

Safety and efficacy of ATSN-201 in patients with X-linked retinoschisis: 12-month dose finding results of the LIGHTHOUSE study

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Everett L¹, Nagiel A^{2,3}, Lam BL⁴, Aleman TS⁵, Lauer AK¹, Berrocal AM⁴, Gregori NZ⁴,
Boye SE^{6,7}, Boye SL⁶, Pardon LP⁷, Yoon D⁷, Kay CN⁸, Fujita KP⁷

1. Casey Eye Institute, Oregon Health & Science University, Portland, OR
2. The Vision Center, Department of Surgery, Children's Hospital Los Angeles, Los Angeles, CA
3. Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA
4. Bascom Palmer Eye Institute, University of Miami, Miami, FL
5. Scheie Eye Institute and The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
6. Department of Pediatrics, University of Florida, Gainesville, FL
7. Atsena Therapeutics, Durham, NC
8. Vitreoretinal Associates, Gainesville, FL



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 - Research to Prevent Blindness Unrestricted Grant
 - NIH P30 EY010572
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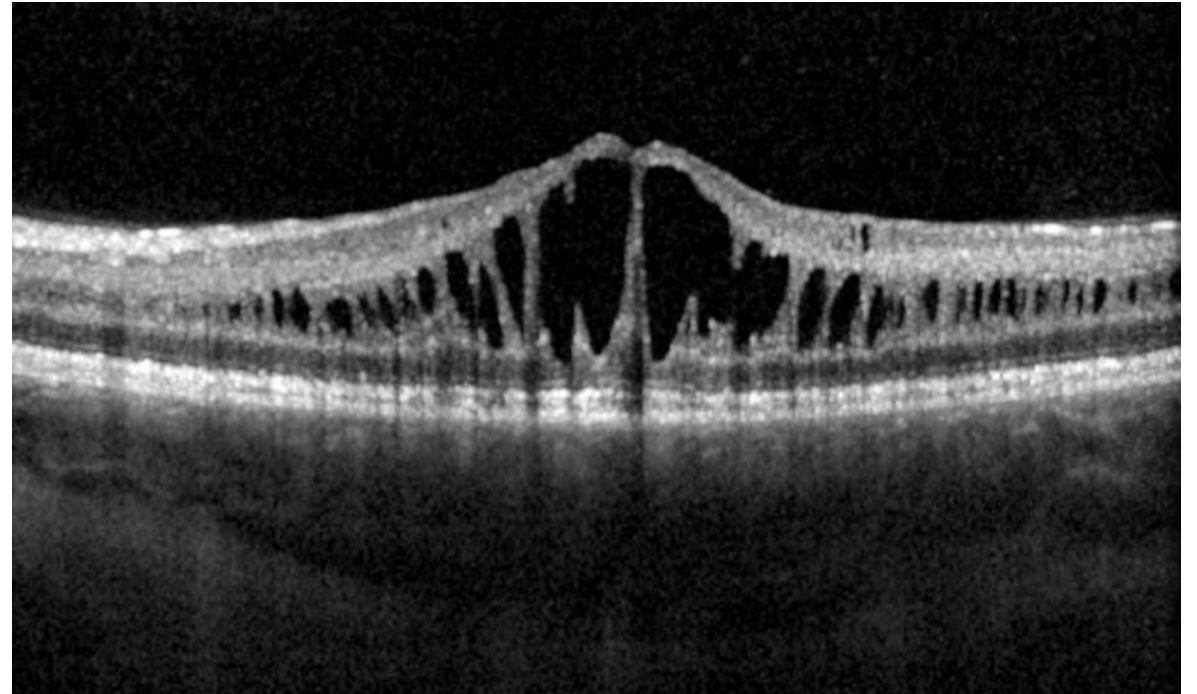
X-Linked Retinoschisis (XLRS)

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

XLRS is caused by mutations in *RS1* gene

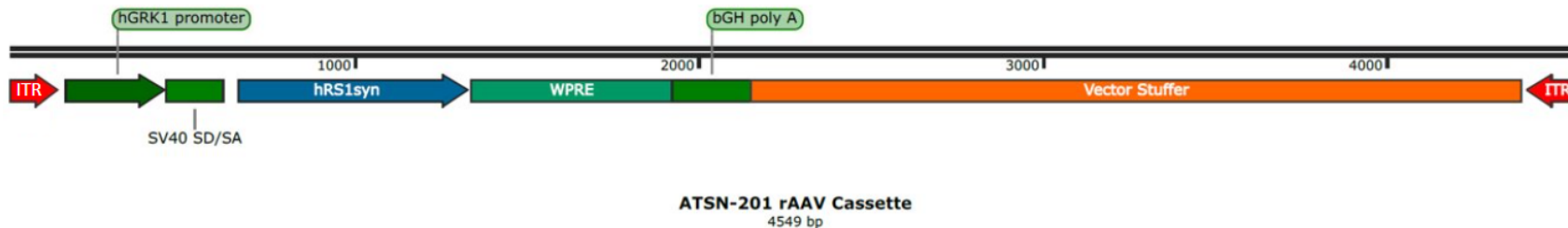
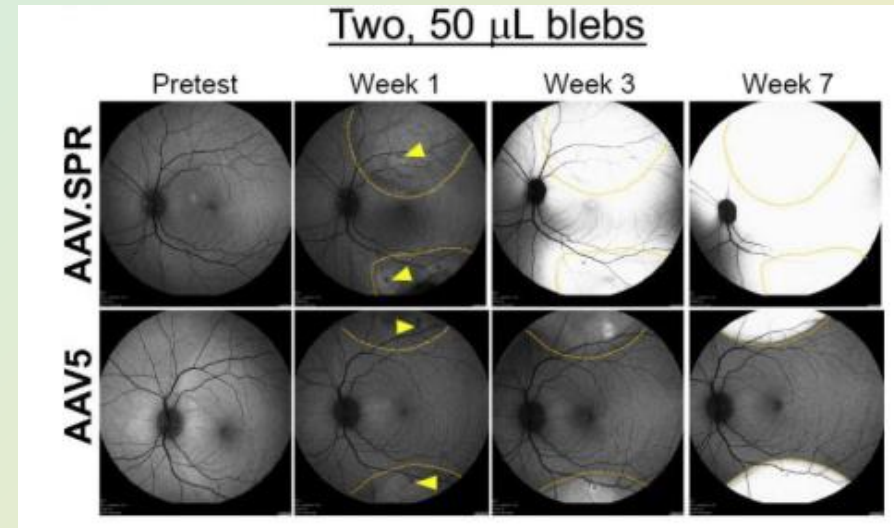
- *RS1* encodes the protein retinoschisin (RS1), expressed primarily in photoreceptors and, to a lesser extent, bipolar cells
- Upon secretion, RS1 binds to inner segments of rods and cones, bipolar cells, and the outer plexiform layer
- RS1 has a role in cell-cell adhesion, fluid balance, and the photoreceptor/bipolar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

