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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Financial Disclosures

- Atsena Therapeutics (employee)

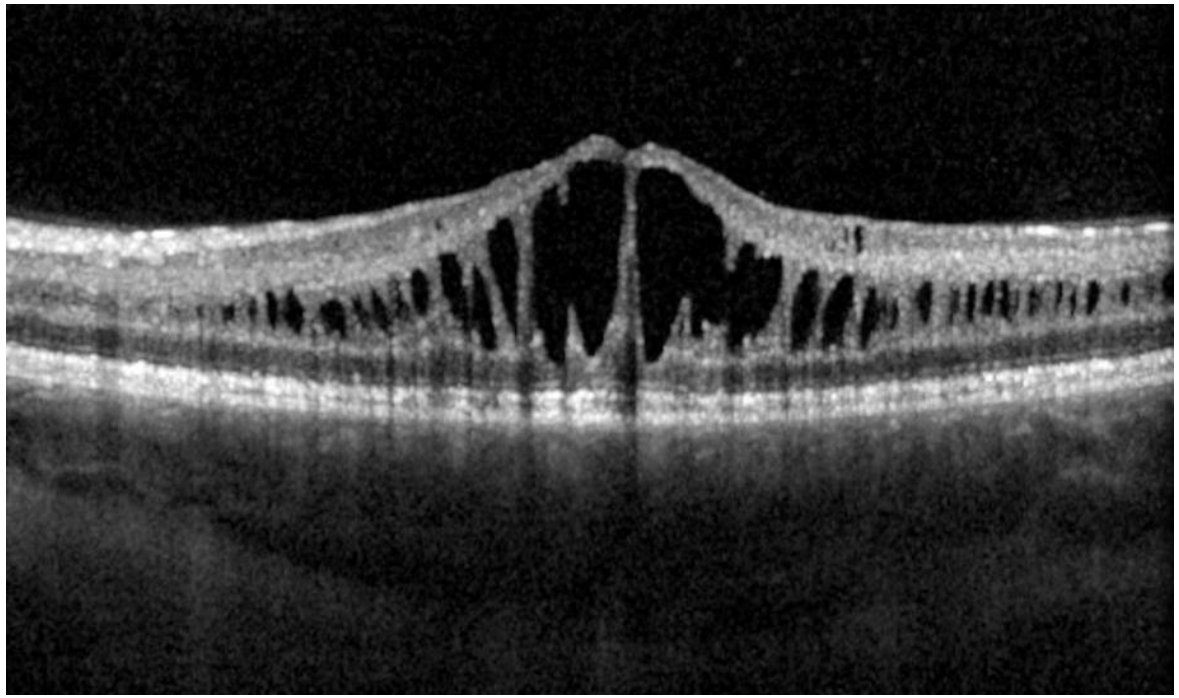
X-Linked Retinoschisis (XLRS)

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**

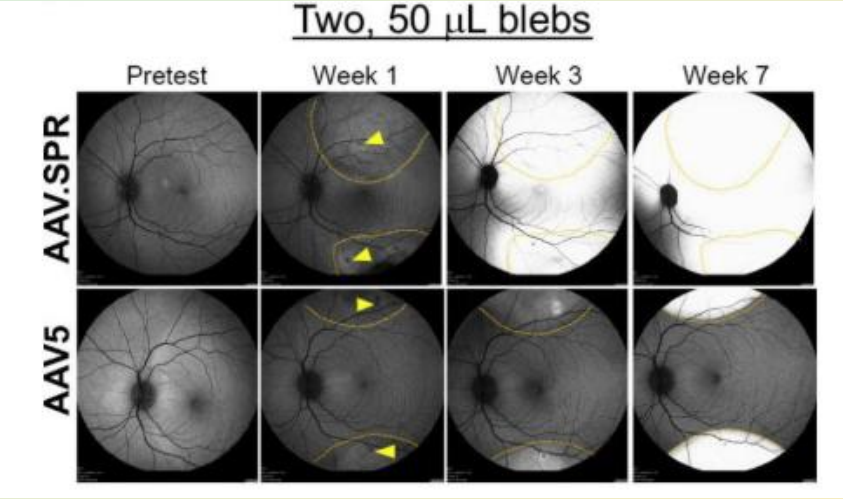
FOVEAL SCHISIS IN XLRS

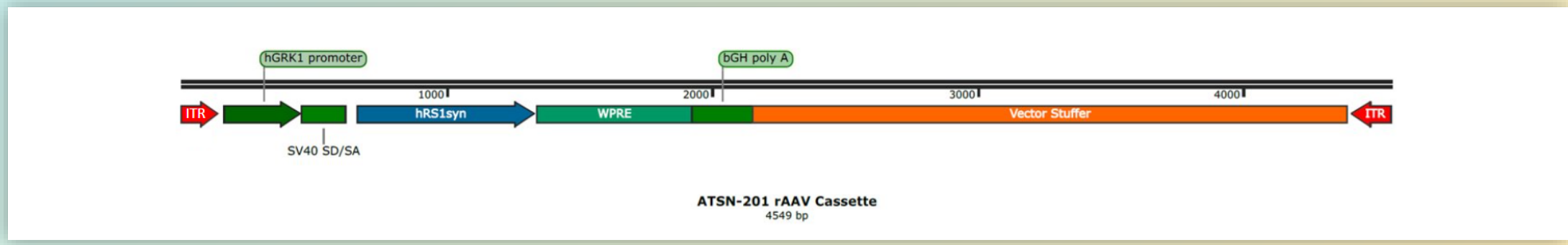


Molday RS, Kellner U, and Weber HFB. 2012.

