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

Kay CN[1], Everett L[2], Nagiel A[3,4], Lam BL[5], Lauer AK[2], Berrocal AM[5], Gregori NZ[5], Boye SE[6], Boye SL[6], Pardon LP[7], Yoon D[7], Fujita KP[7]

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

Financial Disclosures: Christine Kay

- Atsena Therapeutics
  - Consultant
  - Equity
- RegenxBio:
  - Investigator/surgeon
- Gyroscope:
  - Investigator/surgeon
- Foundation Fighting Blindness
  - Investigator/clinical trial funding
- Alkeus
  - Investigator/clinical trial funding
  - Consultant
- Opus
  - Consultant
- Kodiak
  - Investigator
- Beacon Therapeutics
  - Investigator/clinical trial funding
- Kiora Pharmaceuticals
  - Consultant/Advisory Board
  - Equity
- Nightstar Therapeutics/Biogen:
  - Investigator/surgeon
- Novartis:
  - Consultant
- Iveric Bio:
  - Investigator/clinical trial funding
- ProQR Therapeutics:
  - Investigator/clinical trial funding
- MeiraGTx/Janssen:
  - Investigator/surgeon
- Janssen:
  - Investigator
- 4D Therapeutics
  - Investigator
  - Consultant
- Guidepoint:
  - Consultant
- Adverum
  - Consultant
- Stealth Therapeutics:
  - Investigator funding
- Belite Bio:
  - Investigator funding
- Nanoscope Therapeutics:
  - Consultant
- NEI:
  - Investigator funding
- EyeBio:
  - Investigator funding
- EyePoint:
  - Investigator funding
- Sanofi:
  - Investigator funding

X-Linked Retinoschisis (XLRS)

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

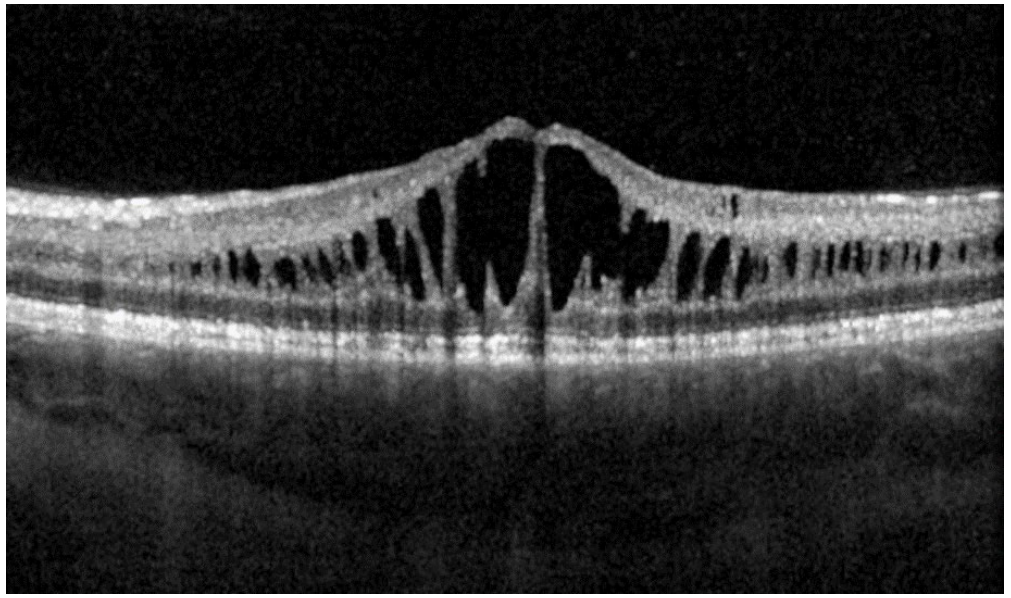
XLRS is caused by mutations in *RS1* gene

- Results in **loss of vision** due to splitting of retinal layers and increased **risk of retinal detachment**
- ***RS1*** **encodes the protein retinoschisin (RS1)**, expressed primarily in photoreceptors and, to a lesser extent, bipolar cells
- RS1 has a role in **cell-cell adhesion, fluid balance, and the photoreceptor/bipolar cell synapse**

ATSN-201 subretinal gene therapy

- Introduces the **functional human retinoschisin (*hRS1*) gene**
- Human rhodopsin kinase promoter targets **photoreceptors**
- **AAV.SPR capsid spreads beyond bleb margins**

FOVEAL SCHISIS IN XLRS



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

XLRS Phase 1/2 Clinical Trial Design (NCT05878860)