FOVEAL SCHISIS IN XLRS



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
- AAV.SPR capsid spreads beyond bleb margins →
- Human rhodopsin kinase promoter
- Human *RS1* transgene (*hRS1syn*)
- Poly-adenylation signal derived from bovine growth hormone, all flanked by inverted terminal repeats



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

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	1.1E10 vg/eye
✓	2	High dose (N=3), ≥ 18 years	3.8E10 vg/eye
✓	3	Mid dose (N=3), ≥ 18 years	2.3E10 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 (12-month data)

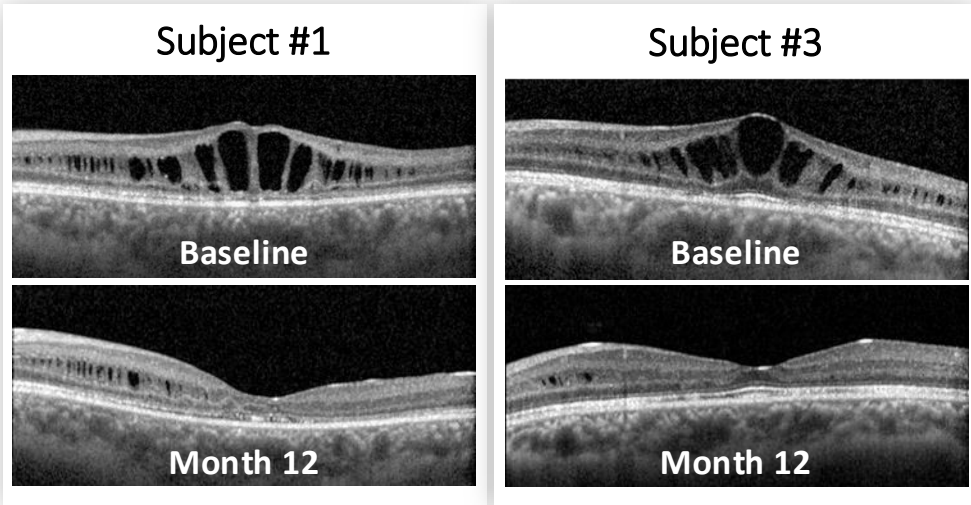
Data cutoff: 13 February 2026

- **Total of 90 TEAEs reported in cohorts 1-3**
 - 87 Grade 1-2 in severity
 - 46 related to surgical procedure
- **No treatment-related SAEs**
 - 1 SAE of fever of unknown origin with negative workup (7 months after treatment)
- **Subretinal deposits at high (N=3) and mid doses (N=1) improved with transient reintroduction of topical or oral corticosteroid treatment**
- **No DLTs and no instances of macular hole formation or retinal detachment**
- **No subjects have discontinued from the study**

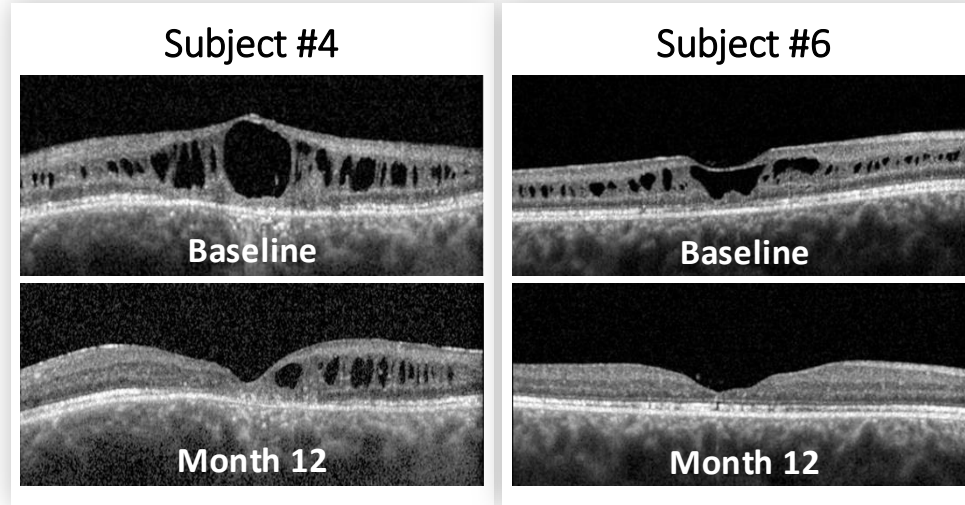
	Cohort 1 N=3	Cohort 2 N=3	Cohort 3 N=3	Total N=9
# of Events				
Any TEAE	29	33	28	90
Any Serious TEAE	1	0	0	1
Any Severe TEAE	1	2	0	3
Severity				
Grade 1	21	15	19	55
Grade 2	7	16	9	32
Grade 3	1	2	0	3
Grade 4 or 5	0	0	0	0
Related to ATSN-201				
Possibly / Probably / Definitely Related	3	9	6	18
Not Related / Unlikely to be Related	26	24	22	72
Related to Surgical Procedure				
Possibly / Probably / Definitely Related	20	17	9	46
Not Related / Unlikely to be Related	9	16	19	44

7 of 9 treated eyes had closure of foveal schisis

Cohort 1 (Low Dose)



