Safety and Efficacy of ATSN-201 Dose Escalation in Patients with X-Linked Retinoschisis (XLRS)

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OHSU

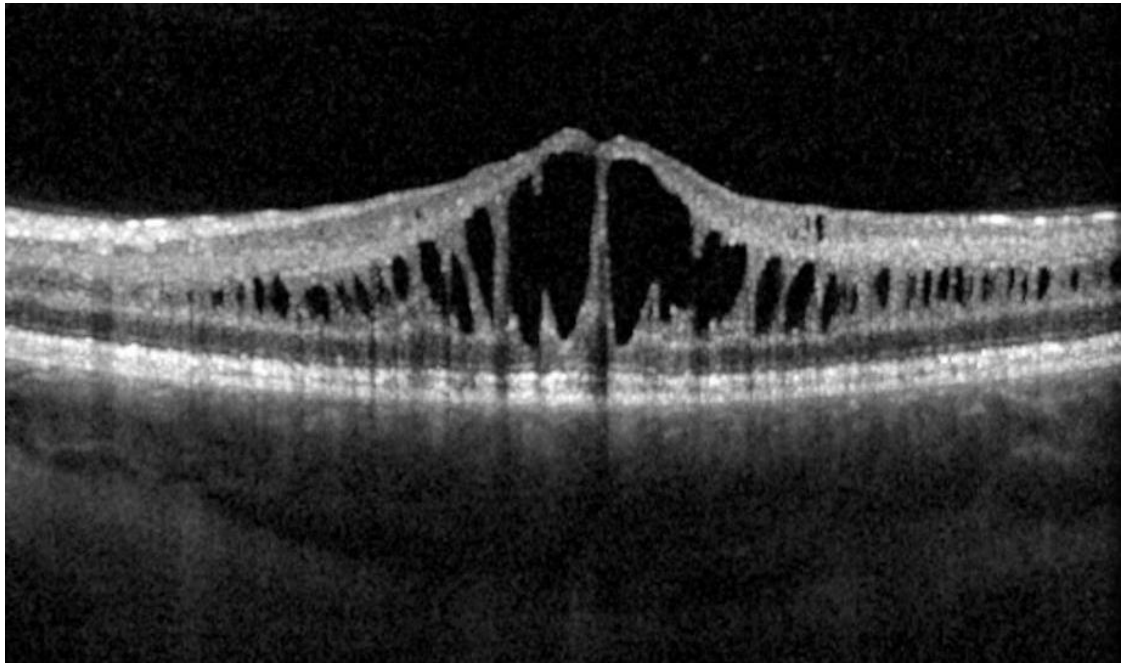
X-Linked Retinoschisis (XLRS)

XLRS is one of the most common causes of juvenile macular degeneration in males

XLRS is caused by pathogenic *RS1* variants

- ***RS1* encodes the protein retinoschisin (RS1)**, expressed primarily in photoreceptors and, to a lesser extent, bipolar cells
- Upon secretion, RS1 **binds to inner segments of rods and cones, bipolar cells**, and the outer plexiform layer
- RS1 has a role in **cell-cell adhesion, fluid balance, and the photoreceptor/bipolar cell synapse**
- Defects in *RS1* result in **loss of vision** due to splitting of retinal layers and increased **risk of retinal detachment**

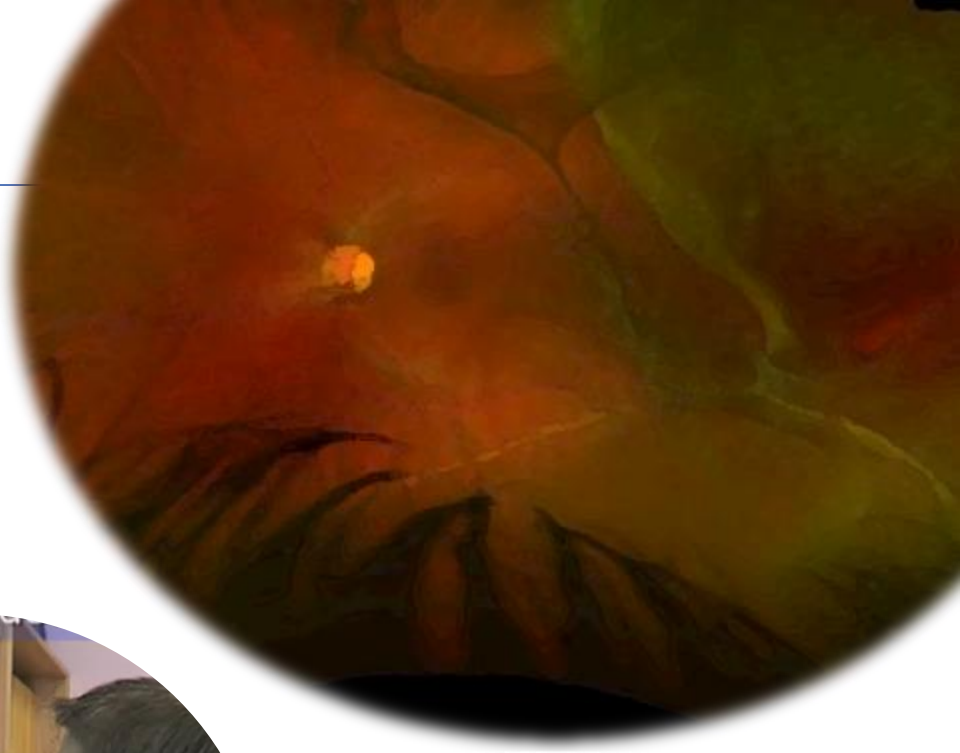
FOVEAL SCHISIS IN XLRS

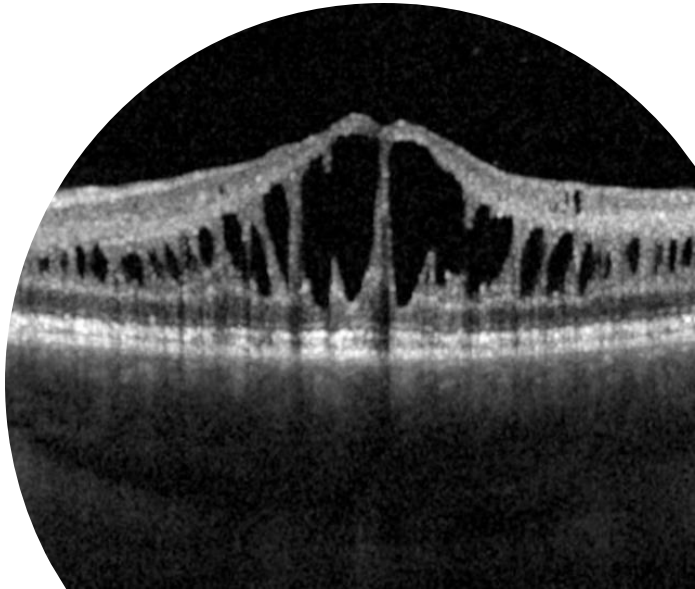


Molday RS, Kellner U, and Weber HFB. 2012.

Patient experience with XLRS

- XLRS affects **~35,000 people in the United States and Europe**
- As an X-linked disease, occurs primarily in **males**
- Young boys usually present with reduced vision by **early elementary school**
- Typically present with BCVA of **20/40 to 20/120**
- **Vision slowly deteriorates throughout life** and may progress to legal blindness (20/200) in the 5th or 6th decade of life
- Patients are at **risk of retinal detachment** and **vitreous hemorrhage**; they are are told to avoid activities that can cause trauma
- Increased surgical risk due to fragile retina: **avoid foveal detachment** with subretinal gene therapy
- No effective treatments

