



OpRegen® - A Therapeutic Expert Discussion of the First-Reported Finding of Retinal Tissue Regeneration in Dry-AMD with Geographic Atrophy

Forward-Looking Statements

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AMD is the **leading cause** of
irreversible vision loss in the US

Source: aao.org

Brian Culley, CEO

OpRegen Highlights

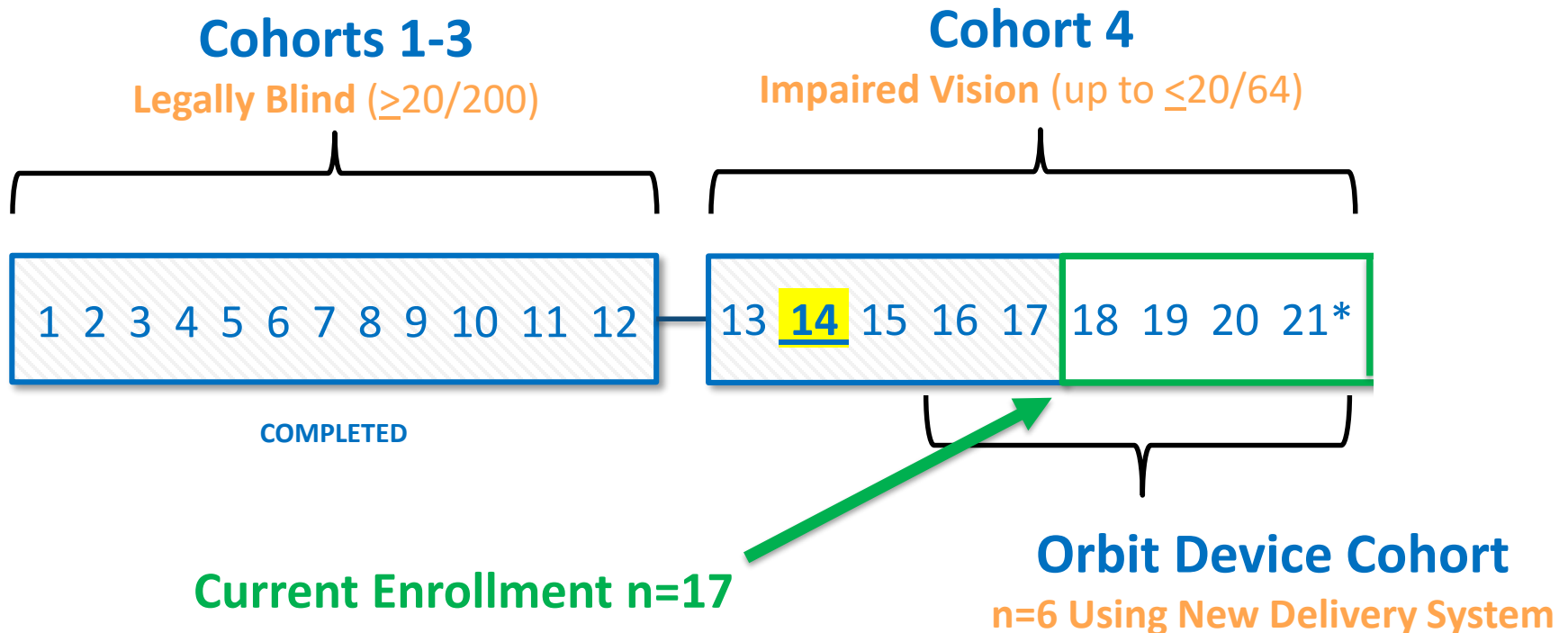
- Product is comprised of transplanted allogeneic RPE cells
- Currently in a phase 1/2a clinical trial (17 patients treated)
- In-house cGMP production
- >99% pure RPE cells
 - NIH-approved cell line
 - Established >20 years ago
 - Extensively characterized
 - No genetic modifications performed
- Ready-to-use formulation
 - No dose preparation or washing
 - From frozen cells to injection device in 5 minutes
- Commercial production path
 - Current production is 2,500 clinical doses/batch
 - Higher scale-up in larger reactors



Ongoing Phase 1/2a Clinical Trial in Dry AMD

Purpose: Safety and efficacy of subretinally transplanted RPE cells

Design: Open label, single-arm, multi-center at 5 sites





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Source: aao.org

Therapeutic Experts Introduction

Jordi M. Monés, MD, PhD,

- **Director, Institut de la Macula and Director, Principal Investigator and one of the founder governors of the Barcelona Macula Foundation**
- **MD and PhD: Universitat de Barcelona, Spain**
- **Ophthalmology residency: Institut Barraquer, Barcelona, Spain**
- **Retinal fellowship: Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, USA**
- **Retinal fellowship: Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Mexico**
- **Widely published in peer-reviewed scientific journals and specialty books and has given more than 300 talks at international congresses and meetings. Dr. Monés is a member of 12 scientific societies, being one of the few retinal specialists who belongs to all the four major retina societies: The Macula Society, The Retina Society, The Club Jules Gonin and The American Society of Retina Specialists**

Michael S. Ip, MD

- **Chief of the Vitreoretinal Surgery Service at the Doheny Eye Centers, UCLA Stein Eye Institute, Medical Director of the Doheny Image Reading Center (DIRC)**
- **BS: Tufts University**
- **MD: New York University School of Medicine, New York, NY**
- **Ophthalmology residency: University of Pittsburgh School of Medicine, Pittsburgh, PA**
- **Vitreoretinal clinical and research fellowship: New England Eye Center, Tufts University, Cambridge, MA**
- **Board Certified American Board of Ophthalmology**
- **Author of hundreds of articles in leading professional journals and books and is a principal investigator or co-principal investigator on several multi-million-dollar national research enterprises**



AMD is the **leading cause** of
irreversible vision loss in the US

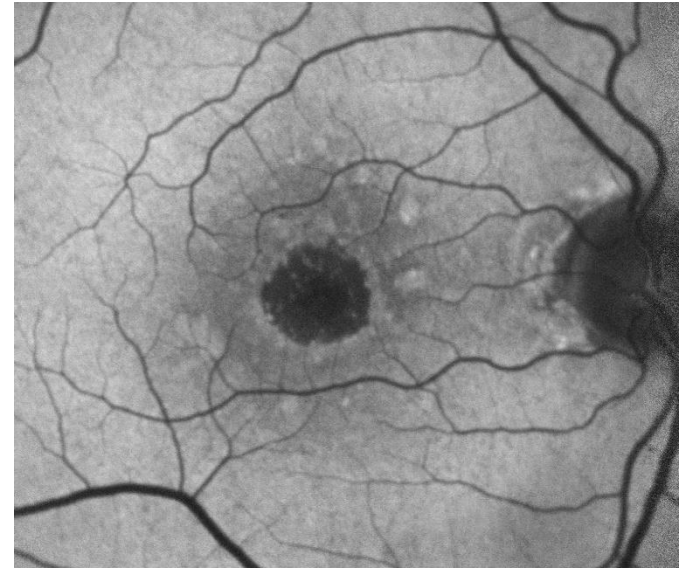
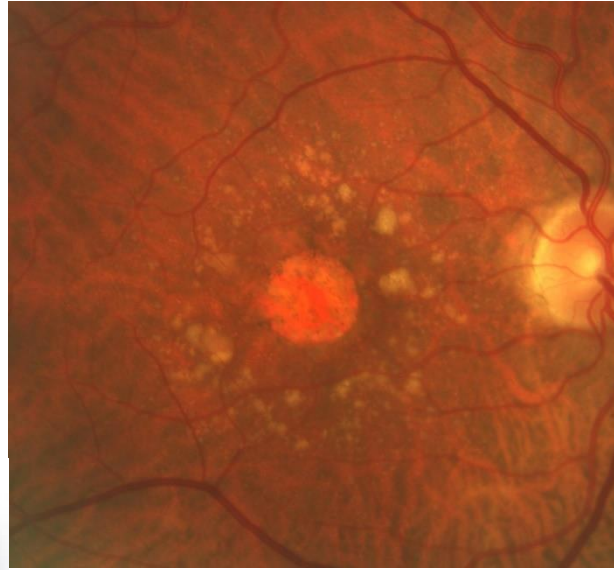
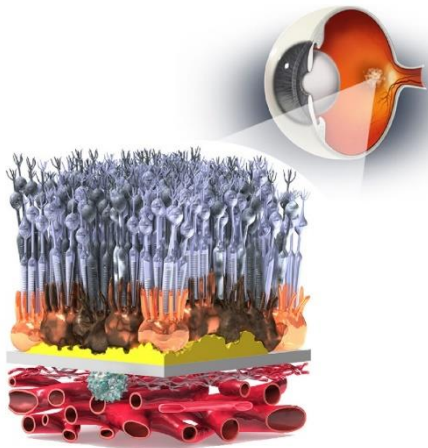


Source: aao.org

Overview of OpRegen (Patient #14)

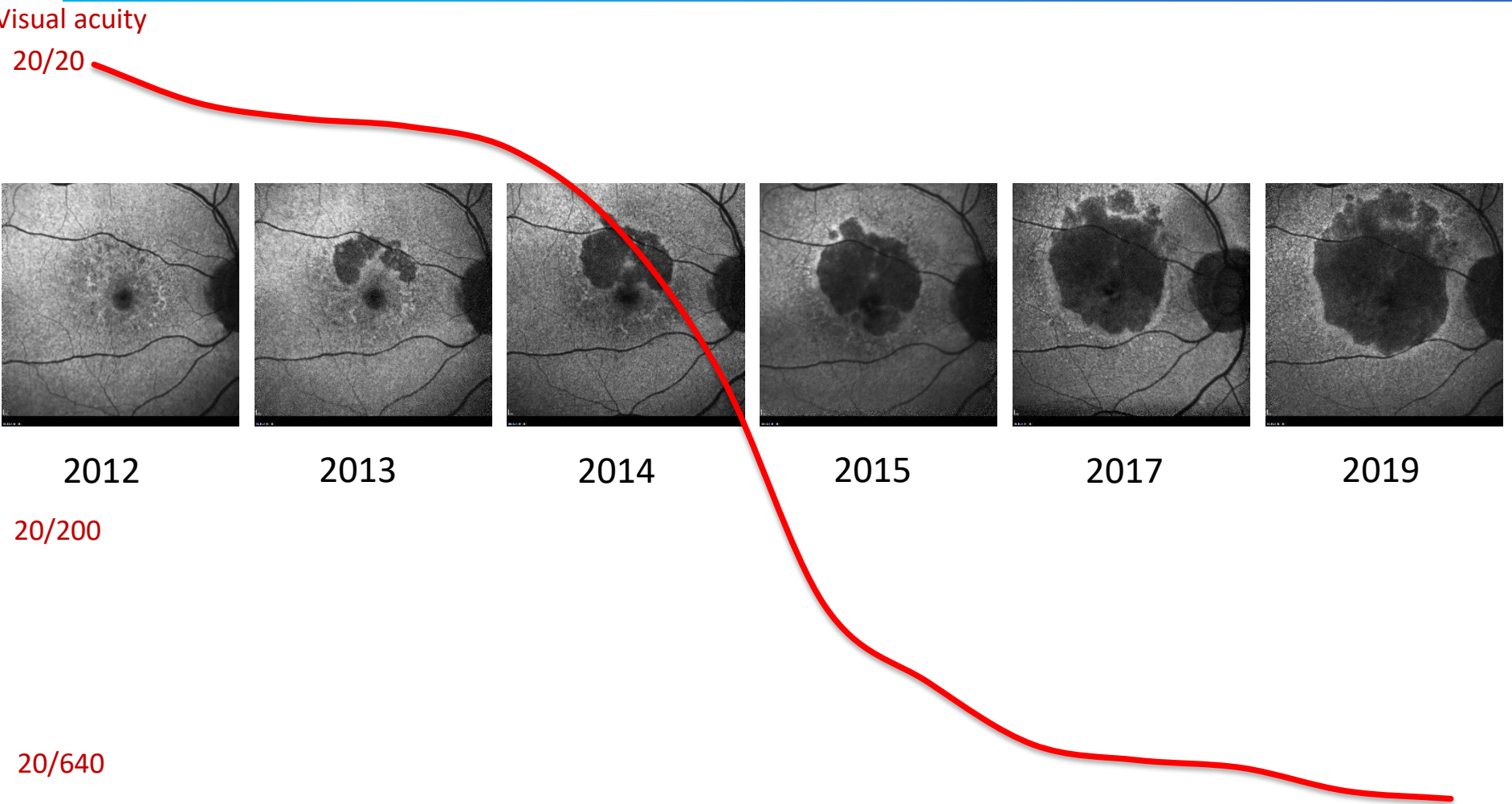
Jordi M. Monés, MD, PhD

Atrophic Dry Age-Related Macular Degeneration



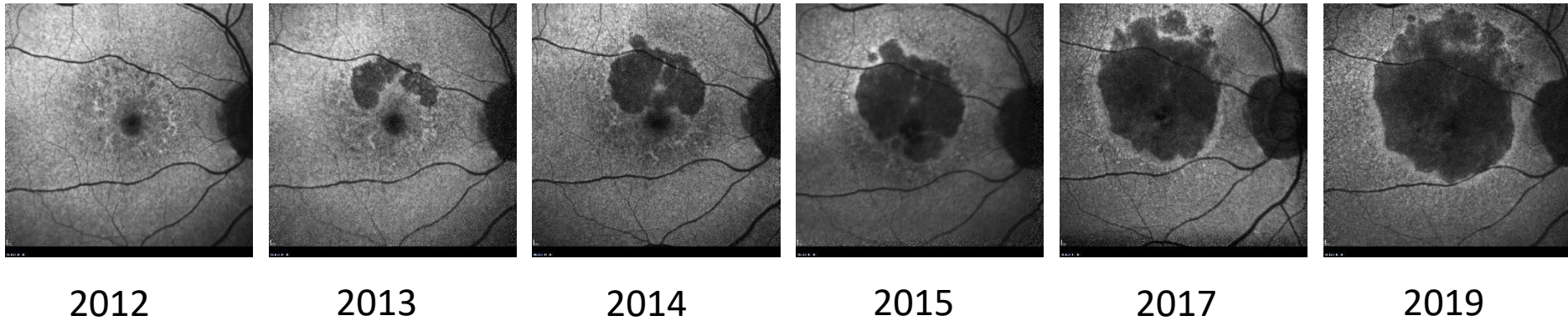
Atrophic dry AMD involves the loss of retina cells (RPE) and photoreceptors in an area of geographic atrophy (GA), causing impaired vision and blindness

Atrophic Age-Related Macular Degeneration (AMD) (image courtesy of Dr. Jordi Monés)



Progressive destruction of the retina... that leads to blindness in few years

Atrophic Age-Related Macular Degeneration (AMD) (image courtesy of Dr. Jordi Monés)



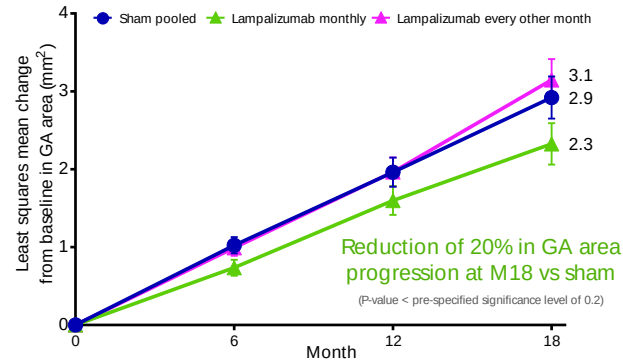
It is a true epidemic, affecting 1 out of 4 people 80 years of age or older...

...and currently it has no treatment

Current Investigational Therapies for GA Aim to Slow-Down the Rate of Growth

DELAYING THERAPIES: Anti Factor D, Lampalizumab

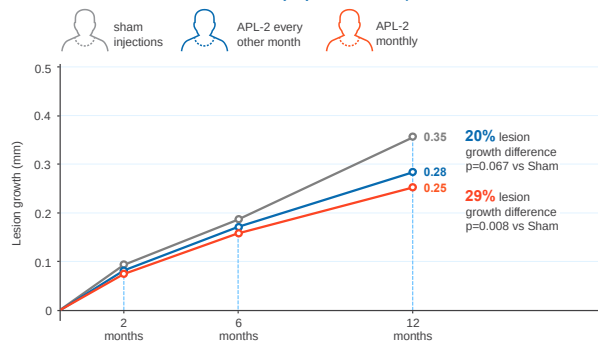
Positive treatment effect observed in the lampalizumab monthly group beginning at Month 6 through Month 18 in **Adjusted Mean Change in GA**



Total area of GA at baseline similar across groups: ~3.4 DA.
*Based on the mITT population with LOCF data. Adjusted mean is the least squares (LS) mean from the stratified analysis of variance (ANOVA) model adjusted for baseline GA. Vertical bars are ± 1 standard error of the LS mean.