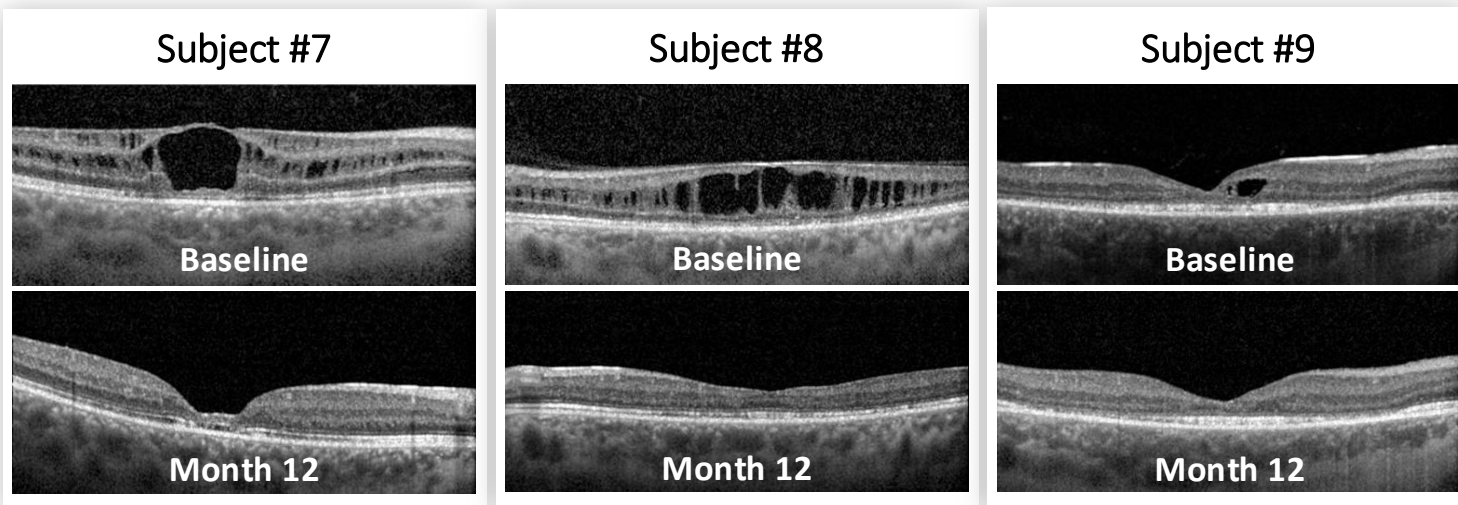
Cohort 2 (High Dose)



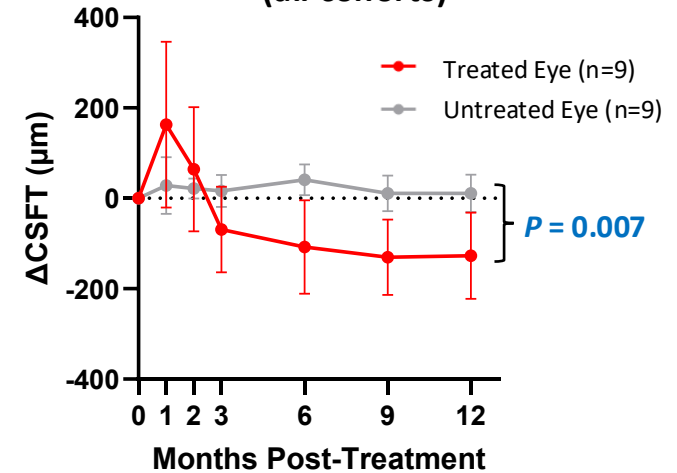
For the 2 treated eyes without foveal schisis closure:

- 1 had blebs placed further in the **periphery**
- 1 developed **ERM** following intra-operative laser

Cohort 3 (Mid Dose)

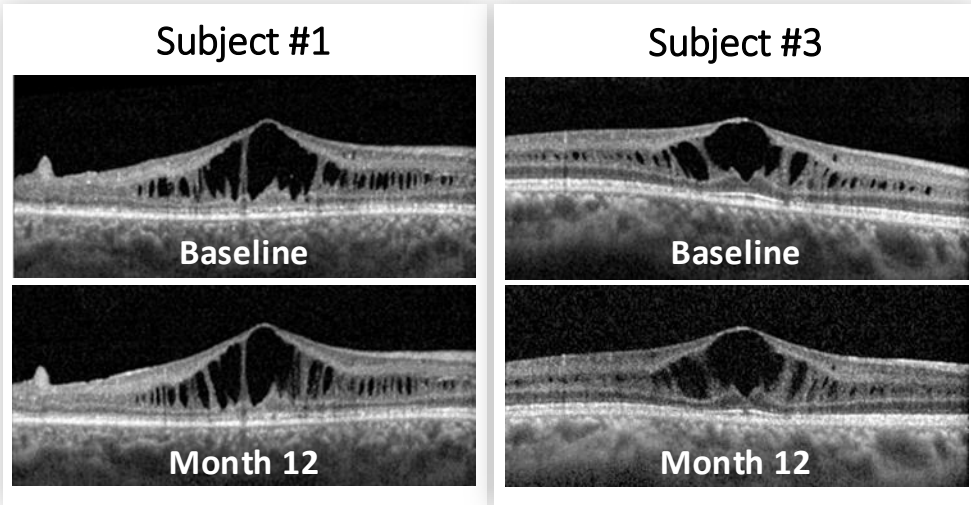


Change in retinal thickness over time (all cohorts)