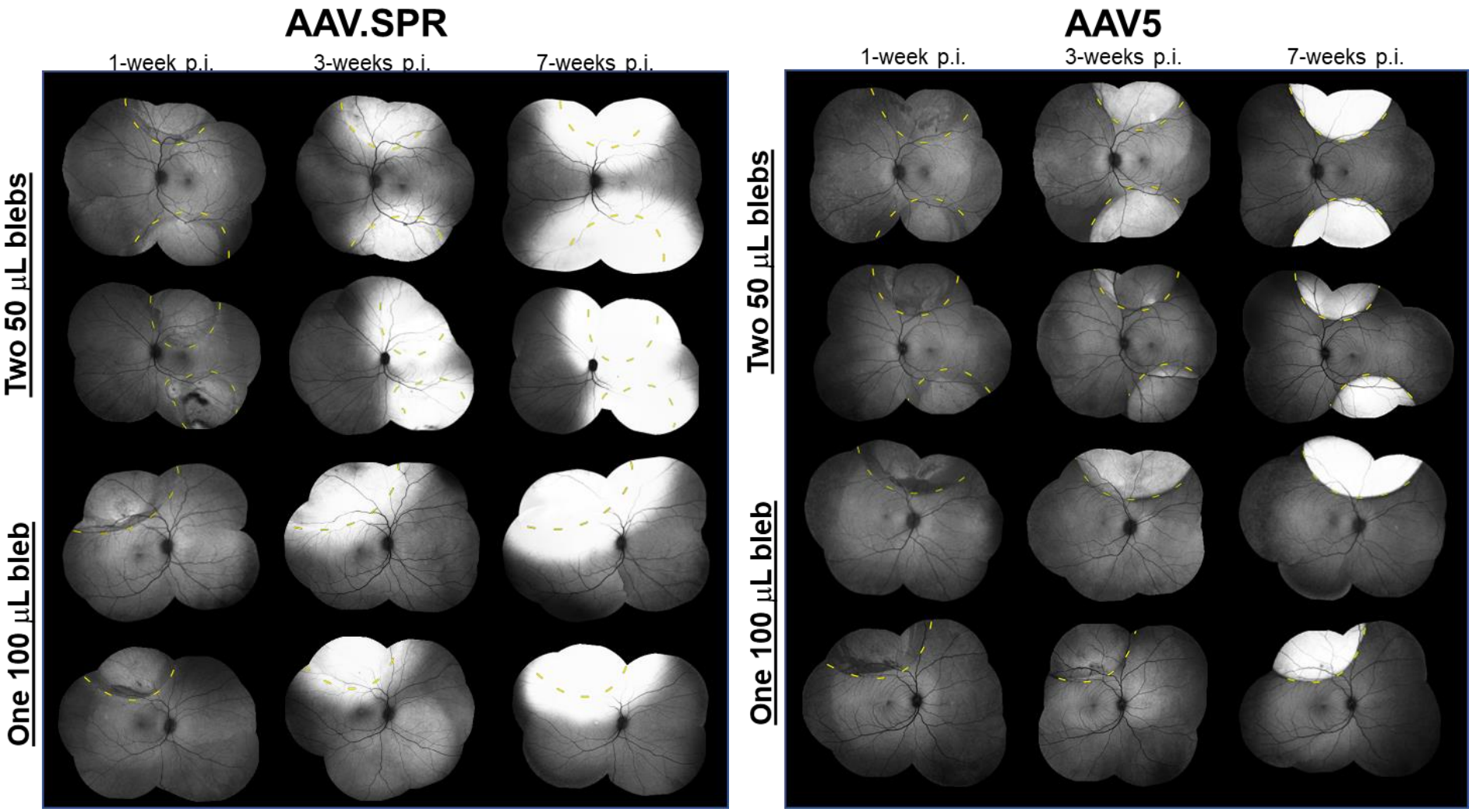




Molday RS, Kellner U, and Weber HFB. 2012.
Stavrakas et al. *Therapeutic Advances in Ophthalmology*. 2024;16.

AAV.SPR is a novel, laterally spreading AAV

Non-human primate (NHP) studies



- AAV.SPR promotes transgene expression (GFP) **7-12 mm beyond the borders** of the original subretinal injection bleb (yellow dotted lines)
- **AAV.SPR transduces foveal cones without the need for subfoveal injection**
- AAV.SPR transduces much larger areas of the retina
- Efficient foveal cone transduction is achieved with either one (100µL) or two (50µL) peripheral subretinal injections with AAV.SPR
- Outperforms benchmarks: **AAV5-mediated transgene expression is restricted to region of retinal detachment** and does not transduce foveal cones following peripheral subretinal injection

ATSN-201 subretinal gene therapy for XLRS

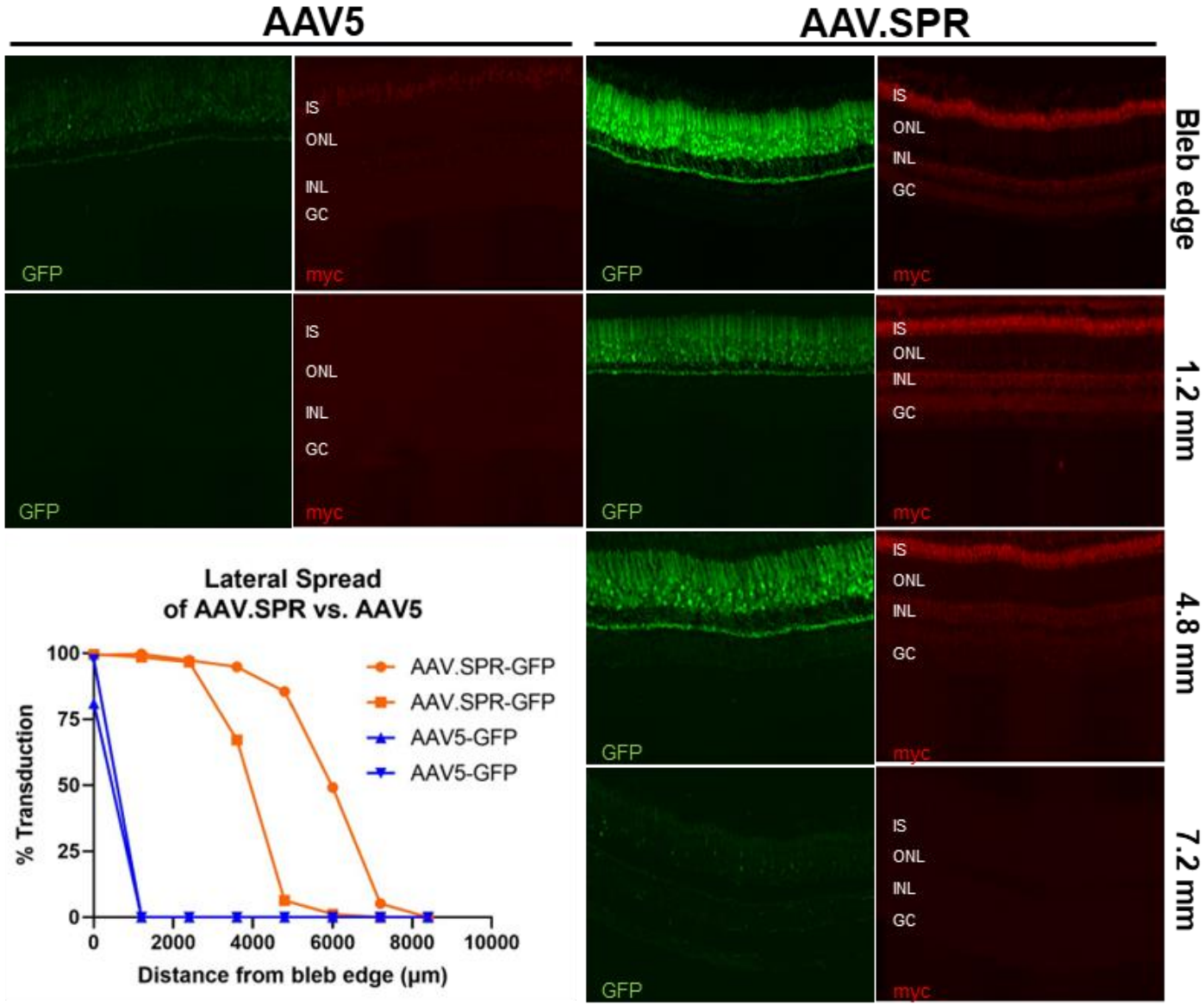
- **ATSN-201** (rAAV.SPR-hGRK1-*hRS1syn*) is a **subretinal gene therapy** product being developed to **introduce the functional human retinoschisin (*hRS1*) gene to photoreceptors**
  - Human rhodopsin kinase promoter
  - Wildtype human *RS1* transgene
  - Poly-adenylation signal derived from bovine growth hormone
- **AAV.SPR capsid**
  - **Does not bind to elements in the extracellular matrix (heparin sulfate, sialic acid)**
  - **Highly neurotrophic (photoreceptors > RPE)**

ATSN-201 rAAV Cassette
4549 bp

bGH = bovine growth hormone; hGRK1 = human rhodopsin kinase;
hRS1syn = synthetic human retinoschisin with synonymous point mutations;
ITR = inverted terminal repeat;
poly A = polyadenylation;
rAAV = recombinant adeno-associated virus;
SV40 SD/SA = simian virus 40 splice donor/splice acceptor;
WPRE = woodchuck hepatitis virus post-transcriptional regulatory element

AAV.SPR enables spread of RS1 outside region of local bleb placement

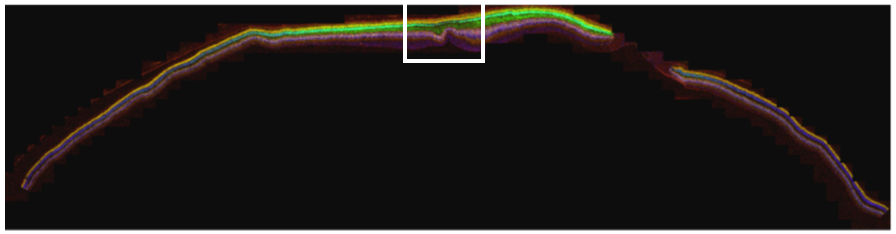
- Co-injected AAV-GFP and AAV-mycRS1 vectors (packaged in either AAV5 or AAV.SPR) into NHP.
- Examined retinal cross sections at equal distances away from bleb margins.
- Despite RS1 being a secreted protein, myc expression is only seen where there is also GFP, meaning mycRS1 is only locally secreted.
- Thus, AAV.SPR is needed to enable spread of RS1 into the central macula from a peripheral bleb.

