

Phase I/IIa Clinical Trial of Subretinally Transplanted Allogeneic Retinal Pigmented Epithelium Cells in Advanced Dry Age-Related Macular Degeneration: Interim Results and Further Insights from Imaging Analyses

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Financial Disclosures

- Consultant: Aerie, Alimera, Allergan, Amgen, Apellis, Clearside, Genentech, OCCURX, Novartis, Regeneron, RegenexBio
- Research Funding: **Lineage Cell Therapeutics**, Apellis, Clearside, Genentech, Novartis

Phase I/IIa Clinical Trial (NCT02286089)

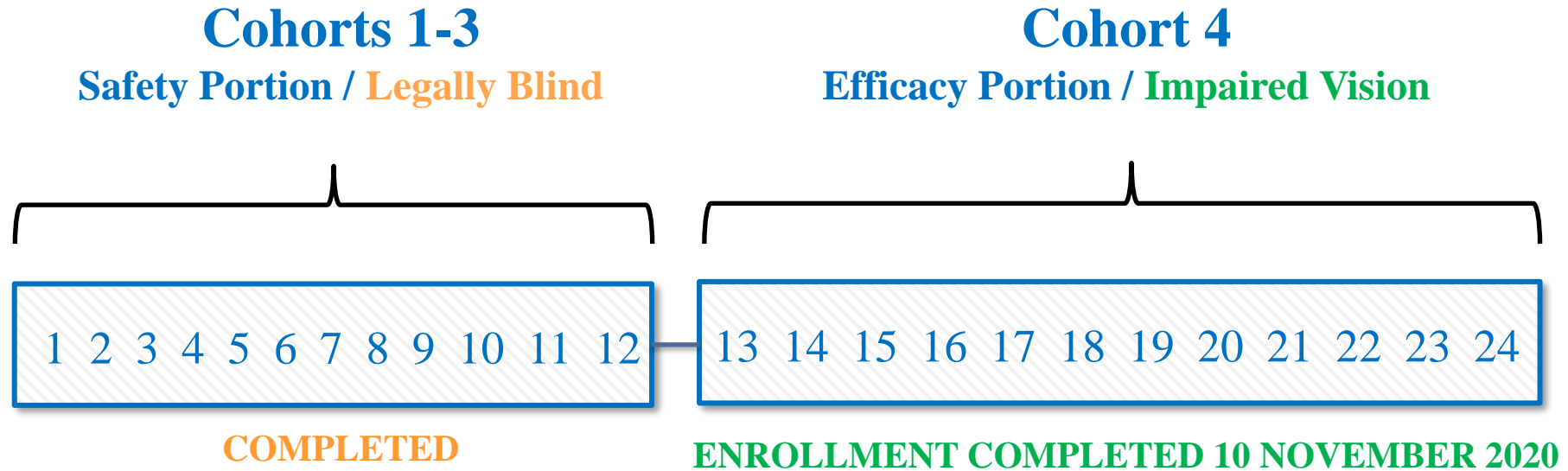
Primary Objective

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

Secondary Objective

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

Study Design



Design:

Open label, single arm, international, multi-center

Dose and Administration:

One 50-100 ul dose of cells injected into the subretinal space

Study Status and Baseline Characteristics

	Cohorts 1-3 (legally blind) n = 12 of 12 planned (<i>complete</i>)	Cohort 4 (better BCVA) n = 12 of 12 planned (<i>complete</i>)
n (%) subjects dropout	2 (17%) (2 medical illness)	1 (12.5%) (Withdrawal of consent/COVID fears)
Age: mean (SD / min - max), yrs	78.3 (\pm 8.2 / 64.8 – 92.2)	75.7 (\pm 8.1 / 60.0 – 87.7)
ETDRS BCVA: mean (SD / min - max)	23.7 (\pm 11.7 / 0 – 39) letters [24 letters \approx 20/400]	44.8 (\pm 7.5 / 28 – 55) letters [45 letters \approx 20/125]
GA area: mean (SD / min - max) via central reader FAF	12.7 (\pm 6.7 / 6 – 30) mm ²	7.4 (\pm 2.9 / 1.4 – 11) mm ²
Mean F/U (min - max), months	46.5 (11 – 60)	20.7 (12 – 40)