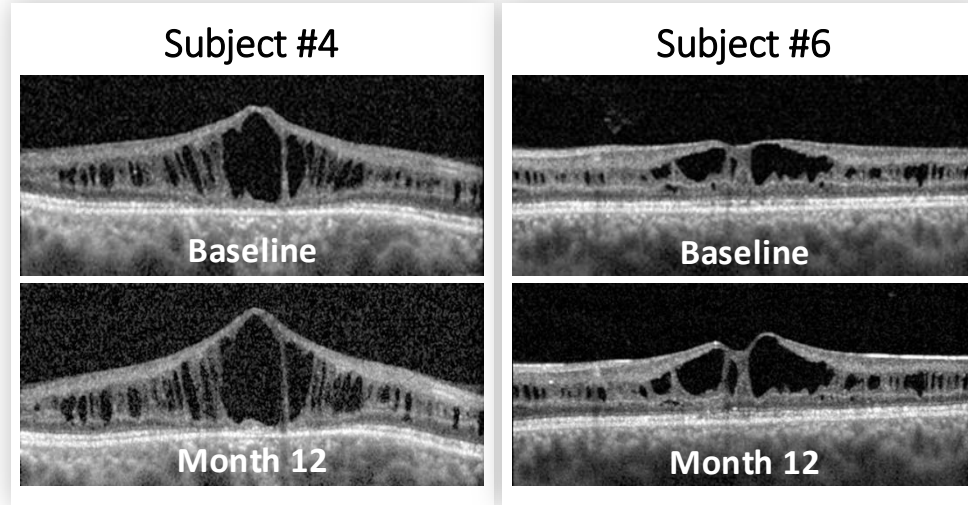


Untreated eyes did not demonstrate foveal schisis closure

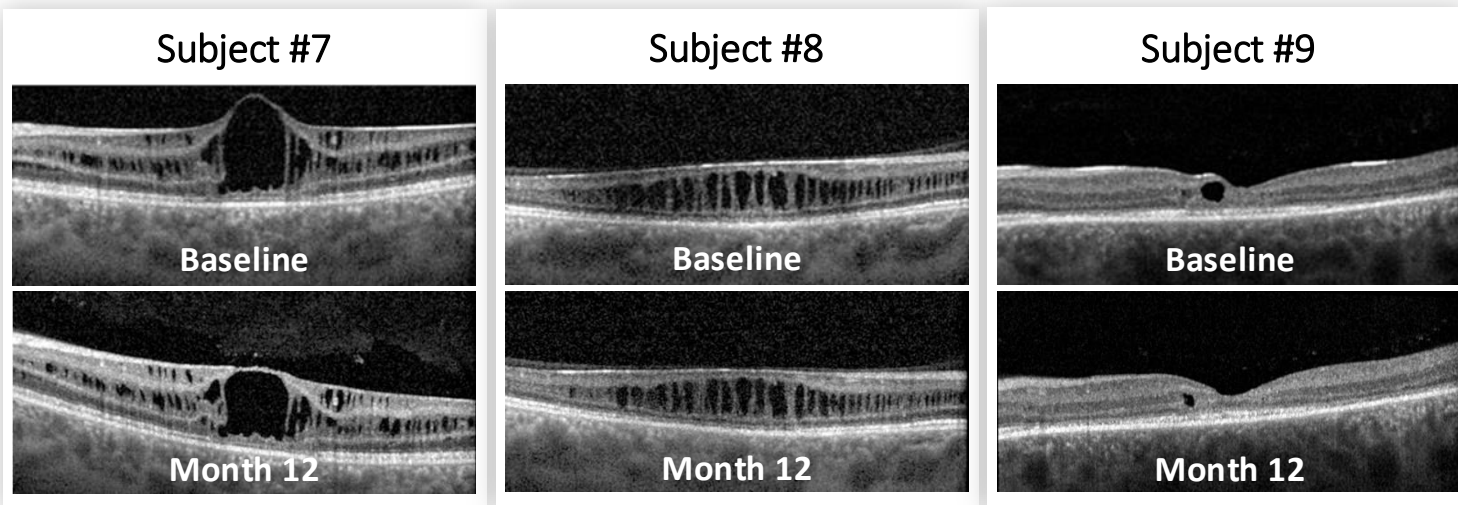
Cohort 1 (Low Dose)



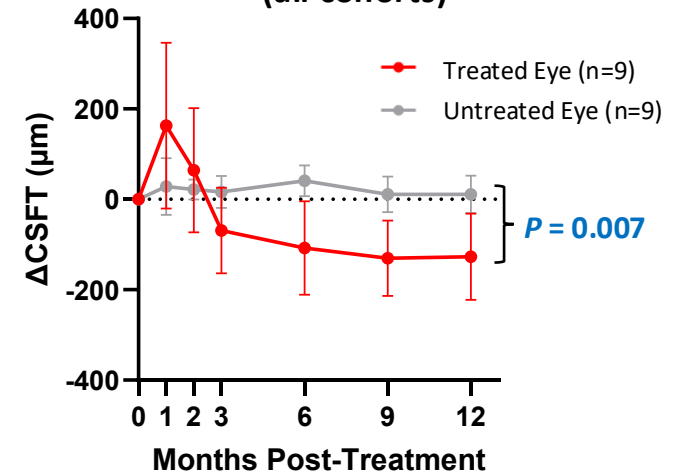
Cohort 2 (High Dose)



Cohort 3 (Mid Dose)



Change in retinal thickness over time (all cohorts)



Eyes with structural improvements generally show improvements in function

Cohort 1 (Low Dose)

Cohort 2 (High Dose)

Cohort 3 (Mid Dose)