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

Data cutoff: 13 February 2026

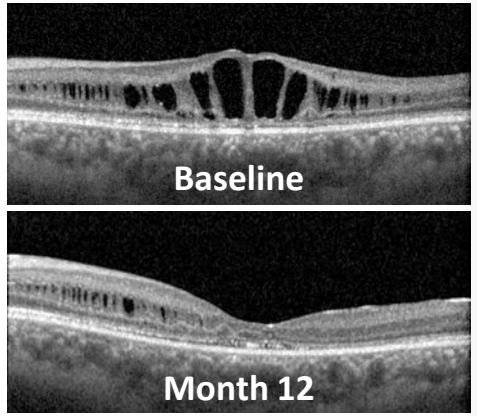
- **Total of 90 TEAEs reported**
  - 87 Grade 1-2 in severity
  - 46 related to surgical procedure
- **No treatment-related SAEs**
  - 1 SAE of fever of unknown origin with negative workup (7 months after treatment)
- **Subretinal deposits at high (N=3) and mid doses (N=1)** improved with transient reintroduction 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)

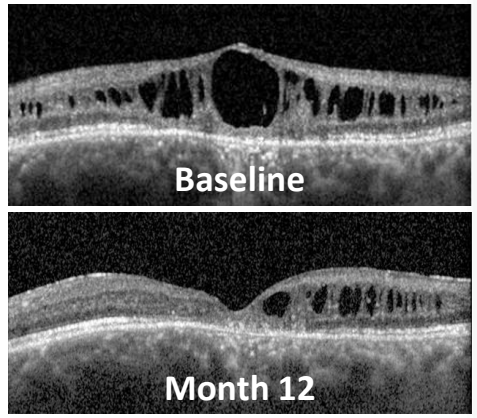
Subject #1



Subject #3

Cohort 2 (High Dose)

Subject #4



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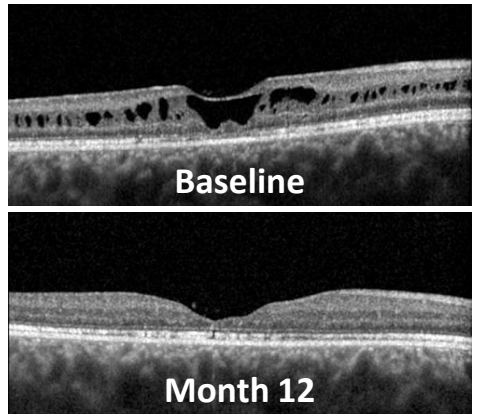
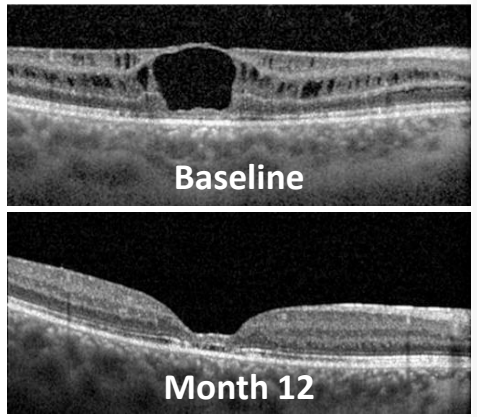


For the 2 treated eyes without foveal schisis closure:

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

Cohort 3 (Mid Dose)

Subject #7



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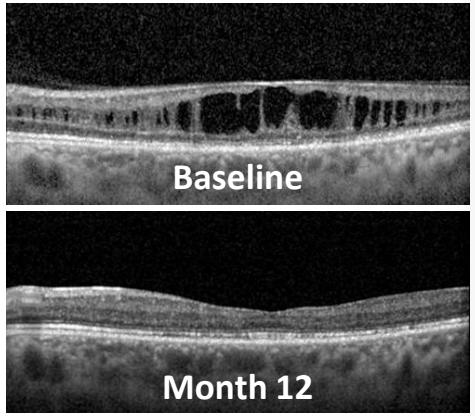

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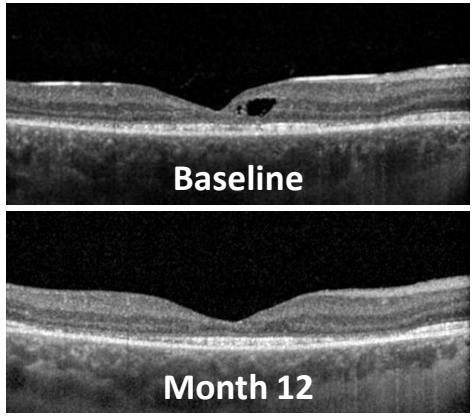
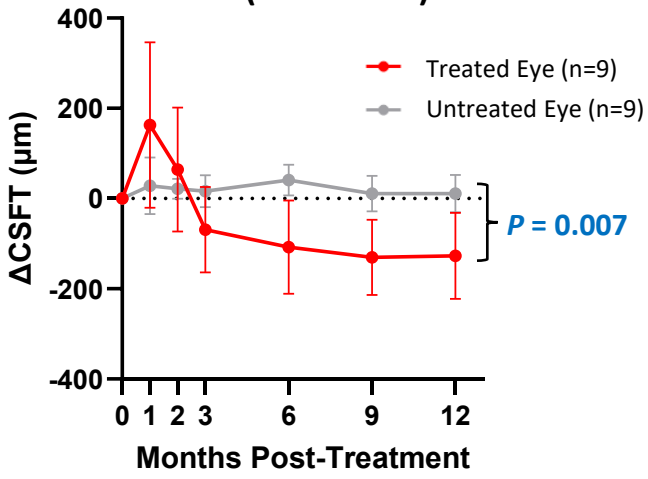