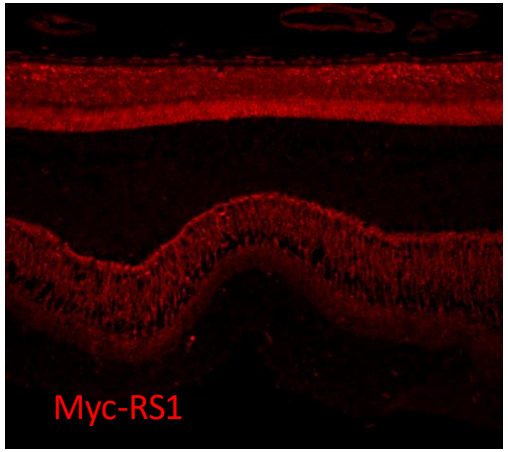


XLRS: Preclinical data using AAV.SPR in NHP and RS1 KO mouse

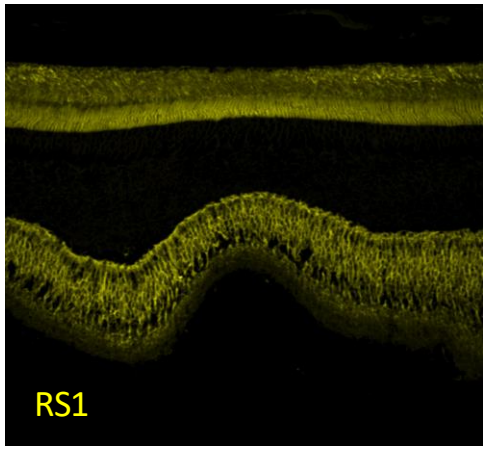
CROSS SECTION OF RETINA

NHP images



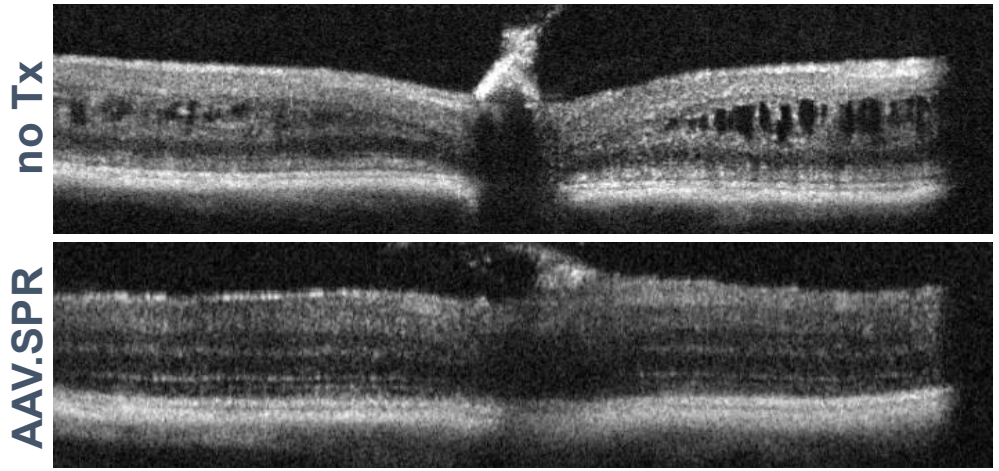


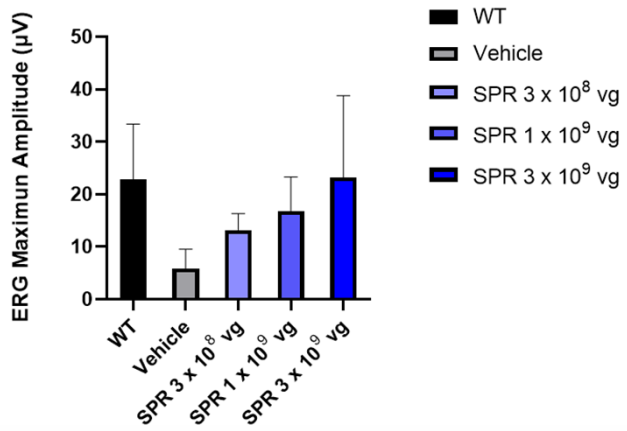
Robust expression in central retina



Myc staining perfectly co-localizes with endogenous RS1

Schisis cavities completely resolved (RS1 KO mouse)





- AAV.SPR capsid enables **safe** and **efficient** delivery of RS1 to the central retina of NHP.
- Preclinical data demonstrate **resolution of schisis cavities** and **restoration of retinal function** to wildtype levels (by ERG) in a RS1 knockout mouse model.

XLRS Phase 1/2 Clinical Trial Design (NCT05878860)

150 µL of ATSN-201 was administered by subretinal injection to the worse-seeing eye, using 2-3 blebs and avoiding foveal detachment

ENROLLED	COHORT	PART A: Dose Escalation	
✓	1	Low dose (N=3), ≥ 18 years	1.5E10 vg/eye
✓	2	High dose (N=3), ≥ 18 years	5.0E10 vg/eye
✓	3	Mid dose (N=3), ≥ 18 years	3.0E10 vg/eye

BASELINE CHARACTERISTICS

	COHORT 1	COHORT 2	COHORT 3
Median age in years (range)	21 (18 to 26)	24 (18 to 60)	26 (24 to 31)
Median Snellen BCVA (range)	20/50 (20/50 to 20/160)	20/100 (20/50 to 20/100)	20/100 (20/40 to 20/125)

Corticosteroid administration: 7-week oral prednisone regimen starting at 1 mg/kg/day, 20 mg triamcinolone acetonide periocular injection, 250 mg IV methylprednisolone, and 28-day topical prednisolone acetate 1% regimen

Key inclusion criteria:

- Male with clinical diagnosis of XLRS caused by **pathogenic or likely pathogenic mutations in *RS1***
- BCVA of **34 to 73 ETDRS letters** (20/200 to 20/40)
- Presence of **foveal (or parafoveal/perifoveal) schisis** in the study eye on OCT

Primary endpoint:

- The incidence of **dose-limiting toxicities (DLTs)** and **treatment-emergent adverse events (TEAEs)** over a 52-week period following a single subretinal dose of ATSN-201 (safety follow-up will continue to 5 years)

Key secondary endpoints:

- **Structural: Optical coherence tomography (OCT)**
- **Functional:**
  - **Microperimetry (MP)**
  - **Best-corrected visual acuity (BCVA)**
  - **Low luminance visual acuity (LLVA)**

ATSN-201 has demonstrated a favorable safety profile

Data cutoff: 5 March 2025

No DLTs and no instances of macular hole formation or retinal detachment

Total of 76 TEAEs reported
- 73 Grade 1-2 in severity
- 46 related to surgical procedure

Cohort 2 (high dose):
- 3 TEAEs of subretinal deposits
- 3 TEAEs of retinal thickening
- 1 TEAE of ERM (significant intra-operative laser)
- Improvement with additional steroids

Cohort 3 (mid dose):
- 1 TEAE of subretinal deposits
- 3 TEAEs of retinal thickening
- Improvement with additional steroids

No subjects have discontinued from the study

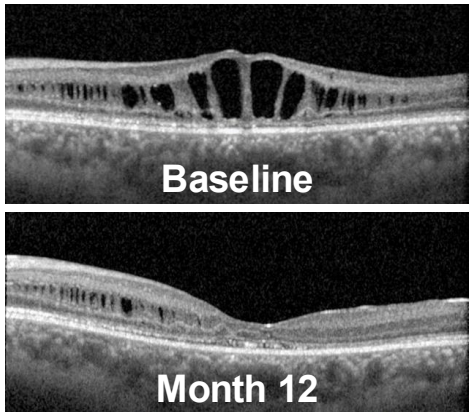
No treatment-related SAEs
- 1 SAE of fever of unknown origin with negative workup (7 months after treatment)

	Cohort 1 N=3	Cohort 2 N=3	Cohort 3 N=3	Total N=9
# of Events				
Any TEAE	29	27	20	76
Any Serious TEAE	1	0	0	1
Any Severe TEAE	1	2	0	3
Severity				
Grade 1	21	14	14	49
Grade 2	7	11	6	24
Grade 3	1	2	0	3
Grade 4 or 5	0	0	0	0
Related to ATSN-201				
Possibly / Probably / Definitely Related	3	10	6	19
Not Related / Unlikely to be Related	26	17	14	57
Related to Surgical Procedure				
Possibly / Probably / Definitely Related	20	17	9	46
Not Related / Unlikely to be Related	9	10	11	30

7 of 9 treated eyes had closure of foveal schisis

Cohort 1 (Low Dose)

Subject #1



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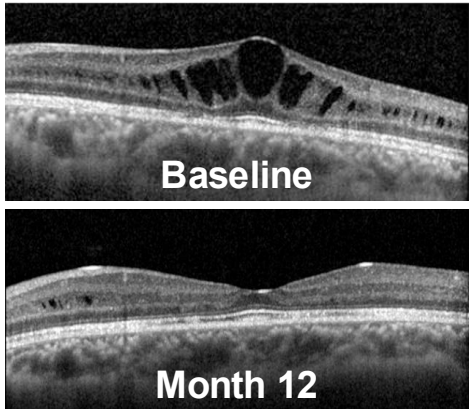
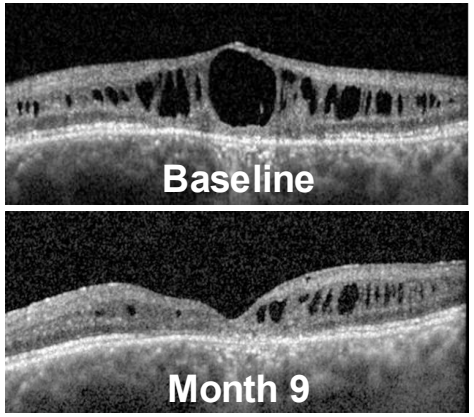
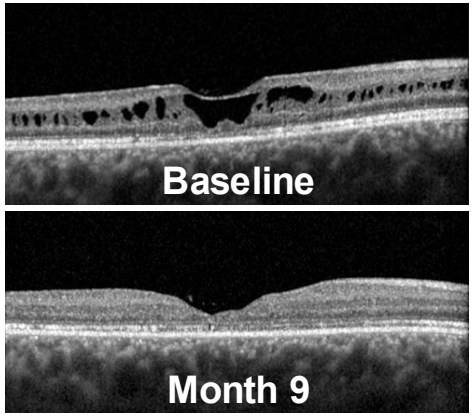


Cohort 2 (High Dose)