Subject #1

Subject #3

Subject #4

Subject #6

Subject #7

Subject #8

Subject #9

Baseline

Baseline

Baseline

Baseline

Baseline

Baseline

Baseline

Month 12

Month 12

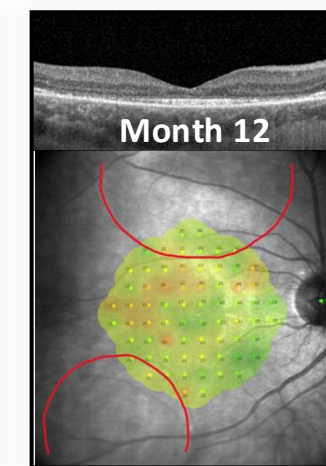
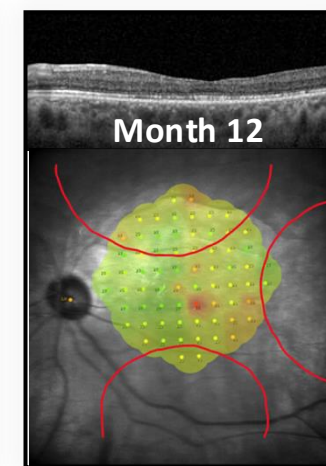
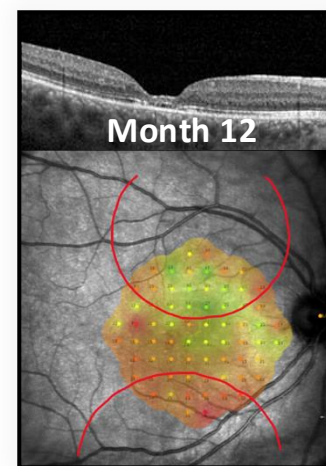
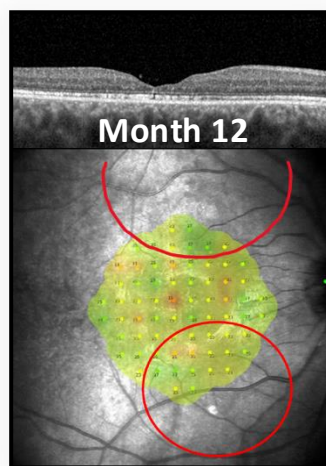
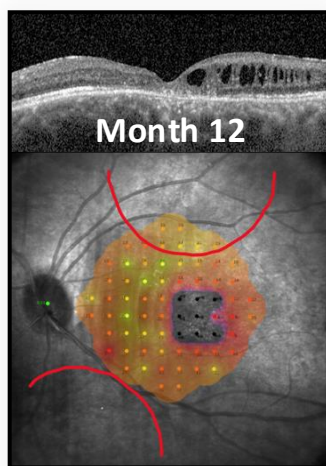
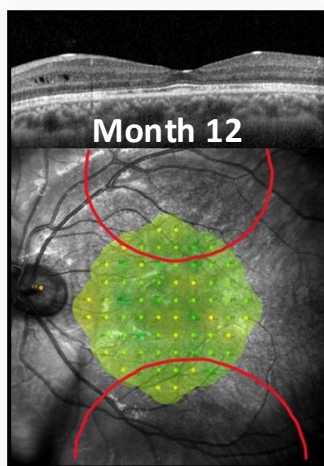
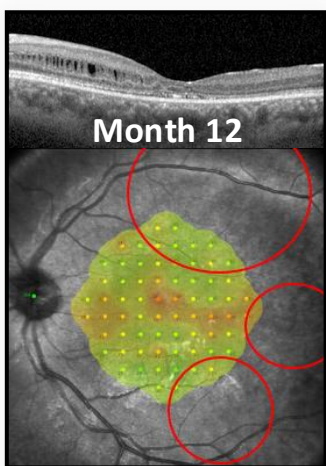
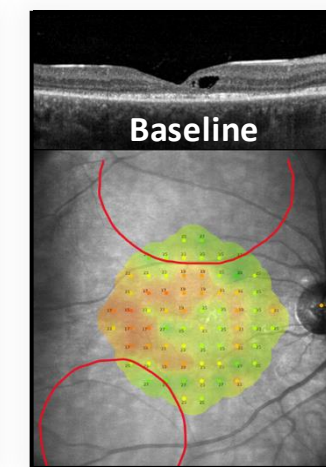
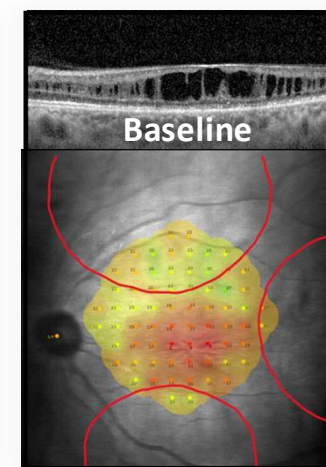
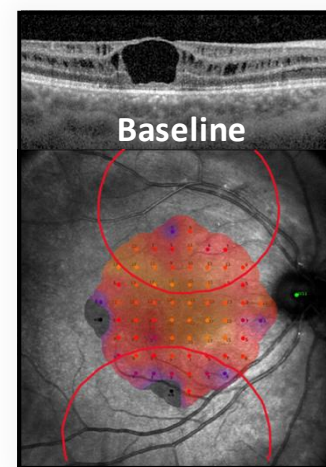
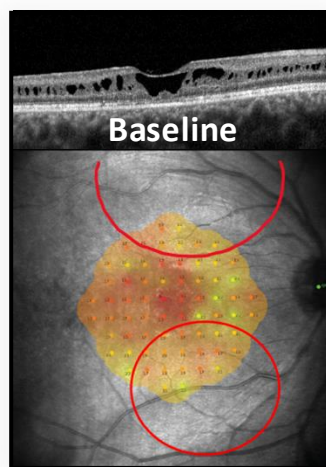
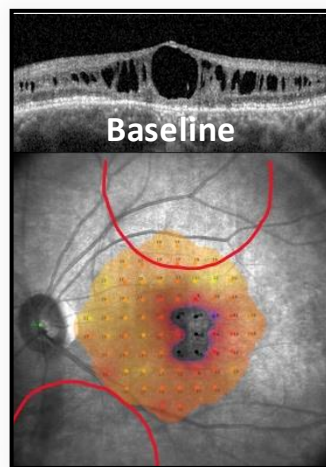
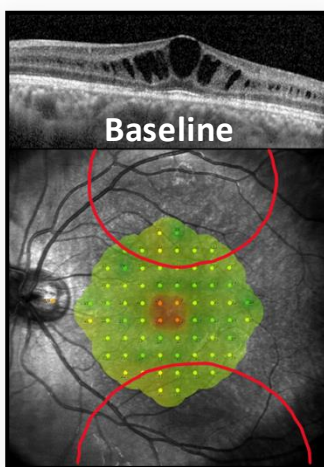
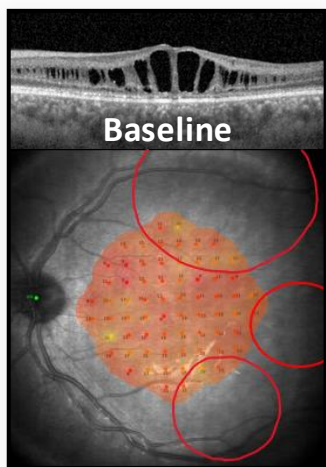
Month 12

Month 12

Month 12

Month 12

Month 12



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

Cohort 1 (Low Dose)

Cohort 2 (High Dose)

Cohort 3 (Mid Dose)