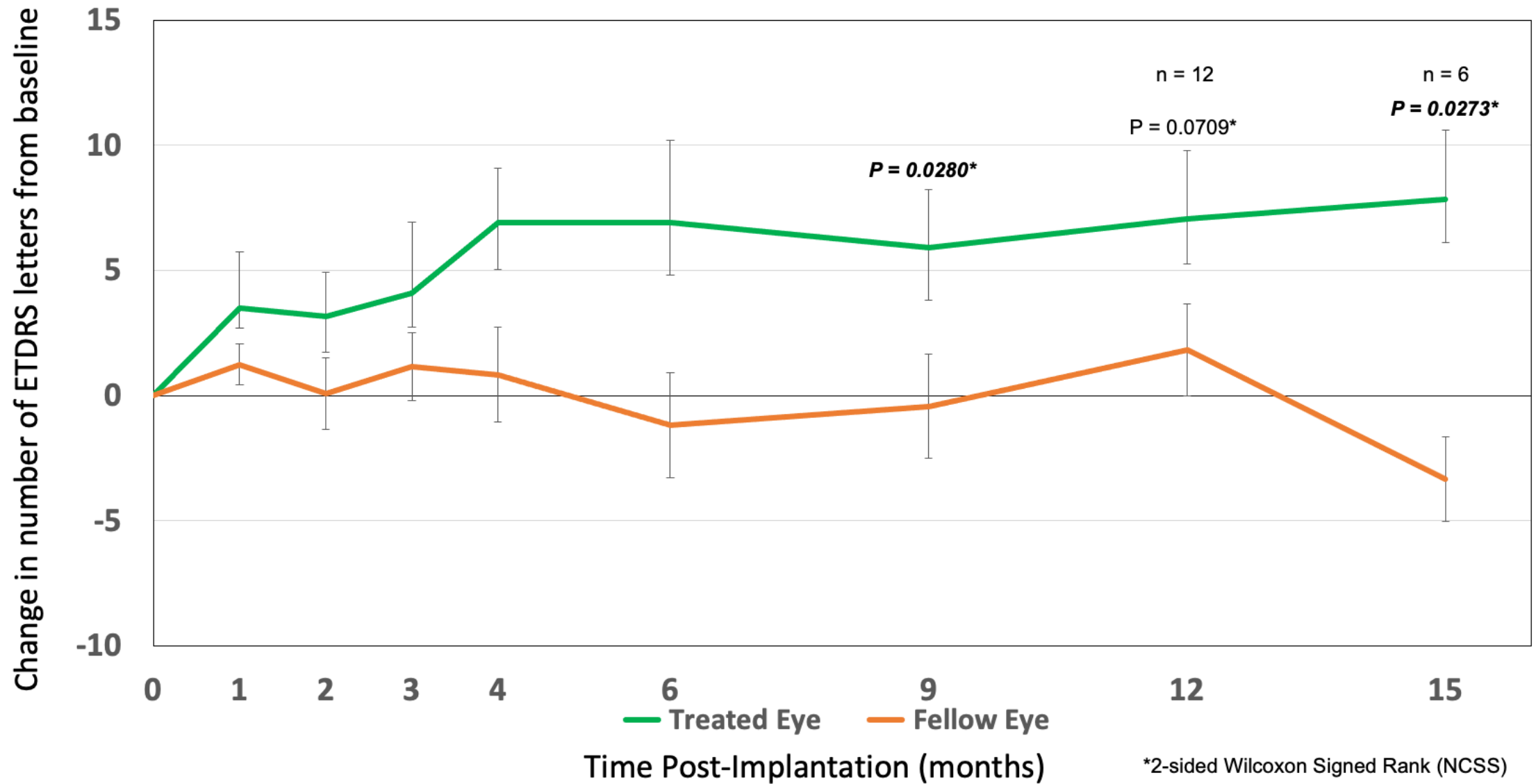
Primary Endpoint (N = 24 patients) Systemic and Ocular Safety and Tolerability

- No unexpected SAEs or AEs, appears well tolerated
- No acute or delayed inflammation, no sustained increased IOP
- All patients (N = 24) reported at least one adverse events (AE)
 - Majority of AEs were mild (333/382; 87%)

