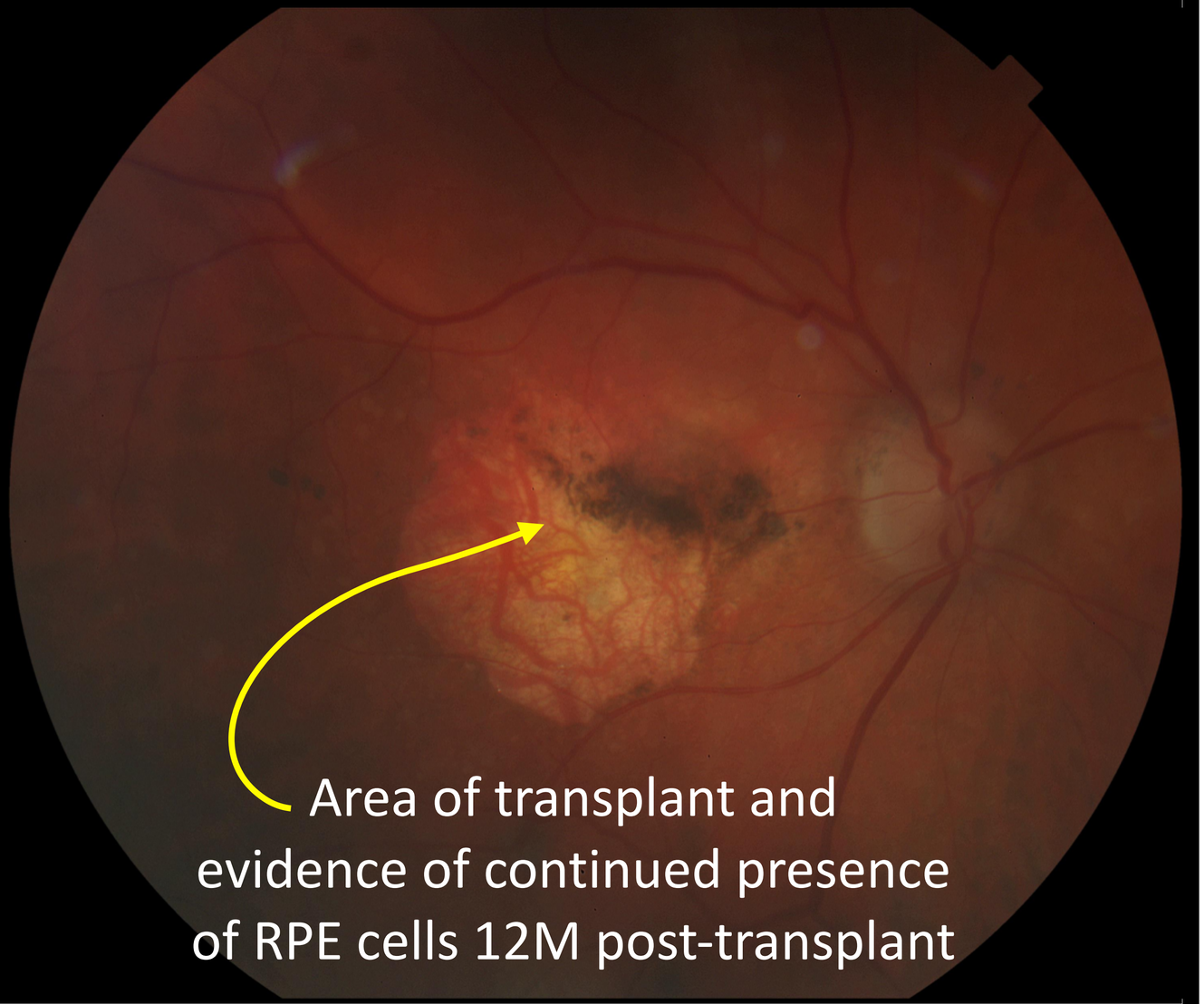
Patient #18 – 12 Months Post-op

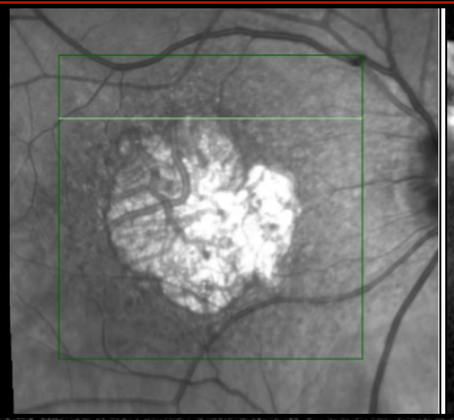
OpRegen TAI delivered via Orbit SDS

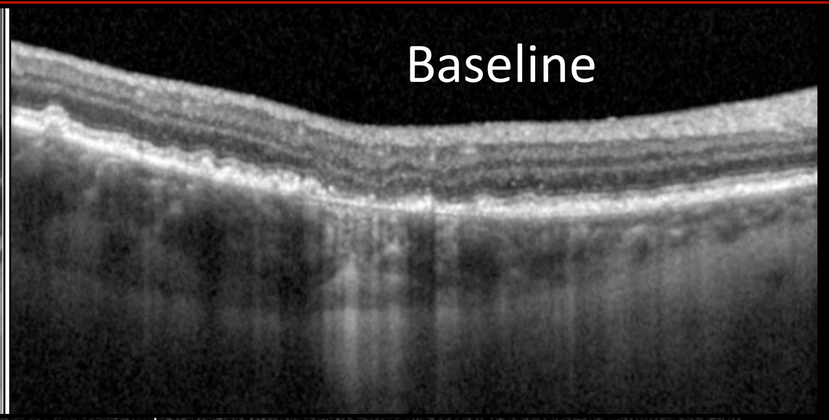


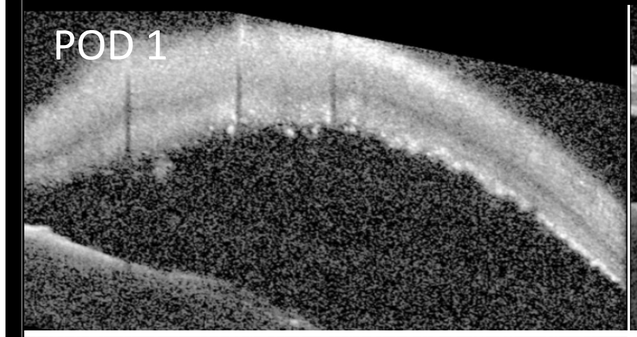


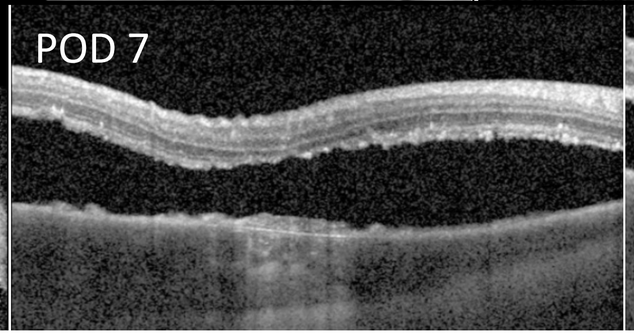
Patient #18 – SRF, Resolved w/o Intervention