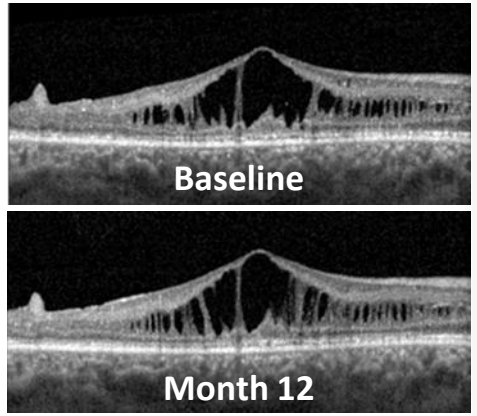
Change in retinal thickness over time (all cohorts)



Untreated eyes did not demonstrate foveal schisis closure

Cohort 1 (Low Dose)

Subject #1



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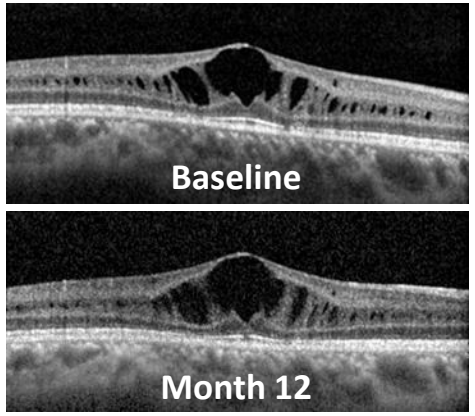
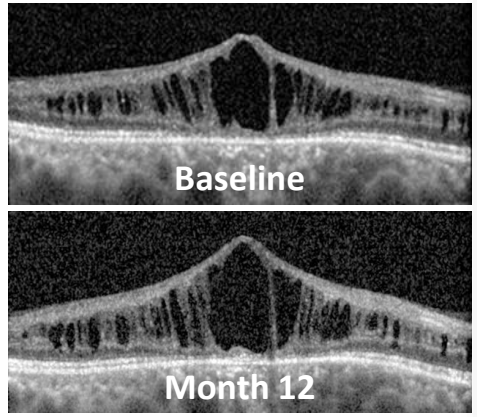


Cohort 2 (High Dose)

Subject #4



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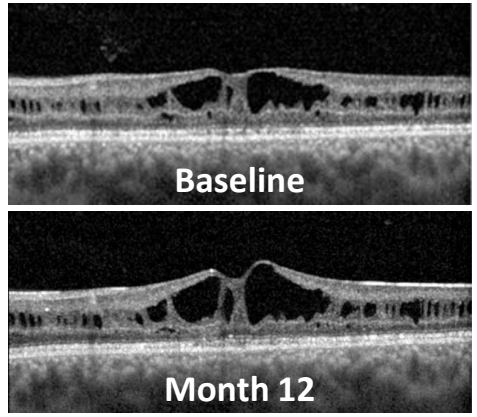
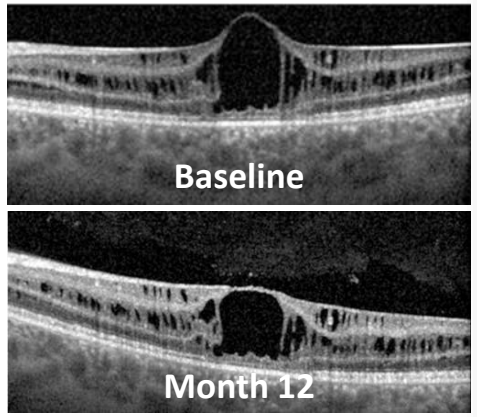


Cohort 3 (Mid Dose)

Subject #7



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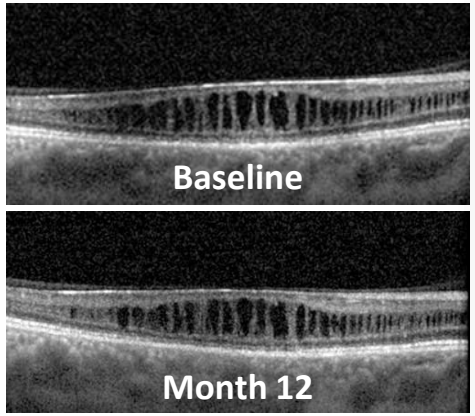