Subject #4

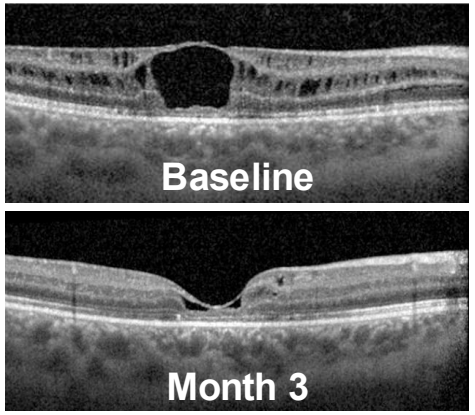


Subject #6



Cohort 3 (Mid Dose)

Subject #7



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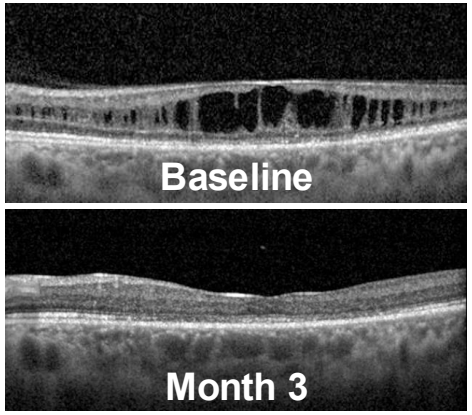
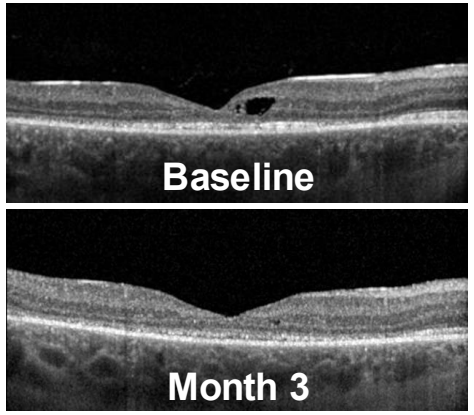


Subject #9



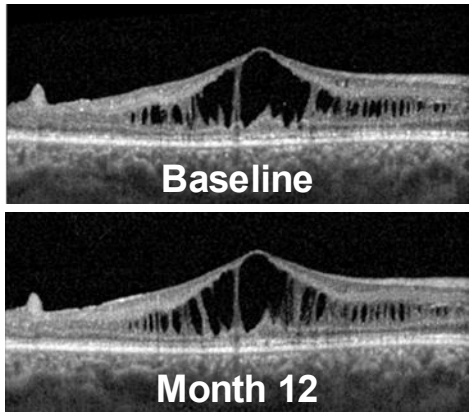
For the 2 treated eyes that did not demonstrate foveal schisis closure:

- **Subject #2** had blebs placed further in the **periphery**
- **Subject #5** developed **ERM** following intra-operative laser

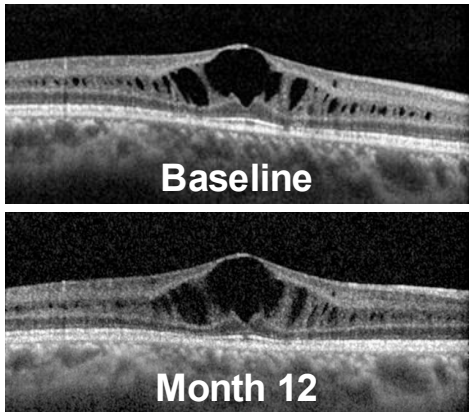
Untreated eyes did not demonstrate foveal schisis closure

Cohort 1 (Low Dose)

Subject #1

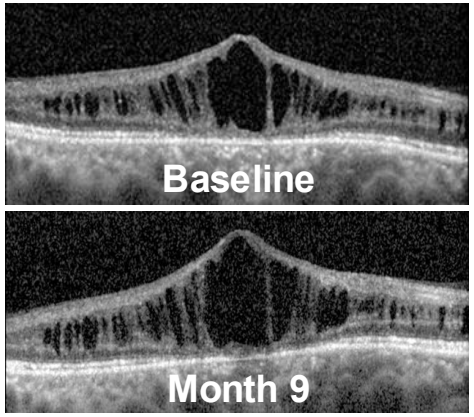


Subject #3

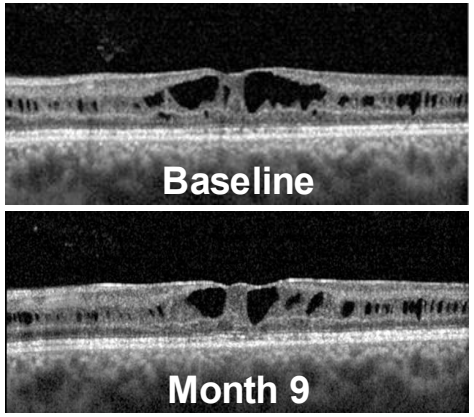


Cohort 2 (High Dose)

Subject #4

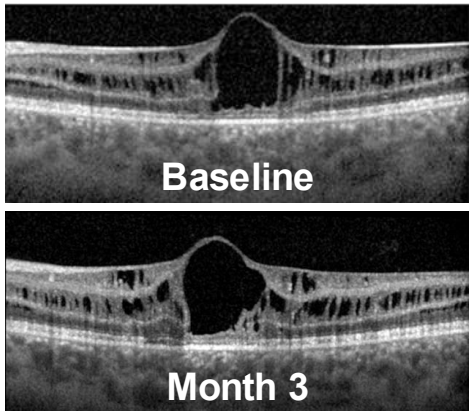


Subject #6



Cohort 3 (Mid Dose)

Subject #7



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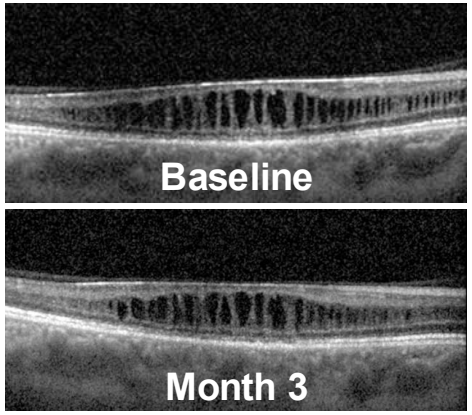

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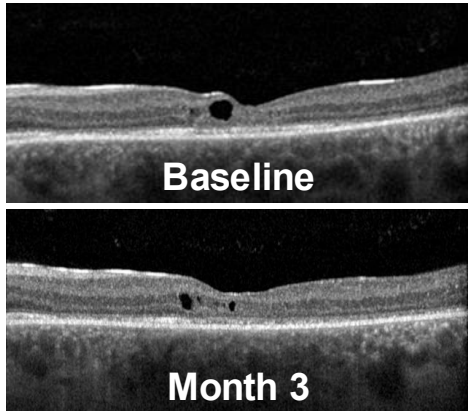
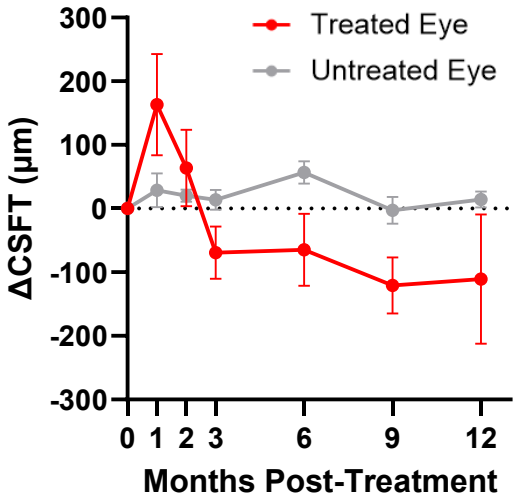


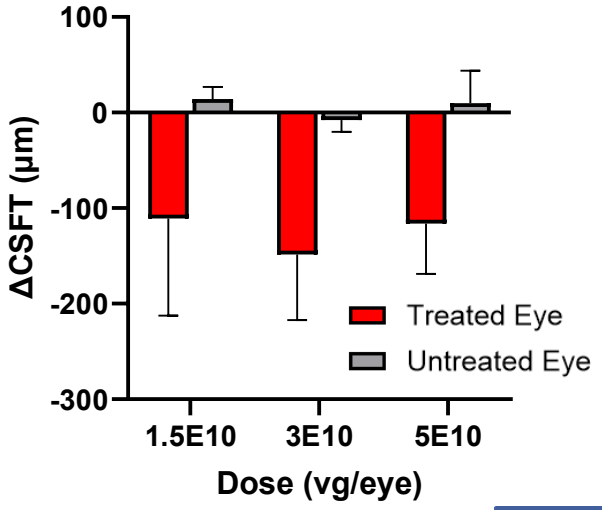
Treated eyes demonstrate a significant reduction in retinal thickness

Data represented as central subfield thickness (CSFT, 1 mm diameter)

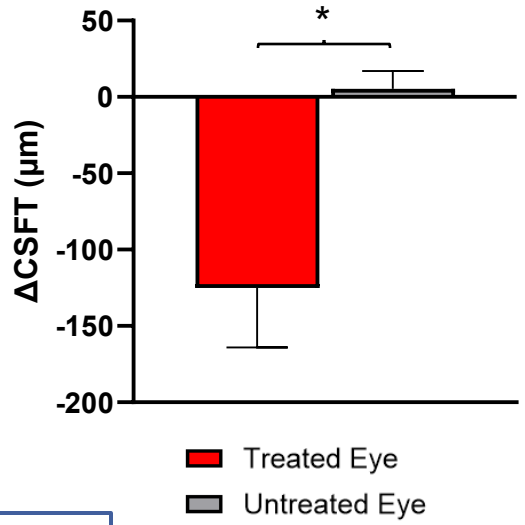
Change in retinal thickness over time



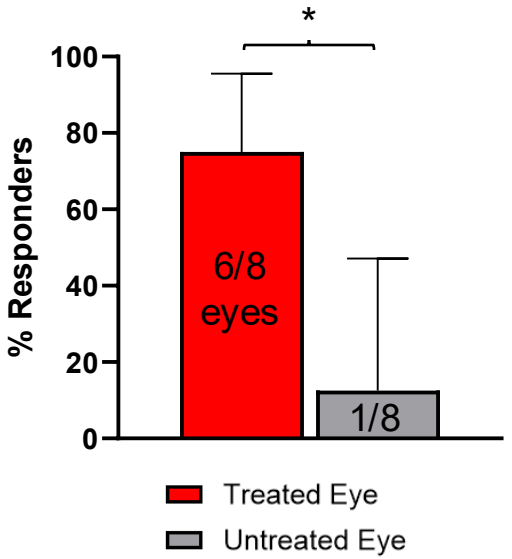
Change in retinal thickness by cohort



Change in retinal thickness for all cohorts combined



% Responders for all cohorts combined



*$P < 0.05$

Data include:

- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

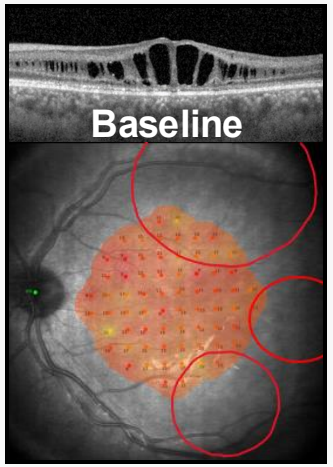
Responder if **decrease in CSFT > repeatability (22%)**
(Subject #9 excluded due to absence of foveal schisis at Baseline)

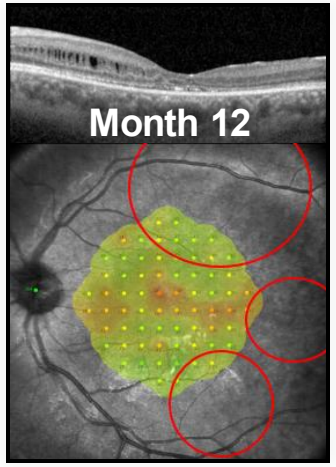
Jeffrey BG, Cukras CA, Vitale S, et al. 2014.

Eyes with structural improvements generally show improvements in function

Cohort 1 (Low Dose)

Subject #1





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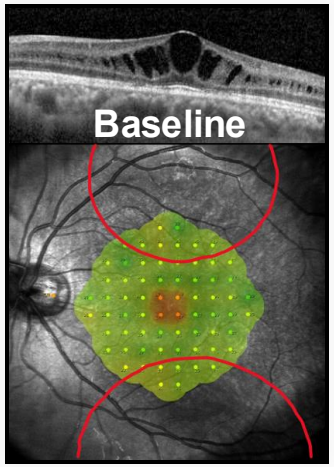
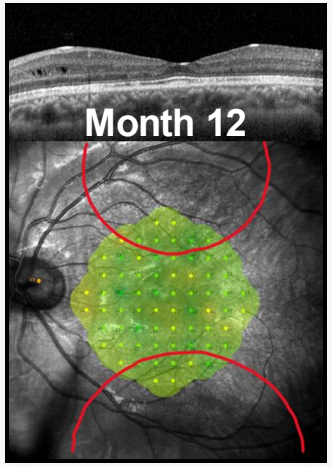
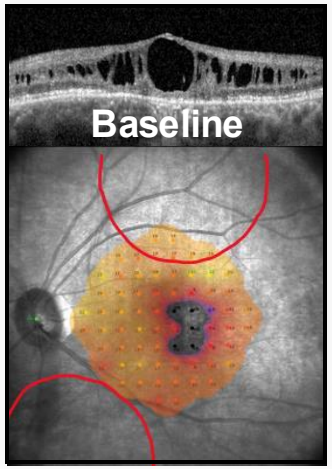
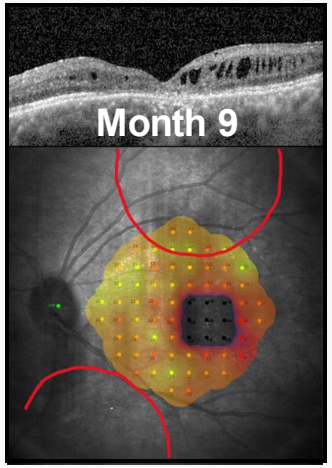




Cohort 2 (High Dose)

Subject #4





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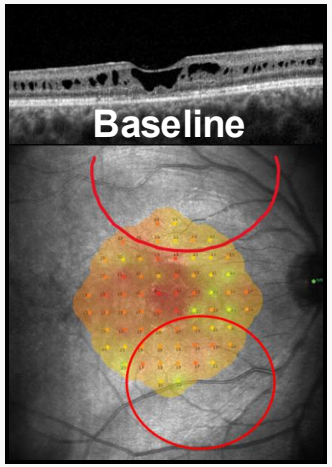
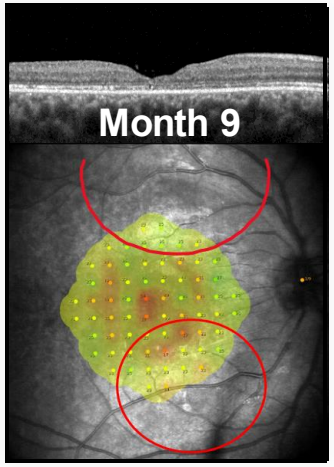
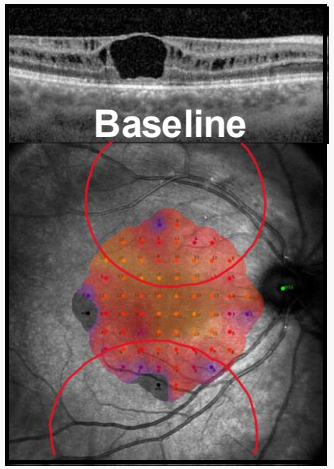
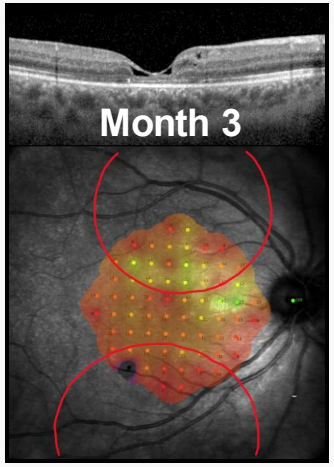




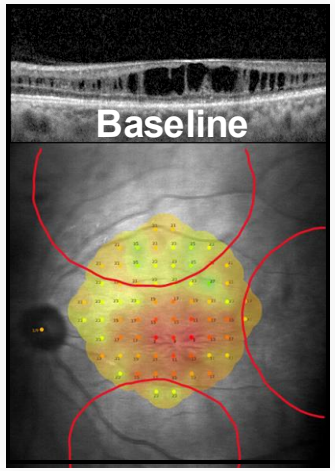
Cohort 3 (Mid Dose)