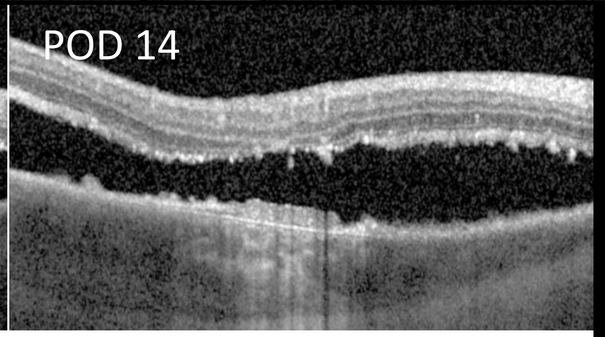
OpRegen TAI delivered via Orbit SDS

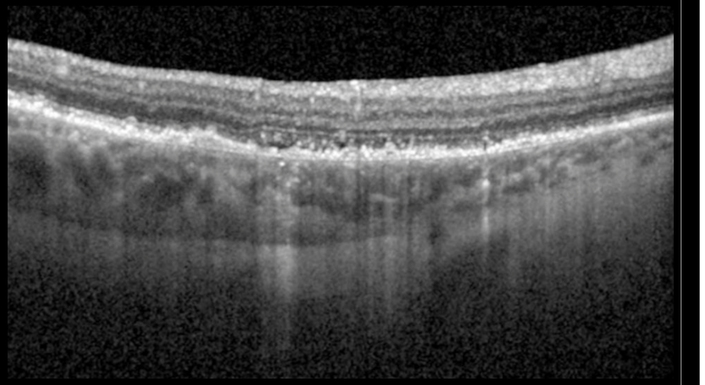


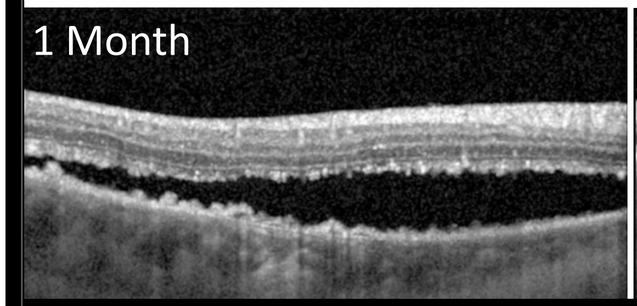


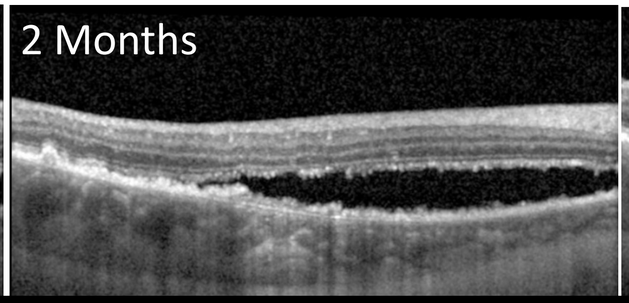


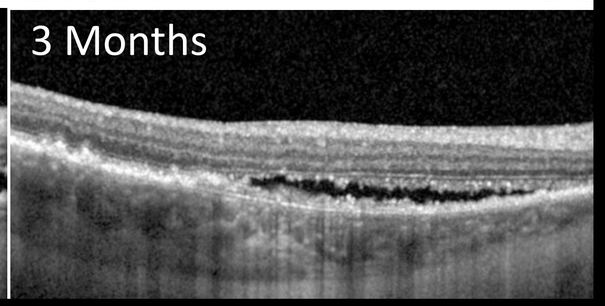






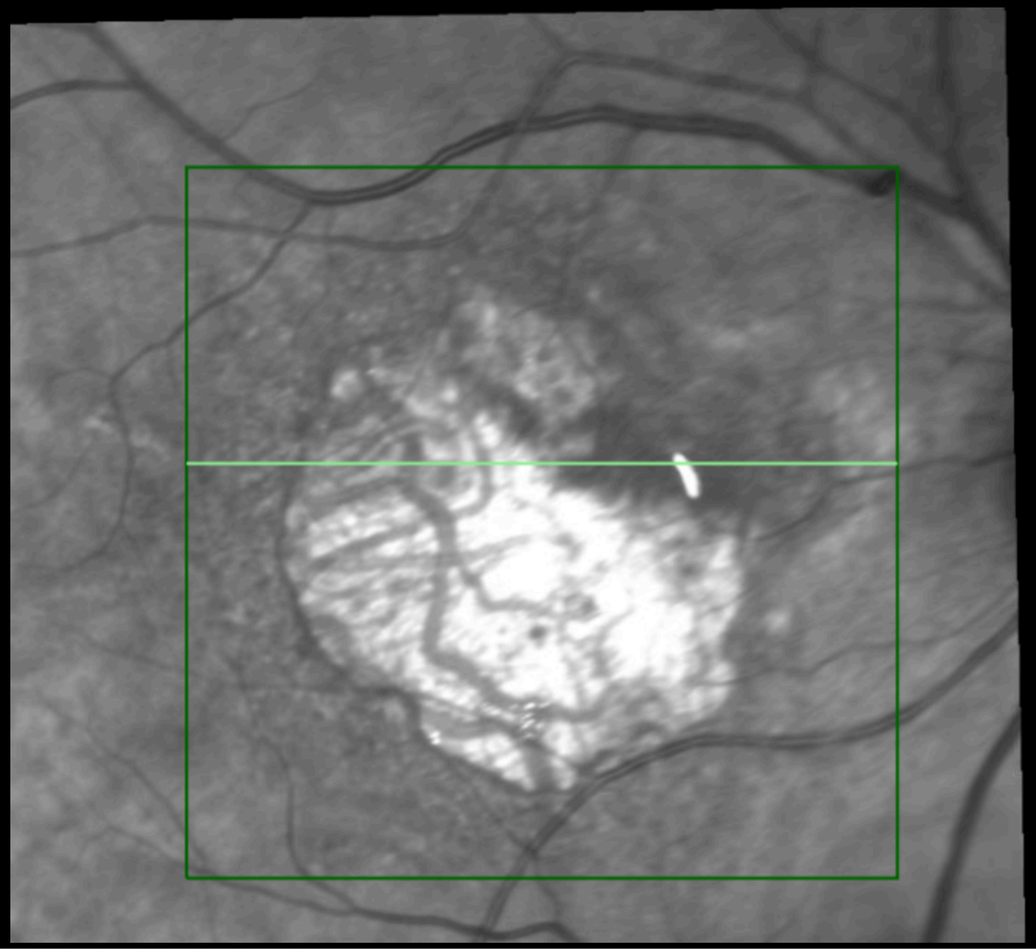


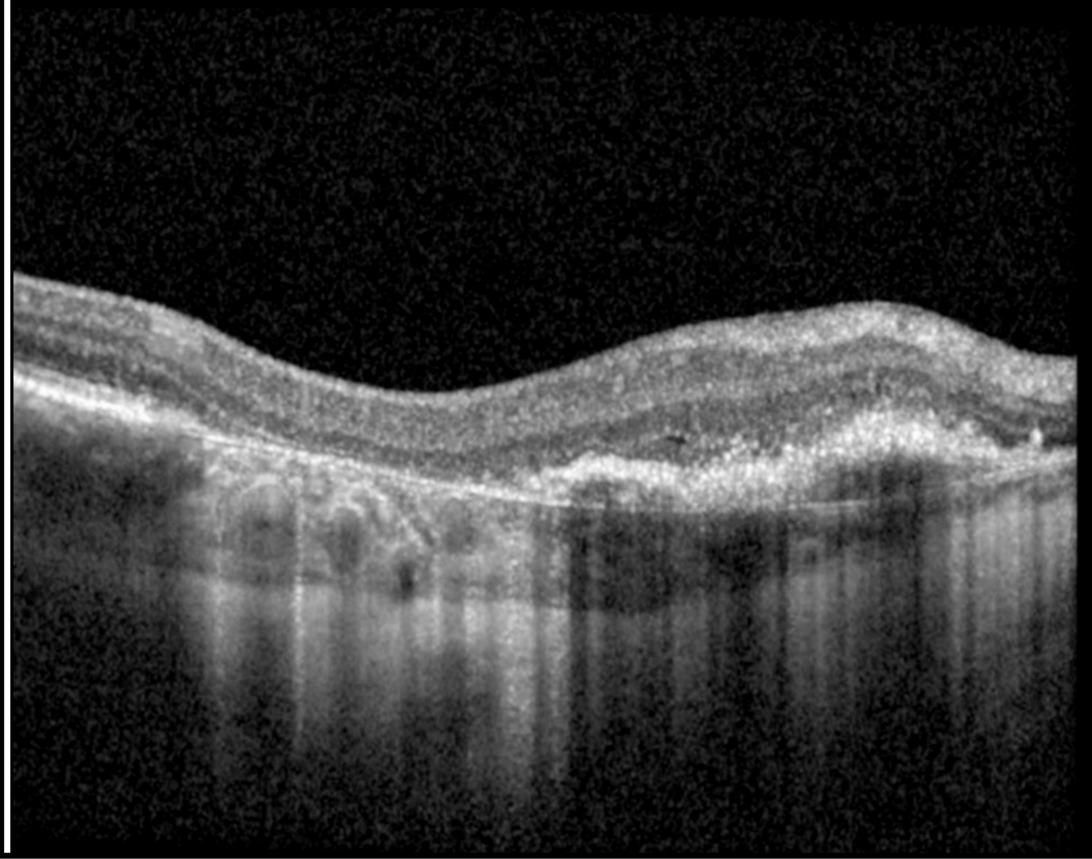




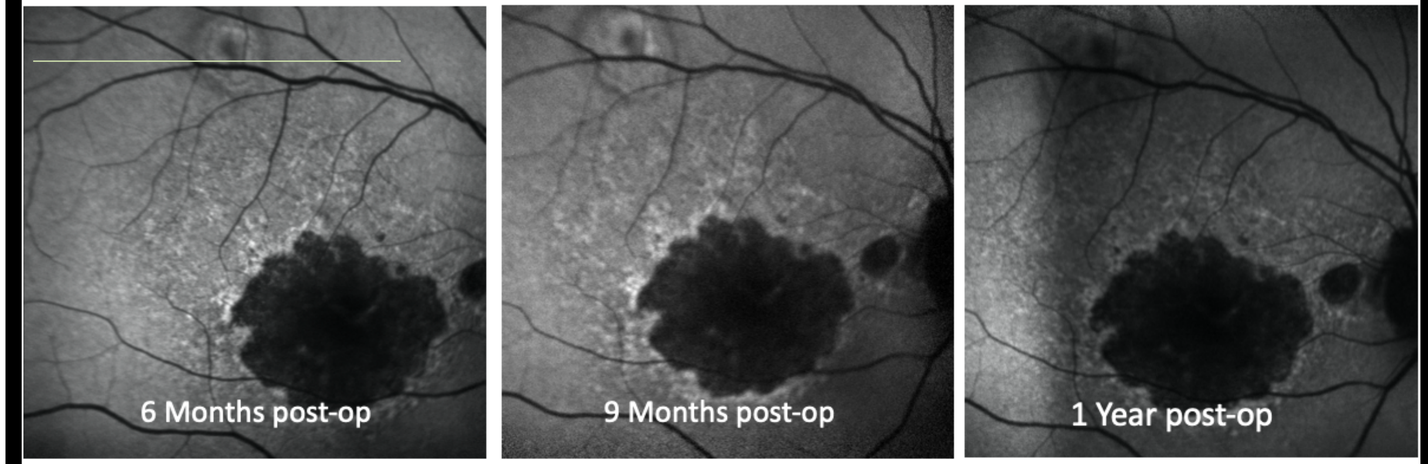
Patient #18 – CNV 15 months post-operative
OpRegen TAI delivered via Orbit SDS

Area of CNV, not in area of needle penetration, noted beginning ~6M post-op, patient responsive to “treat and extend” anti-VEGF therapy

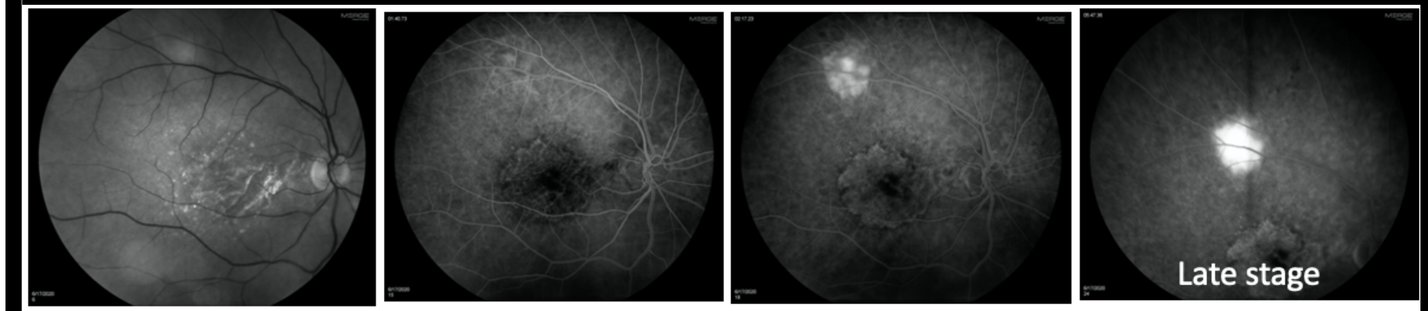




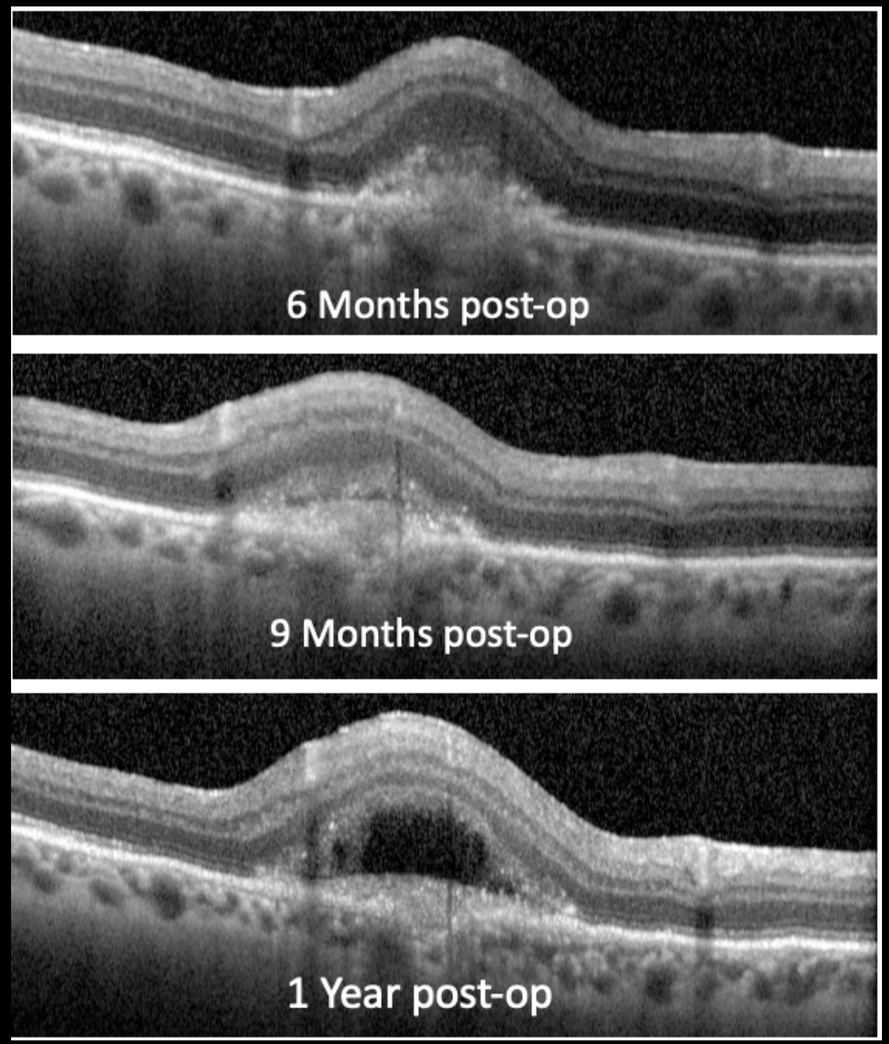
Patient #16 – Type 2 CNV Successfully Treated with anti-VEGF
OpRegen TAI delivered via Orbit SDS



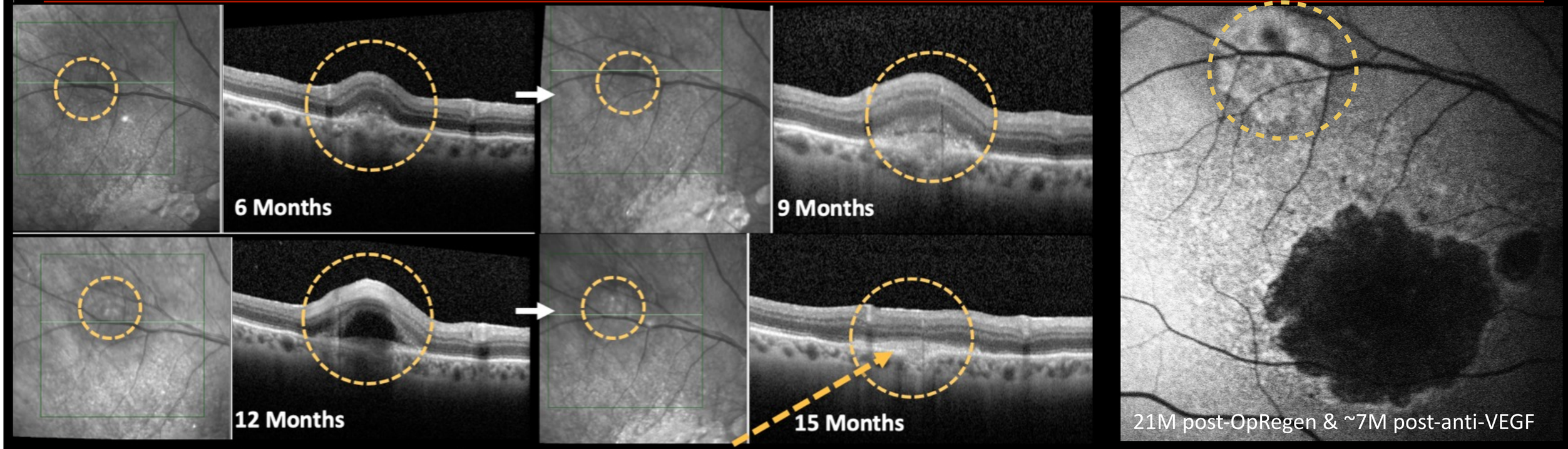
9M post-op - formation of fibrosis with early de-pigmentation in the area of Orbit SDS needle penetration, which had expanded at 1-year post-op with SRF



On FA, the lesion filling begins in the arteriovenous and venous stage, with max staining at late stage – also suggesting choroidal pathology – Type 2 CNV



Patient #16 – Type 2 CNV Successfully Treated with anti-VEGF
OpRegen TAI delivered via Orbit SDS