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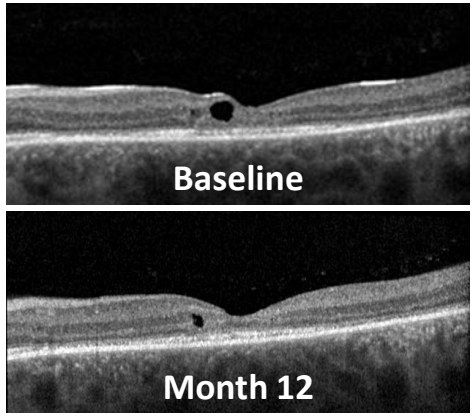
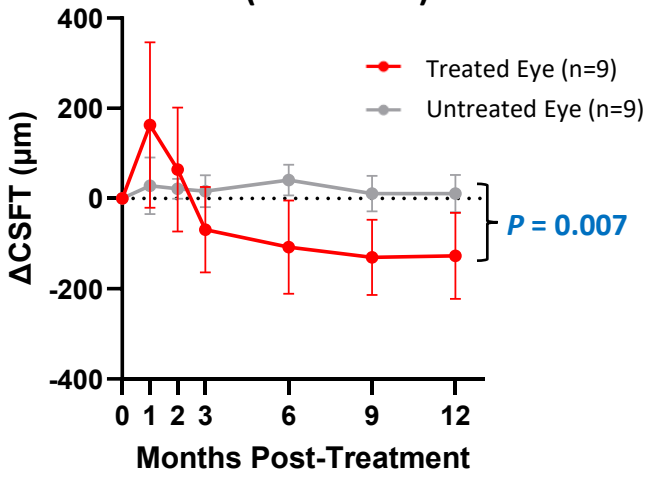
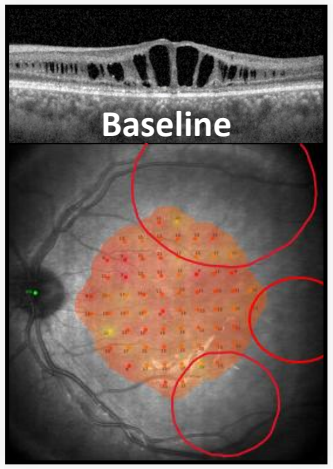
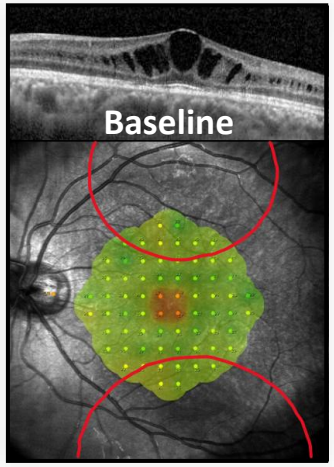
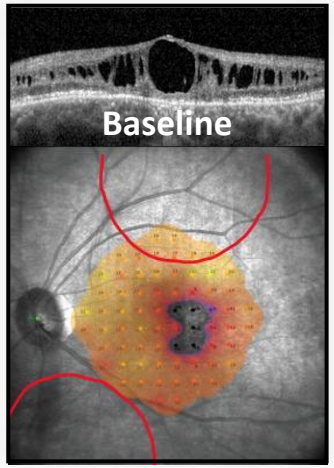
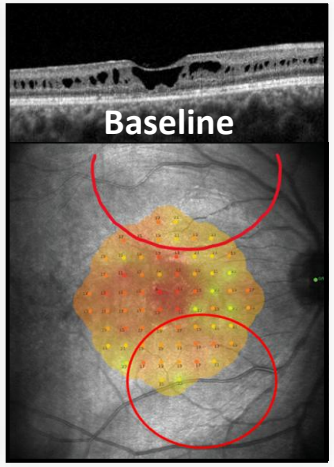
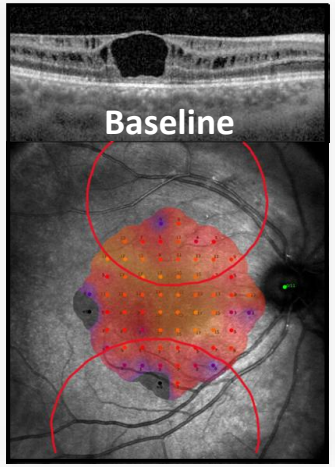
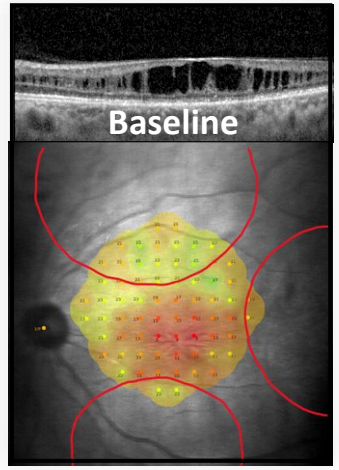
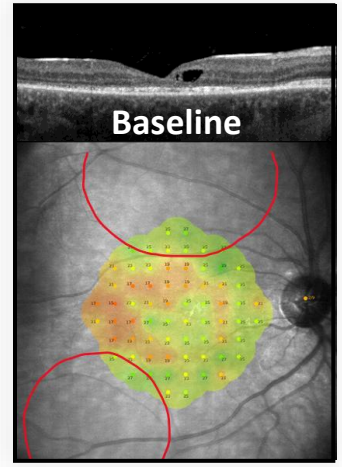
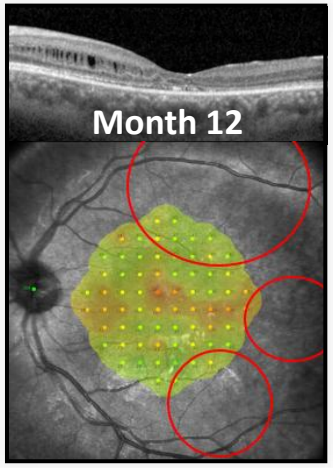
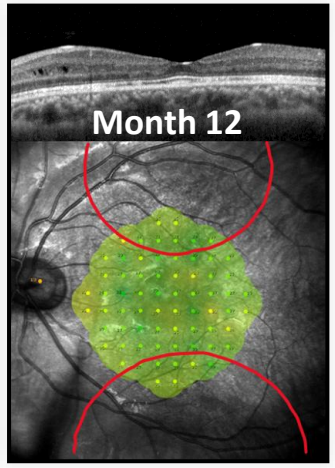
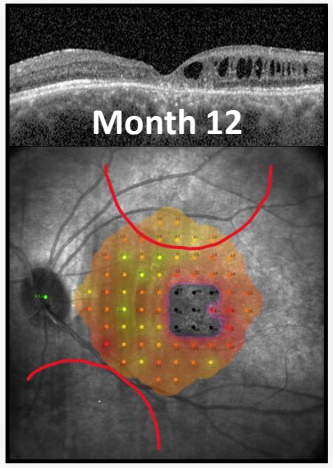
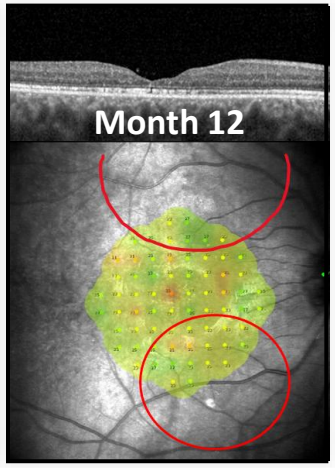
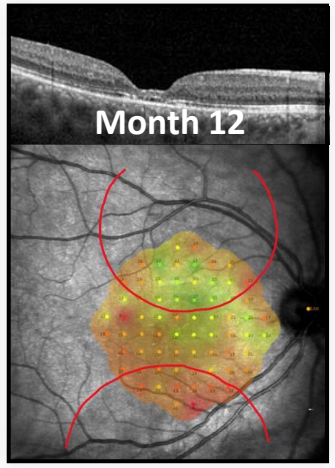
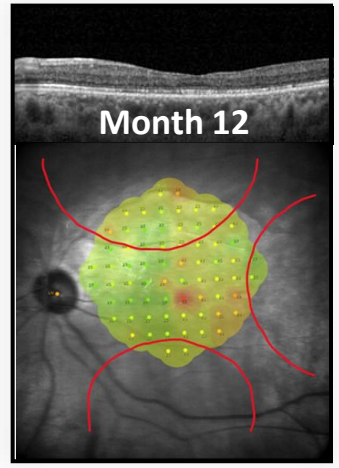
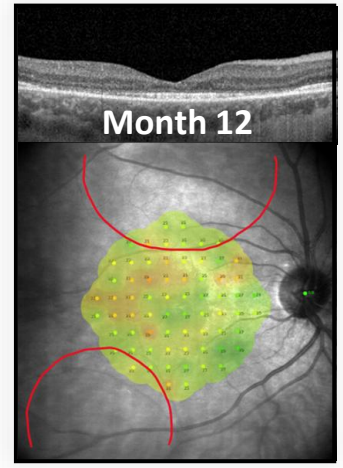