APL-2 slows GA growth at 12 months (square root)

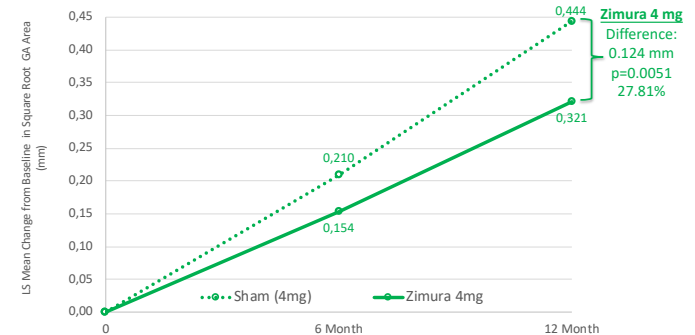


Apellis

Modified Intent to Treat population (mITT). Observed, Mixed-Effect Model

12

Primary Efficacy Endpoint Achieved: Zimura 4 mg vs. Sham



Based on LSMEANS from MMR Model. ITT Population Hochberg procedure used for significance testing

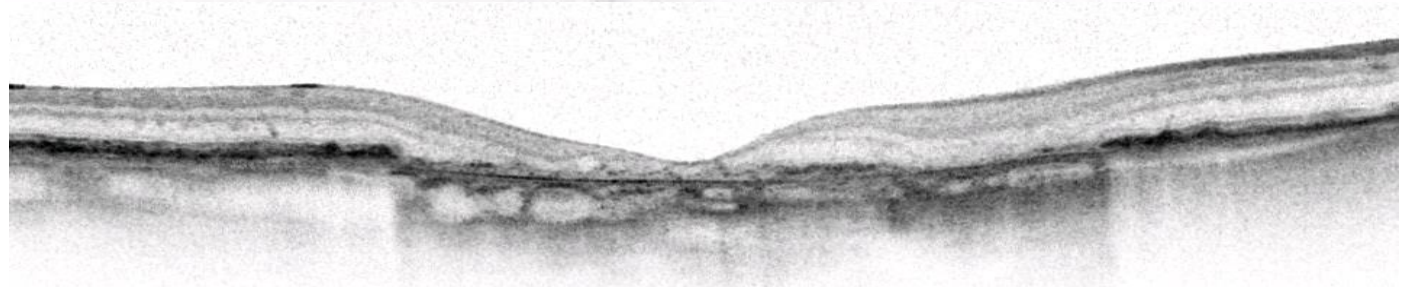
27

Natural History: Progressive Destruction of RPE, ELZ, ELM and ONL

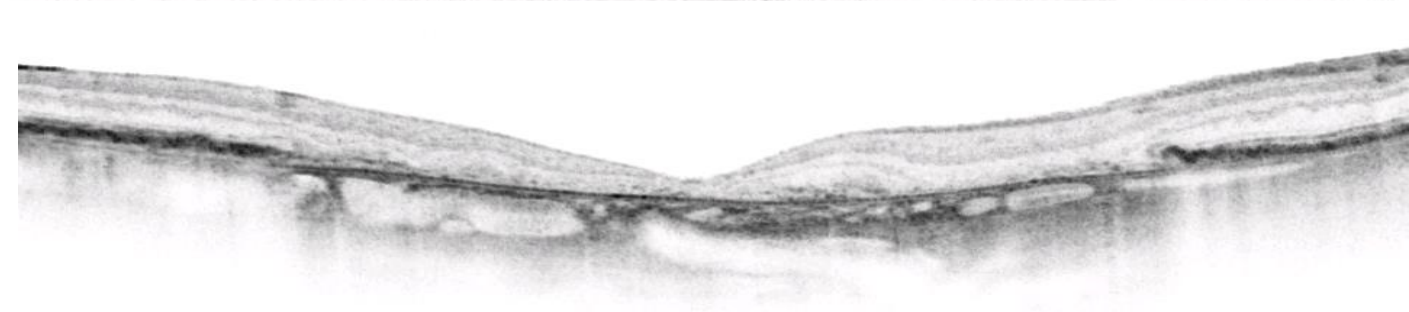
2010



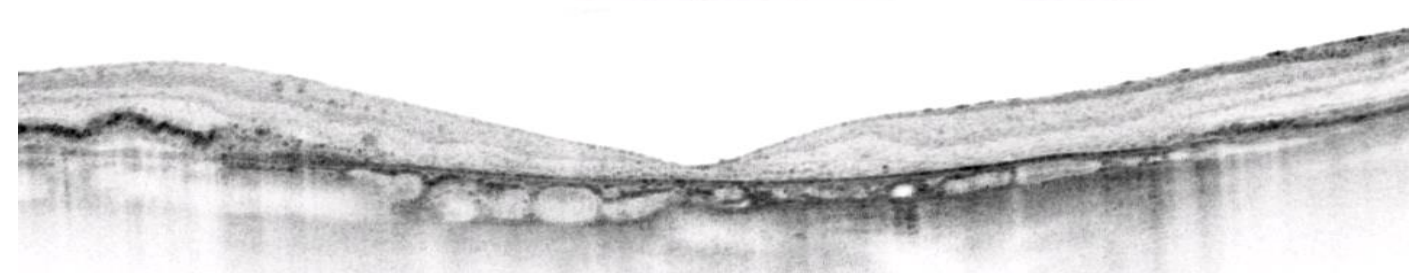
2013



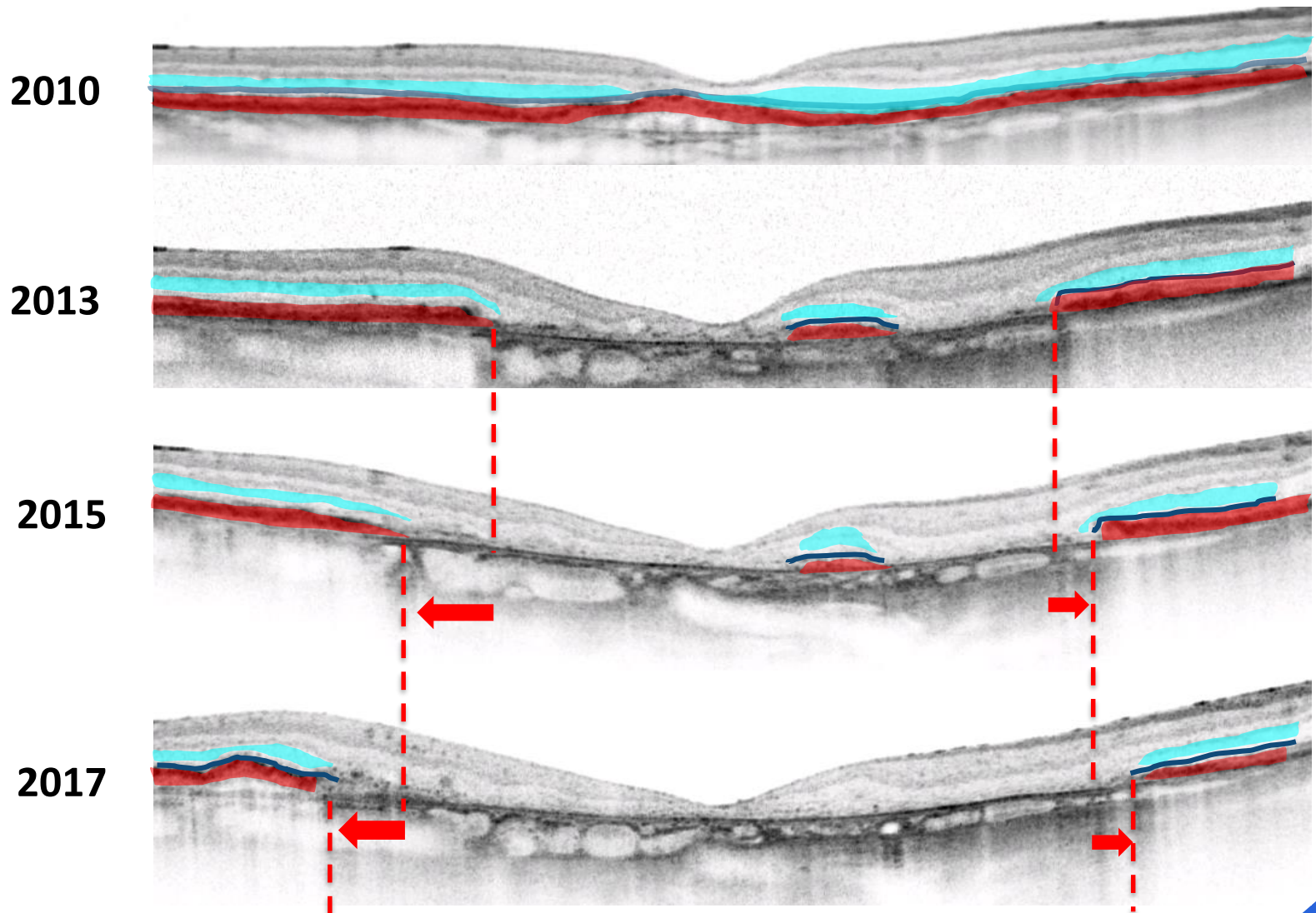
2015



2017

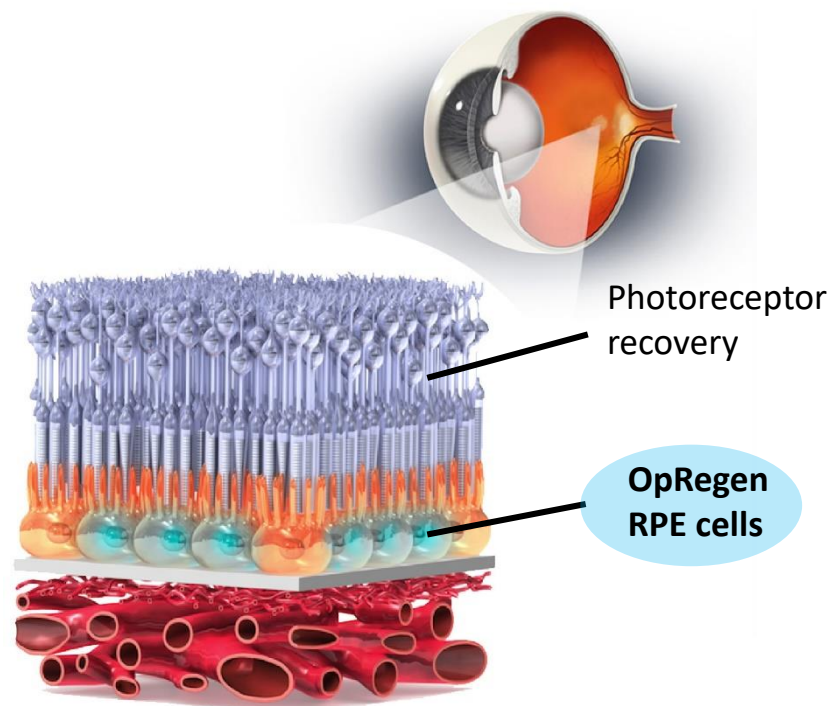
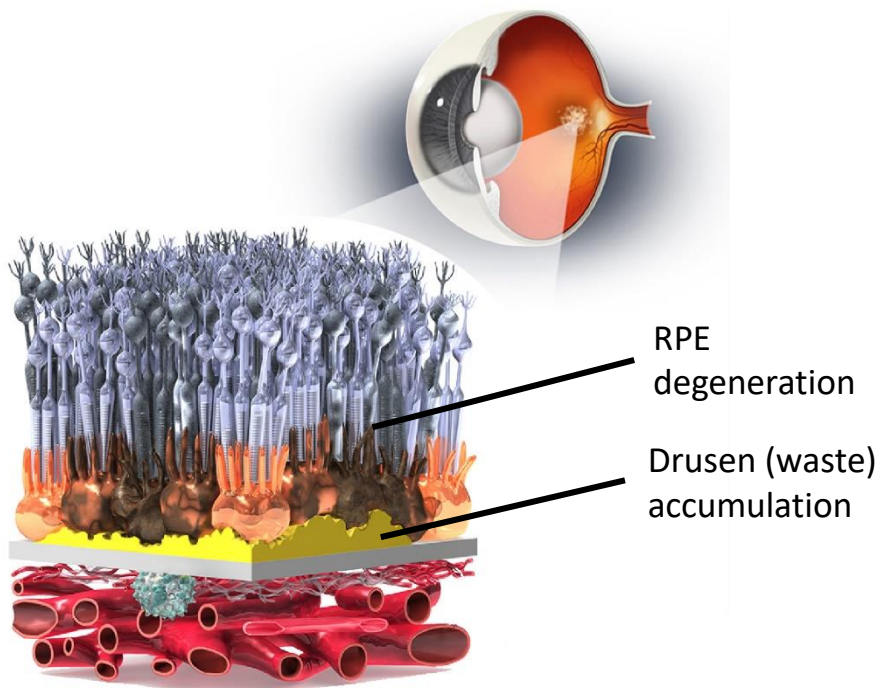


Natural History: Progressive Destruction of RPE, ELZ, ELM and ONL



OpRegen Transplant Rationale

- Atrophic dry AMD involves the loss of retina cells (RPE) in an area of geographic atrophy (GA), causing impaired vision and blindness
- OpRegen is a suspension of **RPE cells** delivered to the sub-retinal space to restore activity and support photoreceptors



Patient Background

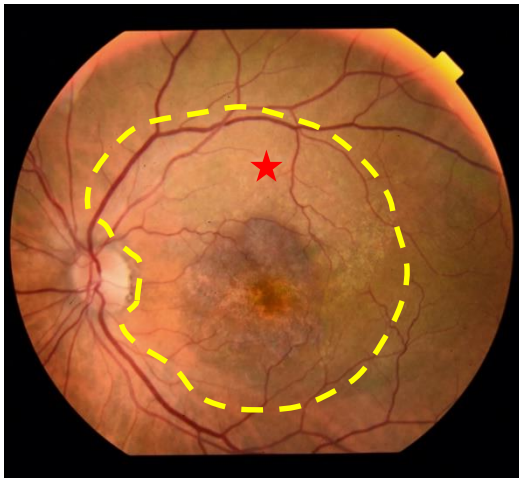
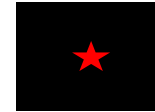
- **OpRegen patient #14 (2nd patient in Cohort 4)**
- **80-year-old female**
- **Ocular medical history**
 - >20-year history of AMD
 - Treated eye (OS):
 - BCVA 20/80 (54 Letters)
 - GA size 8.139 mm² per Central Reader
 - ~2 years prior was ~2.7 mm² per Central Reader
 - Fellow eye (OD)
 - BCVA 20/63 (61 Letters)
 - GA size 6.959 mm² per Central Reader
- **Pseudophakic (OU)**