- Administration of single anti-VEGF at month 12
- Inactive CNVM out to 21M post-OpRegen (7 months post-anti-VEGF) follow up
- Asymptomatic scarring, likely at site of needle penetration, most clearly visible via FAF

Cohort 4
Clinical Efficacy Assessments
BCVA and GA (Structure/Function)

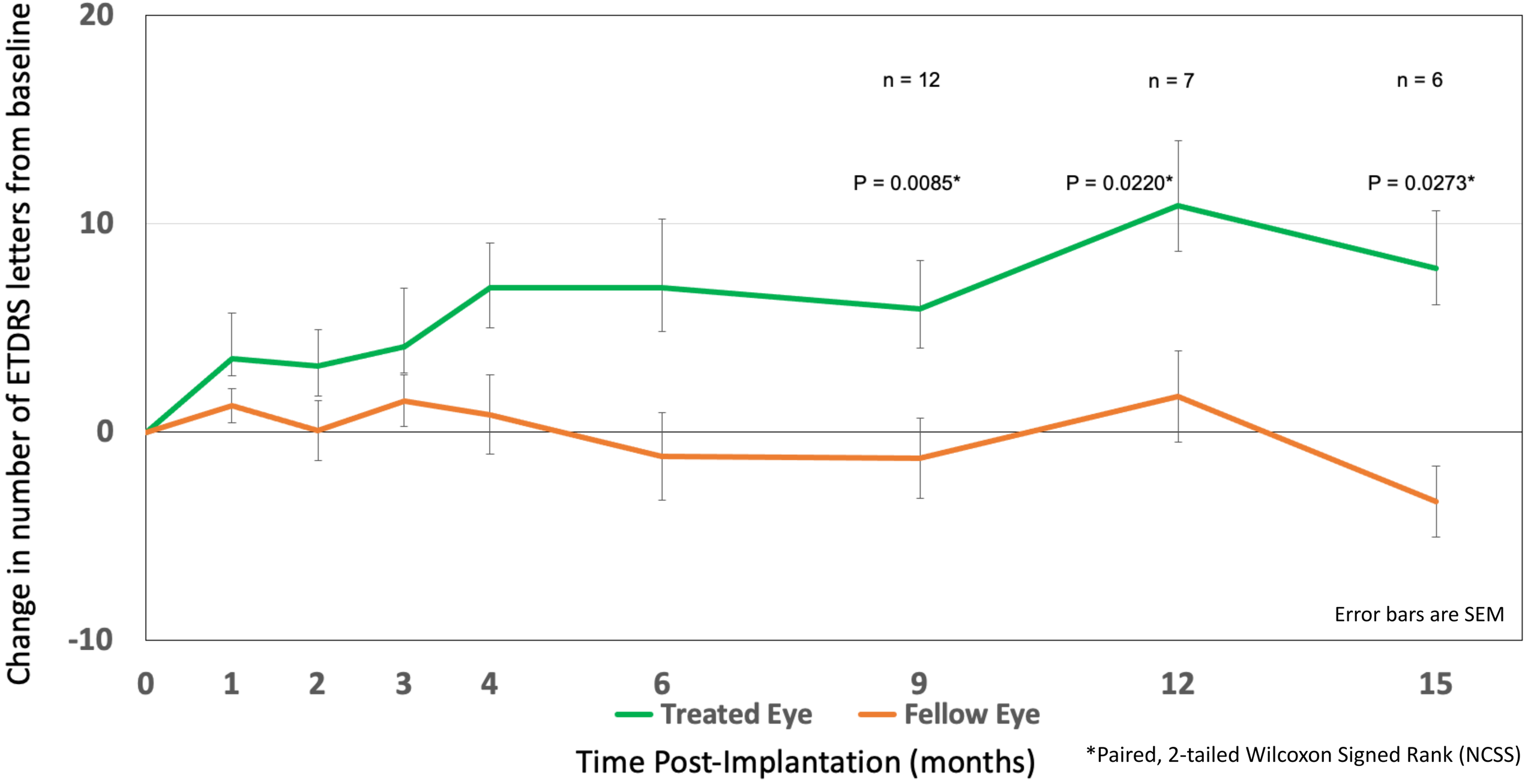
N = 12 Better VA (≤ 20/64 and ≥ 20/250)

n = 3 delivered via PPV, original OpRegen formulation

n = 2 delivered via PPV, OpRegen “Thaw and Inject”

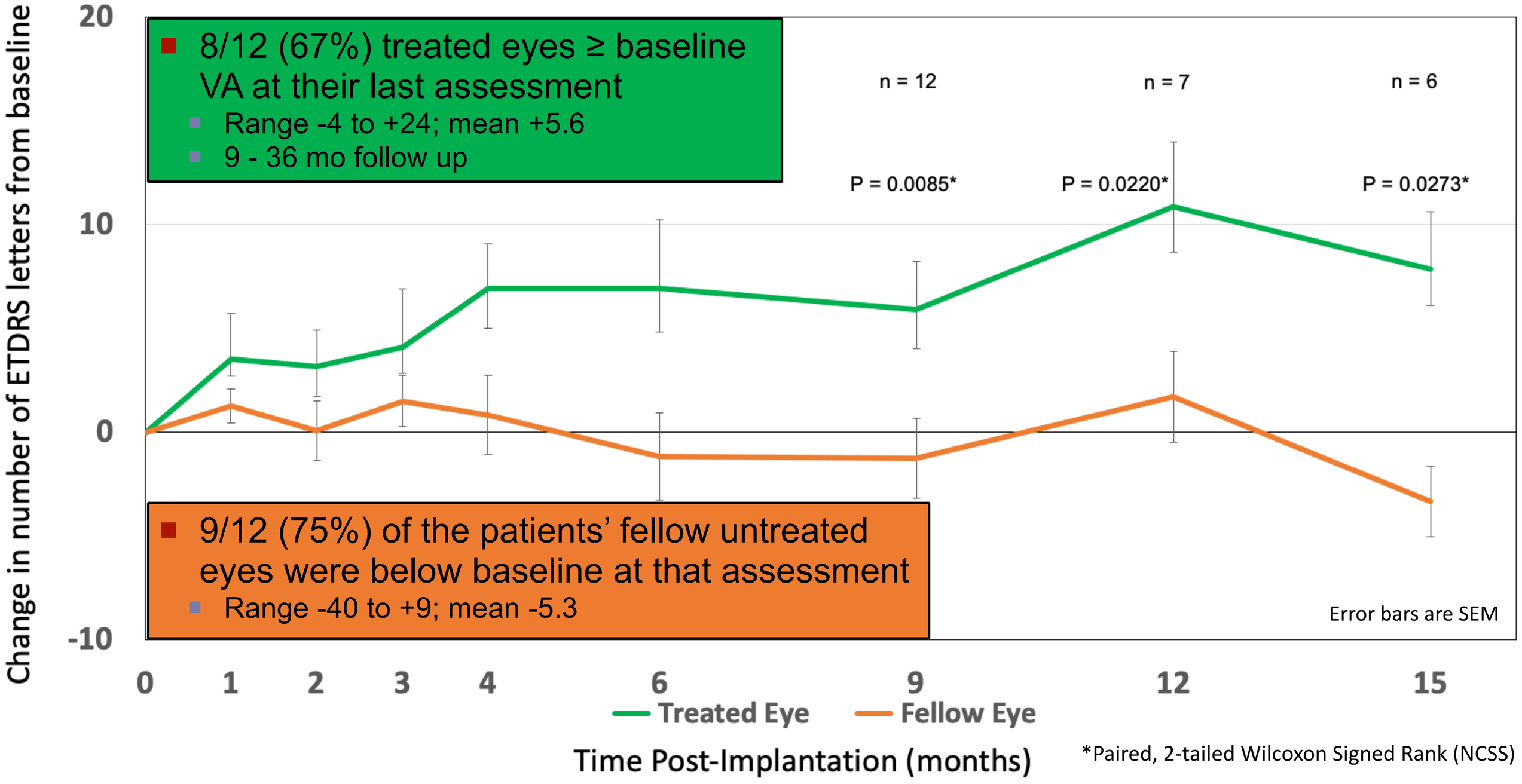
n = 7 delivered via Orbit SDS, OpRegen “Thaw and Inject”

Mean Change in Cohort 4 BCVA – Treated and Fellow Eye



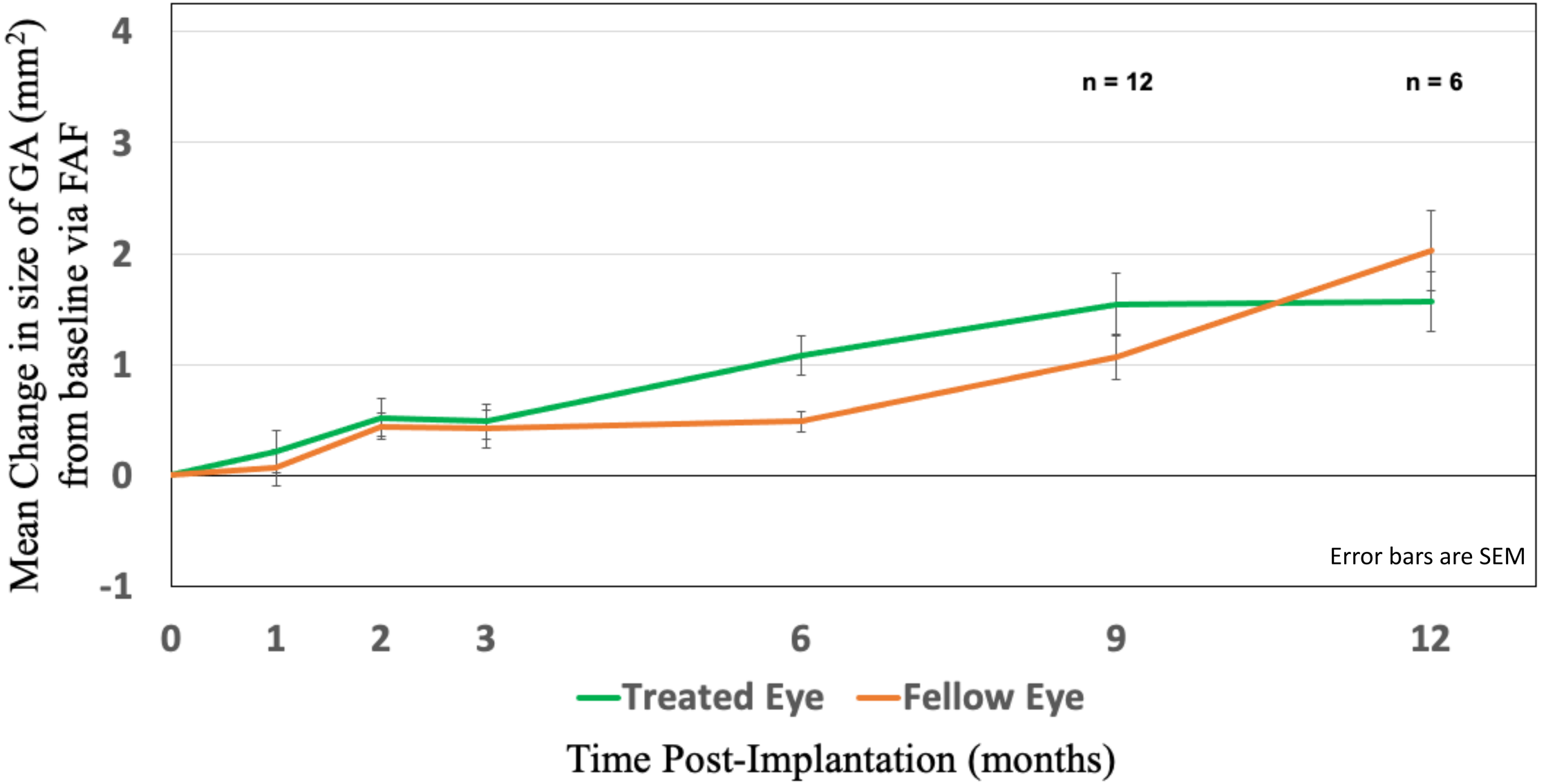
*Paired, 2-tailed Wilcoxon Signed Rank (NCSS)