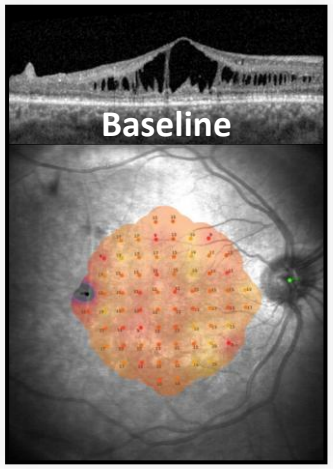
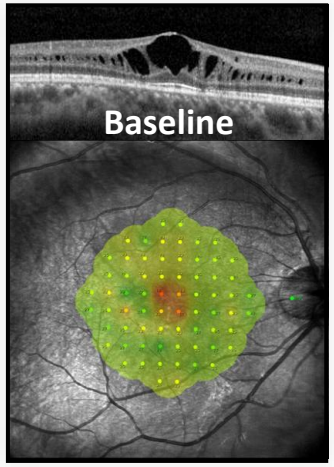
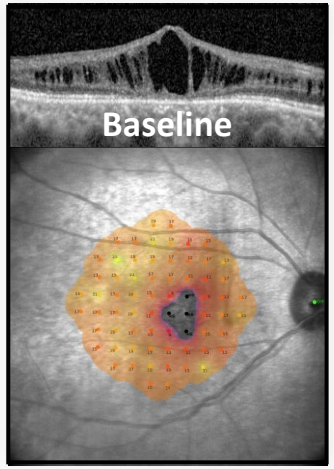
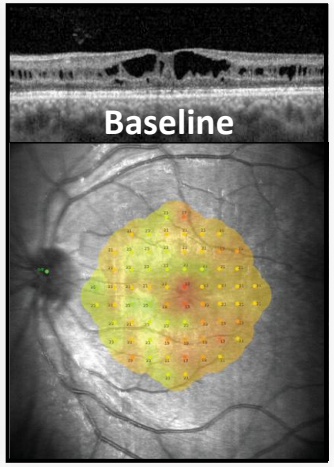
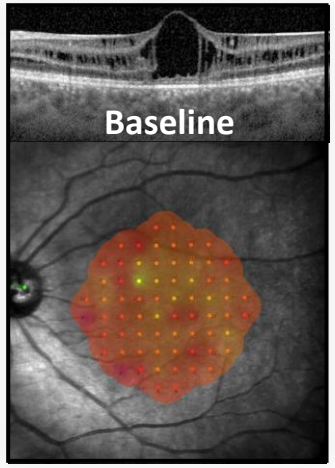
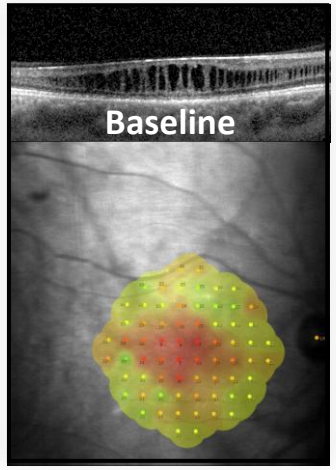
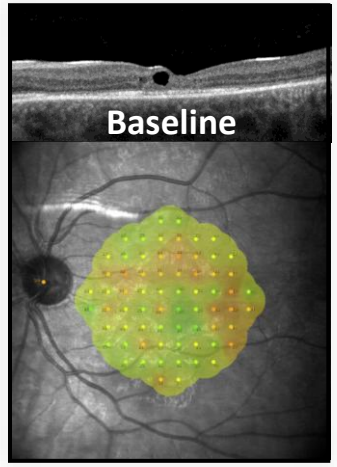
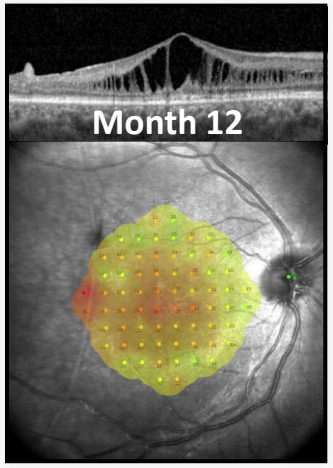
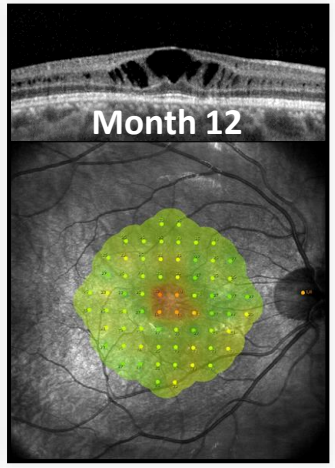
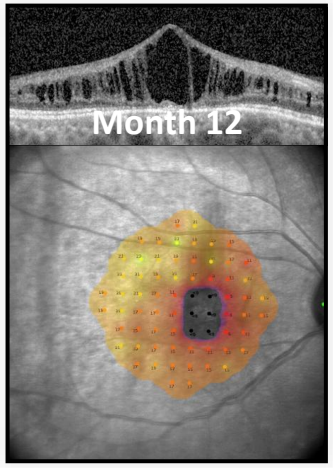
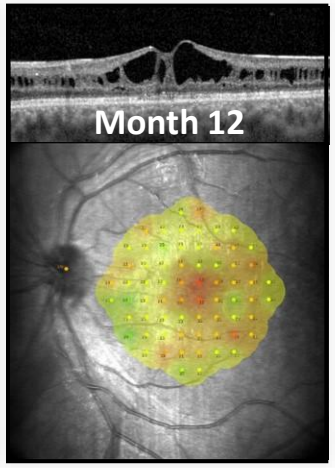
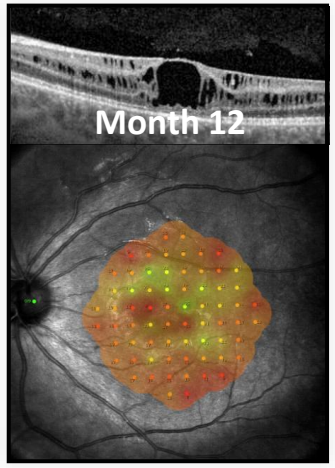
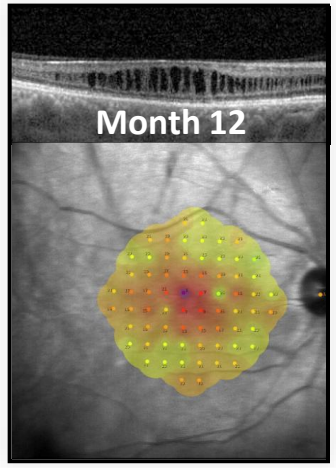
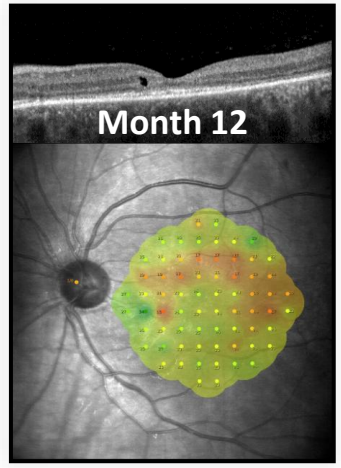
Change in retinal thickness over time (all cohorts)