Location of OpRegen Implantation Bleb for Patient #14

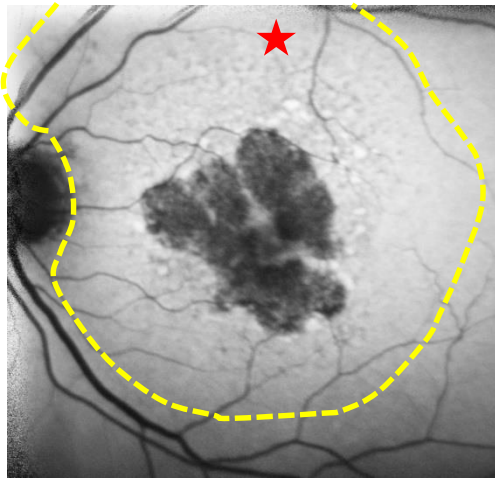
Subretinal bleb border



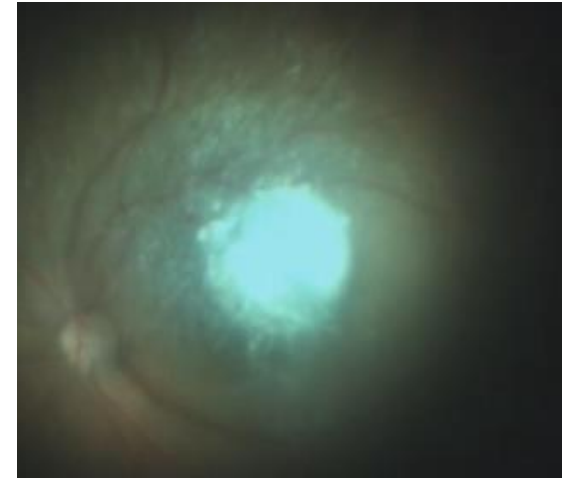
Precise implantation location



**Color fundus
photography (CFP)**



**Fundus
Autofluorescence (FAF)**

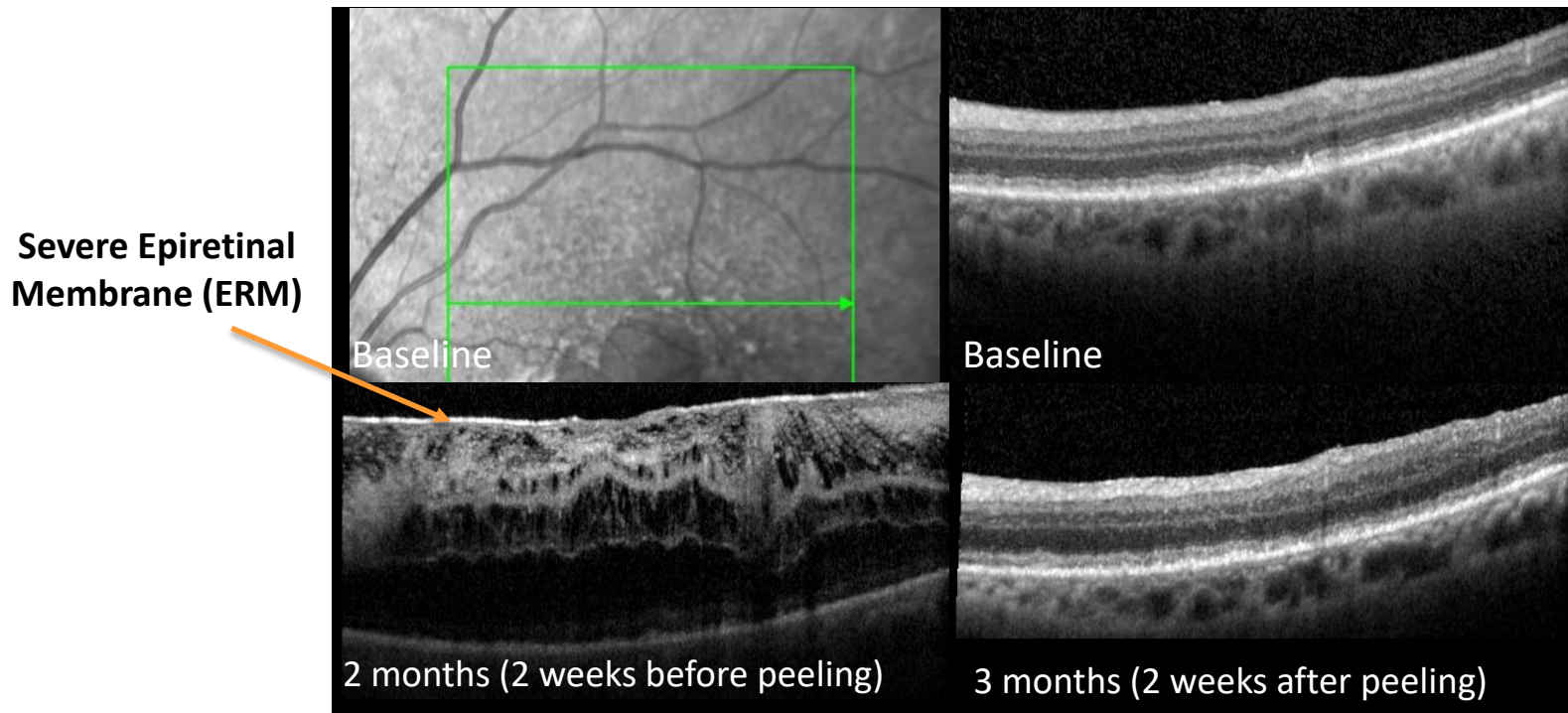


**Surgical bleb post-
OpRegen implant**

IR and OCT Sample Images (Baseline, Pre- and Post-ERM Peel)

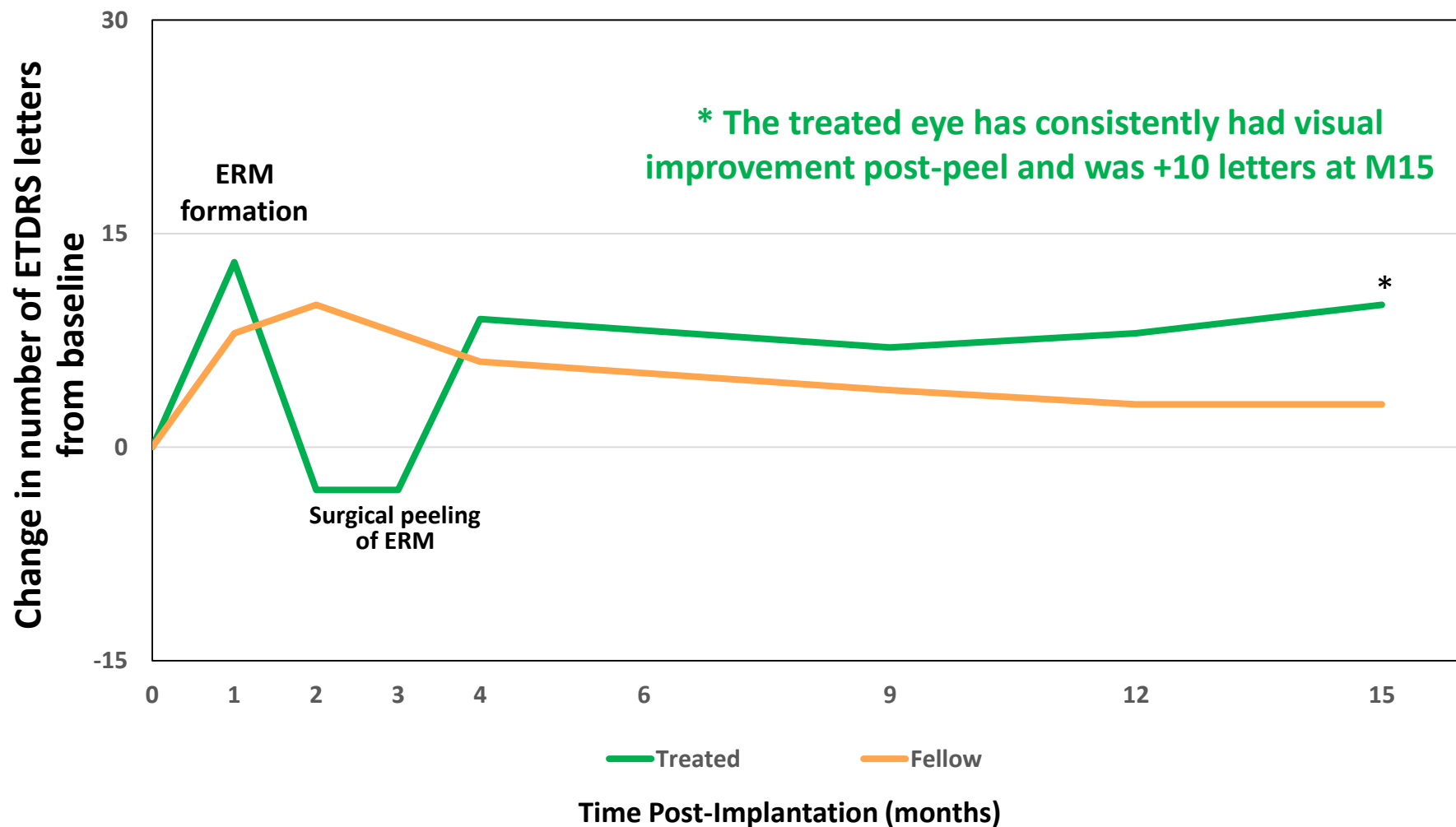
Relevant post-OpRegen transplant ocular AEs included

- **Progressive ERM that ultimately required surgical intervention**
- **Rapid restoration of vision and more normal retinal structure following the ERM peel**

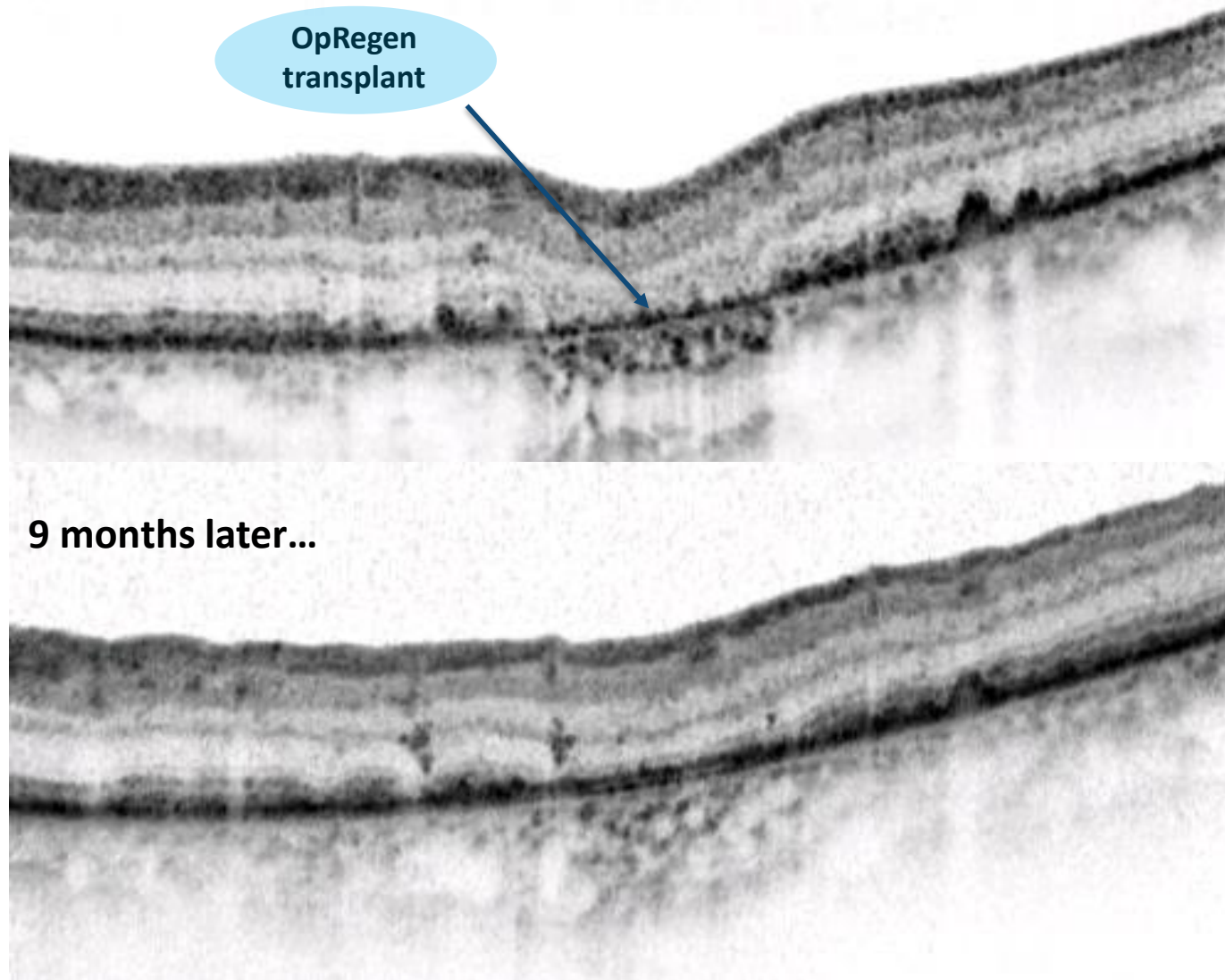


Improved BCVA Following OpRegen Treatment & Surgical Removal of ERM

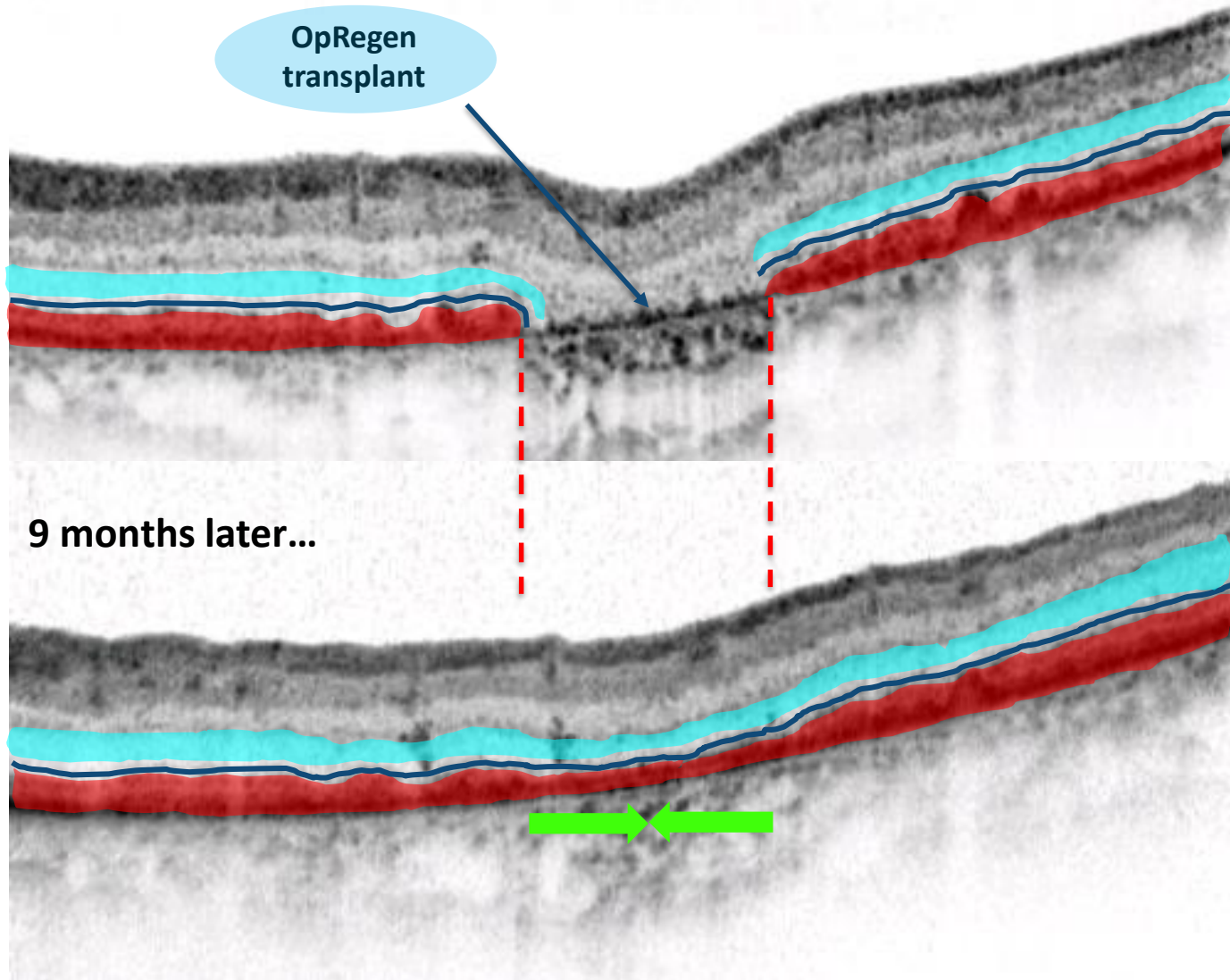
Individual Changes in BCVA – Treated vs. Fellow