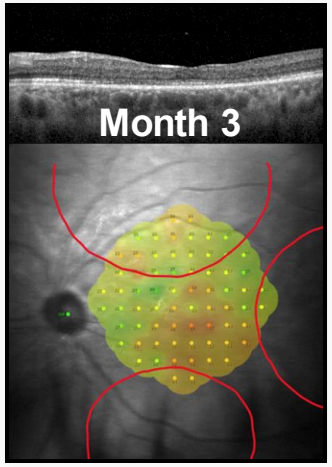
Subject #7



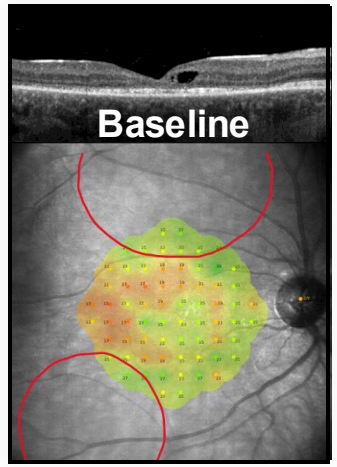


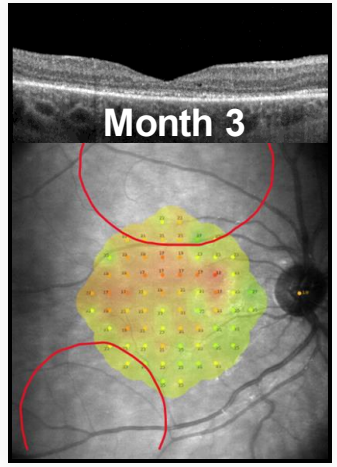
Subject #8



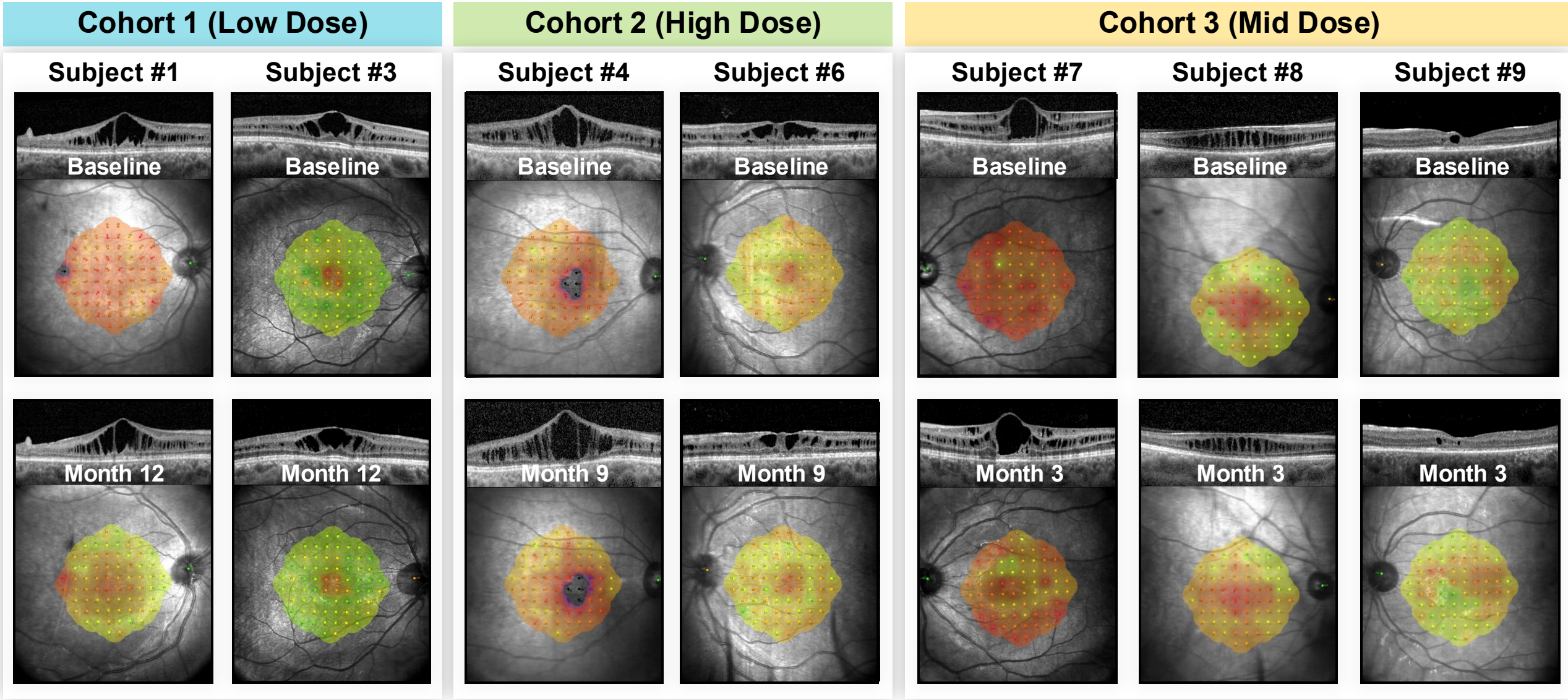


Subject #9





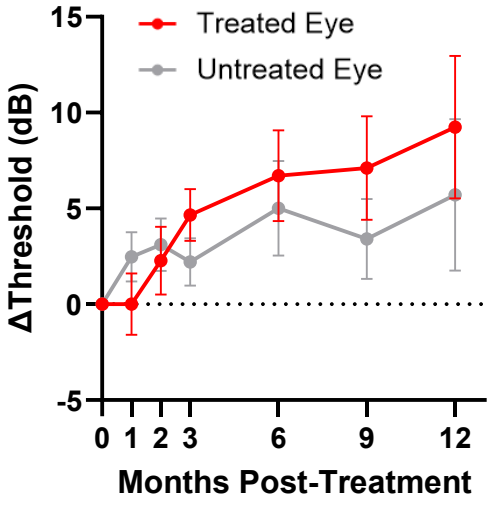
Untreated eyes changed minimally, with some showing a possible learning effect



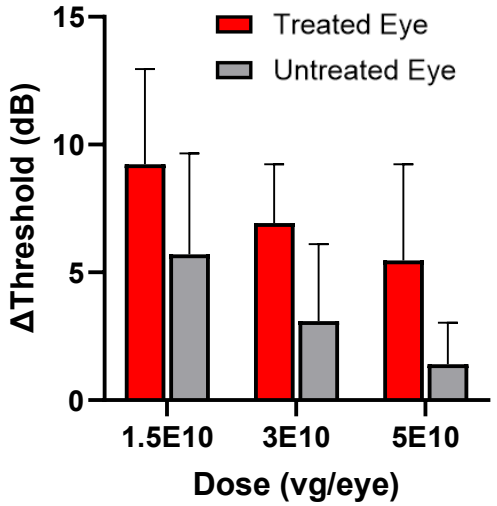
Treated eyes demonstrate improvements in MP compared to untreated eyes

Data represented as average of 5 loci with lowest sensitivity at Baseline (19 dB cutoff, additional loci included if tied)

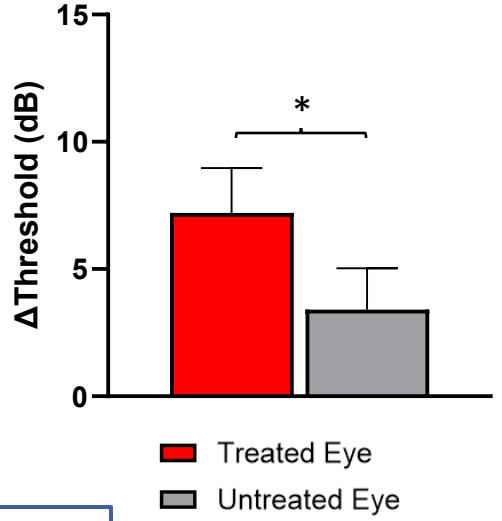
Change in retinal sensitivity over time



Change in retinal sensitivity by cohort



Change in retinal sensitivity for all cohorts combined



% Responders for all cohorts combined

*$P < 0.05$

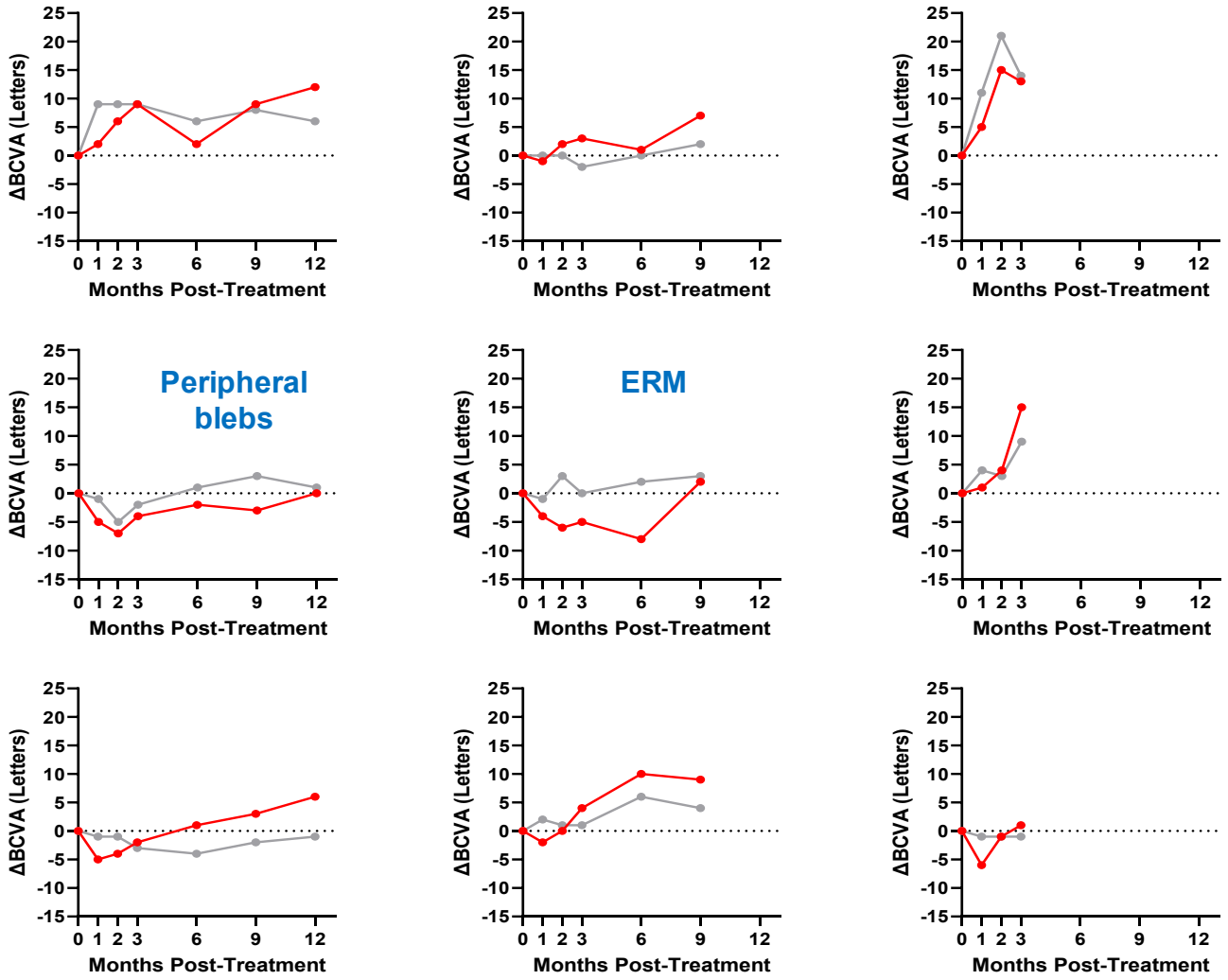
Data include:

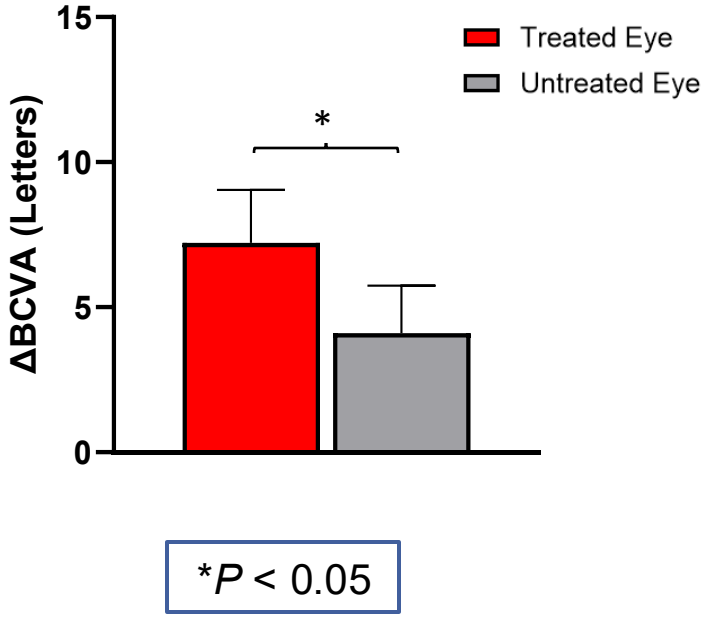
- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

Responder if **selected loci improved by ≥ 7dB on average** *(scotomatous points excluded, additional loci included if tied)*

BCVA generally improves post-treatment

Cohort 1 (Low Dose) | **Cohort 2 (High Dose)** | **Cohort 3 (Mid Dose)**





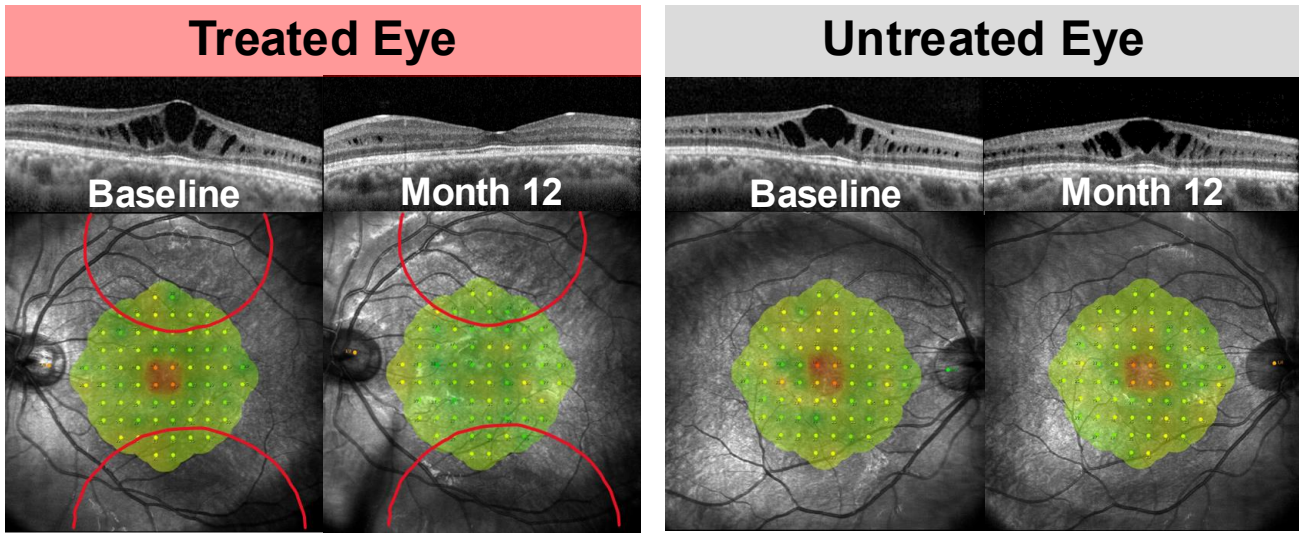
*$P < 0.05$

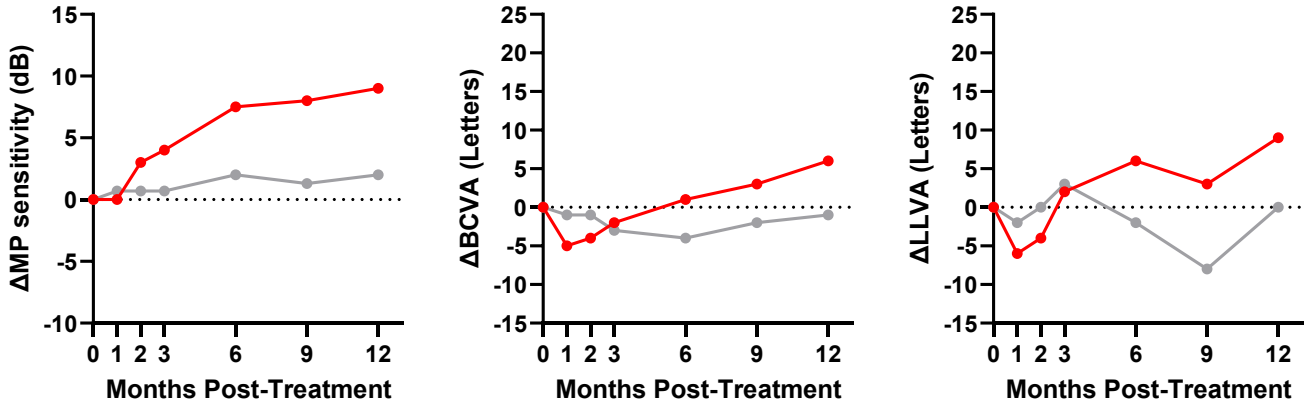
Data include:

- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

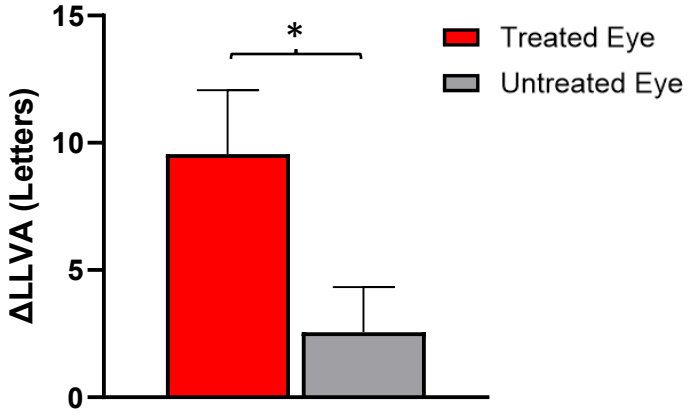
LLVA results are aligned with other measures of function

Cohort 1 (Low Dose): Subject #3





All Cohorts



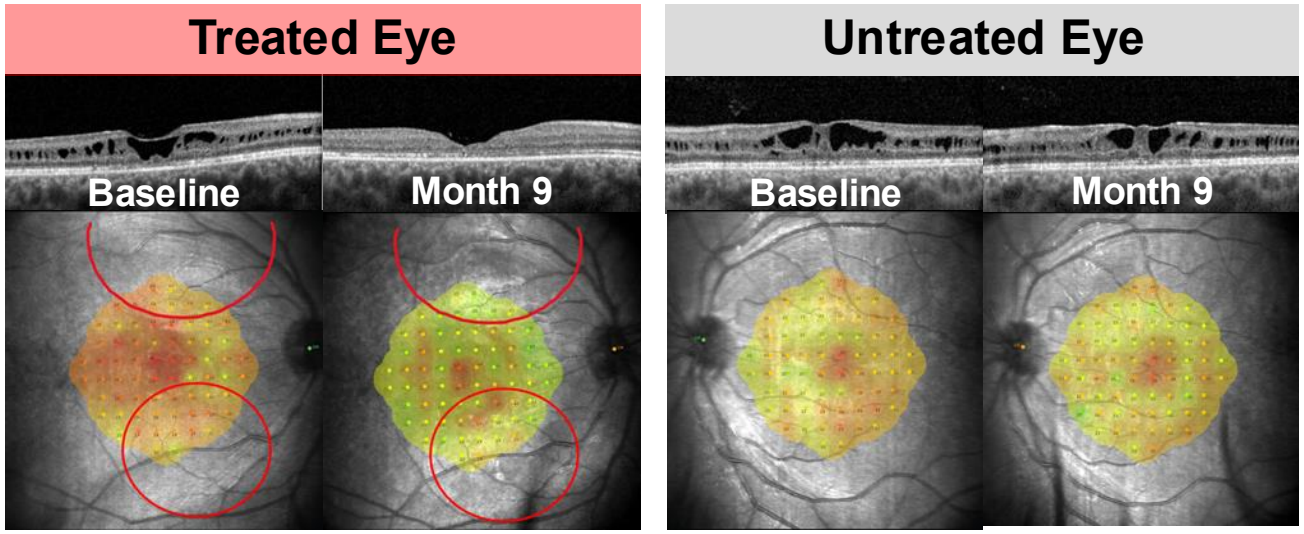
*$P < 0.05$

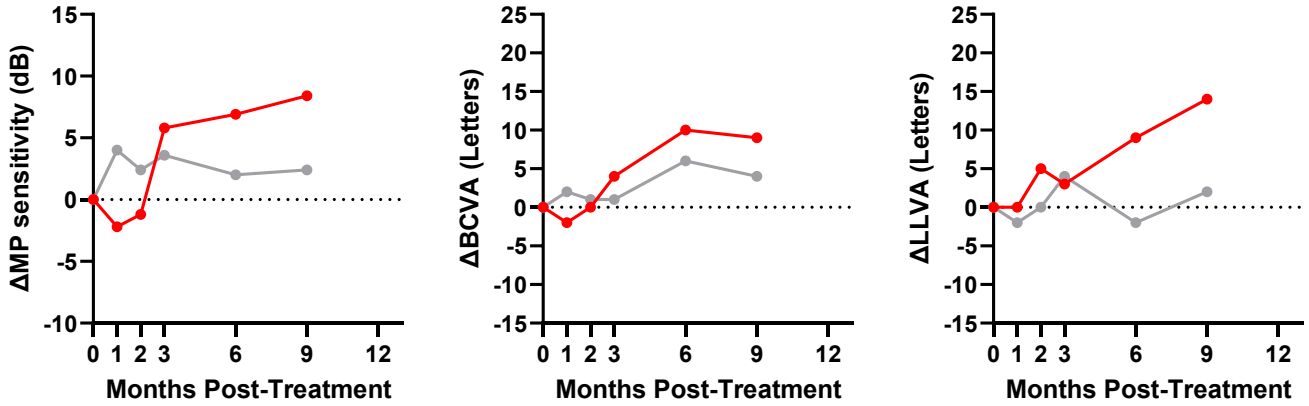
Data include:

- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

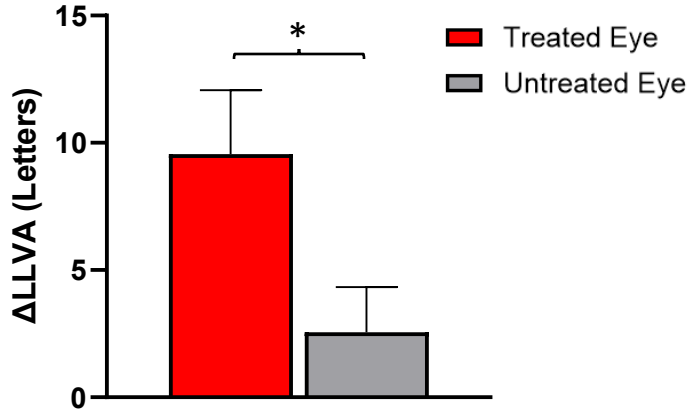
LLVA results are aligned with other measures of function

Cohort 2 (High Dose): Subject #6





All Cohorts



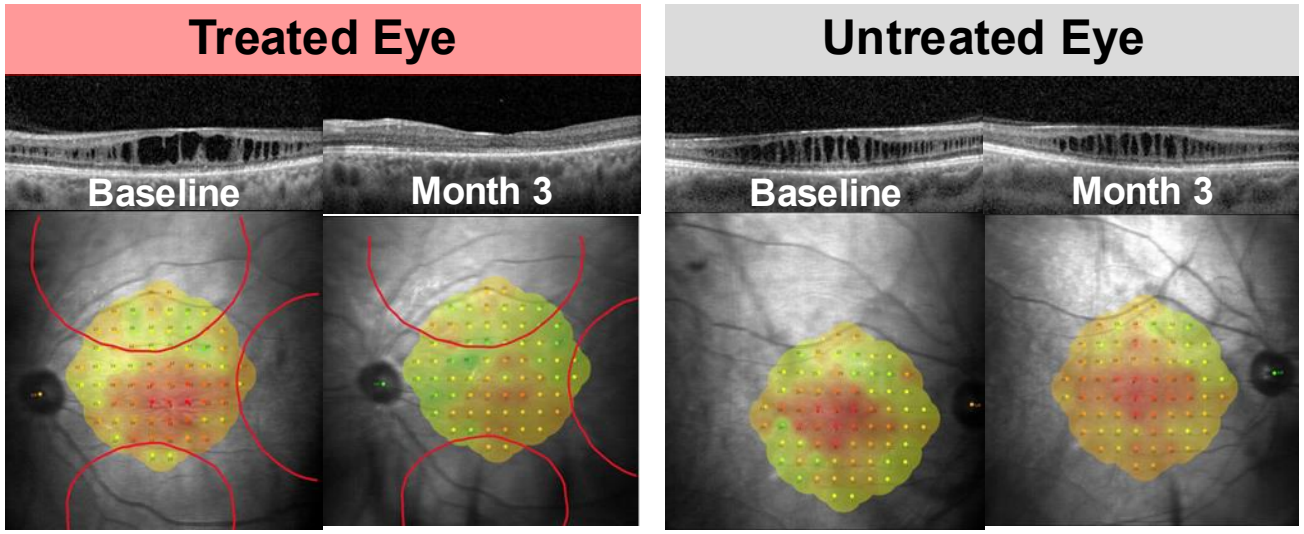
*$P < 0.05$

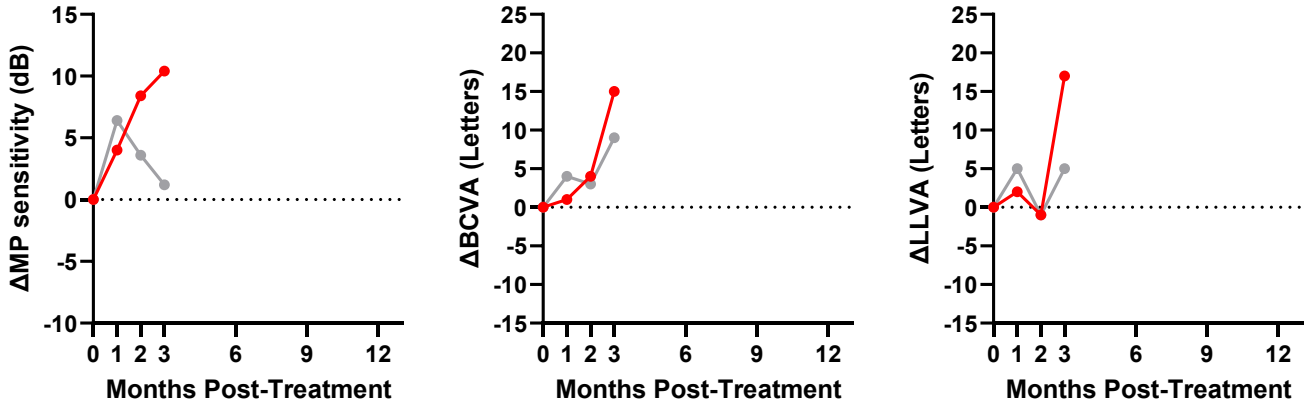
Data include:

- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

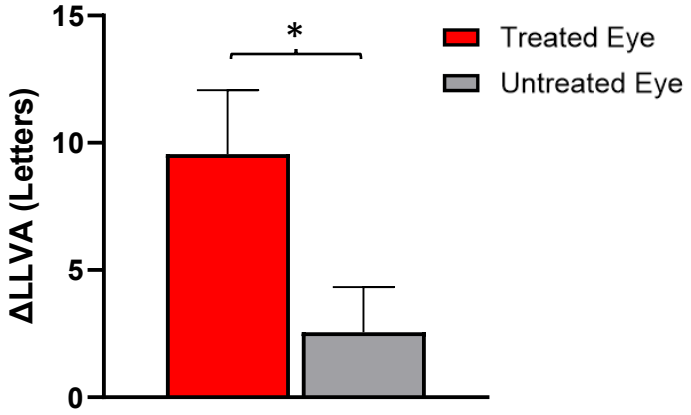
LLVA results are aligned with other measures of function

Cohort 3 (Mid Dose): Subject #8





All Cohorts



*$P < 0.05$

Data include:

- **Cohort 1** through **12 months**
- **Cohort 2** through **9 months**
- **Cohort 3** through **3 months**

Currently enrolling Part B (Dose Expansion)

ENROLLED	COHORT	PART A: Dose Escalation	
✓	1	Low dose (N=3), ≥ 18 years	1.5E10 vg/eye
✓	2	High dose (N=3), ≥ 18 years	5.0E10 vg/eye
✓	3	Mid dose (N=3), ≥ 18 years	3.0E10 vg/eye

ENROLLED	COHORT	PART B: Dose Expansion	
→	4	Control (N=3), ≥ 18 years	No intervention
		Low volume (N=3), ≥ 18 years	1.5E10 vg/eye
		High volume (N=3), ≥ 18 years	2.3E10 vg/eye
	5	TBD (N=3), ≥ 6 and < 18 years	TBD

Cohort 4 (Adult)

- Enrolling 9 subjects, randomized 1:1:1 into:
  - **Control**
    - No intervention
    - Optional cross-over after 12-month Main Study Period
  - **Low Volume**
    - **150 µL** of 1.0E11 vg/mL (1.5E10 vg/eye)
    - Administered in **~two 75 µL blebs**
  - **High Volume**
    - **225 µL** of 1.0E11 vg/mL (2.3E10 vg/eye)
    - Administered in **~three 75 µL blebs**

Cohort 5 (Pediatric)

- Will enroll 3 subjects
- Subjects will receive either the low or high volume from Cohort 4

ATSN-201 (rAAV.SPR-hGRK1-*hRS1syn*)
is a subretinal gene therapy product being developed to introduce the functional human retinoschisin (*hRS1*) gene to photoreceptors

SAFETY

- A **low dose** of 1.5 x 10^{10} vg/eye is **well-tolerated** through 1 year post-treatment
- **Subretinal deposits** and **transient retinal thickening** have been observed at higher doses (improvement with additional steroids)
- Majority of adverse events **Grade 1-2** in severity and related to the **surgical procedure**
- **One serious adverse event** to date
  - Unrelated to study drug or procedures
- **No dose-limiting toxicities**
- Subretinal injection, avoiding foveal detachment, can be **safely performed in patients with XLRS**

EFFICACY

- Preliminary evidence of **efficacy at all 3 dose levels**
- **Majority of treated eyes** demonstrated **closure of foveal schisis**
- Of the 2 subjects without a substantial decrease in central retinal thickness:
  - One subject had **bleb placement further in the periphery** and had only central macular schisis
  - One subject required intra-operative laser and developed an **ERM**
- **Improvements in visual function (MP, BCVA, LLVA)** observed in eyes demonstrating closure of foveal schisis, relative to untreated eyes.

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OHSU

Questions & Discussion