Mean Change in Cohort 4 BCVA – Treated and Fellow Eye

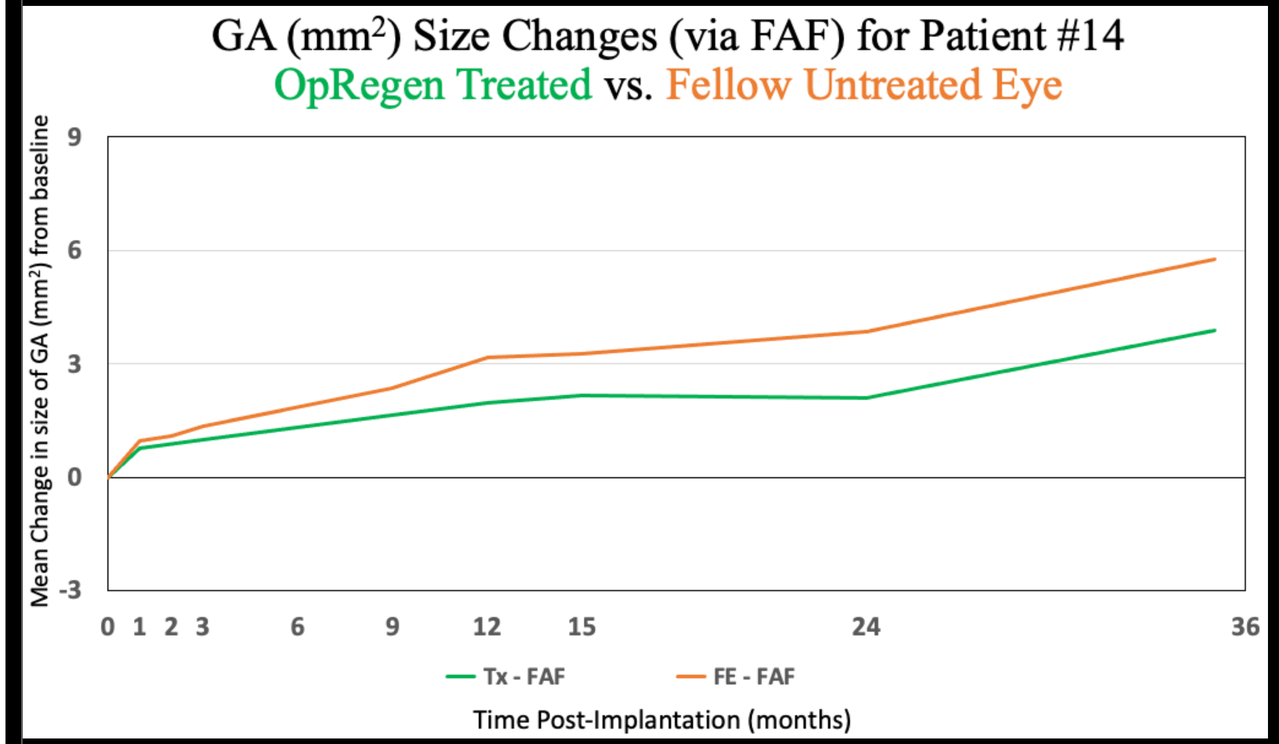


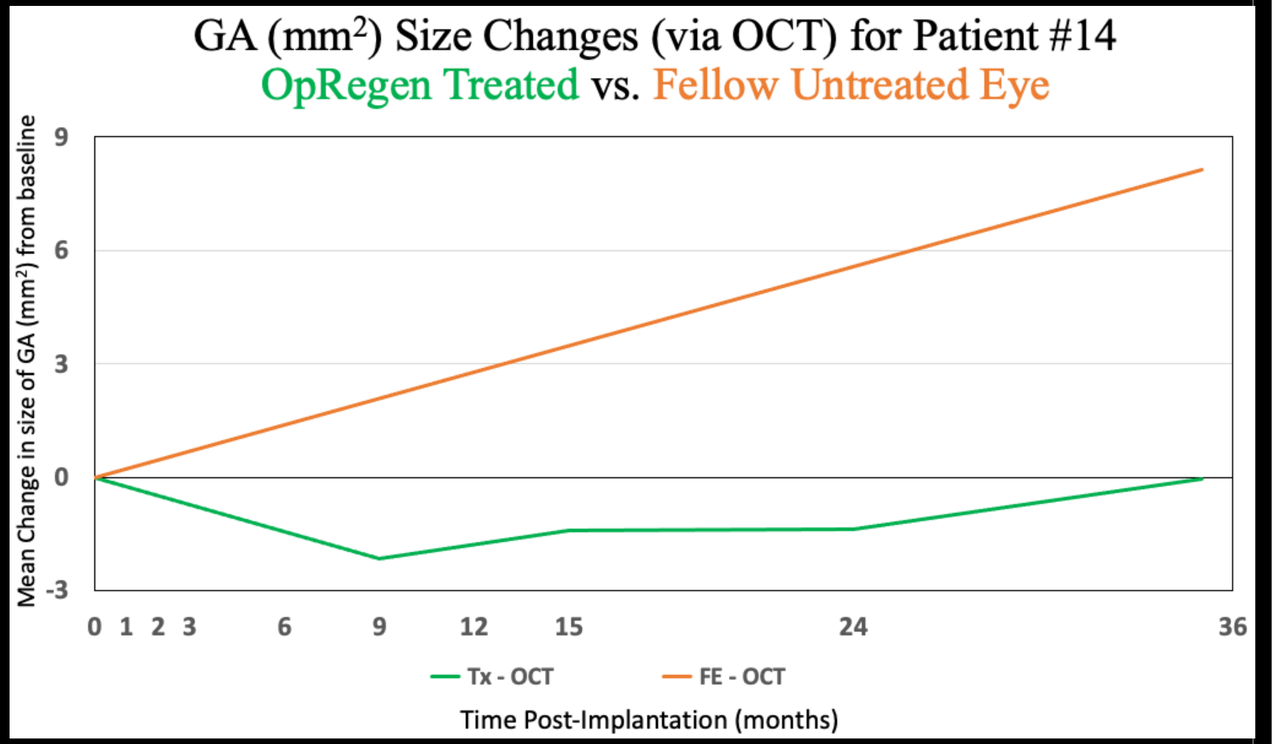
*Paired, 2-tailed Wilcoxon Signed Rank (NCSS)

Mean Change (SEM) in Cohort 4 GA (mm^2) via FAF Treated and Fellow Eye



Patient #14 – Changes in GA Size (FAF vs OCT)
OpRegen original formulation delivered via PPV



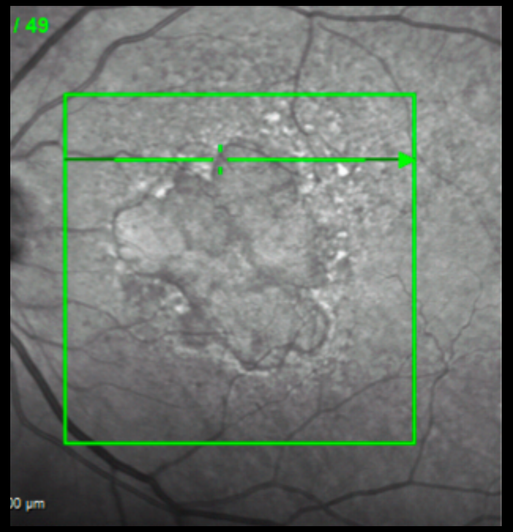


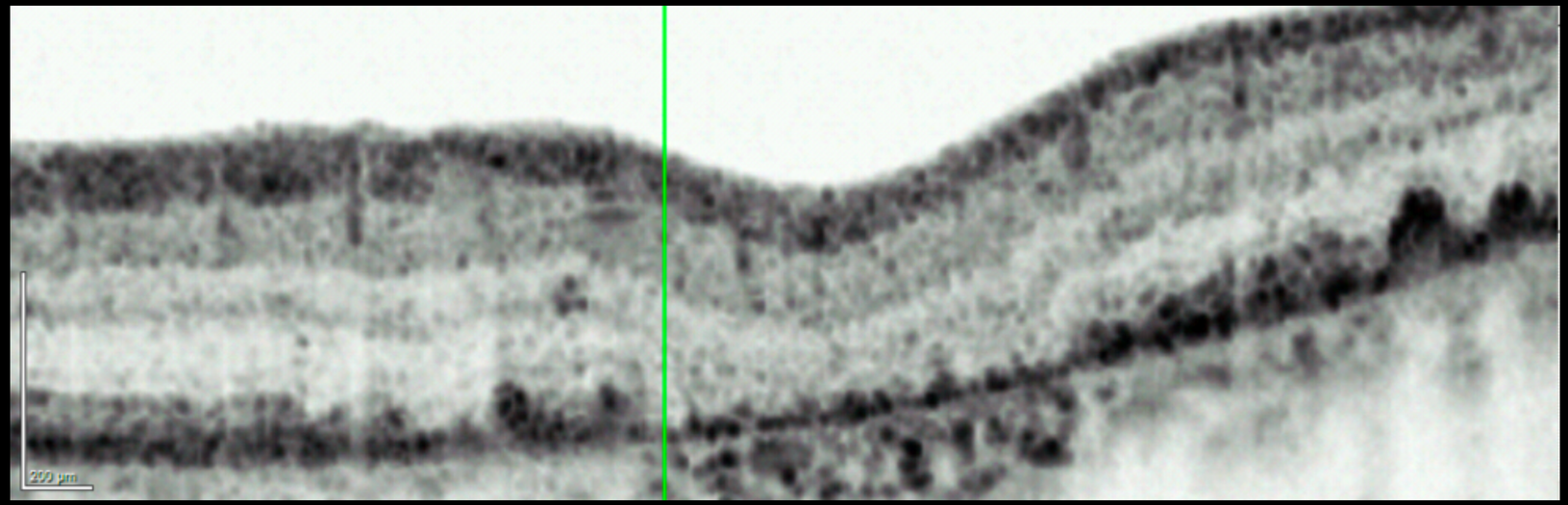
- External limiting membrane (ELM), outer nuclear layer (ONL), and retinal pigment epithelium (RPE) layers mapped
- All elements had to be present to determine the total area of atrophy after OpRegen
- FAF is a poor tool to assess RPE cell therapy due to the lack of lipofuscin and other accumulated waste products in the newly implanted cells, which are therefore not detectable via FAF

OCT analyses courtesy of Jordi Monés, MD, PhD

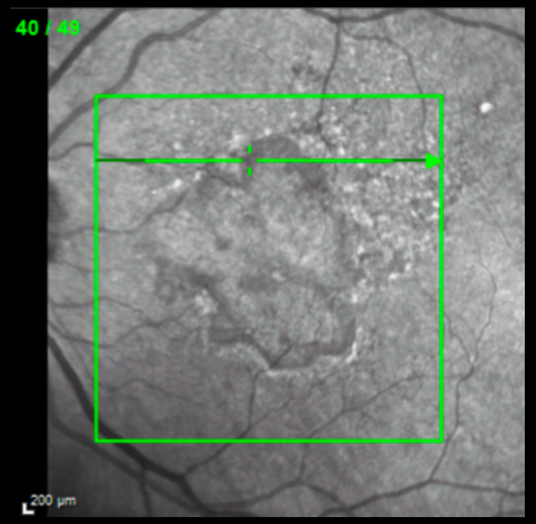
Patient #14 – Changes in Area of Atrophy Post-Tx
OpRegen original formulation delivered via PPV

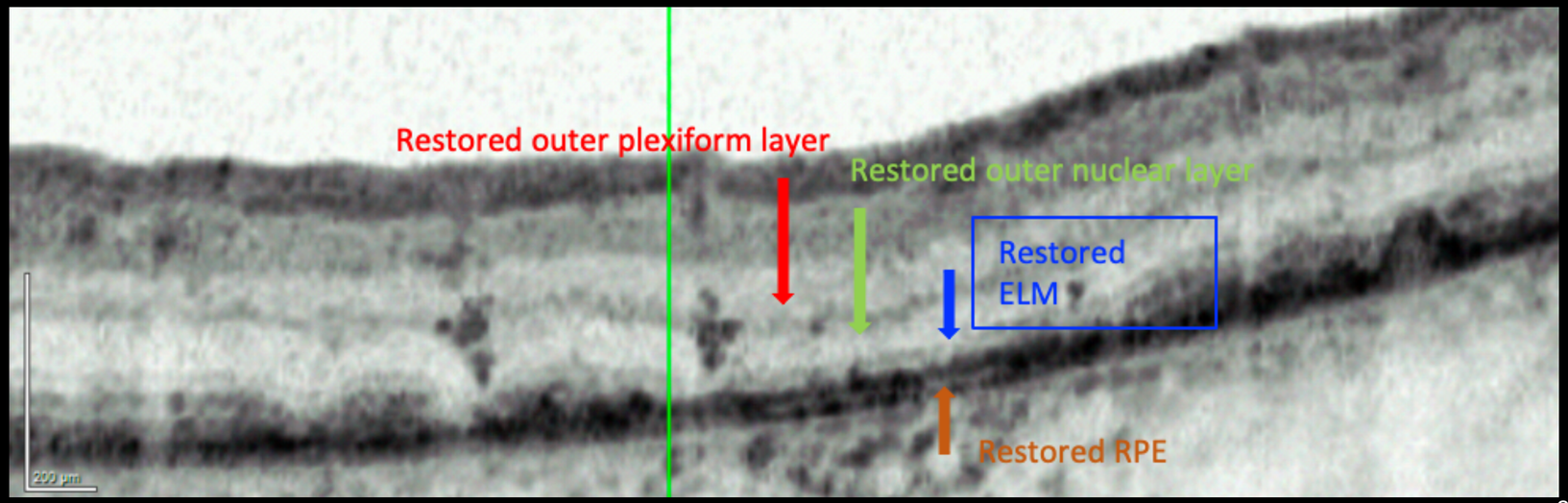
Baseline
54 letters read
(~20/80)





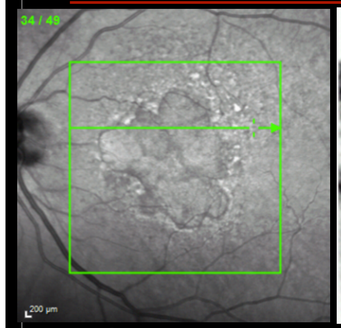
Month 9
61 letters read
(~20/63)