Subject #1

Subject #3

Subject #4

Subject #6

Subject #7

Subject #8

Subject #9

Baseline

Baseline

Baseline

Baseline

Baseline

Baseline

Baseline

Month 12

Month 12

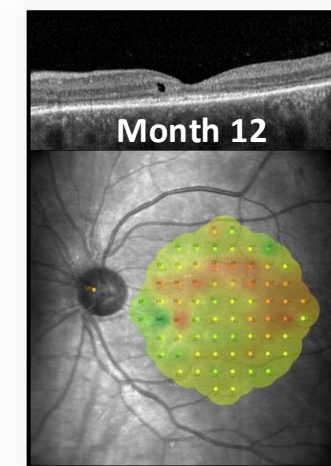
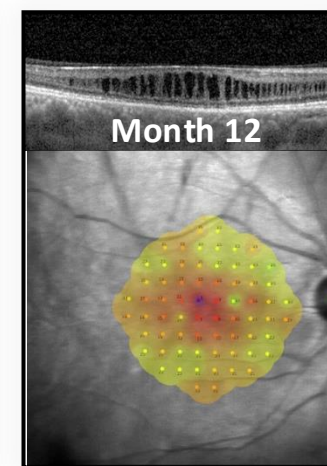
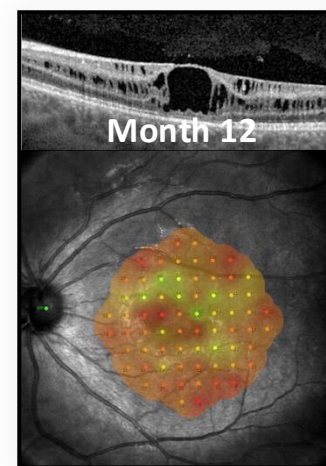
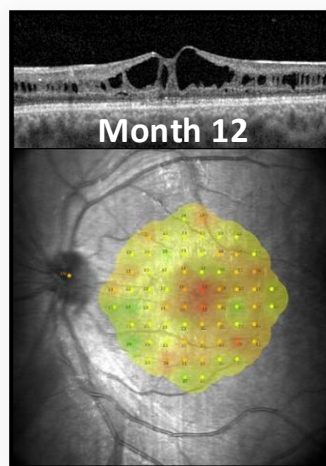
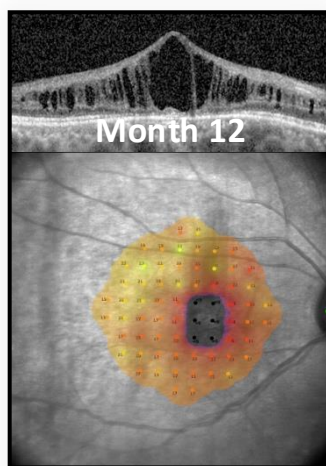
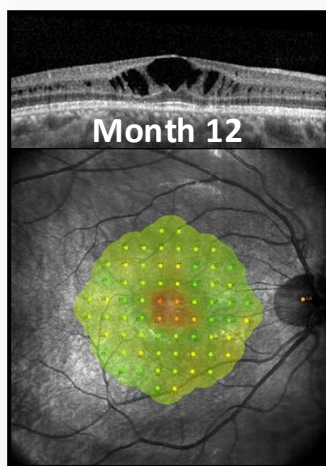
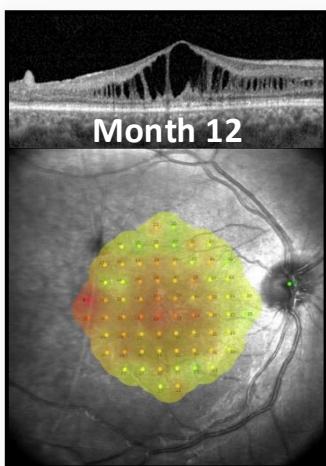
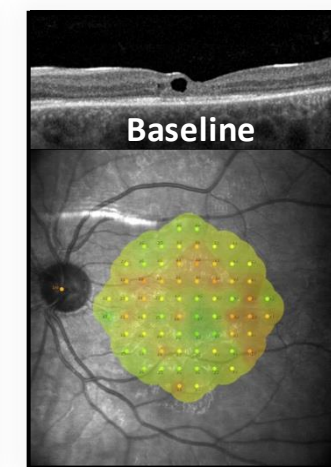
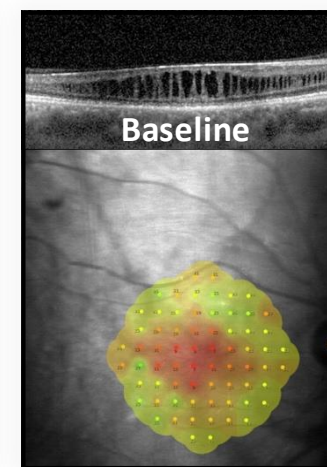
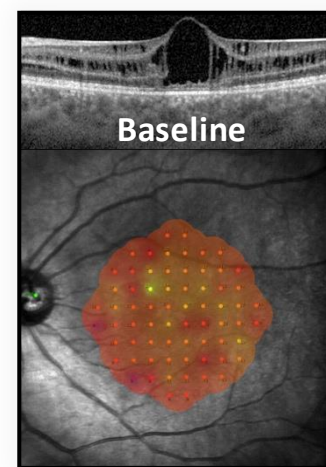
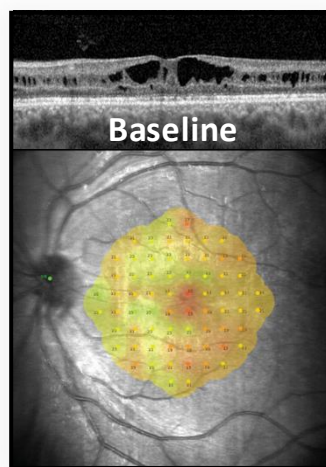
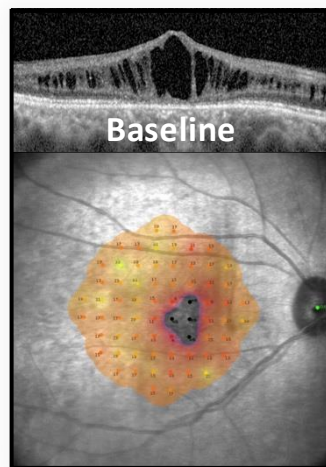
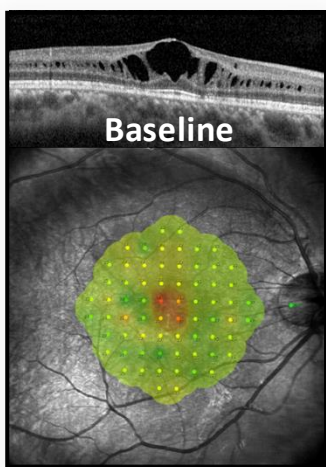
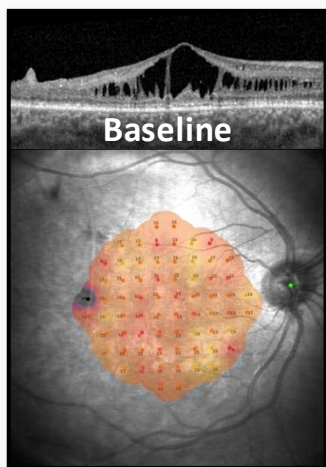
Month 12

Month 12

Month 12

Month 12

Month 12



BCVA and LLVA generally improve post-treatment

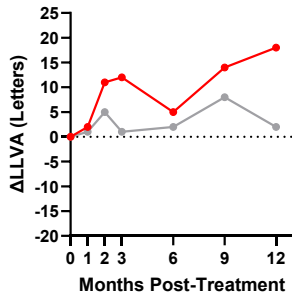
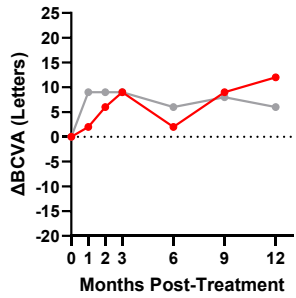


Cohort 1 (Low Dose)