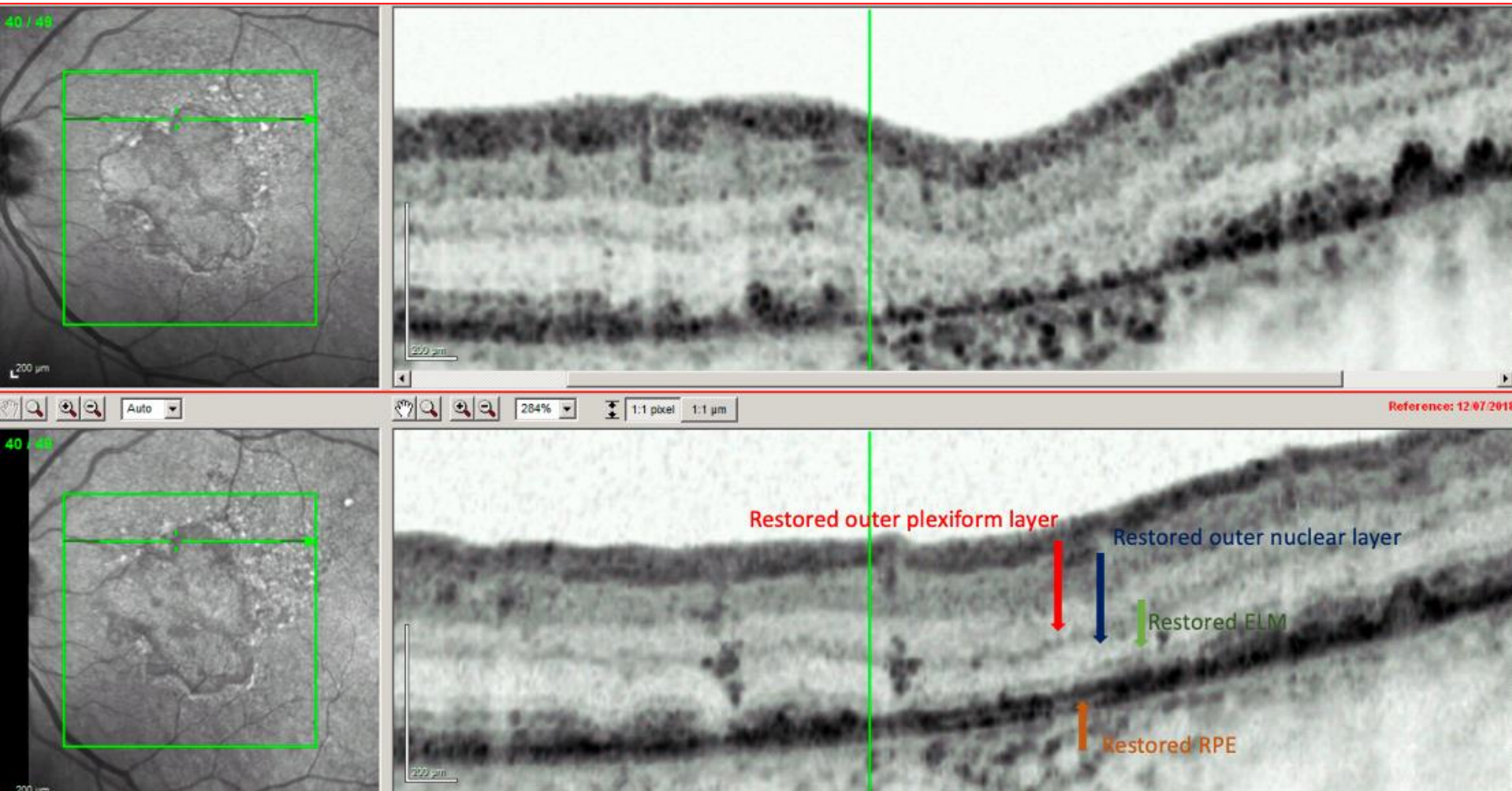
OpRegen RPE Cell Transplant Results Patient #14



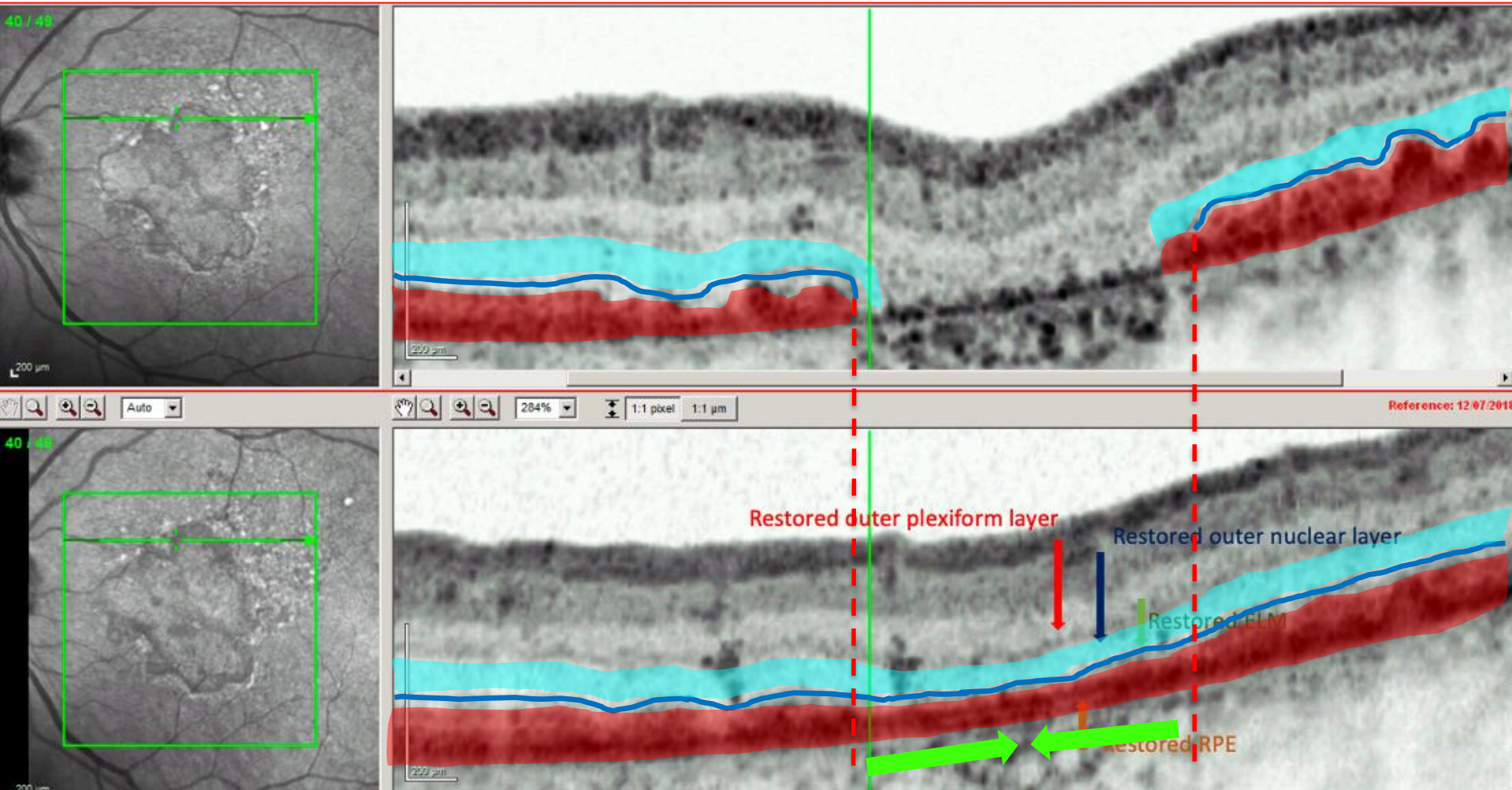
OpRegen RPE Cell Transplant Results Patient #14



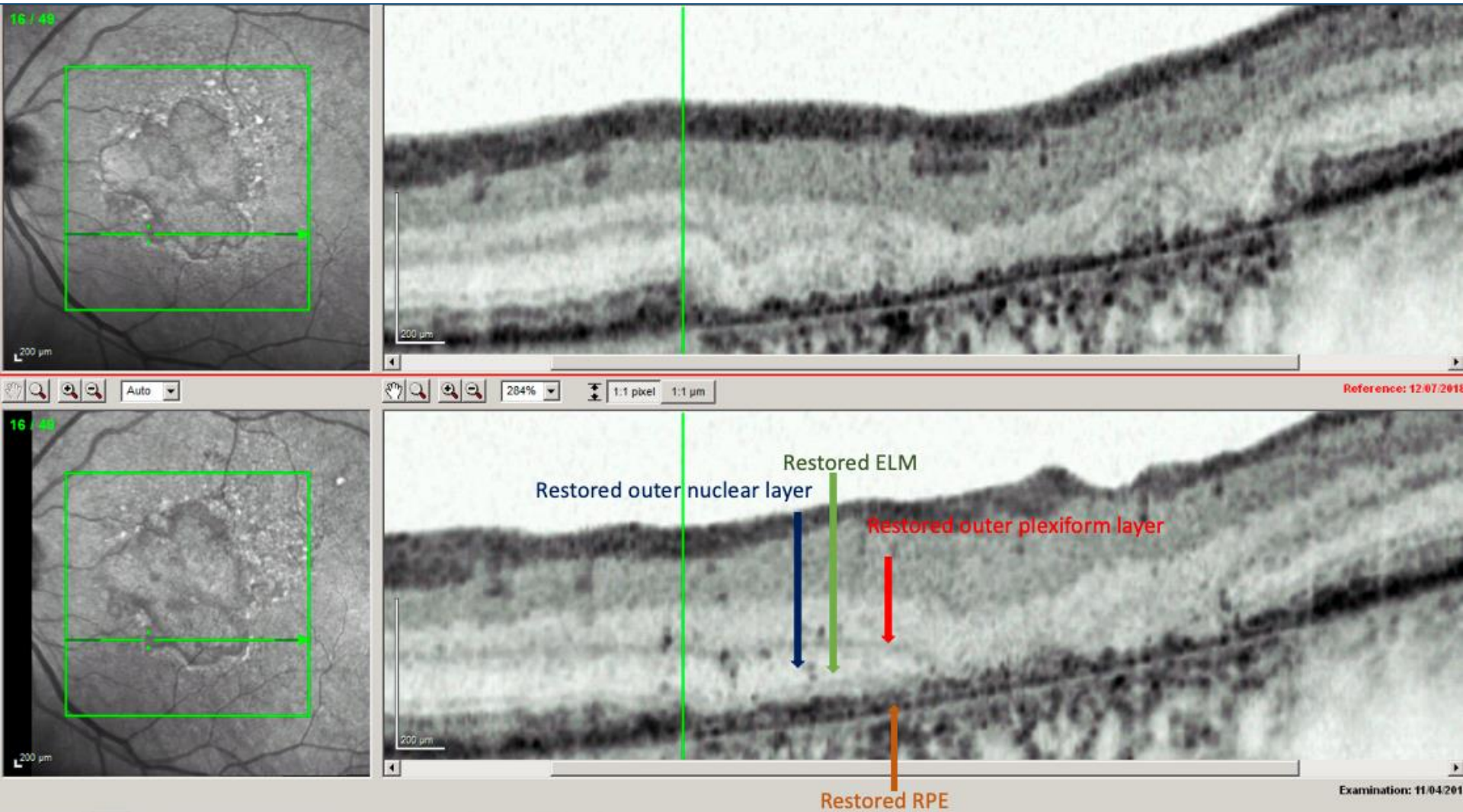
Consistent Findings of Retinal Regeneration (New ONL, ELM, ELZ and RPE) No Matter the Location of the Scan, Through 360°