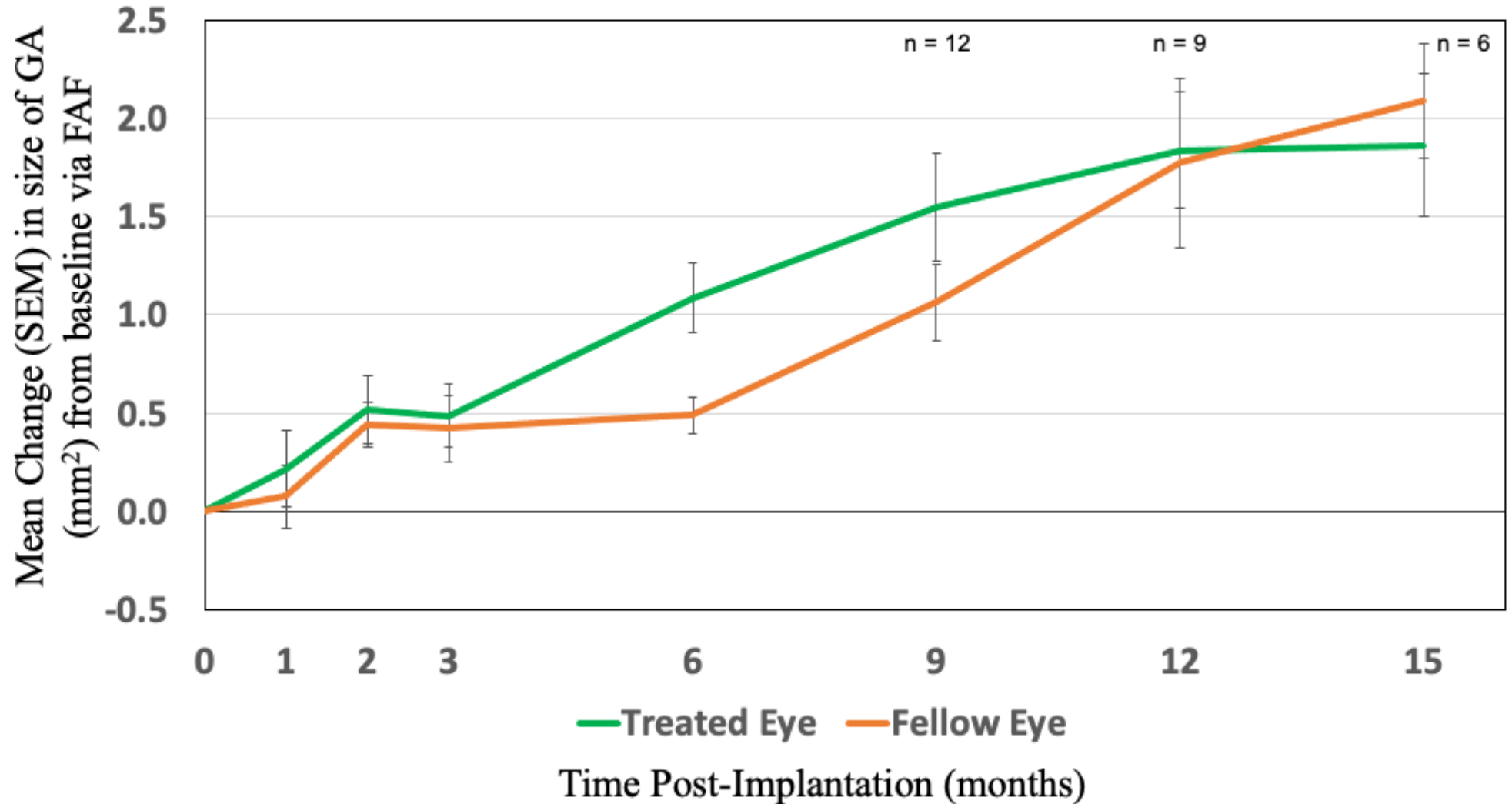
Primary Endpoint (N = 24 patients) Systemic and Ocular Safety and Tolerability (*continued*)

AE Term	Numbers of Patients Reporting (n/24; %) and Relevant Details
Limited Subretinal Hemorrhage	5/24; 20.8% (asymptomatic & spontaneously resolved)
Any form of Macular Fibrosis (ERM)	16/24; 66.7% (majority were mild to moderate in severity)
Subretinal Pigmentation	13/24; 54.2% (potentially a positive finding)
Subretinal Fluid, persisting >24h	8/24; 33.3% (majority resolved <72 hrs, none required treatment)
CNV	4/24; 16.7% <ul style="list-style-type: none"> • One (1) began >2 yrs post-op, responsive to regular anti-VEGF treatment • One (1) Type 2 CNV – 6M post-op at retinal puncture site, successfully treated with single administration of an anti-VEGF • Two others at area of GA occurred <6M post-op and receive anti-VEGF as clinically indicated, appear responsive to date
Lamellar or macular hole	3/24; 12.5% (two were associated with ERM, one other resolved without treatment or sequelae)
Retinoschisis	3/24; 12.5%
Retinal tear/retinal detachment	2/24; 8.3%

Mean Change (SEM) in Cohort 4 BCVA – Treated and Fellow Eye



Mean Change (SEM) in Cohort 4 GA (mm²) (SEM) via FAF – All Treated and Fellow Eyes