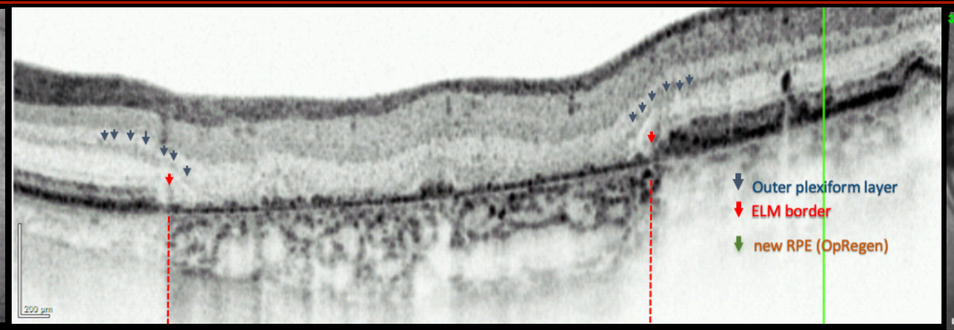




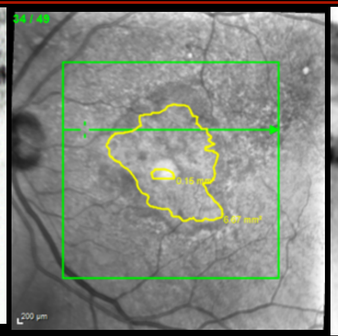
OCT analyses courtesy of Jordi Monés, MD, PhD

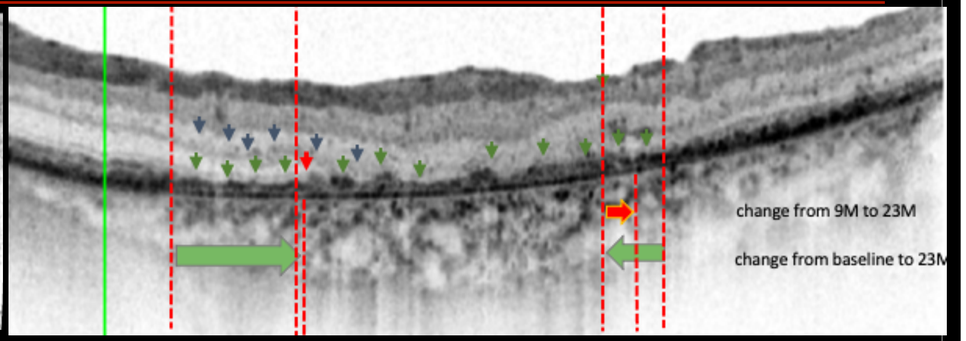
Patient #14 – Changes in Area of Atrophy Post-Tx
OpRegen original formulation delivered via PPV



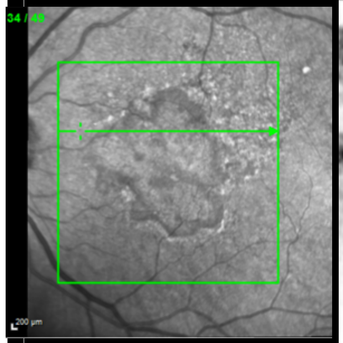


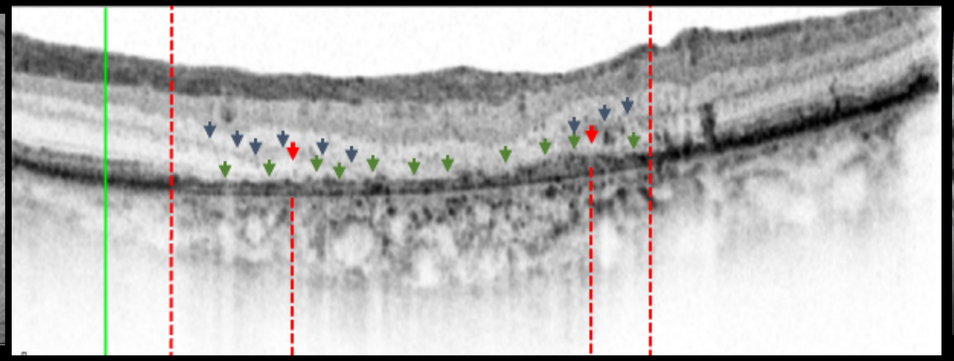
Baseline
54 letters (~20/80)



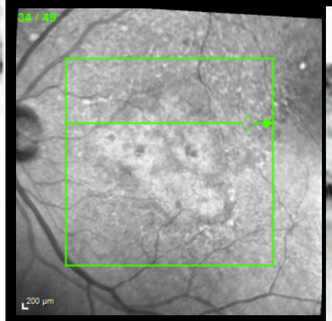


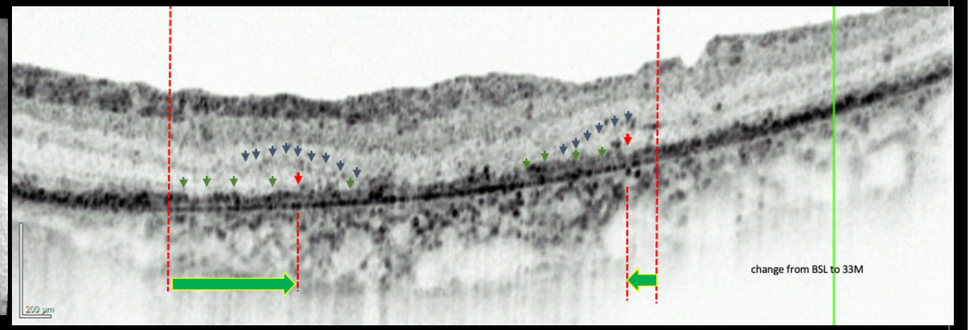
Month 23
66 letters (~20/50)





Month 9
61 letters (~20/63)





Month 33
50 letters (~20/100)

Outer plexiform layer
ELM border
New RPE layer

OCT analyses courtesy of Jordi Monés, MD, PhD

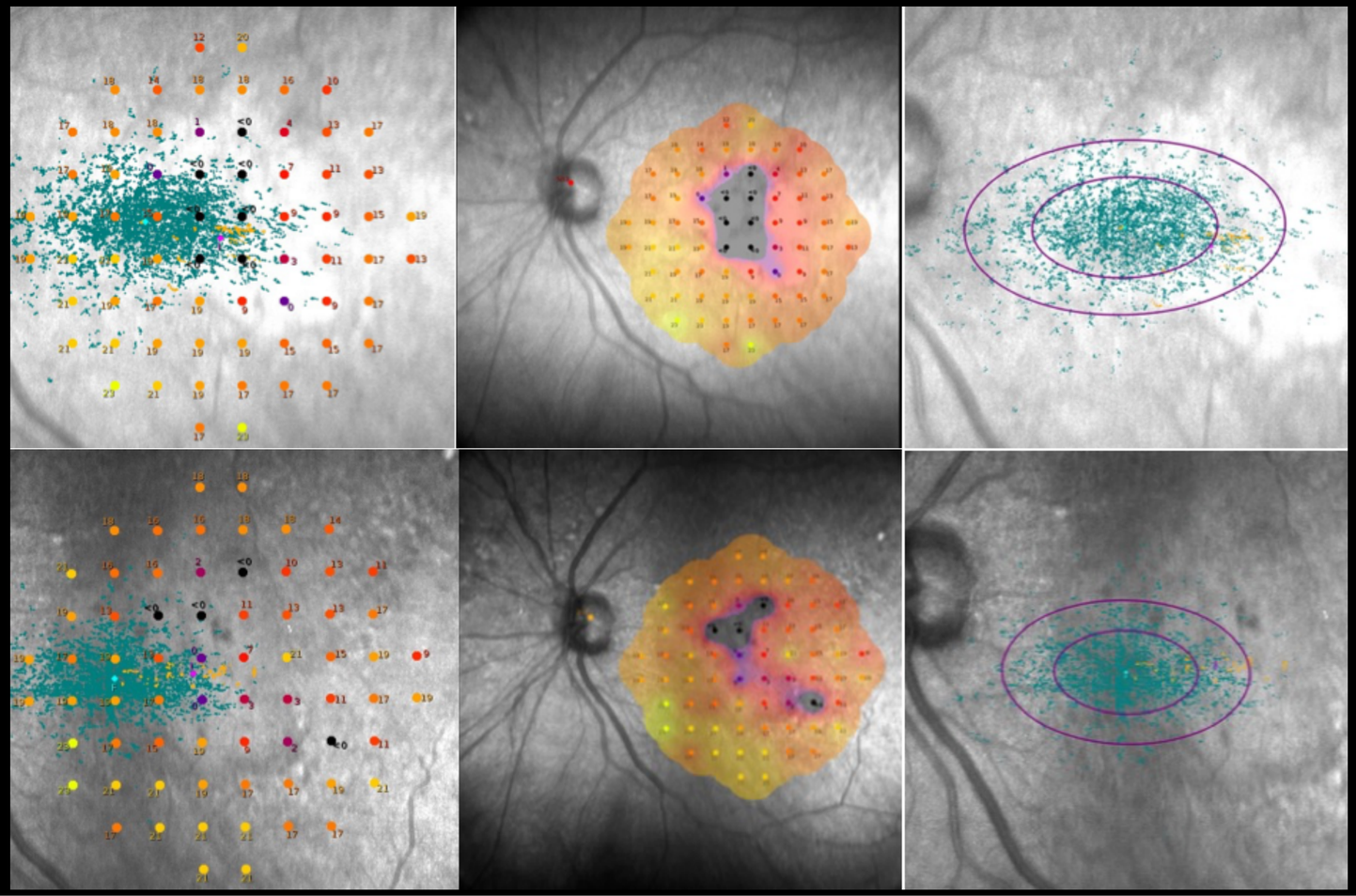
Patient #14 – Changes to Microperimetry
OpRegen original formulation delivered via PPV

Month 0 Baseline
54 letters (~20/60)

Unable to fixate to perform microperimetry.

Month 23
66 letters
(~20/50)

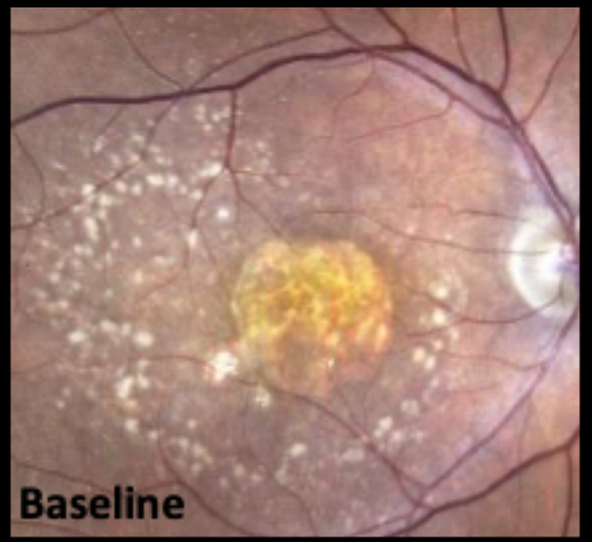
Month 33
50 letters
(~20/100)

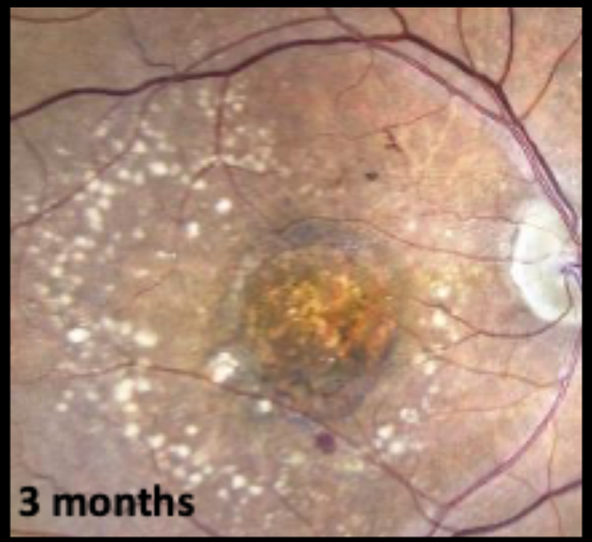


Patient #21 – Changes to Area of GA & Drusen

OpRegen TAI delivered via PPV

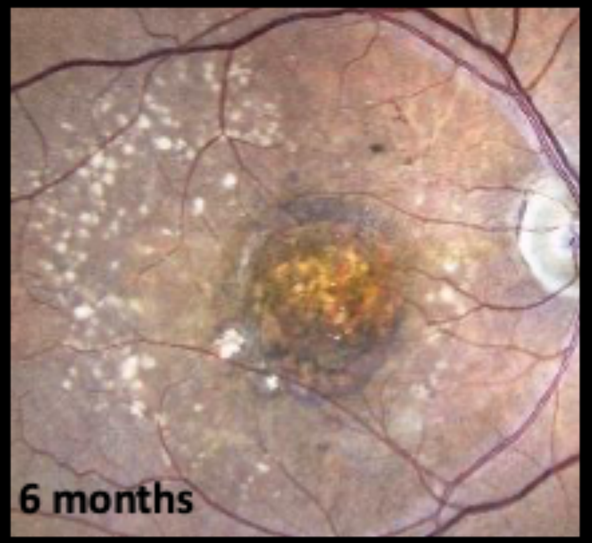
Baseline
49 letters
(~20/100)