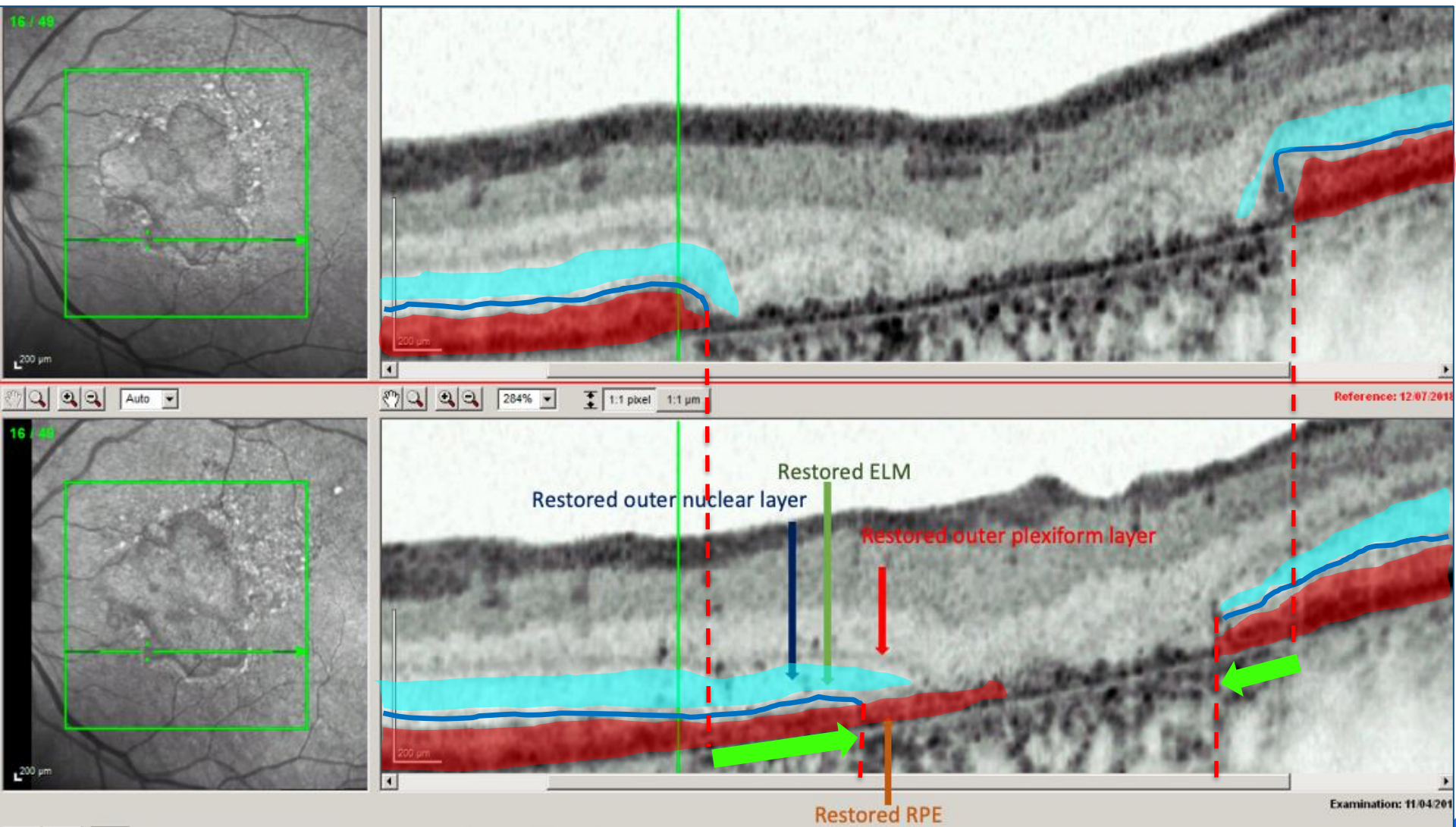
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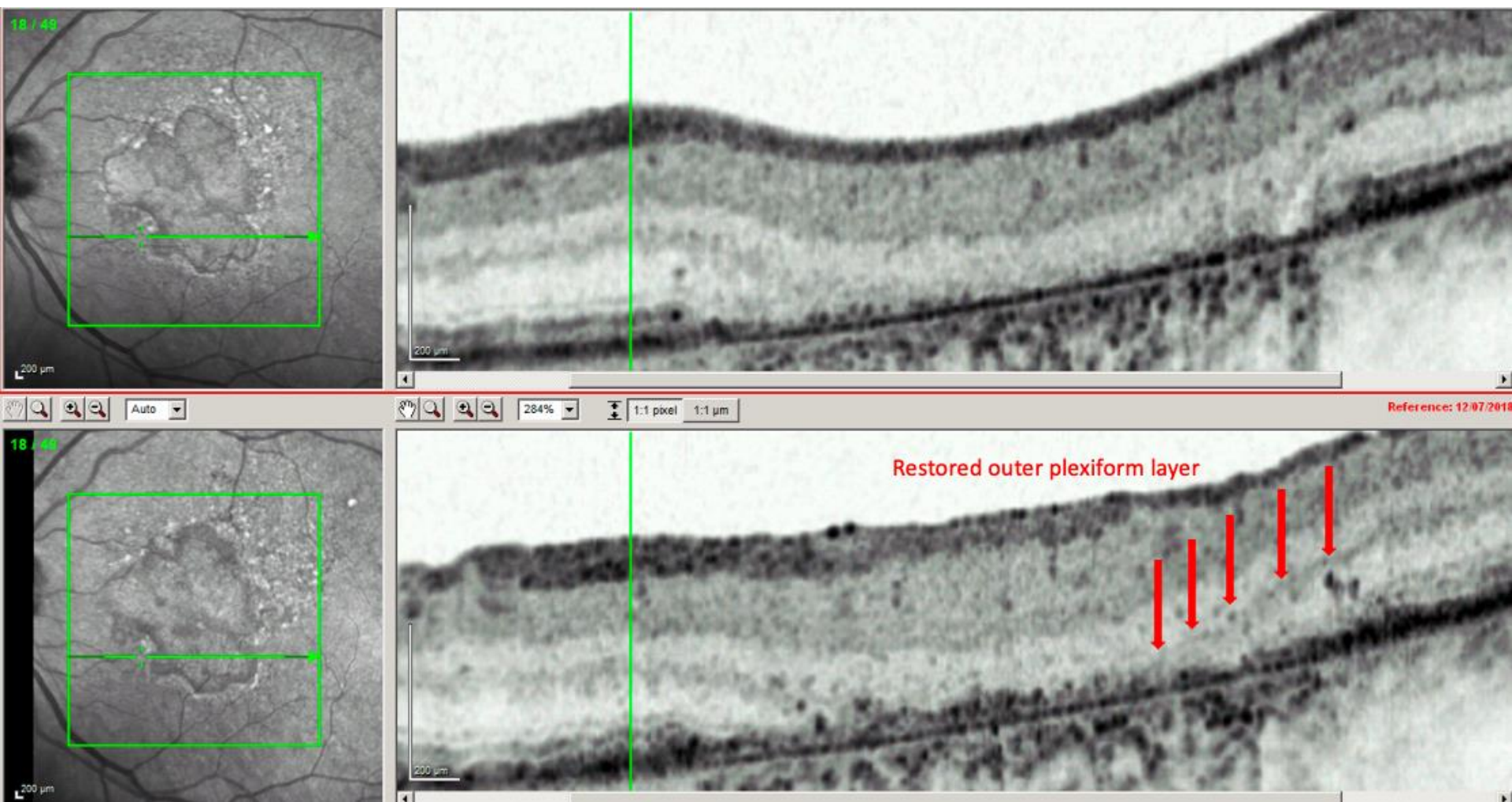
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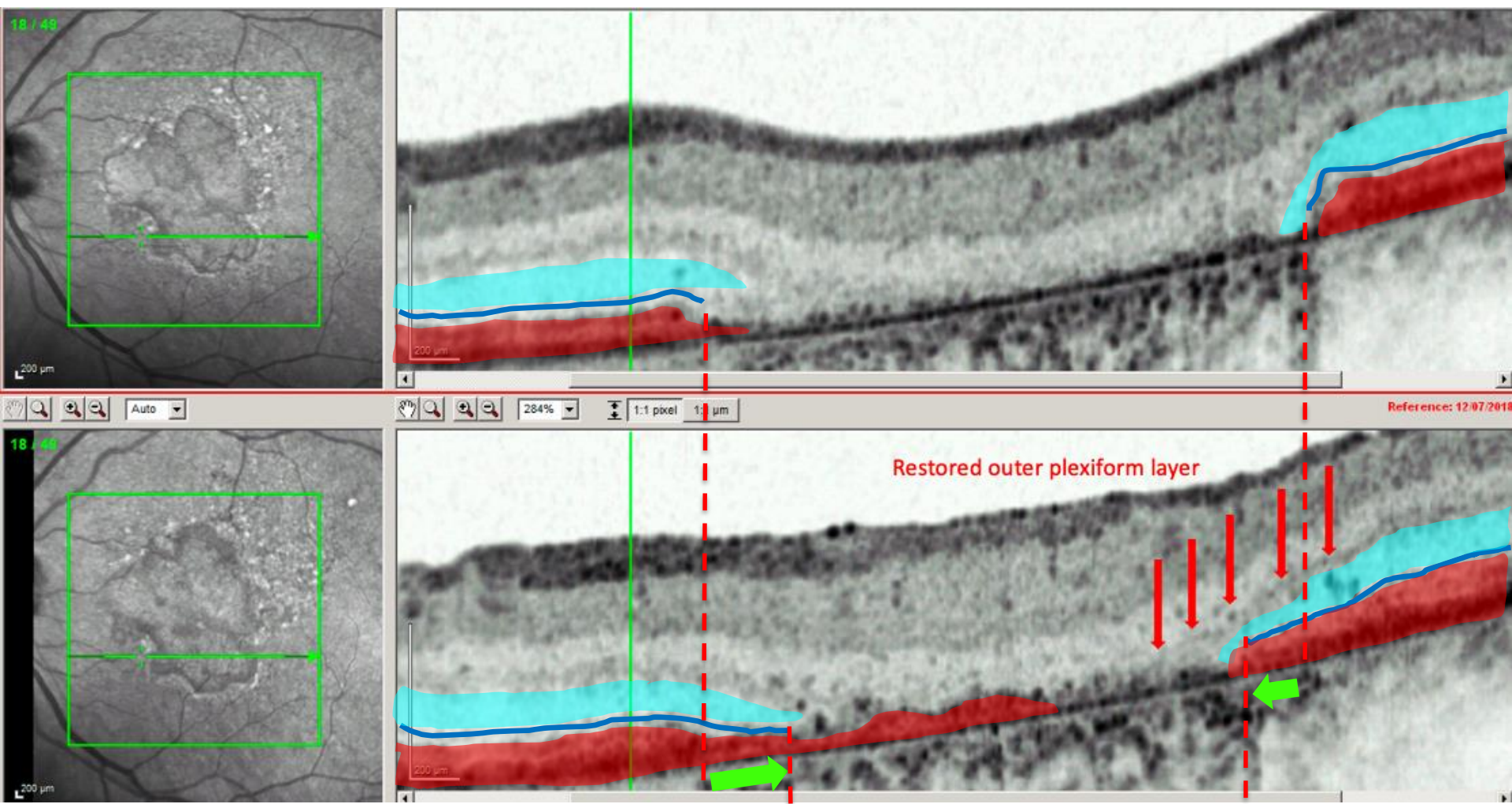
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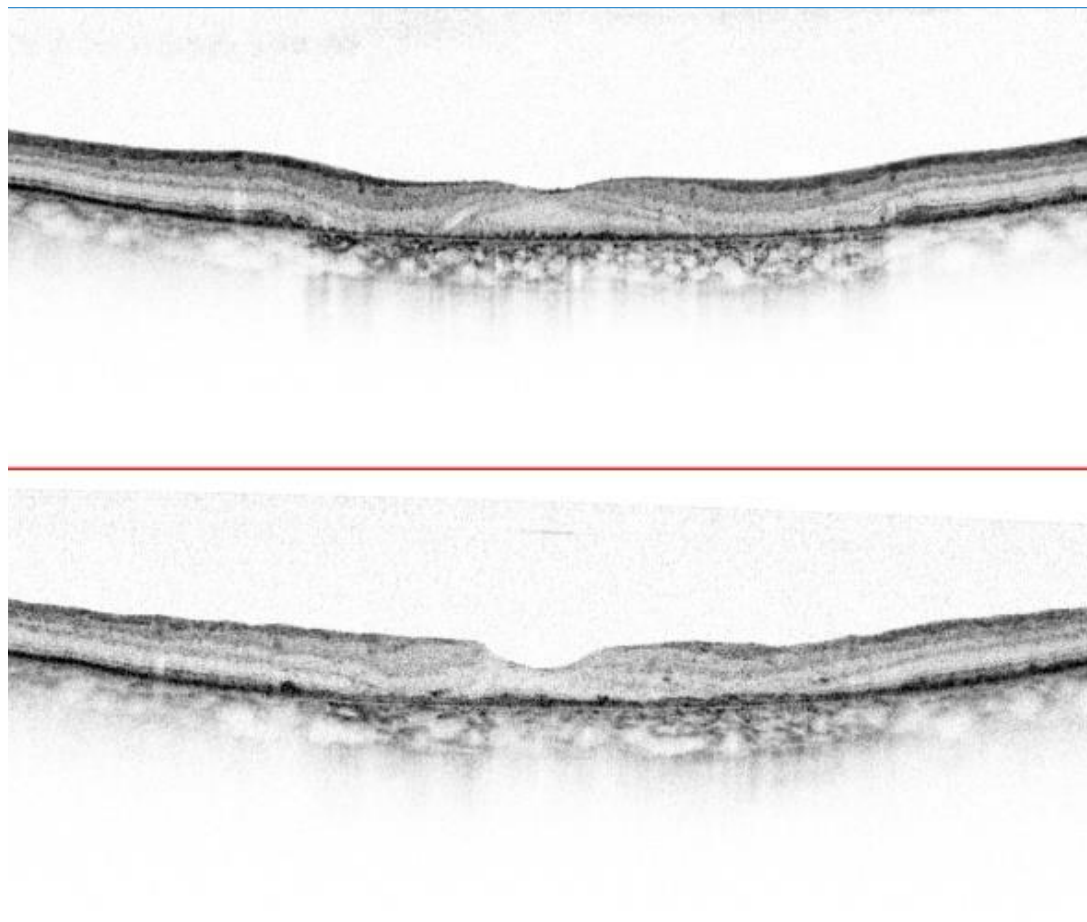
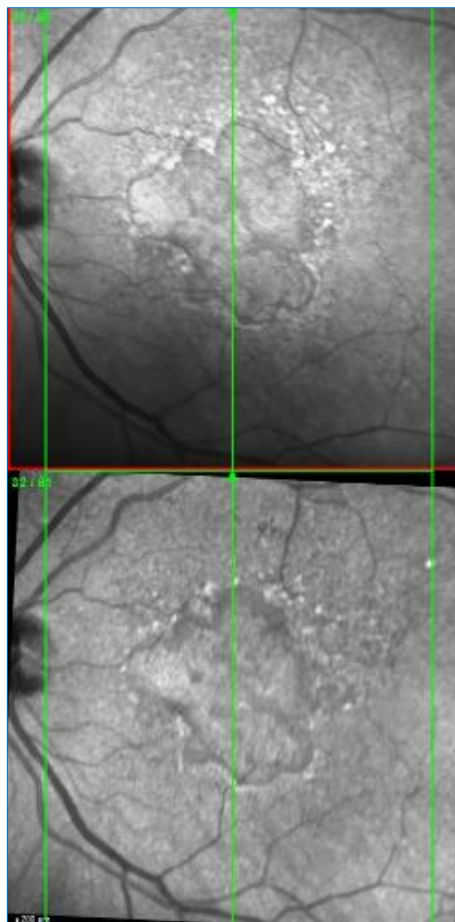
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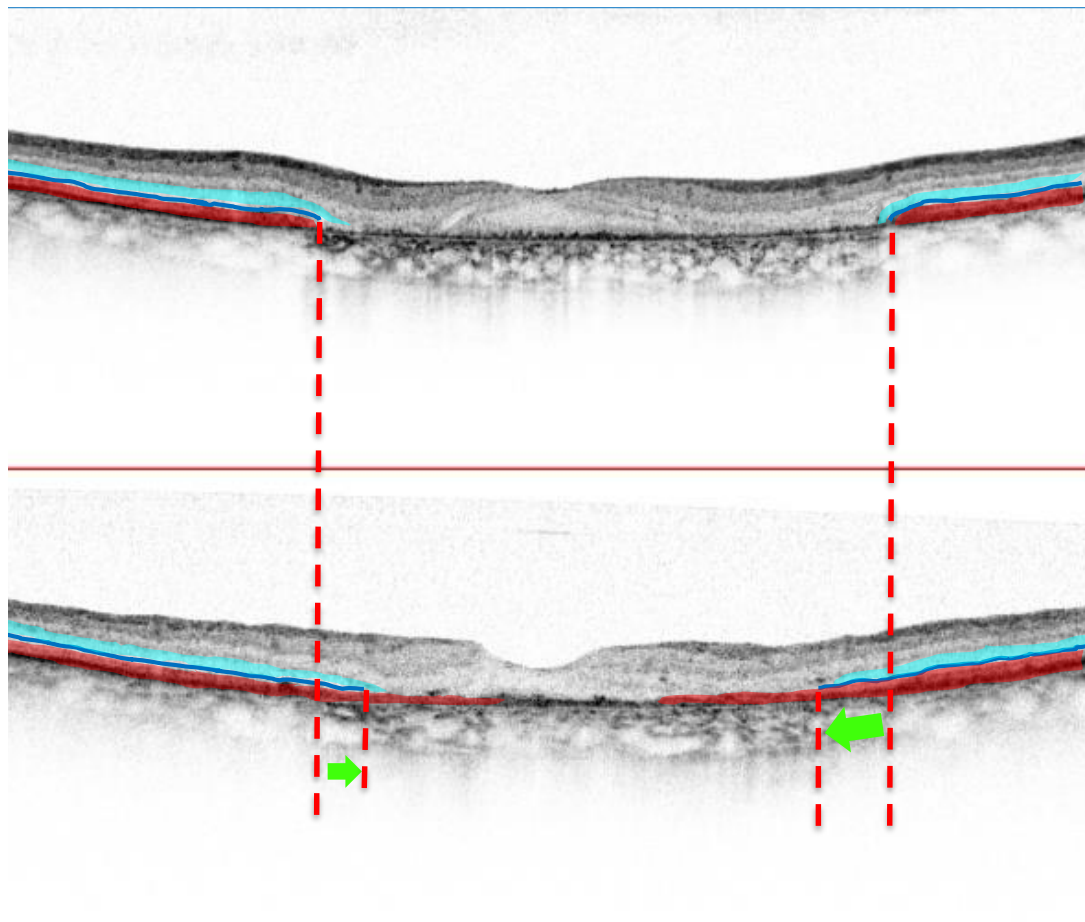
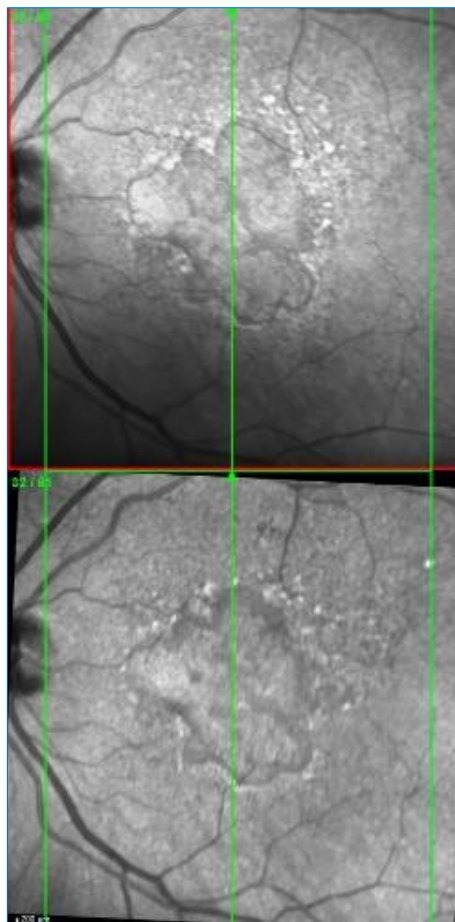
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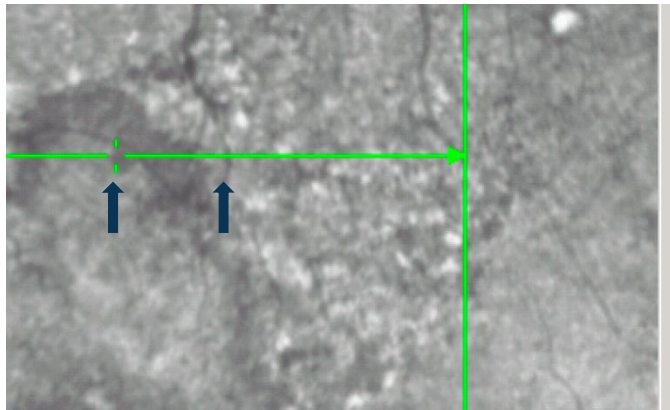
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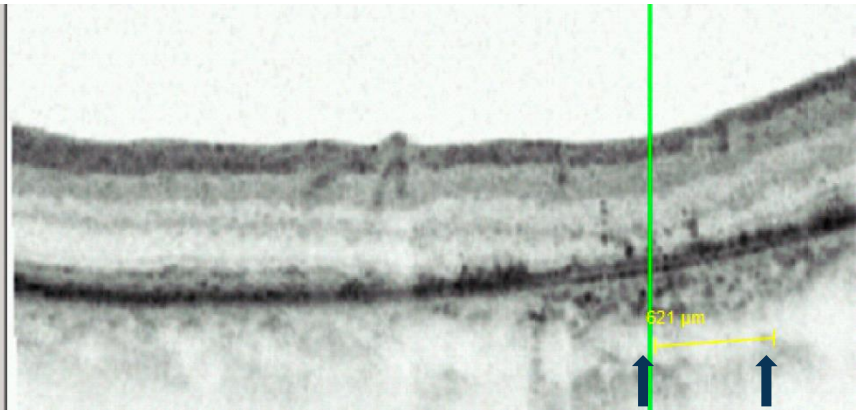
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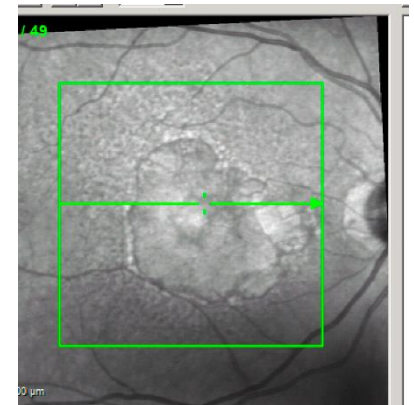
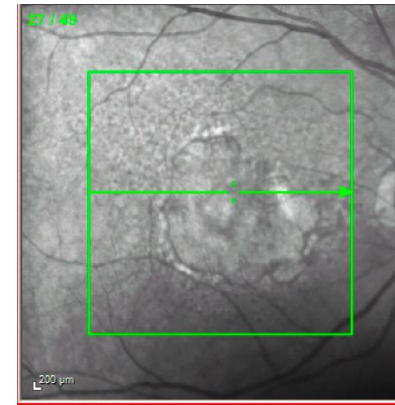
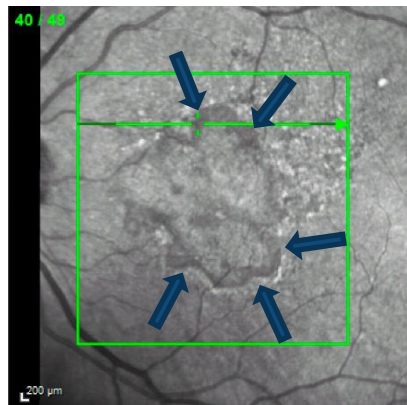
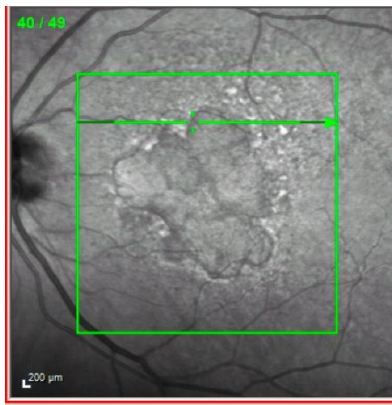
New Gray Rim at IR Image: A Finding Corresponding to the Area of Retinal Restoration