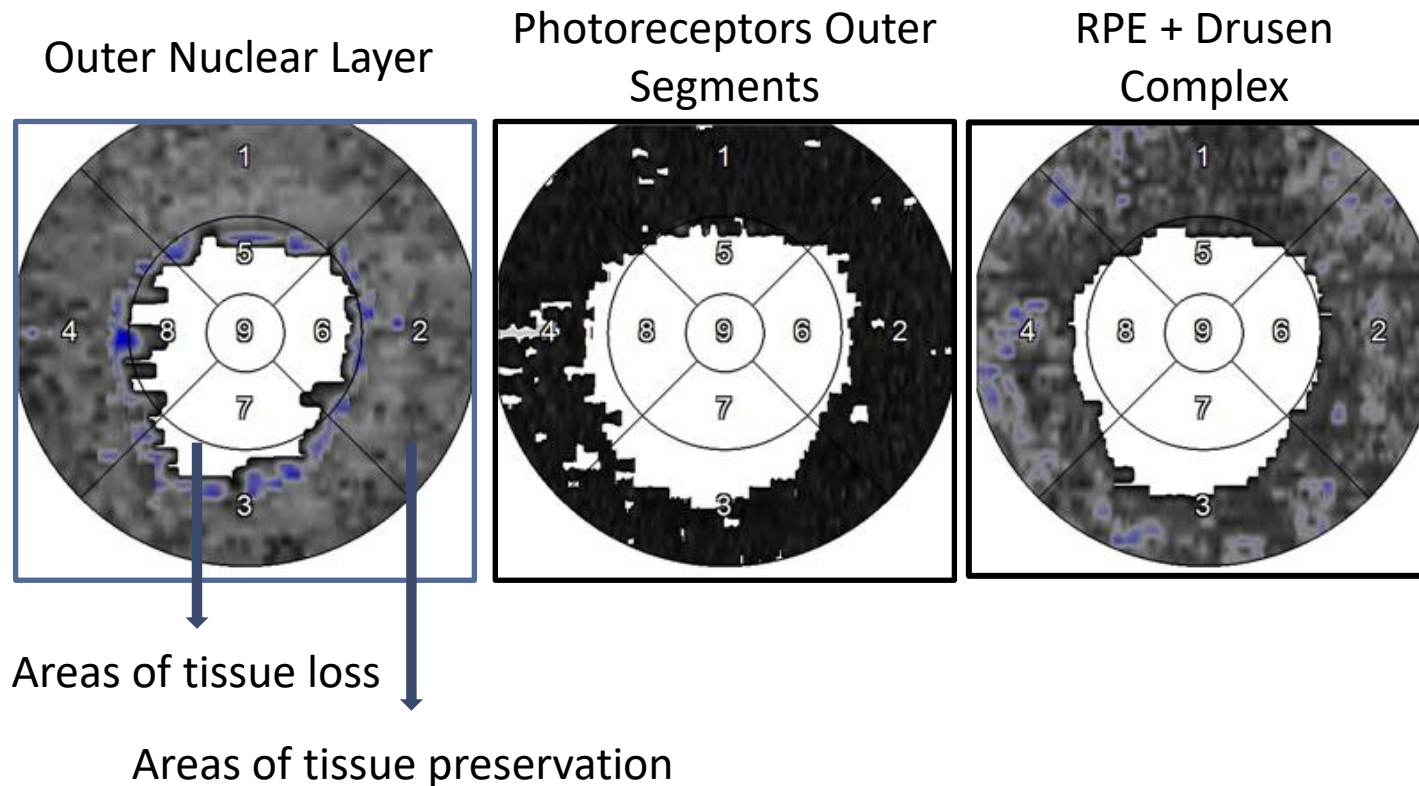
FAF is a poor tool to assess RPE cell therapy due to the lack of lipofuscin and other accumulated waste products in the newly implanted cells, which are therefore not detectable via FAF

Analyses of Images by Doheny Image Reading and Research Lab (DIRRL)

- SD-OCT images were captured using
 - Spectralis (Spectralis; Heidelberg Engineering, Inc., Heidelberg, Germany)
 - Macular volume consisting of 512x49 equally spaced B-scans within a 20x20 degree field centered on the fovea
- Retinal layers in all B-scans were manually segmented for thickness and area measurements using 3D-OCTOR (developed at Doheny Eye Institute)
 - Validated, part 11-compliant, image-grading software tool
 - Graders use a computer mouse to draw the boundaries of all structures of interest to gather quantitative information in eyes with complex disease