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
						
						

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

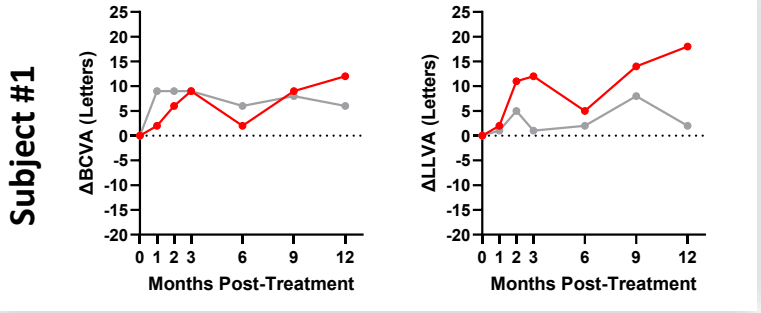
Cohort 1 (Low Dose)		Cohort 2 (High Dose)		Cohort 3 (Mid Dose)		
Subject #1	Subject #3	Subject #4	Subject #6	Subject #7	Subject #8	Subject #9
						
						

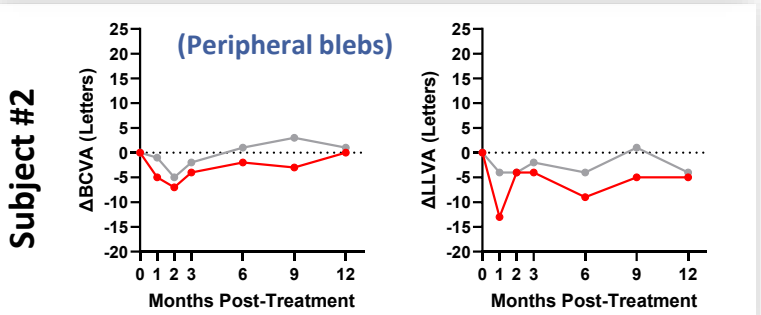
BCVA and LLVA generally improve post-treatment