OS STUDY EYE



OD FELLOW EYE



- Enlarged gray rim (arrows) around all the area of atrophy following OpRegen treatment, which corresponds to RPE with ELM and ONL, was observed at Month 9
- No similar images were found in the fellow eye

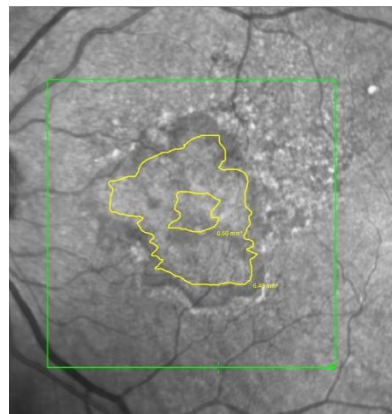
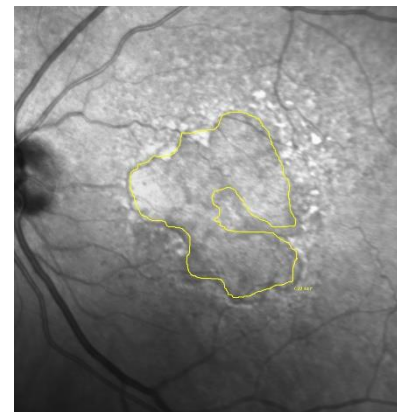
OCT Guided Calculation of Atrophy Boundaries Over Time

- Measurements of the area of atrophy have been performed, manually guided by the OCT features and overlaid on the infrared (IR) images
 - Measuring by FAF is not appropriate, since OpRegen RPE cells do not have autofluorescence and FAF doesn't take into the account the status of ELM/ONL
 - Measuring only from IR is not sufficient, which is why we used also OCT features
 - The criteria to exclude areas from the atrophy have been some evidence of preservation of ELM and ONL
 - Features only of RPE have not been used, ELM and ONL had to have been present

May 2017
Historical



July 2018
Baseline



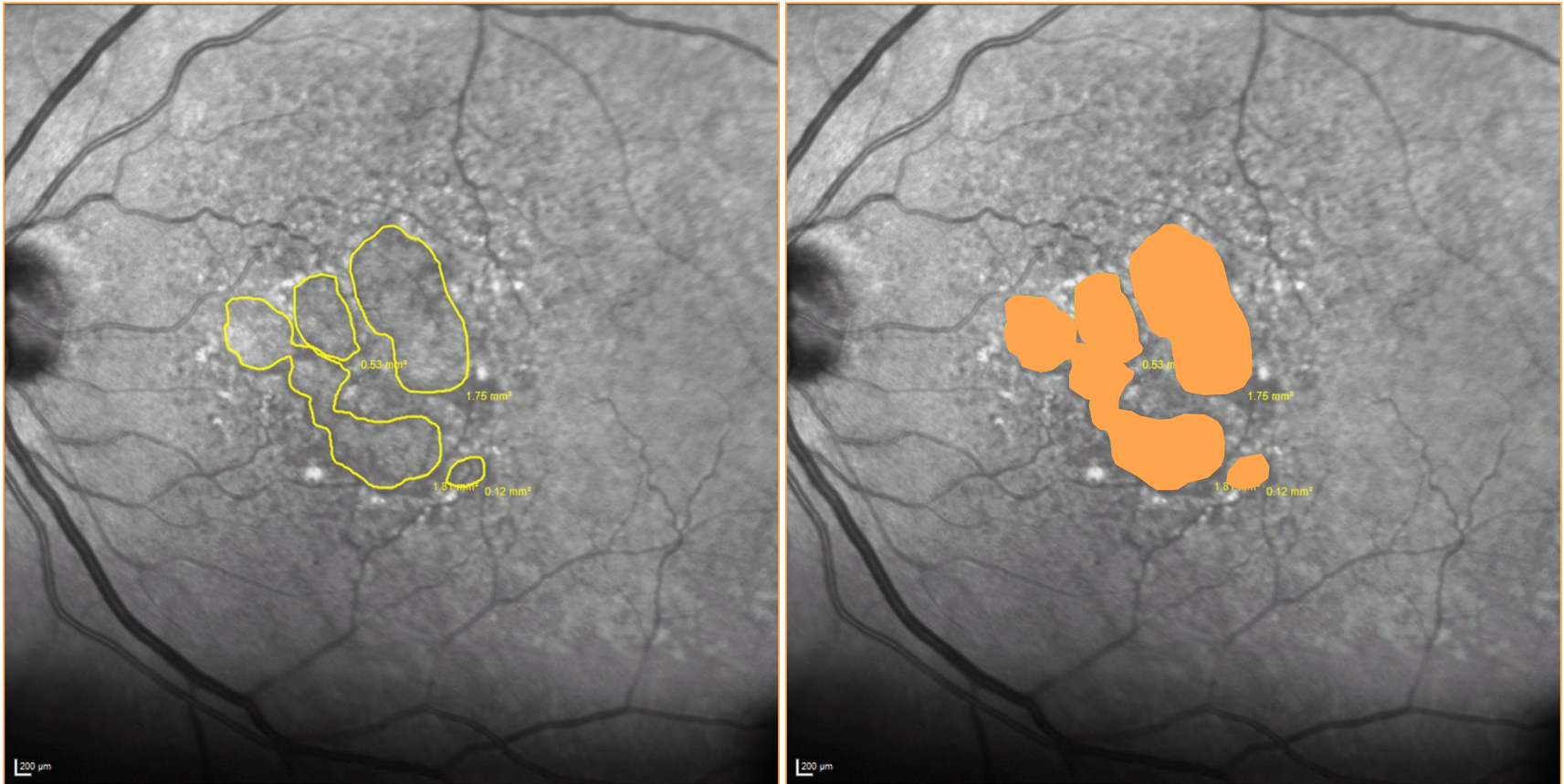
April 2019
9M post-Tx



October 2019
12M post-Tx

Progression of Atrophic Lesion Over Time – Historical Reference

Historical data (May 2017)
4.21 mm² (sqrt 2.05)



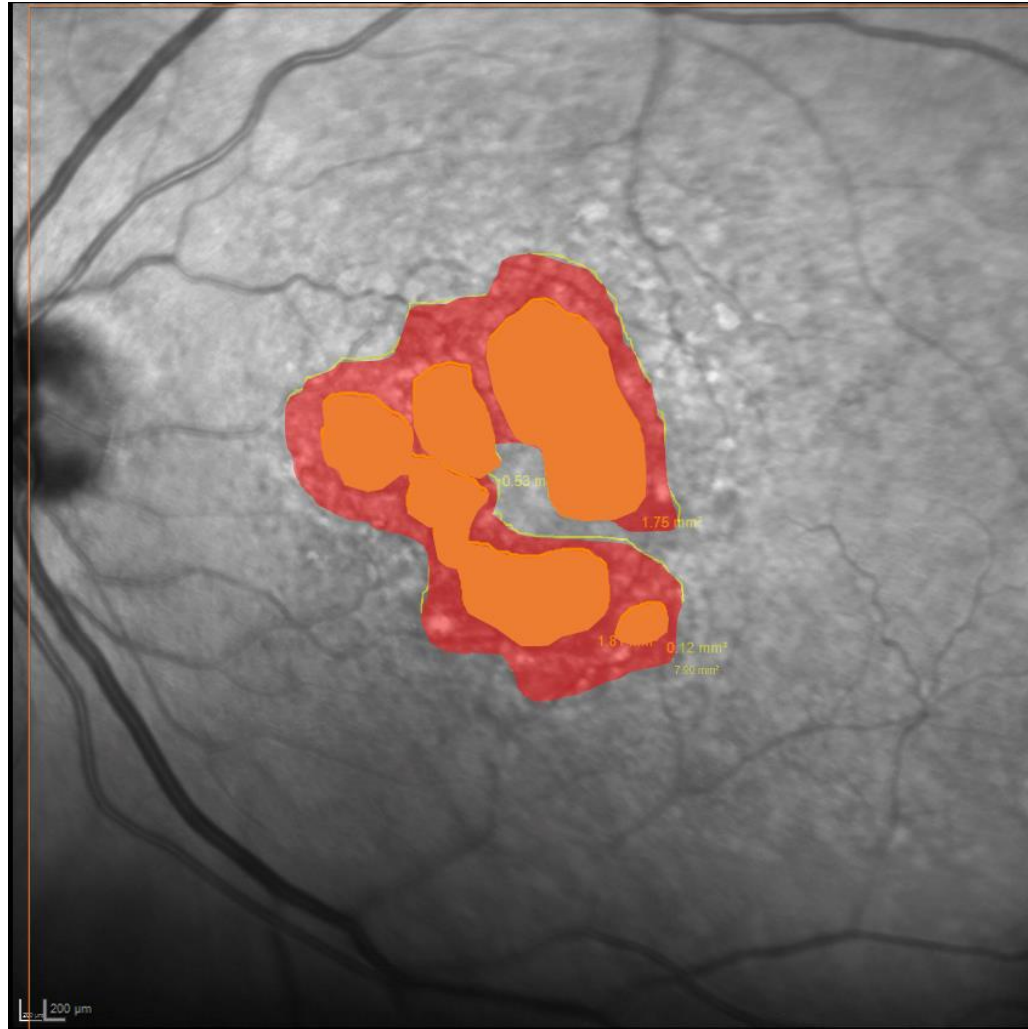
Progression of Atrophic Lesion Over Time – Baseline

Baseline (July 2018)
7.90 mm² (sqrt 2.8)



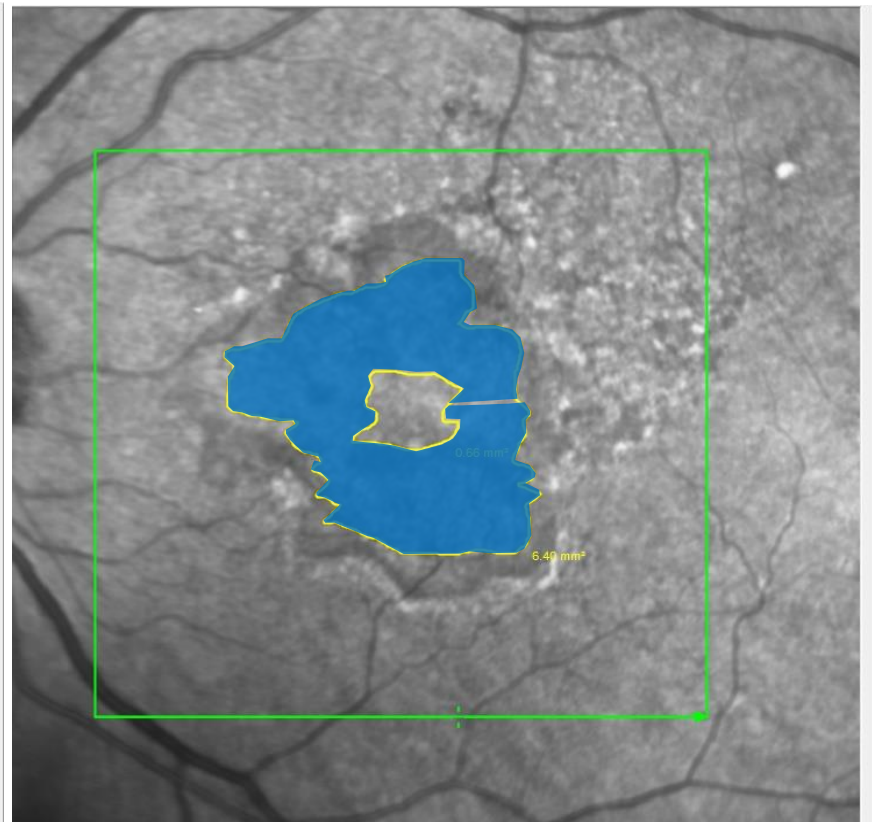
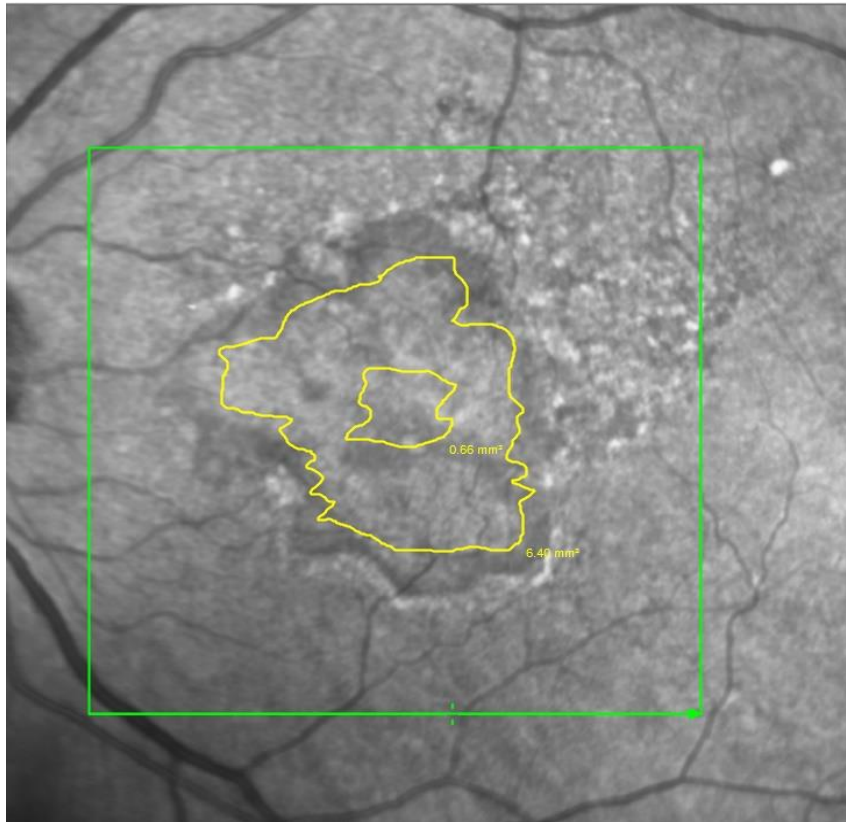
Rate of Atrophy Progression – Historical to Baseline