Illustration of Thickness and Area Maps Generated from 3D-OCTOR Grading

Areas in white represent absence or loss of various retinal tissues of interest, while areas in gray or black show areas of preserved retinal tissue

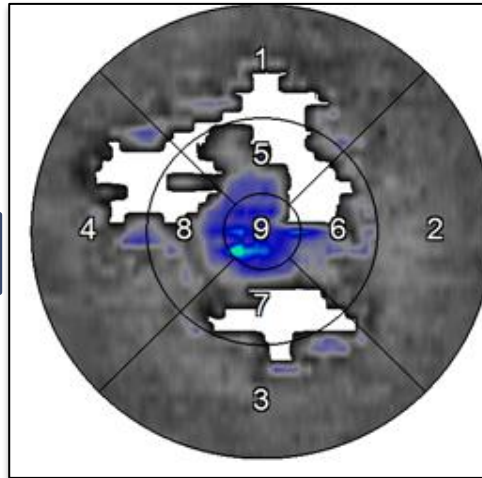


Outer Nuclear Layer (ONL) – Area (mm²) (preserved area)

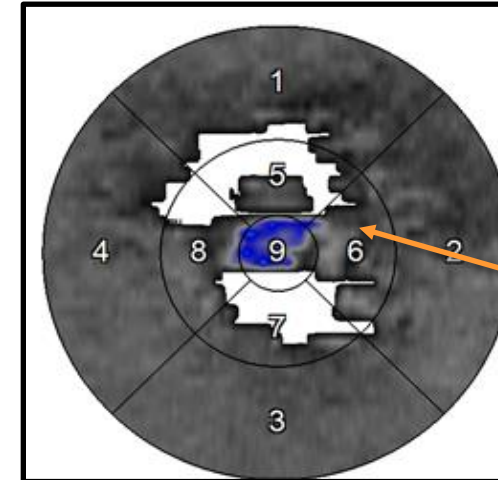
Patient #14 - potential restoration

Baseline –
36.14 mm²

Study Eye



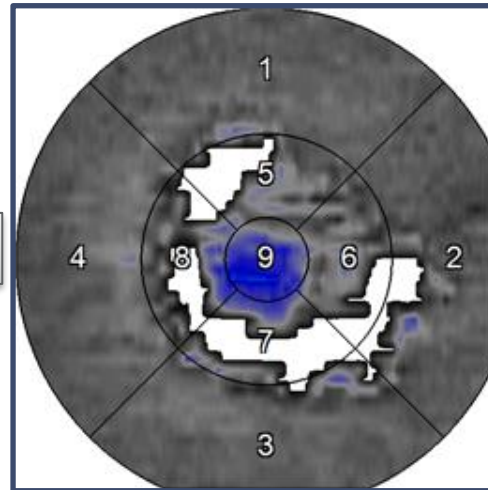
Month 12 –
36.59 mm²



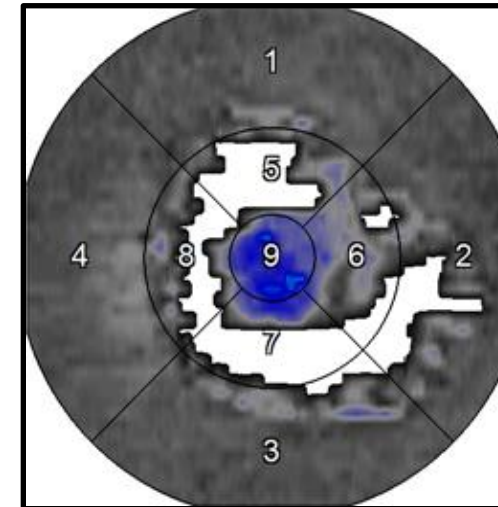
Example of
an improved
region of ONL
area

Baseline –
31.11 mm²

Fellow Eye



Month 12 –
30.09 mm²

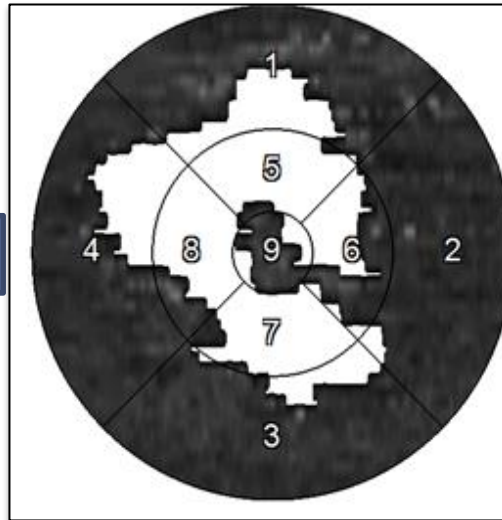


Increased RPE + Drusen Complex – Area (mm²) (preserved area)