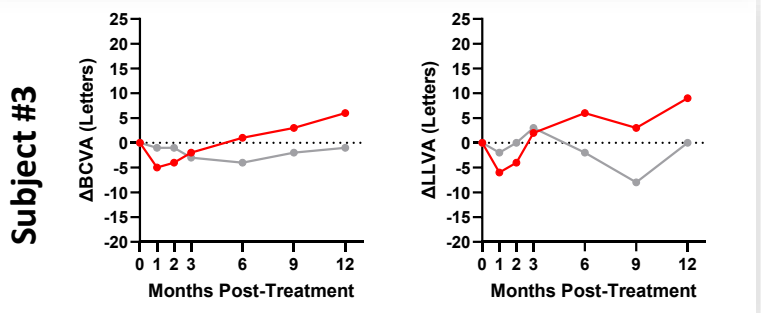
Treated Eye
Untreated Eye

Cohort 1 (Low Dose)

Change in BCVA



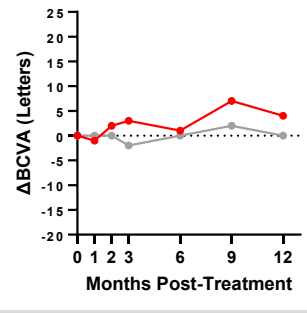


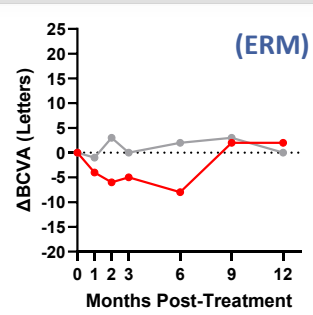


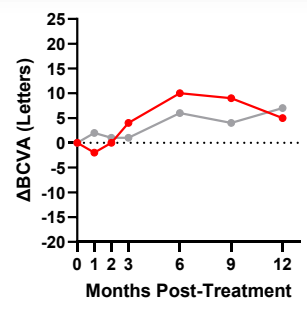
Change in LLVA

Cohort 2 (High Dose)

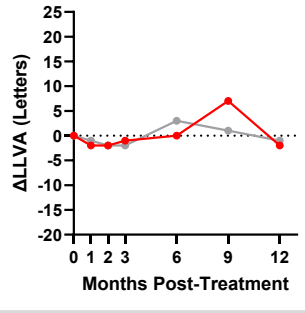
Change in BCVA

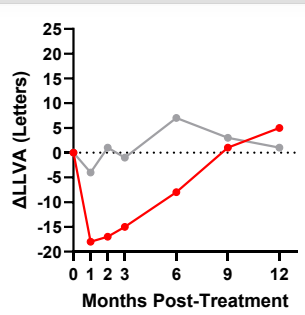


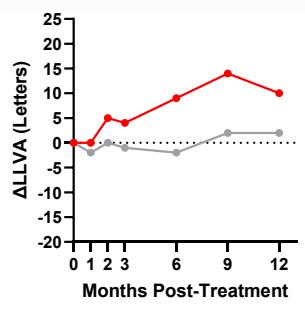




Change in LLVA

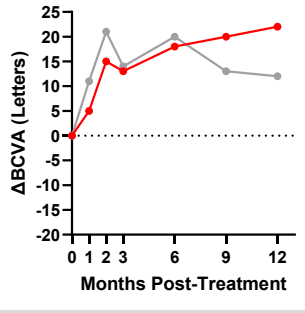


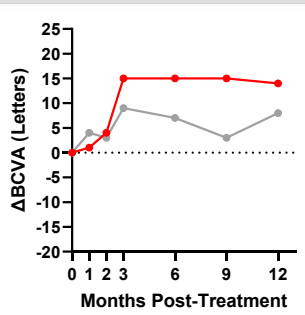


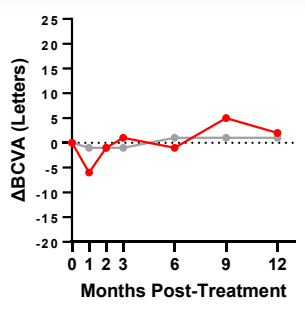


Cohort 3 (Mid Dose)