Change from historical image to Baseline: 0.64 mm SQRT/year



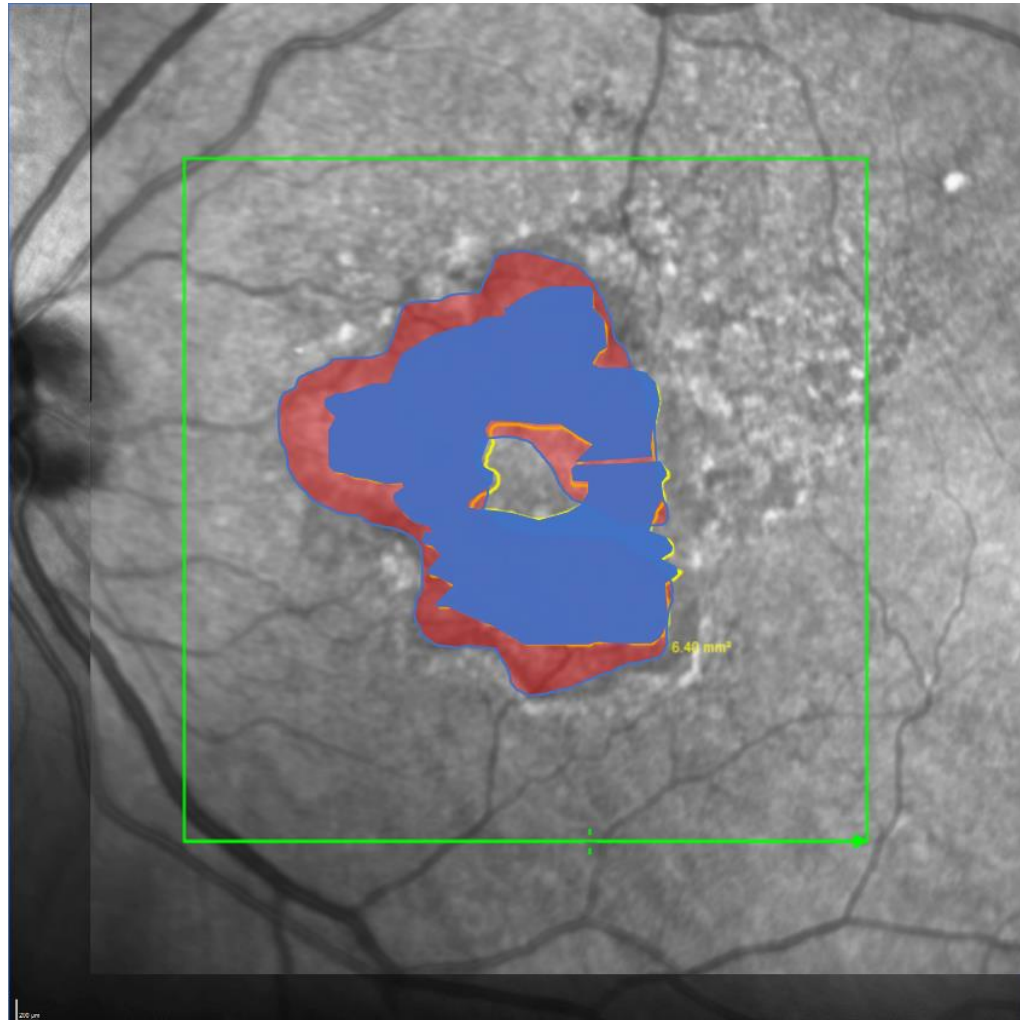
Atrophic Lesion 9 Months Post-OpRegen

9 months post-OpRegen (April 2019)
5.74 mm² (sqrt 2.39)



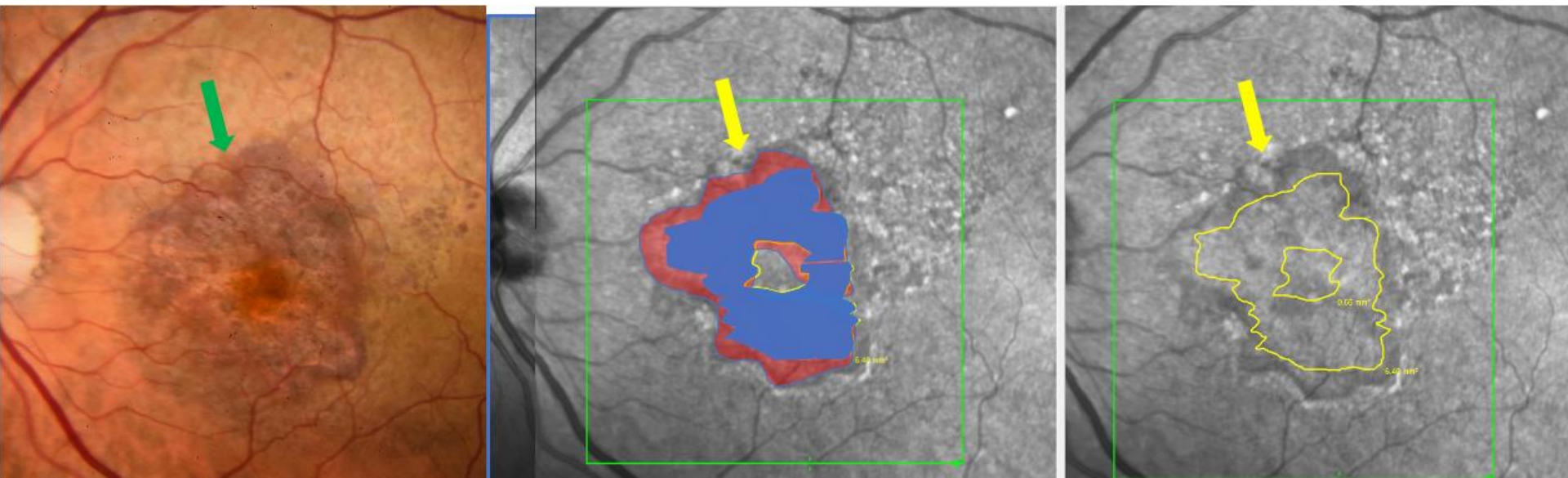
Rate of Atrophy Progression – Baseline to M9 Post-OpRegen Demonstrated Regression

Change from Baseline to M9 post-OpRegen: **- 0.55 mm** SQRT/year

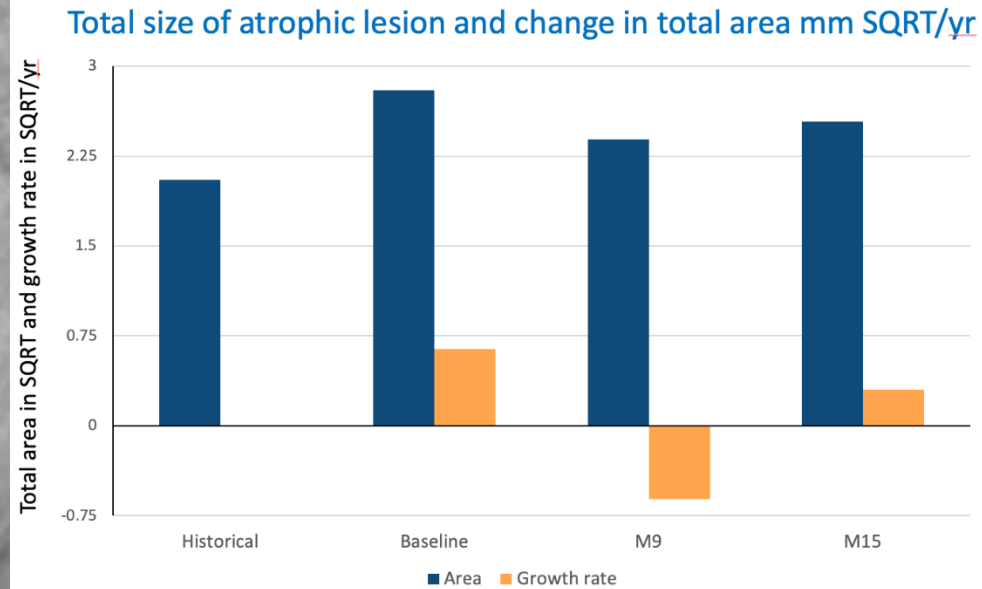
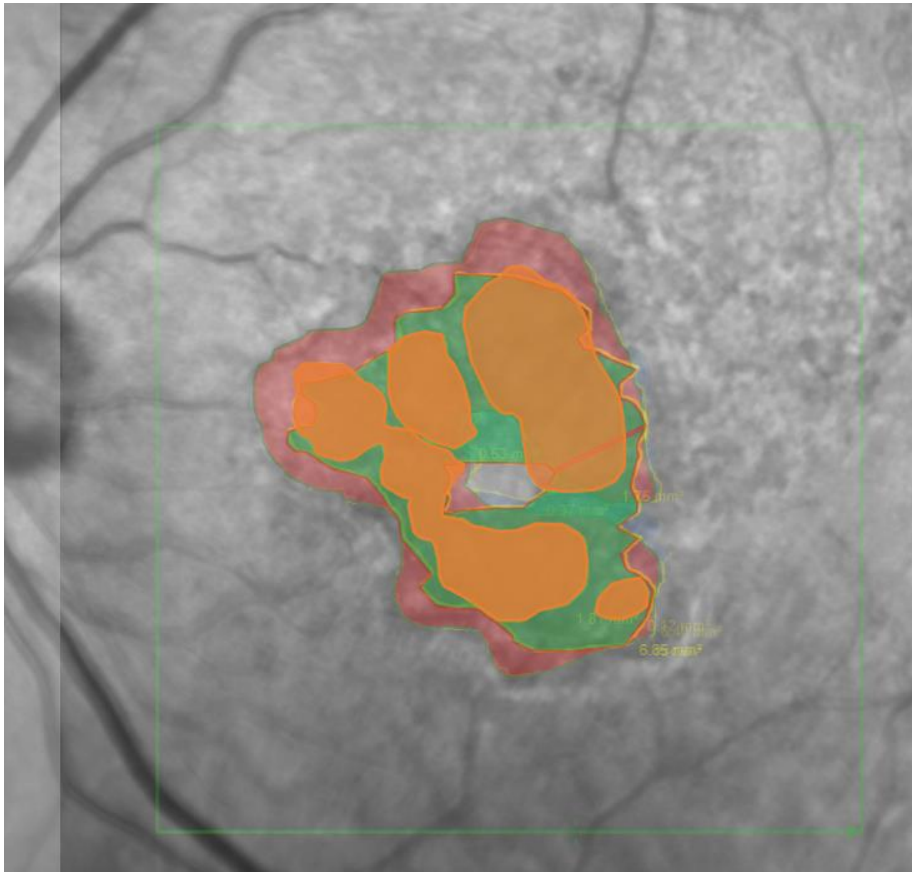


Subretinal Hyperpigmentation Corresponds to Regenerated Outer Retinal Layers

- The grayish band all around the lesion rim (yellow arrows) on IR corresponds to the brownish color visible on the CFP (green arrow) and to the regenerated outer retinal layers on OCT, which was consistently visible on multiple images



Rate of Atrophy Progression Indicated Regression of 27% from Baseline to Month 9





AMD is the **leading cause** of
irreversible vision loss in the US



Source: aao.org

Analyses of OpRegen (Patient #14)

Michael S. Ip, MD and Team

Analyses of OpRegen Subjects 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
- **Muneeswar Gupta Nittala, Swetha Velaga, Ken Marion, Kirstie Baker, Sowmya Srinivas, Ayesha Karamat, Christopher Okonkwo, Michael Ip, Vas Sadda**

Grading of Various Retinal Layers (3D-OCTOR)

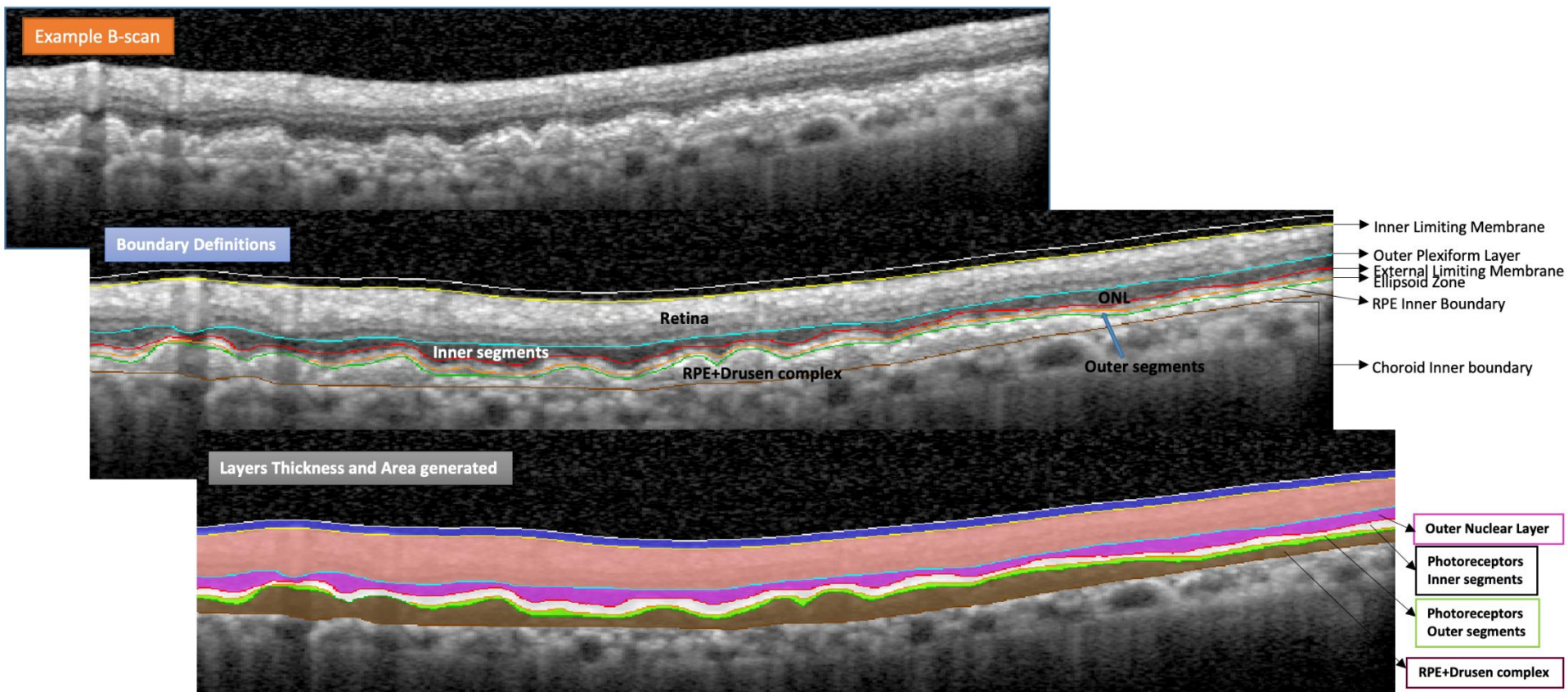


Illustration of Thickness and Area Maps Generated from 3D-OCTOR Grading

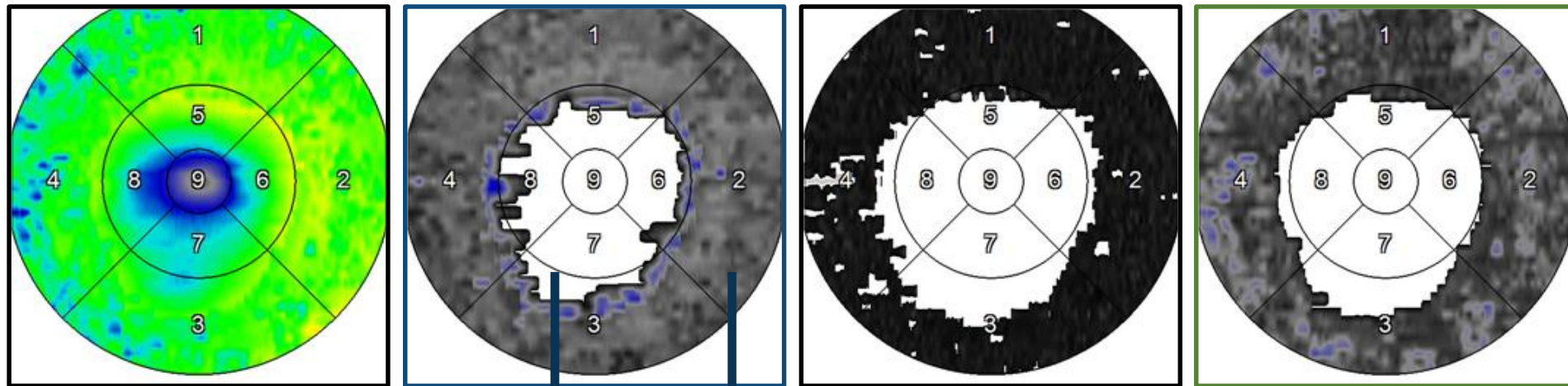
Areas in white or (dark blue/gray for total retina) represent absence or loss of various retinal tissues of interest, while areas in gray or black (green for total retina) show areas of preserved retinal tissue