Patient #14 - potential restoration

Study Eye

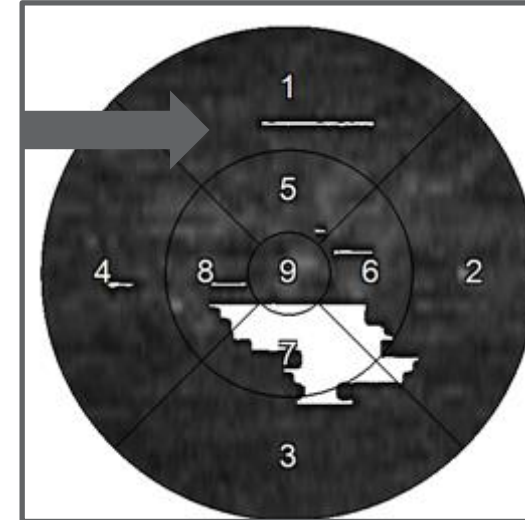
Baseline –
31.85 mm²



Increased RPE +
drusen complex
area in study eye
at Month 12

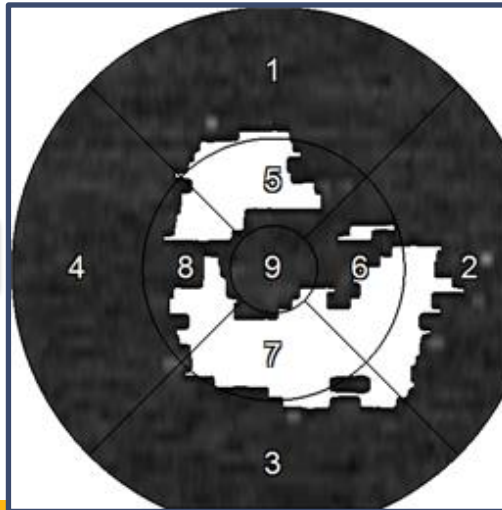


Month 12 –
37.59 mm²

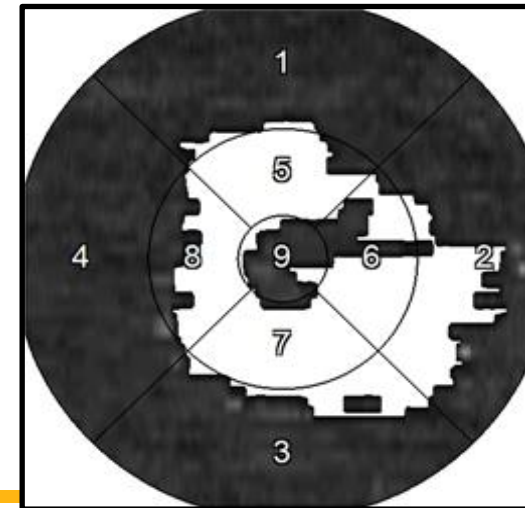


Baseline –
28.66 mm²

Fellow Eye



Month 12 –
26.26 mm²



Baseline to M12 results for Cohort 4

SD-OCT parameters in total macular volume at baseline and Month 12_in **Fellow eye**

Fellow eye at Month 12	Baseline (n = 4 eyes)	Month 12 (n = 4 eyes)	<i>p</i>
Foveal_center_retinal_thickness_Fellow_Eye	197.5 ± 83.87	146.5 ± 28.24	0.5
Sub_foveal_choroidal_thickness_Fellow_Eye	123.67 ± 44.53	112.34 ± 48.51	0.28
ONL_Area_Fellow_Eye	30.77 ± 1.8	30.5 ± 1.29	0.63
ONL_Volume_Fellow_Eye	1.77 ± 0.12	1.81 ± 0.25	0.69
ONL_Thickness_Fellow_Eye	52.97 ± 2.46	54.3 ± 7.16	0.69
IS_Area_Fellow_Eye	26.6 ± 3.98	25.16 ± 3.29	0.22
IS_Thickness_Fellow_Eye	22.94 ± 2.41	18.24 ± 2.98	0.11
IS_Volume_Fellow_Eye	0.77 ± 0.1	0.61 ± 0.1	0.11
EZ_Area_Fellow_Eye	26.13 ± 3.3	24.85 ± 3.26	0.01
EZ_Thickness_Fellow_Eye	13.3 ± 3.35	17.47 ± 3.99	0.15
EZ_Volume_Fellow_Eye	0.45 ± 0.13	0.58 ± 0.14	0.15
RPE+Drusen_Complex_Area_Fellow_Eye	28.33 ± 2.73	26.35 ± 2.43	0.02
RPE+Drusen_Complex_Thickness_Fellow_Eye	23.77 ± 3.43	22.84 ± 5.35	0.55
RPE+Drusen_Complex_Volume_Fellow_Eye	0.8 ± 0.14	0.76 ± 0.18	0.3