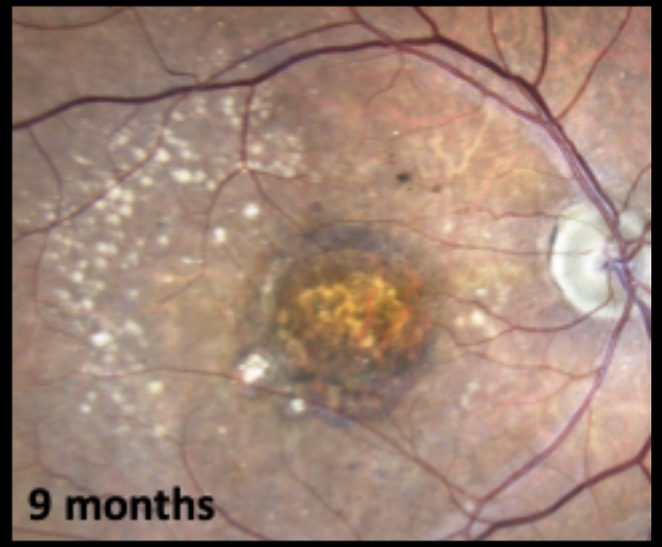




Month 3
45 letters
(~20/125)

Month 6
51 letters
(~20/100)



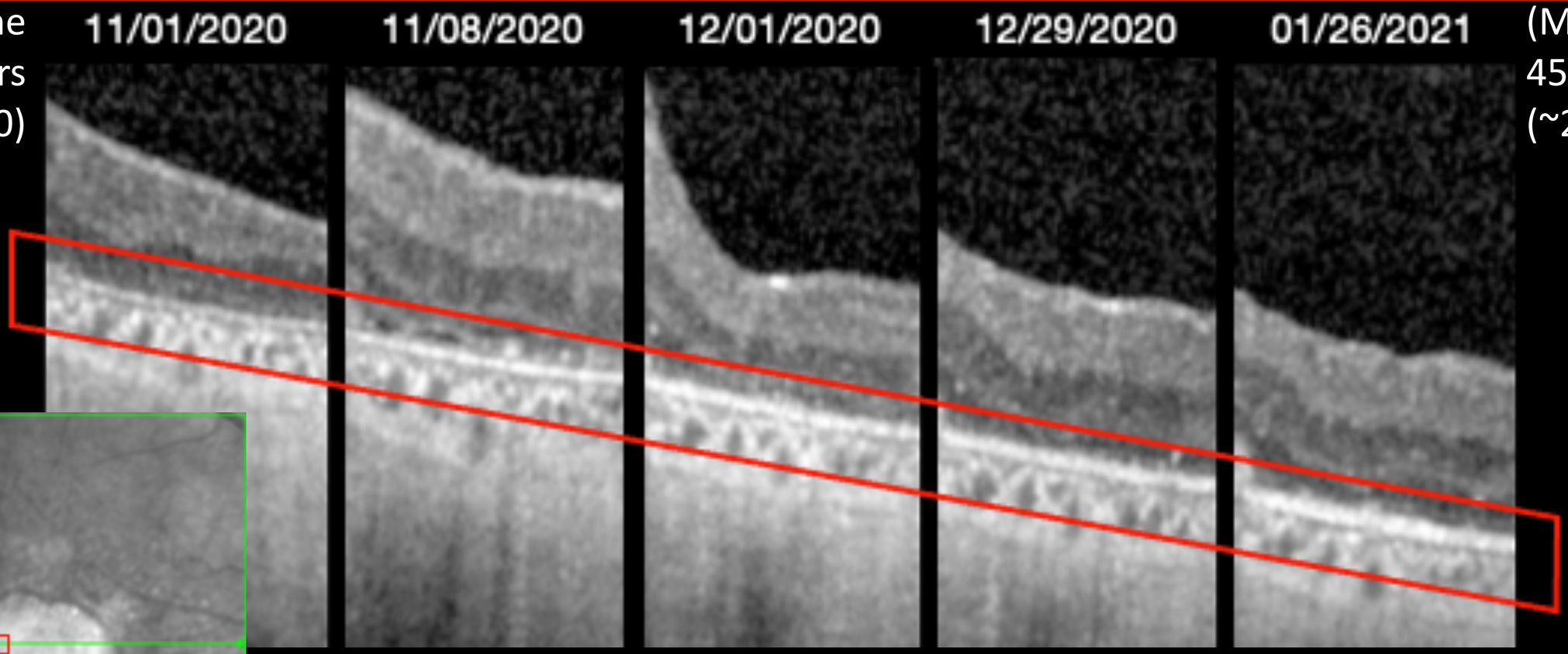


Month 9
50 letters
(~20/100)

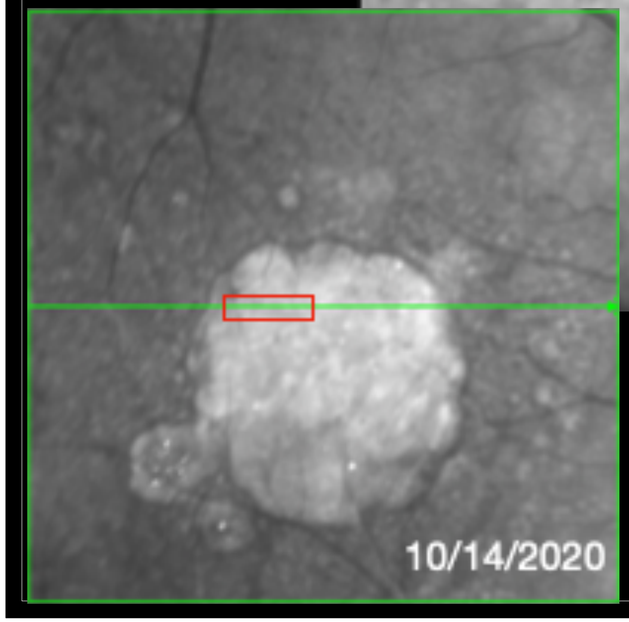
Patient #21 – RPE / Bruch's Thickening

OpRegen TAI delivered via PPV

Baseline
49 letters
(~20/100)



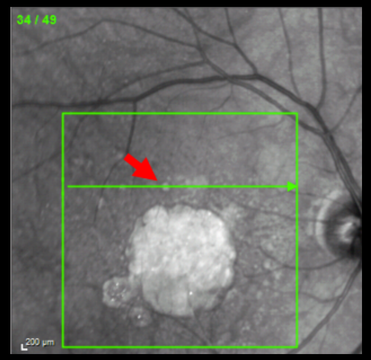
(Month 3)
45 letters
(~20/125)

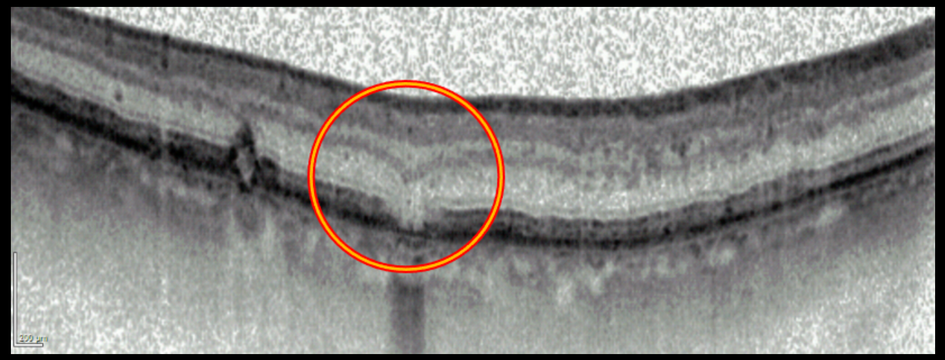


OCT analyses courtesy of Brandon Lujan, MD

Patient #21 – Changes to Areas of iRORA*
OpRegen TAI delivered via PPV

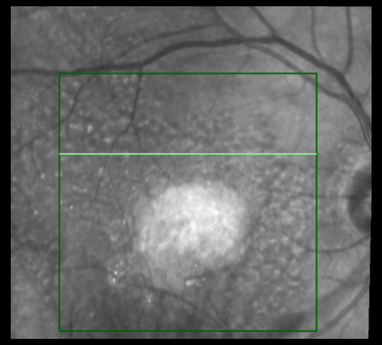
Baseline
49 letters
(~20/100)

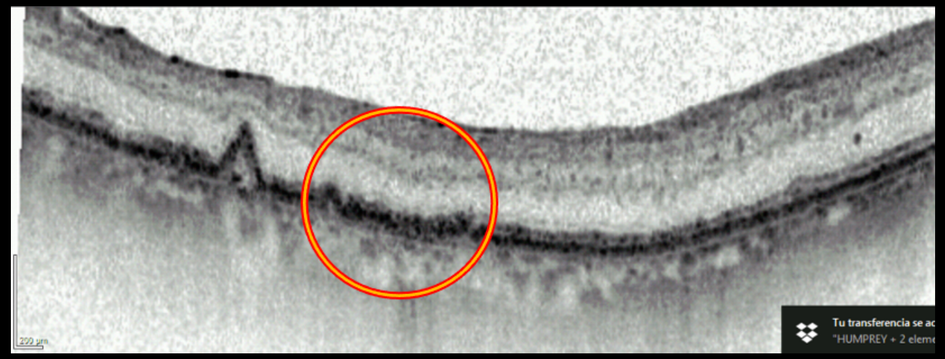




Repair of RPE and ELM discontinuation, and improvement of OPL subsidence

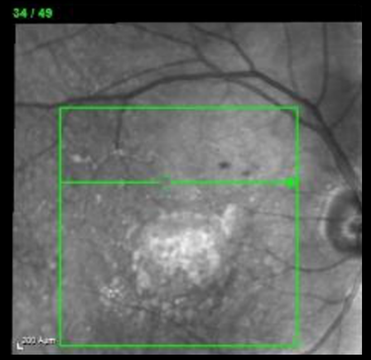
Month 2
40 letters
(~20/160)

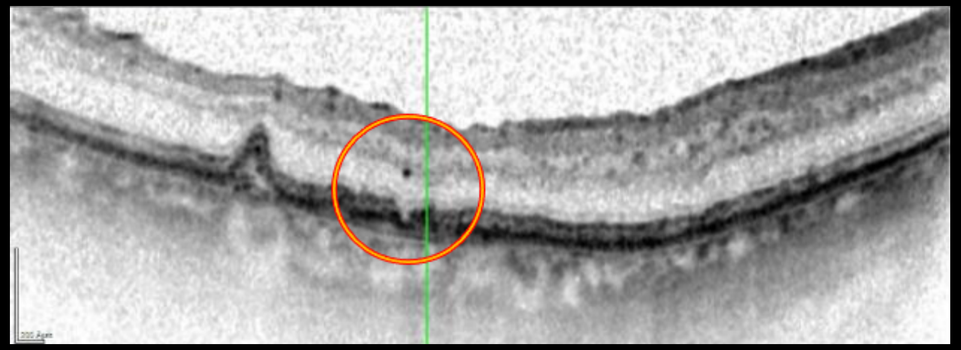




Features suggesting outer retinal regeneration

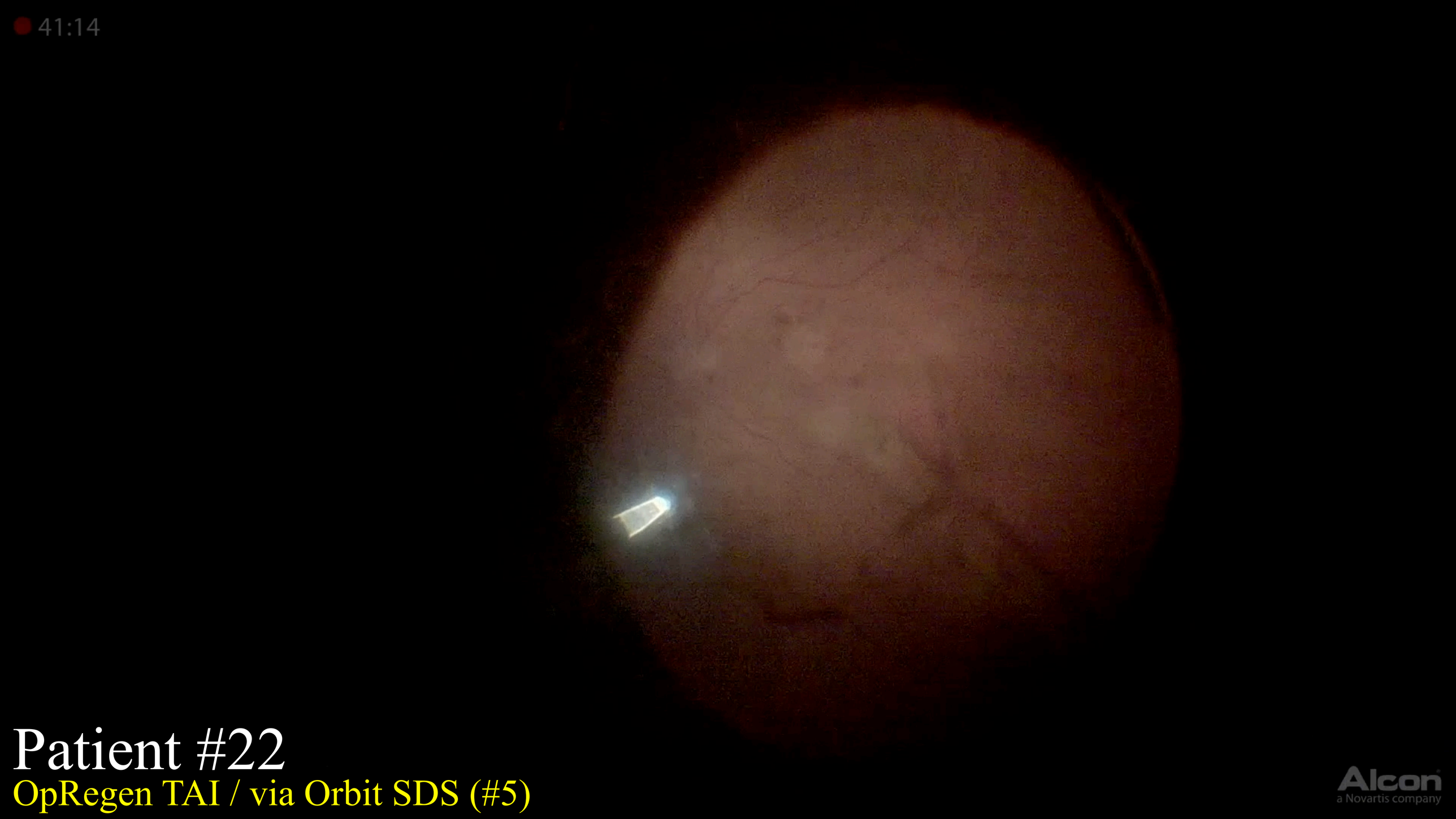
Month 6
51 letters
(~20/100)