Total Retina

Outer Nuclear Layer

Photoreceptors Outer Segments

RPE + Drusen Complex

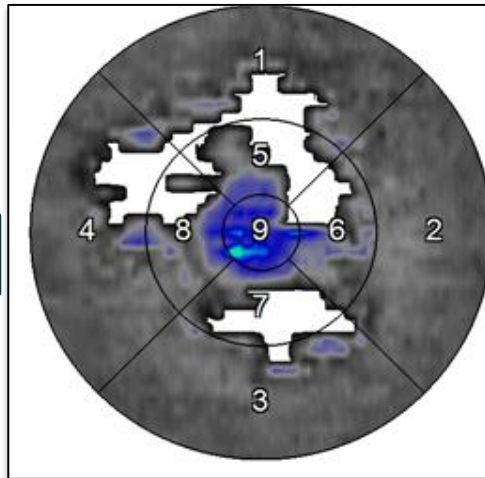


Areas of tissue loss

Areas of tissue preservation

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

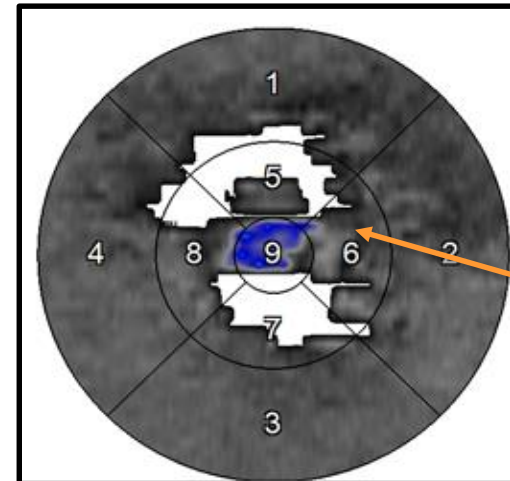
Baseline – 36.14 mm²



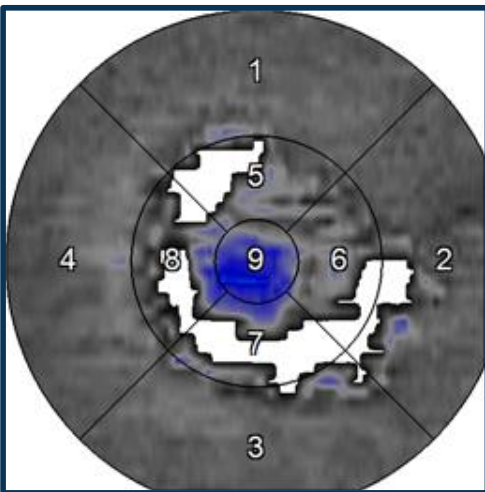
Study Eye



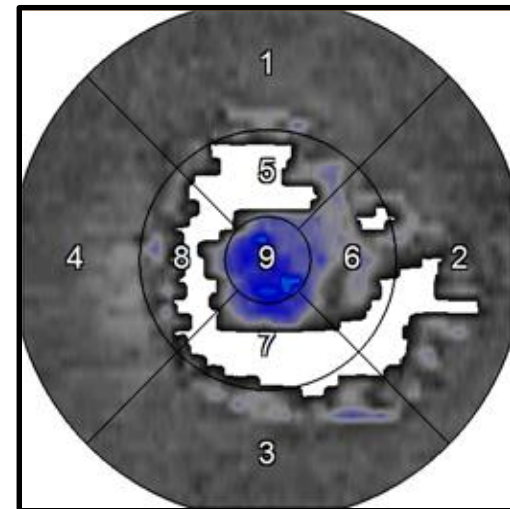
Month 12 – 36.59 mm²



Example of an improved region of ONL area



Fellow Eye



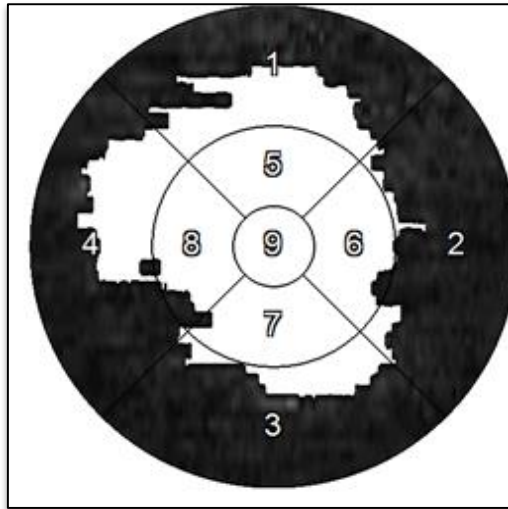
Baseline – 31.11 mm²

Month 12 – 30.09 mm²

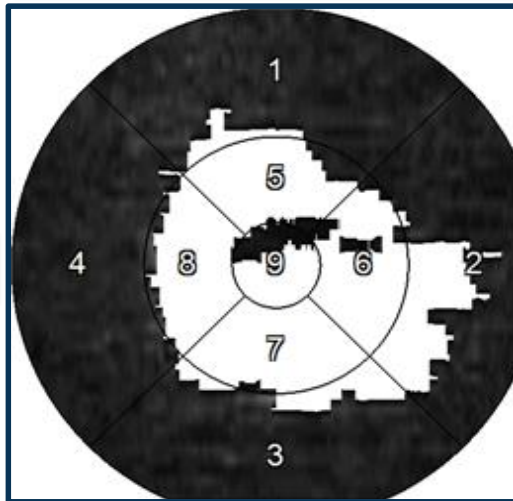
Photoreceptor Outer Segments – Area (mm²) (preserved area)

Study Eye

Baseline – 28.47mm²



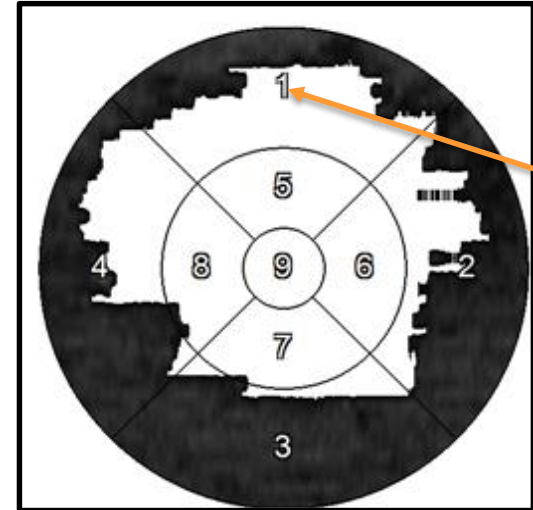
Fellow Eye



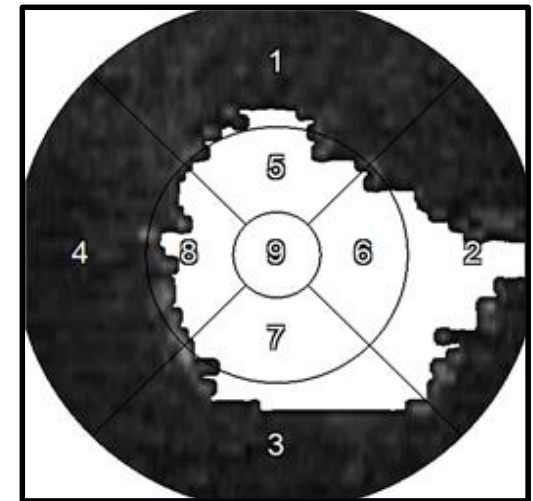
Baseline – 25.39 mm²



Month 12 – 25.79 mm²



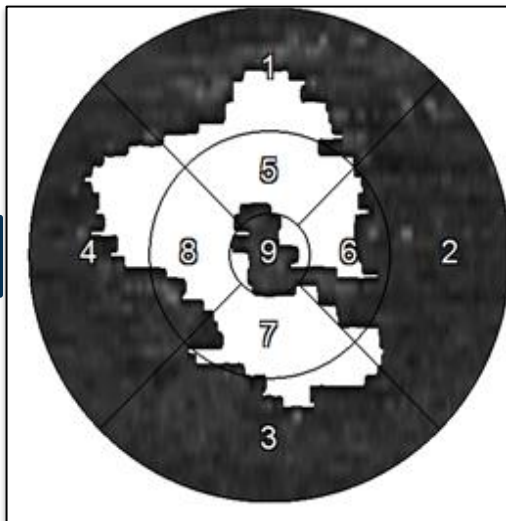
Example of areas with a loss of photoreceptor outer segments



Month 12 – 24.20 mm²

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

Baseline – 31.85 mm²

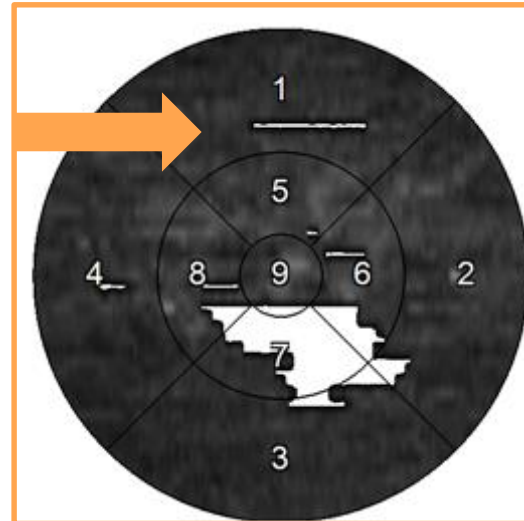


Study Eye

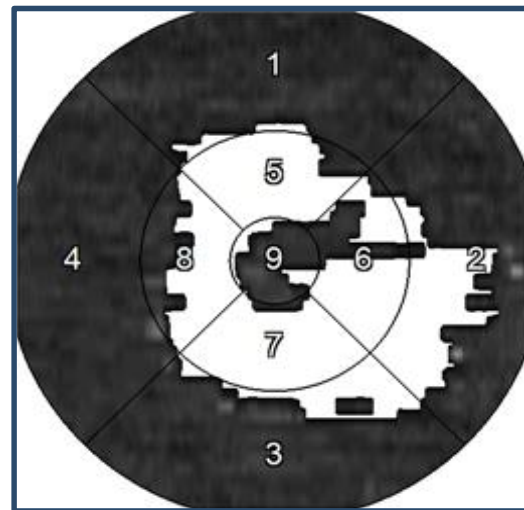
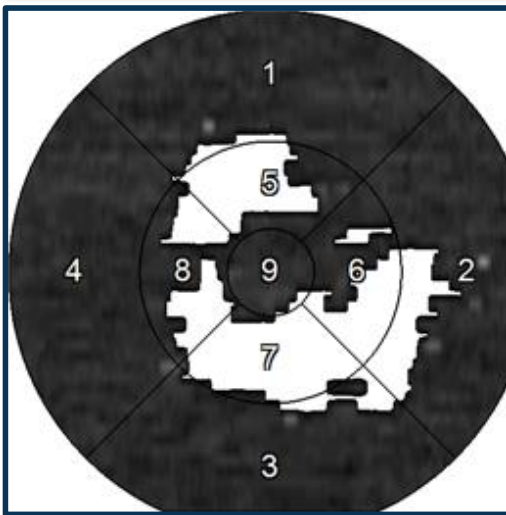
Increased RPE +
drusen complex
area in study eye
at Month 12



Month 12 – 37.59 mm²



Fellow Eye



Baseline – 28.66 mm²

Month 12 – 26.26 mm²

Summary of key 3D-OCTOR findings for OpRegen patient #14

- **RPE + Drusen complex area increased in area at Month 12 when compared to baseline**
- **ONL preserved area increased in study eyes at Month 12 compared to baseline**
- **PRL outer segments loss is persistent at Month 12**
 - Outer segments are traditionally difficult to evaluate and there is significant noise around this measurement



AMD is the **leading cause** of
irreversible vision loss in the US

Source: aao.org

Brian Culley, CEO

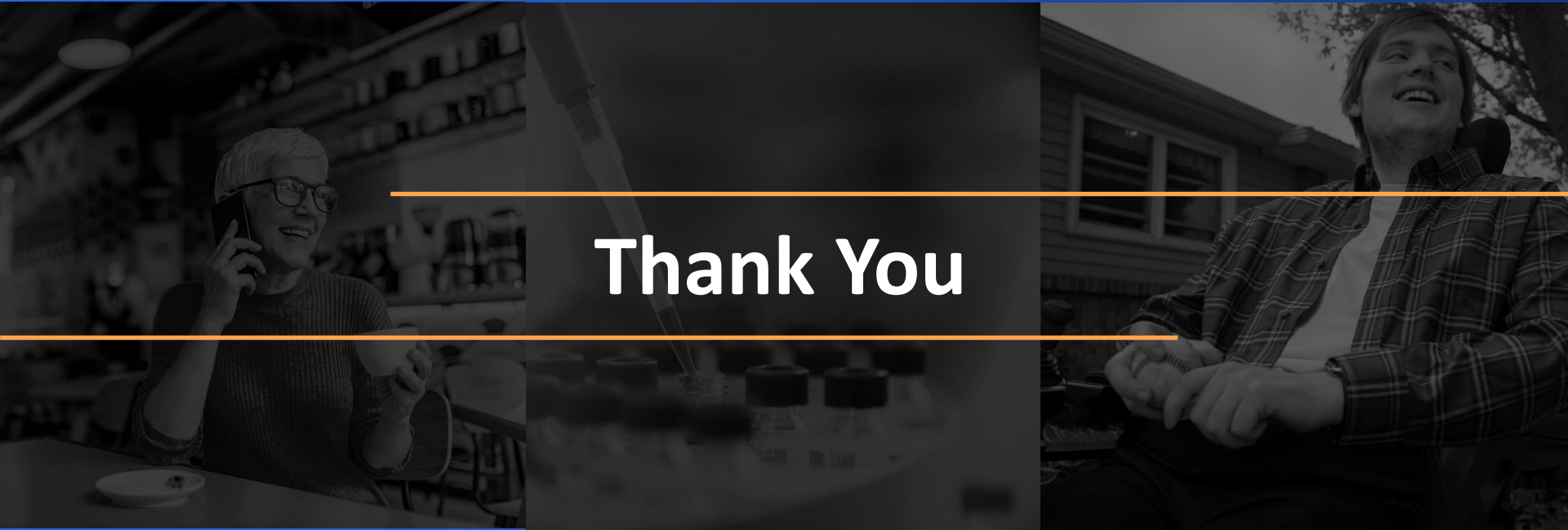
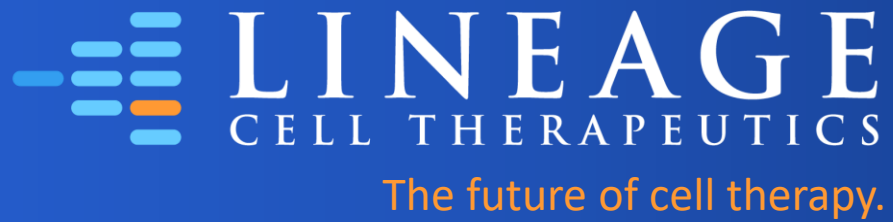
Clinical Findings to Date

- **OpRegen RPE cells have been well-tolerated; no marked, sustained reductions to vision in any patients (n=17)**
- **Most better baseline patients have improved vision at the 1-year time point or last available visit**
 - **Results from patient #14 mean that 1 in 3 of the better vision cohort at 1 year have seen dramatic results**
- **Directionally-positive findings observed across separate assessments and some patients have exhibited signs of:**
 - **Reduced growth of geographic atrophy**
 - **Improved visual acuity**
 - **Improved reading speed**
 - **Improved retina structure**
 - **Reductions in drusen waste material**
 - **Stable engraftment of cells**
- **No reports of acute or delayed inflammation or rejection of OpRegen cells**

Product Positioning

- **OpRegen RPE is being positioned to address a multi-billion commercial opportunity in atrophic dry AMD:**
 - Transplanting RPE cells may provide benefits unreachable by other approaches (complement inhibitors, oxidative stress reduction)
 - The desired patient population is not segmented by discrete dysfunctional pathways; the entire cell is replaced
 - Treatment has been well-tolerated with some patients exhibiting positive changes consistent with the desired treatment effect
 - Patents cover aspects of production, characterization, and formulation
 - Exclusive rights to unique delivery device

OpRegen: Delivering the best cells, the best way,
for the best outcomes.



Thank You

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