Note: Statistical analyses showed significant worsening when comparing values at Baseline to Month 12 in the fellow eye

Baseline to M12 results for Cohort 4

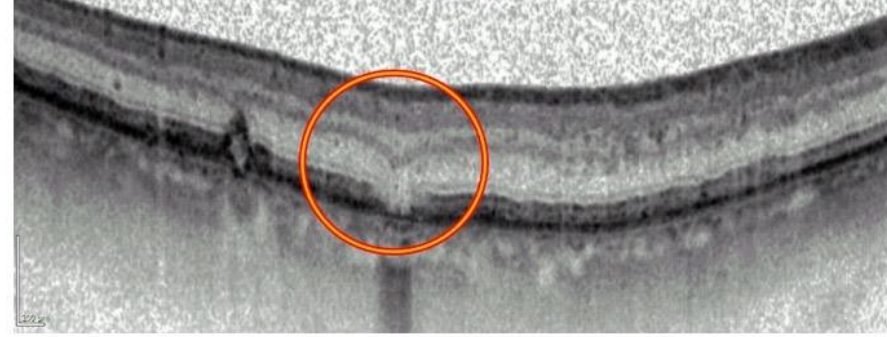
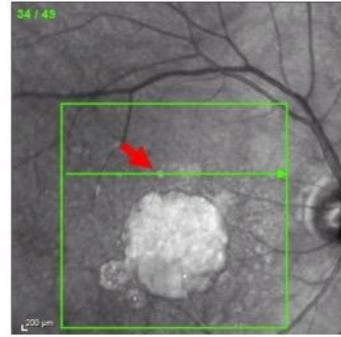
SD-OCT parameters in total macular volume at baseline and Month 12_in **Study eye**

Study eye at Month 12	Baseline (n = 4 eyes)	Month 12 (n = 4 eyes)	<i>p</i>
Foveal_center_retinal_thickness_Study_Eye	188.15 ± 49.14	224.73 ± 107.71	0.47
Sub_foveal_choroidal_thickness_Study_Eye	134.5 ± 22.52	142 ± 41.28	0.72
ONL_Area_Study_Eye	33.25 ± 2.17	34.44 ± 1.39	0.15
ONL_Volume_Study_Eye	2 ± 0.11	2.08 ± 0.3	1
ONL_Thickness_Study_Eye	56.4 ± 5.04	56.13 ± 10.57	0.72
IS_Area_Study_Eye	27.75 ± 0.78	27.78 ± 1.98	0.72
IS_Thickness_Study_Eye	19.25 ± 3.77	17.6 ± 2.42	0.47
IS_Volume_Study_Eye	0.69 ± 0.13	0.66 ± 0.1	0.47
EZ_Area_Study_Eye	26.88 ± 1.84	26.33 ± 2.36	0.47
EZ_Thickness_Study_Eye	12.45 ± 2.12	14.88 ± 2.83	0.07
EZ_Volume_Study_Eye	0.44 ± 0.08	0.55 ± 0.1	0.07
RPE+Drusen_Complex_Area_Study_Eye	29.19 ± 2.15	29.45 ± 1.8	0.47
RPE+Drusen_Complex_Thickness_Study_Eye	26.45 ± 5.48	24.15 ± 2.97	0.28
RPE+Drusen_Complex_Volume_Study_Eye	0.94 ± 0.19	0.9 ± 0.09	0.47