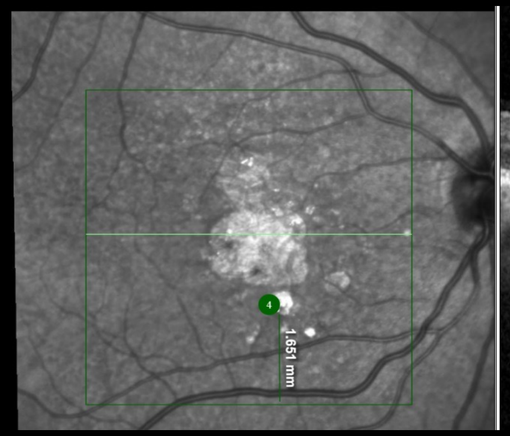
*Incomplete retinal pigment epithelial and outer retinal atrophy

OCT analyses courtesy of Jordi Monés, MD, PhD

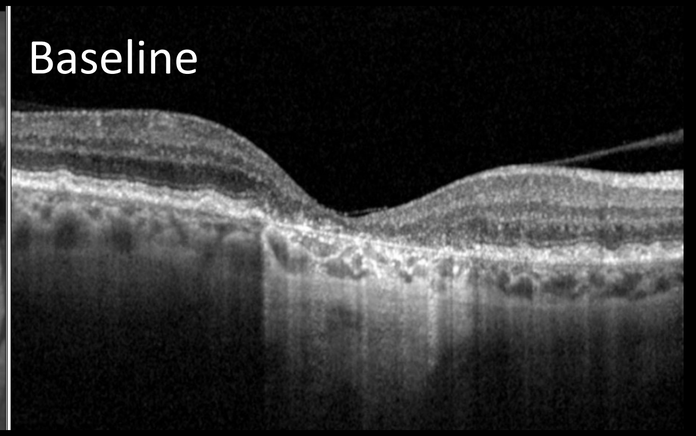

41:14
Patient #22
OpRegen TAI / via Orbit SDS (#5)
Alcon
a Novartis company

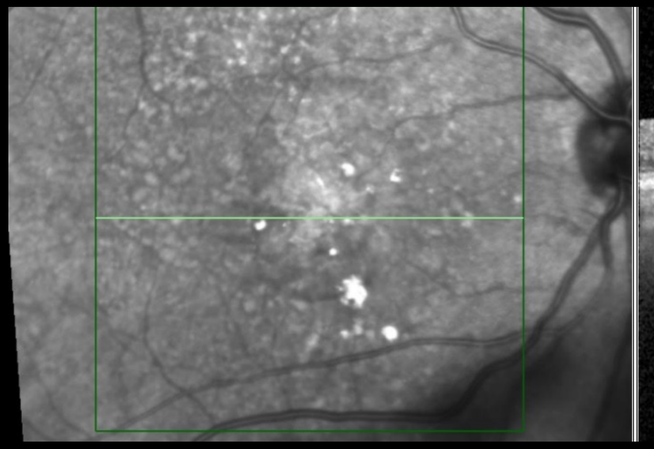
Patient #22 – Autoresolving Incomplete Macular Hole

OpRegen TAI delivered via Orbit SDS

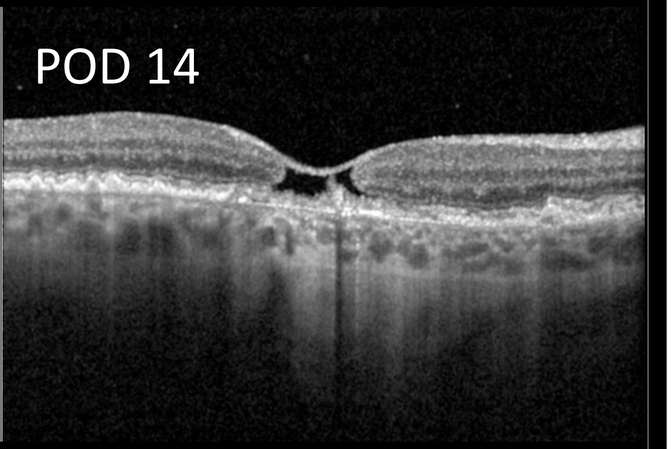


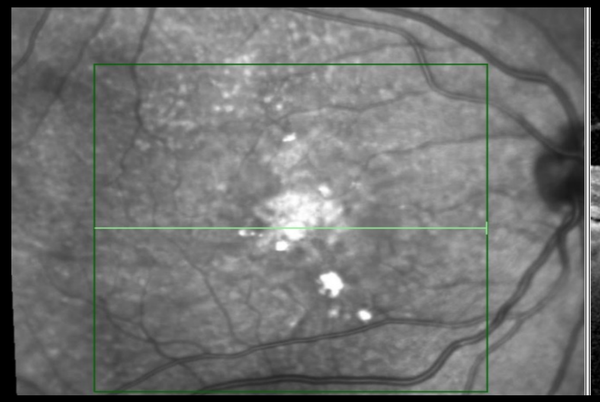
Baseline



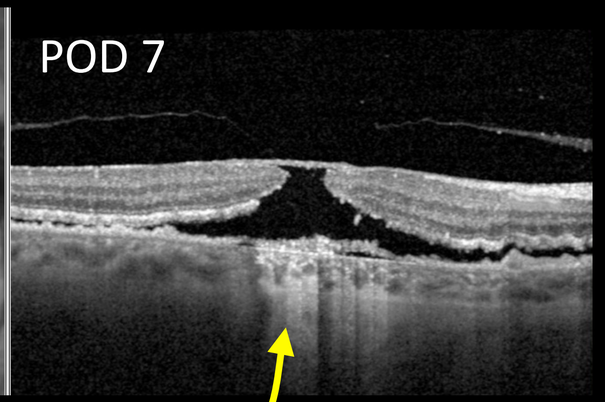


POD 14

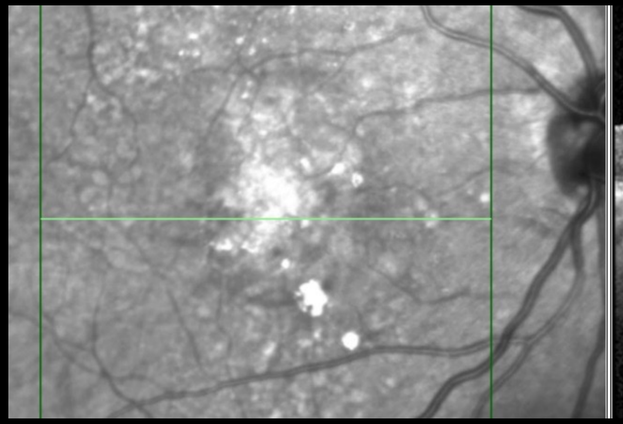




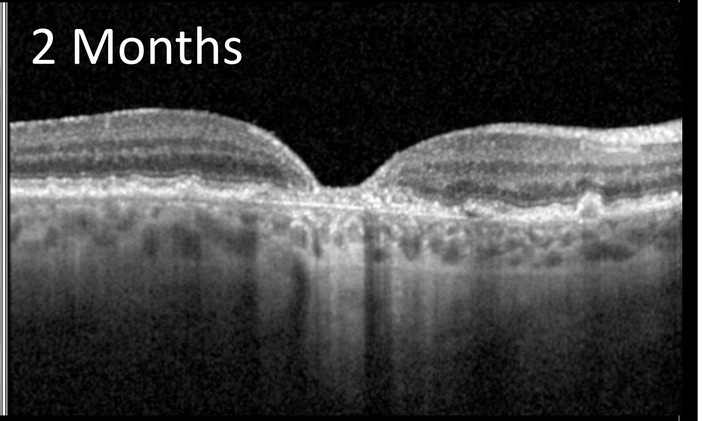
POD 7



Incomplete macular hole with hyaloid & ILM bridge



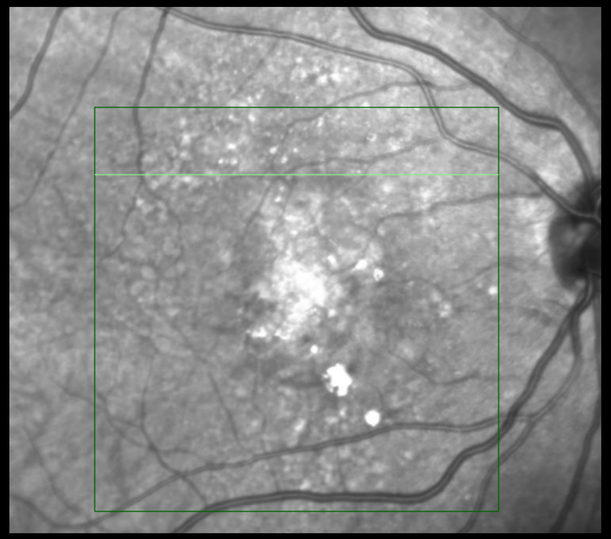
2 Months

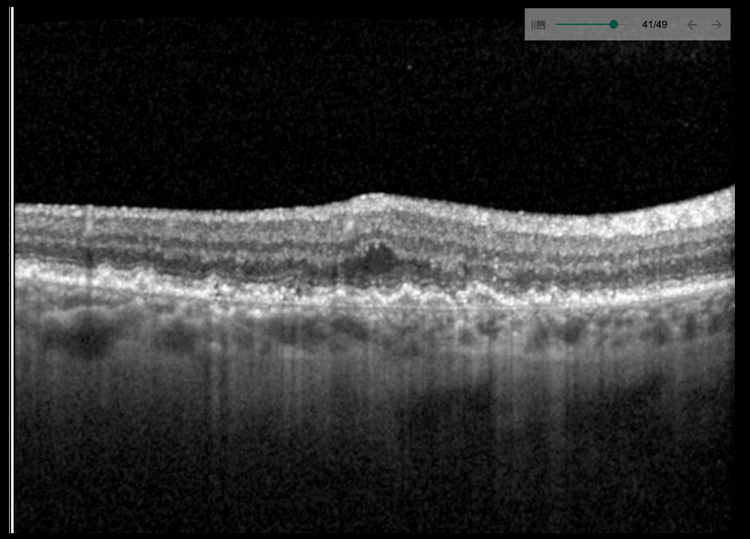


Patient #22 – CNV responsive to anti-VEGF Tx

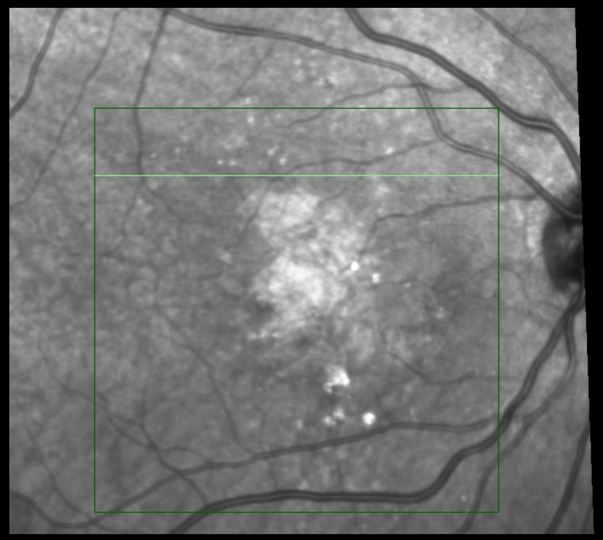
OpRegen TAI delivered via Orbit SDS

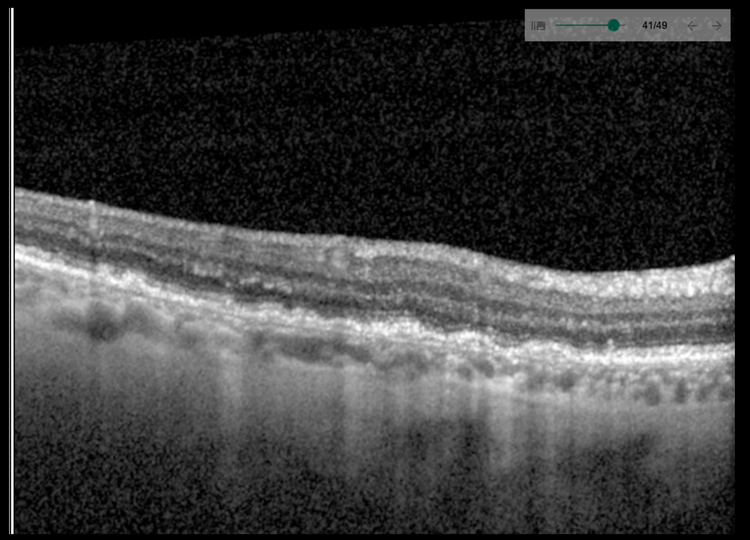
Month 2
56 letters read
(~20/80)