Change in BCVA

Change in LLVA

Subject #1

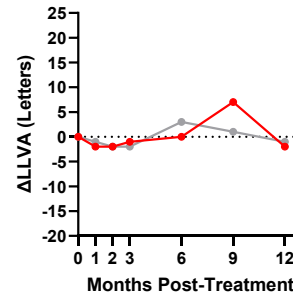
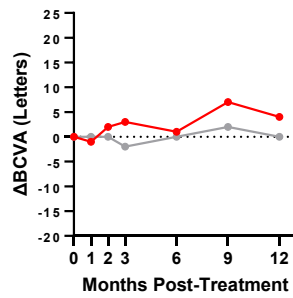


Cohort 2 (High Dose)

Change in BCVA

Change in LLVA

Subject #4

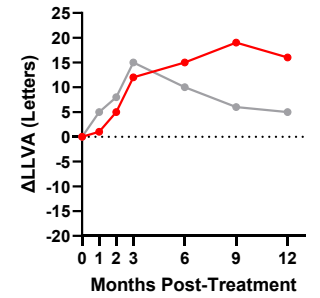
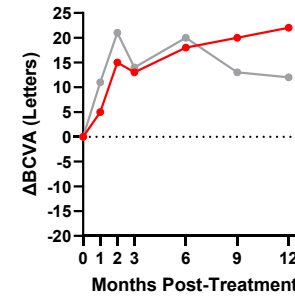


Cohort 3 (Mid Dose)

Change in BCVA

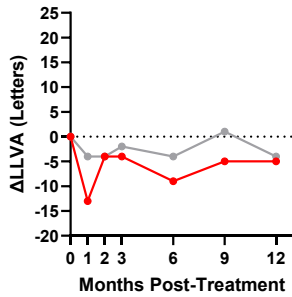
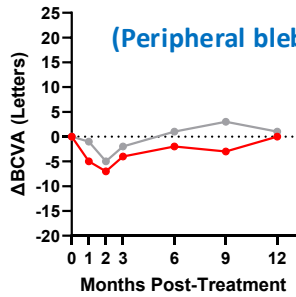
Change in LLVA

Subject #7



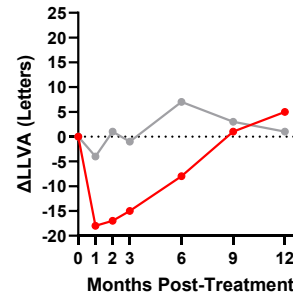
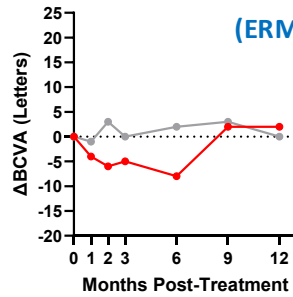
(Peripheral blebs)

Subject #2

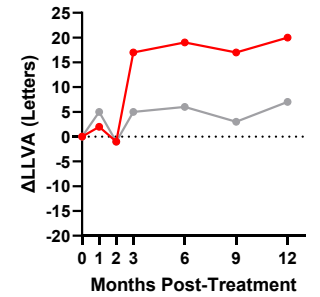
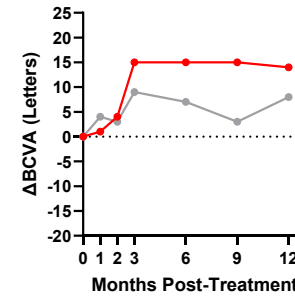


(ERM)

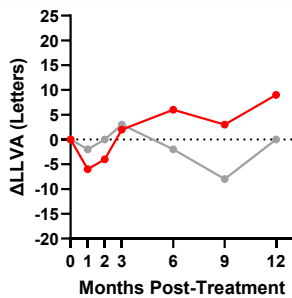
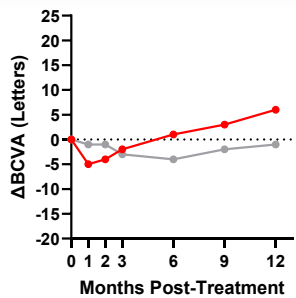
Subject #5



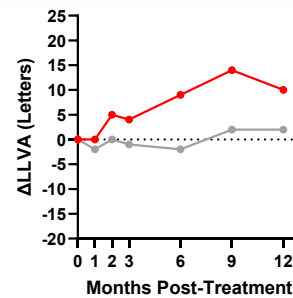
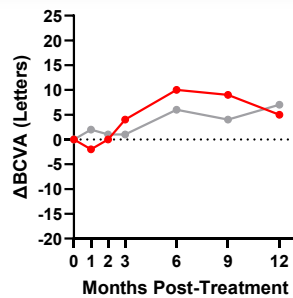
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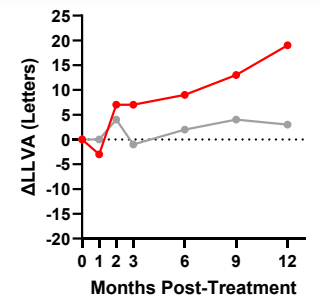
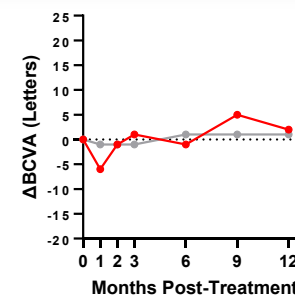
Subject #3



Subject #6



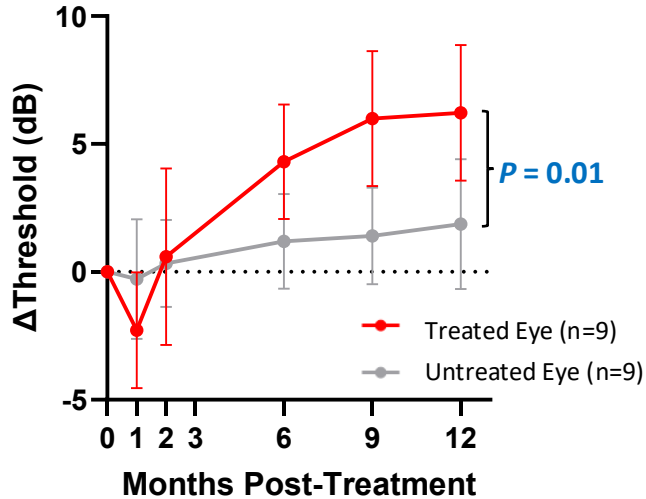
Subject #9



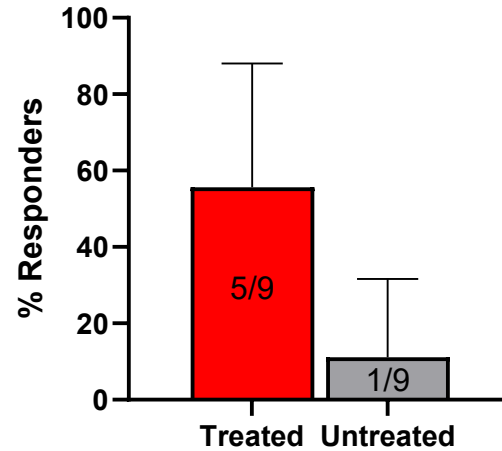
Treated eyes demonstrate greater improvements in visual function