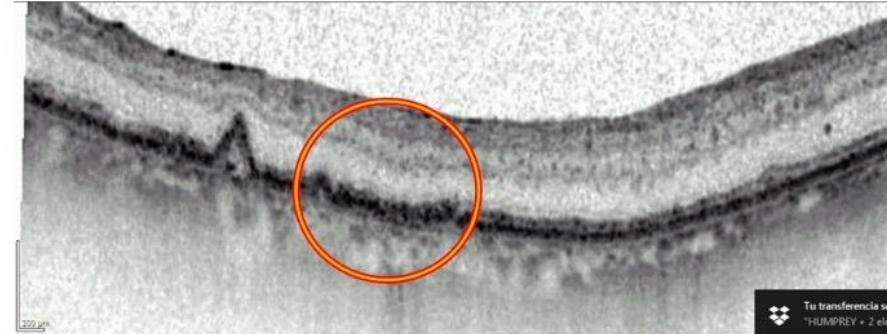
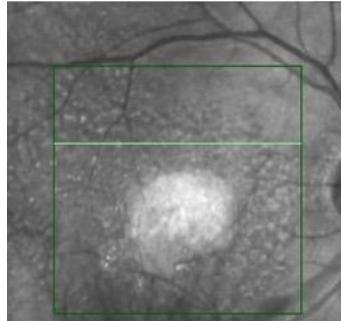
Note: Statistical analyses comparing values at baseline to Month 12 in the treated eye showed stability or trends towards improvement

Possible Resolution of Incomplete RPE and outer retinal atrophy (iRORA) Post-Treatment

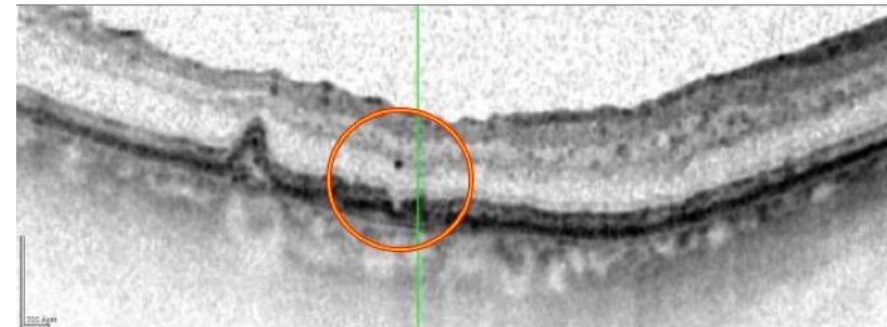
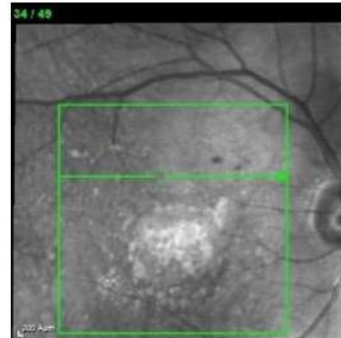
Baseline
49 letters
(~20/100)



Month 2
40 letters
(~20/160)



Month 6
51 letters
(~20/100)



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

Features suggesting
outer retinal
regeneration

OCT analyses courtesy of Jordi Monés, MD, PhD

Conclusions

- In this phase 1/2a clinical trial the RPE subretinal transplantation seemed well-tolerated in all treated participants (N = 24)
- Summary of initial imaging analyses of Cohort 4 showed
 - Fellow eyes had a statistically significant reduction in EZ and RPE/drusen area (M12)
 - Study eyes had a stabilization of EZ and RPE/drusen area (M12)
- Longer term follow up from Cohort 4 and additional analyses (e.g. iRORA lesion resolution, GA directionality) are ongoing
- Earlier intervention and more central placement of the transplanted RPE cells may be beneficial and will need to be evaluated in a future randomized, controlled clinical study

Participating Principal Investigators and Sites

- **Adiel Barak**, Sourasky Medical Center, Tel Aviv, ISR
- **David Boyer**, Retina Vitreous Associates Medical Group Los Angeles, CA. USA
- **Diana V. Do**, Byers Eye Institute, Stanford, Palo Alto, CA. USA
- **Rita Ehrlich**, Rabin Medical Center, Petah Tikva, ISR
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- **H. Richard McDonald**, West Cost Retina Group, San Francisco, CA, USA
- **Christopher Riemann**, CEI, Cincinnati, OH, USA
- **David Telander**, Retinal Consultants Medical Group, Sacramento, CA, USA
- Reading Center: **Merit** (EyeKor), Madison, WI, USA
- Microperimetry: **OIRRC**, Sohail Halim, Sunnyvale, CA, USA
- Supplemental OCT Analyses: Jordi Monés, Brandon Lujan, and Doheny Image Reading and Research Lab (**DIRRL**)

Lineage Acknowledgments

Gary S. Hogge, Avi Ben Shabat,
Jessica Hallinan, Joyce Velez,
Diana Angelini, Yana Aisen

Study Sponsor



DIRRL Acknowledgments

Muneeswar Gupta Nitala, Swetha Velaga, Ken
Marion, Kirstie Baker, Sowmya Srinivas, Ayesha
Karamat, Christopher Okonkwo, Vas Sadda

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