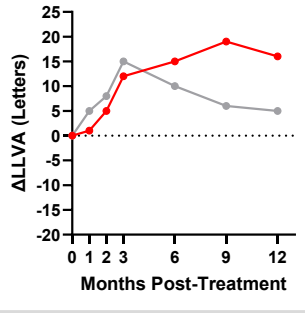
Change in BCVA

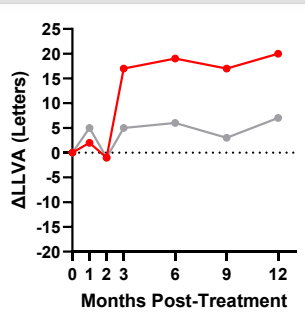


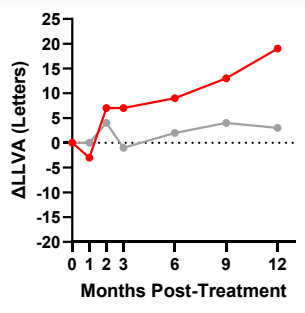




Change in LLVA



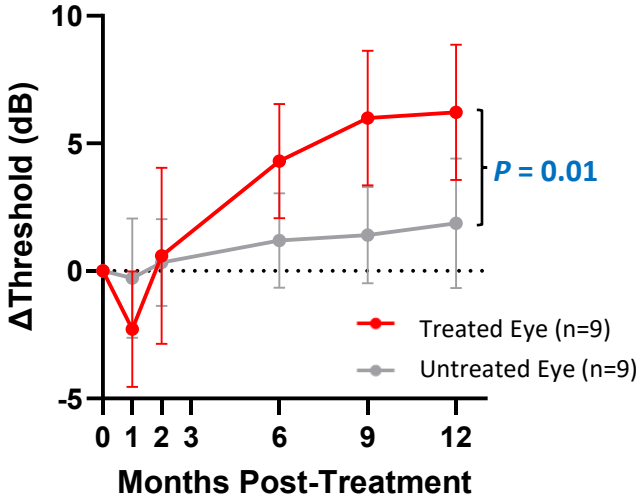




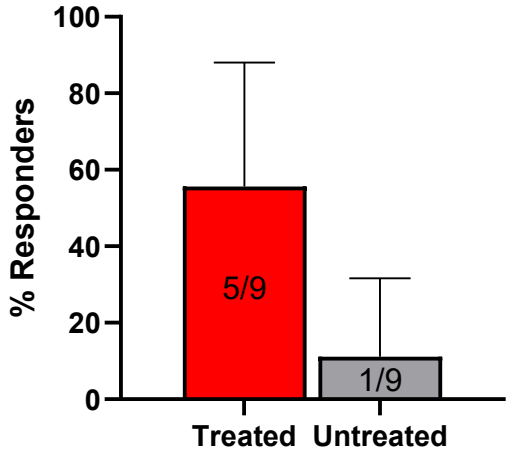
Treated eyes demonstrate greater improvements in visual function

Microperimetry[a]

Change in retinal sensitivity over time (all cohorts)

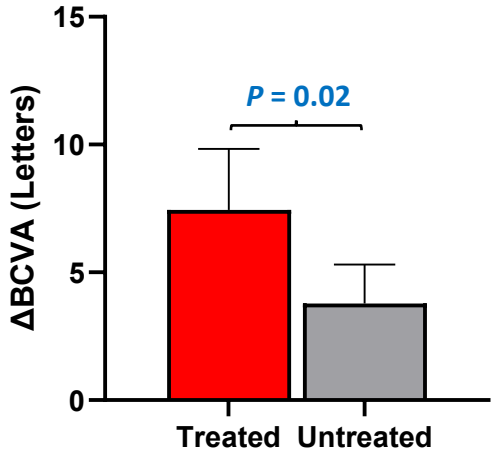


% Responders[b] for all cohorts combined (Month 12)

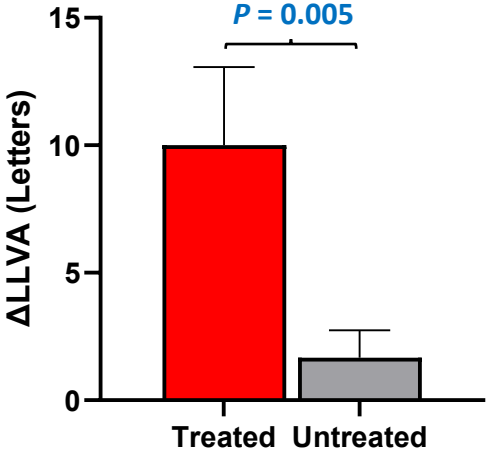


Visual Acuity

Change in BCVA for all cohorts combined (Month 12)



Change in LLVA for all cohorts combined (Month 12)



[a]*MP threshold calculated as the mean sensitivity across the subset of* ***central 16 loci with baseline > 0 dB and ≤ 19 dB***

[b]Responder 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

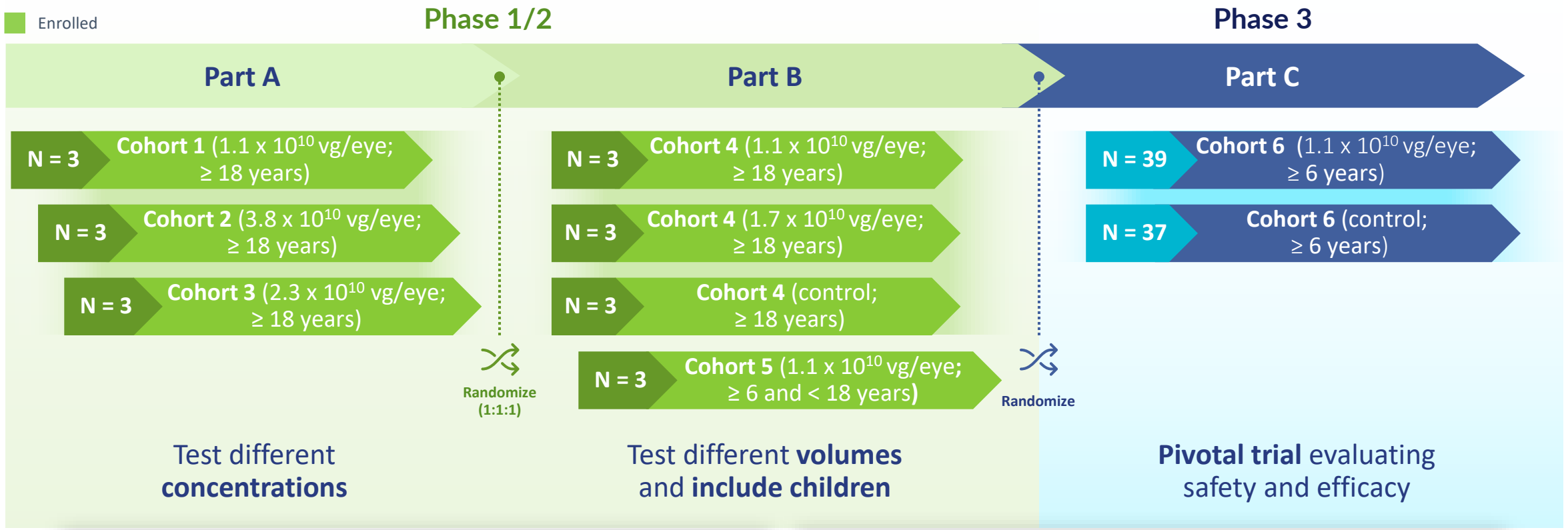
SAFETY

- A **low dose** of 1.1 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

- 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

Questions?