Microperimetry^a

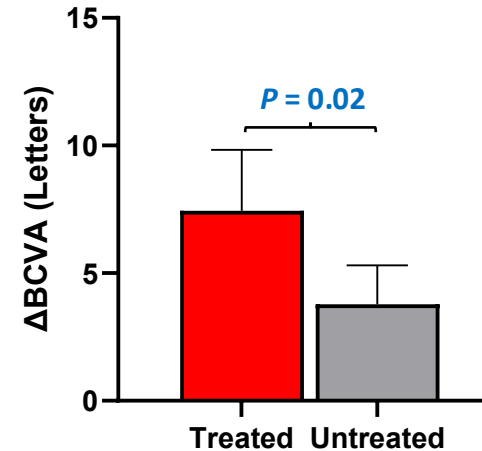
Change in retinal sensitivity over time (all cohorts)



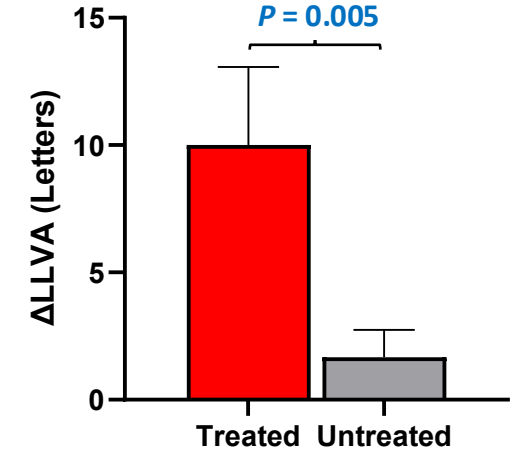
% Responders^b for all cohorts combined (Month 12)



Change in BCVA for all cohorts combined (Month 12)



Change in LLVA for all cohorts combined (Month 12)



^aMP threshold calculated as the mean sensitivity across the subset of central 16 loci with baseline > 0 dB and ≤ 19 dB

^bResponder if MP threshold **improved by ≥ 7dB**

ATSN-201 (rAAV.SPR-hGRK1-hRS1syn)

is a subretinal gene therapy product being developed to introduce the functional human retinoschisin (*hRS1*) gene to photoreceptors

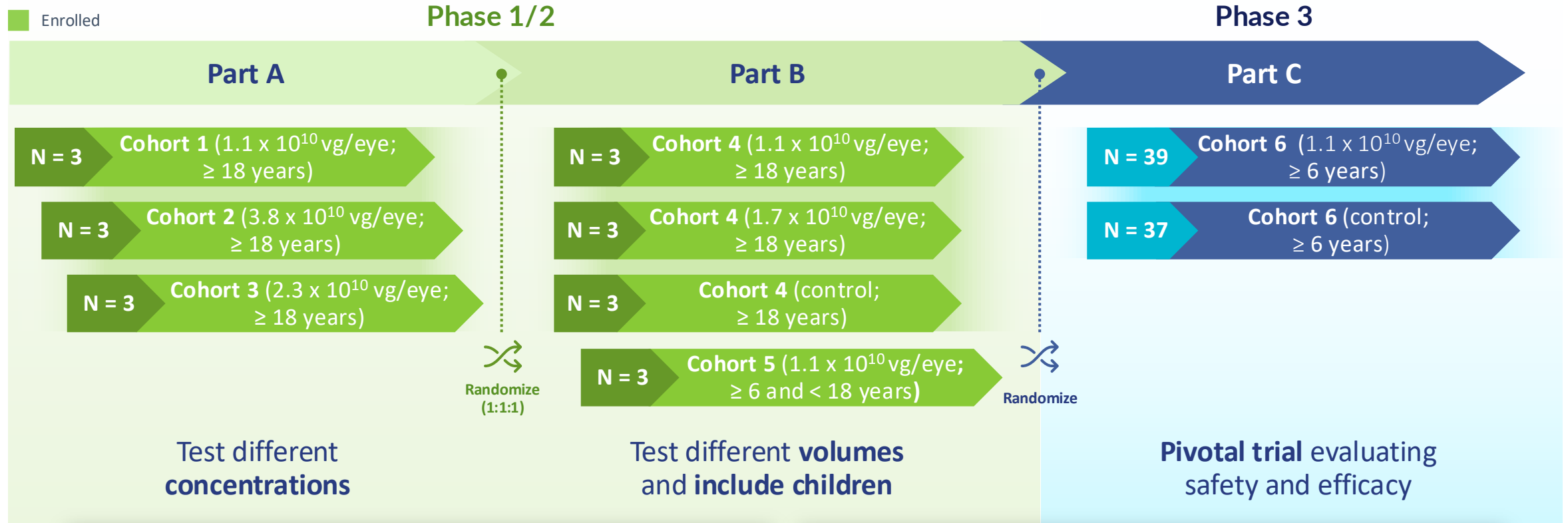
SAFETY

- A **low dose** of 1.1×10^{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

- 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 **blebs further in the periphery** and **high body weight** with transient post-treatment **inflammation** (possible underdosing of steroid)
 - 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

LIGHTHOUSE Phase 1/2/3 Clinical Trial Design and Current Status



PARTS A & B

Main Study Period: 12 months

Primary Endpoint: Safety & Tolerability

Secondary Endpoints: OCT, Microperimetry, BCVA, LLVA

PART C (PIVOTAL)

Main Study Period: 12 months

Primary Endpoint: Microperimetry

Key Secondary Endpoints: OCT, BCVA, LLVA

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Atsena Therapeutics Team
Clinical trial subjects and families



An architectural rendering of a modern building at dusk. The building features a prominent glass facade with a central section that is illuminated with a green glow. A large white diamond shape is overlaid on the left side of the image, containing the text "Questions & Discussion". The scene includes a courtyard with plants and a cable car in the sky.

**Questions &
Discussion**