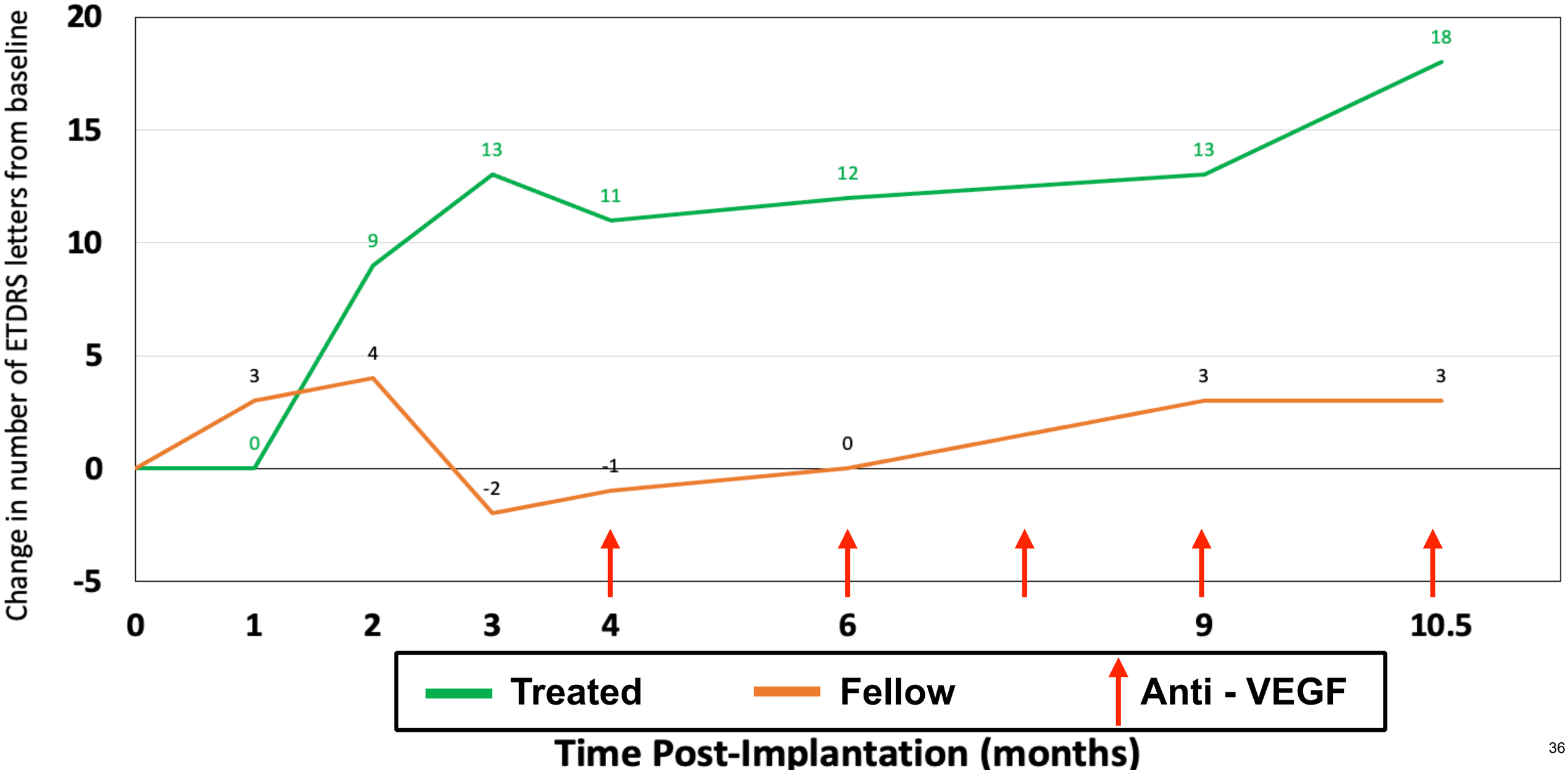
Month 9
60 letters read
(~20/63)





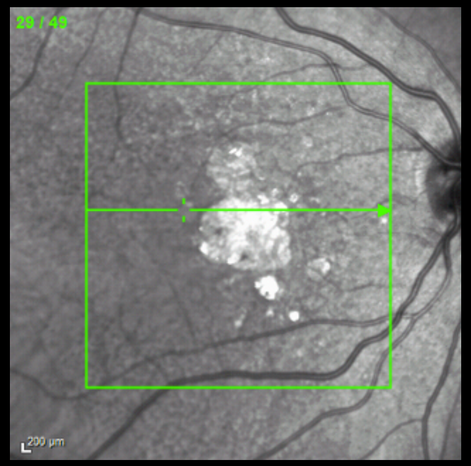
BCVA Changes for Patient #22 (via Orbit SDS)

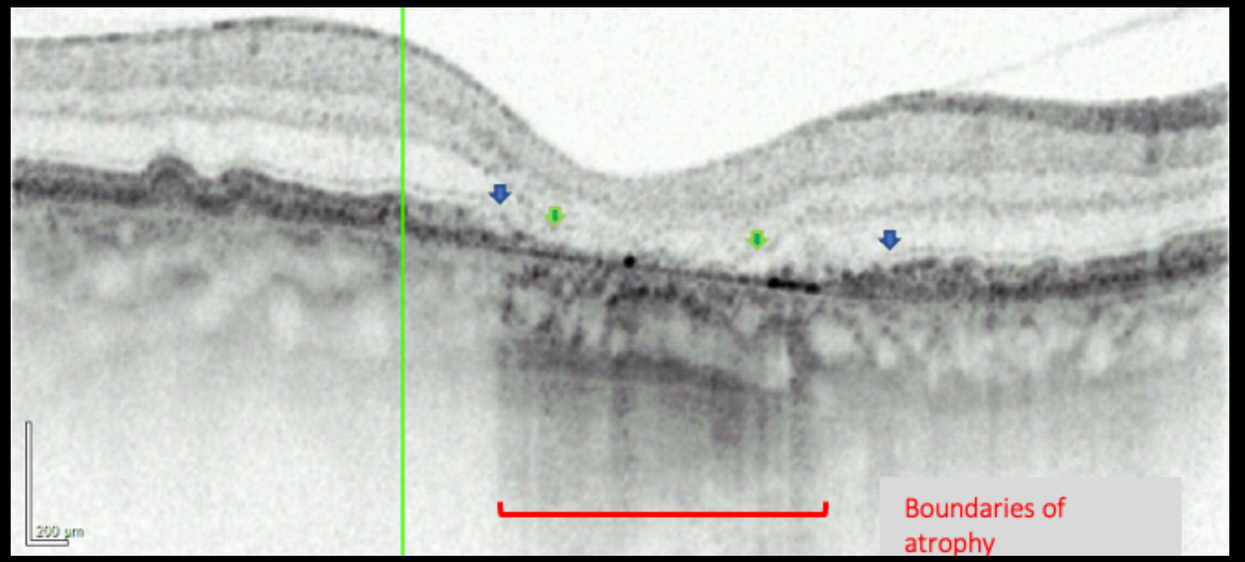
Treated vs. Fellow Eye



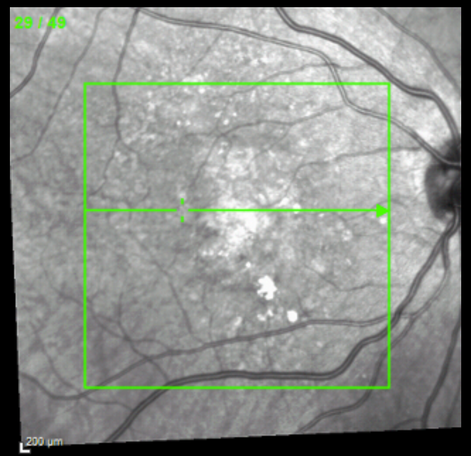
Patient #22 – Structural Changes to area of GA
OpRegen TAI delivered via PPV

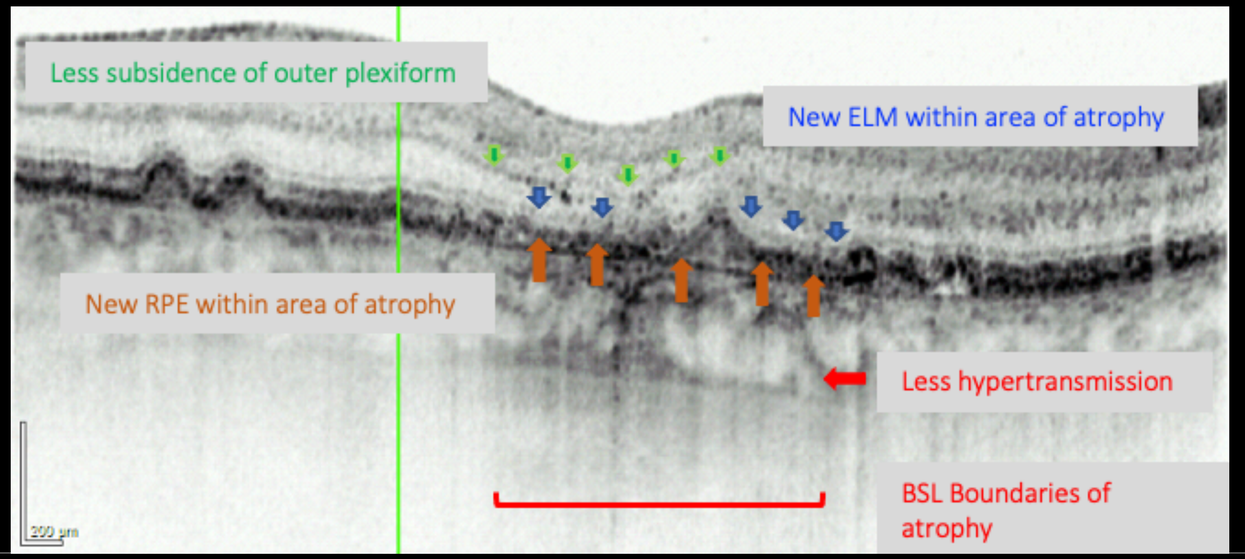
Baseline
47 letters
(~20/125)





Month 3
60 letters
(~20/63)





Outer plexiform layer
ELM border
New RPE layer

OCT analyses courtesy of Jordi Monés, MD, PhD

Acknowledgements for OCT Analyses

Jordi M. Monés, MD, PhD

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Preliminary substudy data presented at Virtual International Retinal Imaging Symposium 2021
June 4-5, 2021

Conclusions

Previously Reported Observations Continue To Hold True

- OpRegen continues to be well-tolerated in all 24 treated patients
- ERMs (15/17, 3 operated) and RD (2/17) after PPV / retinotomy, and CNVM (3/7) after Orbit SDS were the most important ocular AE and have excellent treatment options
- The OpRegen TAI formulation was utilized and well tolerated in 9 cohort 4 patients (7 via Orbit SDS and 2 via PPV)
- OCT analyses (in addition to FAF) may inform our understanding of GA progression

Discussion and Conclusions (*continued*)

- Sustained subretinal pigmentation continues to suggest OpRegen durability especially considering . . .
- . . . Signals of improving anatomy *and* function
  - Reductions in drusen
  - Restoration of outer layers in some patients
  - Possible slowing of GA progression in some patients
  - Visual acuity improvements appear clinically important and statistically significant
  - VFQ-25 scores, microperimetry and reading speed have improved in some patients
- ***Earlier intervention and more central placement of the transplanted OpRegen cells may be beneficial***

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- OCT analyses: Brandon J. Lujan, Lujan Imaging LLC
- Supplemental OCT Analyses: Doheny Image Reading and Research Lab (DIRRL) (Michael S. Ip, Muneeswar Gupta Nitala, Swetha Velaga, Vas Sadda, Ken Marion, Kirstie Baker, Sowmya Srinivas, Ayesha Karamat, Christopher Okonkwo)

Study Sponsor

LINEAGE CELL THERAPEUTICS

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We wish to thank all patients who are participating in this study