Data cutoff: 4 September 2024

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

BASELINE CHARACTERISTICS

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

Drug administered as a one-time subretinal injection (150 uL) ATSN-201 into study eye using 2 blebs and avoiding foveal detachment

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

Study eye = worse-seeing eye

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)

Safety Summary: Overview

Data cutoff: 4 September 2024

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

Total of 53 TEAEs reported

- Majority Grade 1-2 in severity
- 38 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

No subjects have discontinued from the study

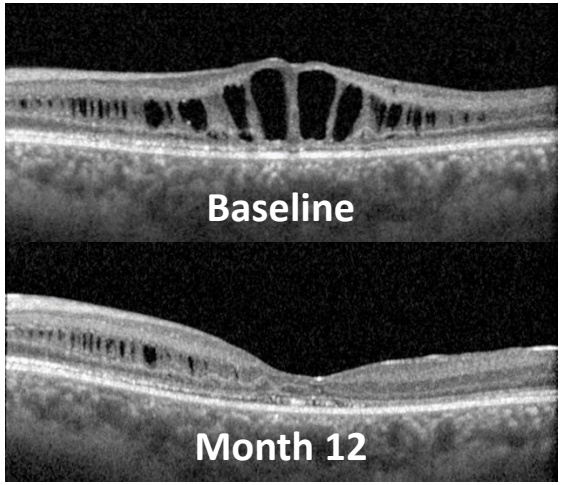
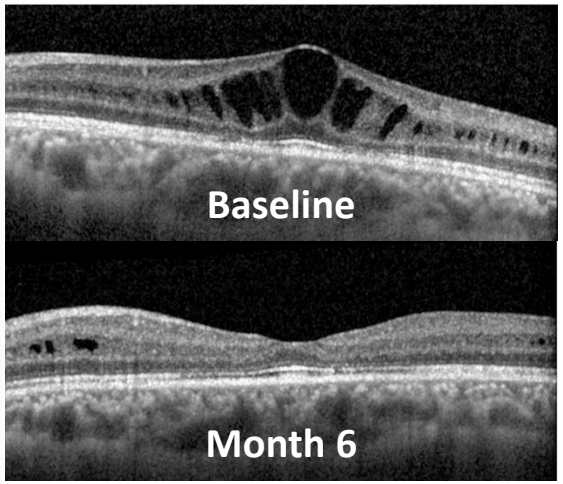
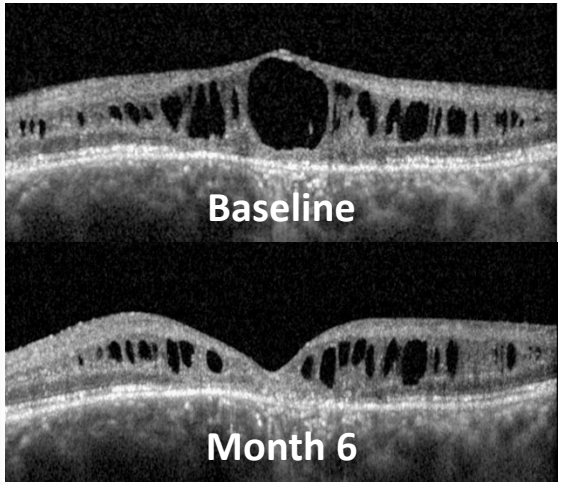
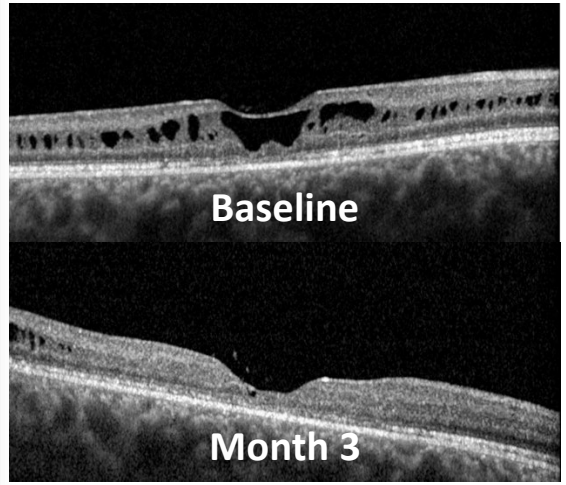
No treatment-related SAEs

- 1 SAE of fever of unknown origin with negative workup
  - 7 months after treatment
  - **Unrelated to ATSN-201 or study procedures**

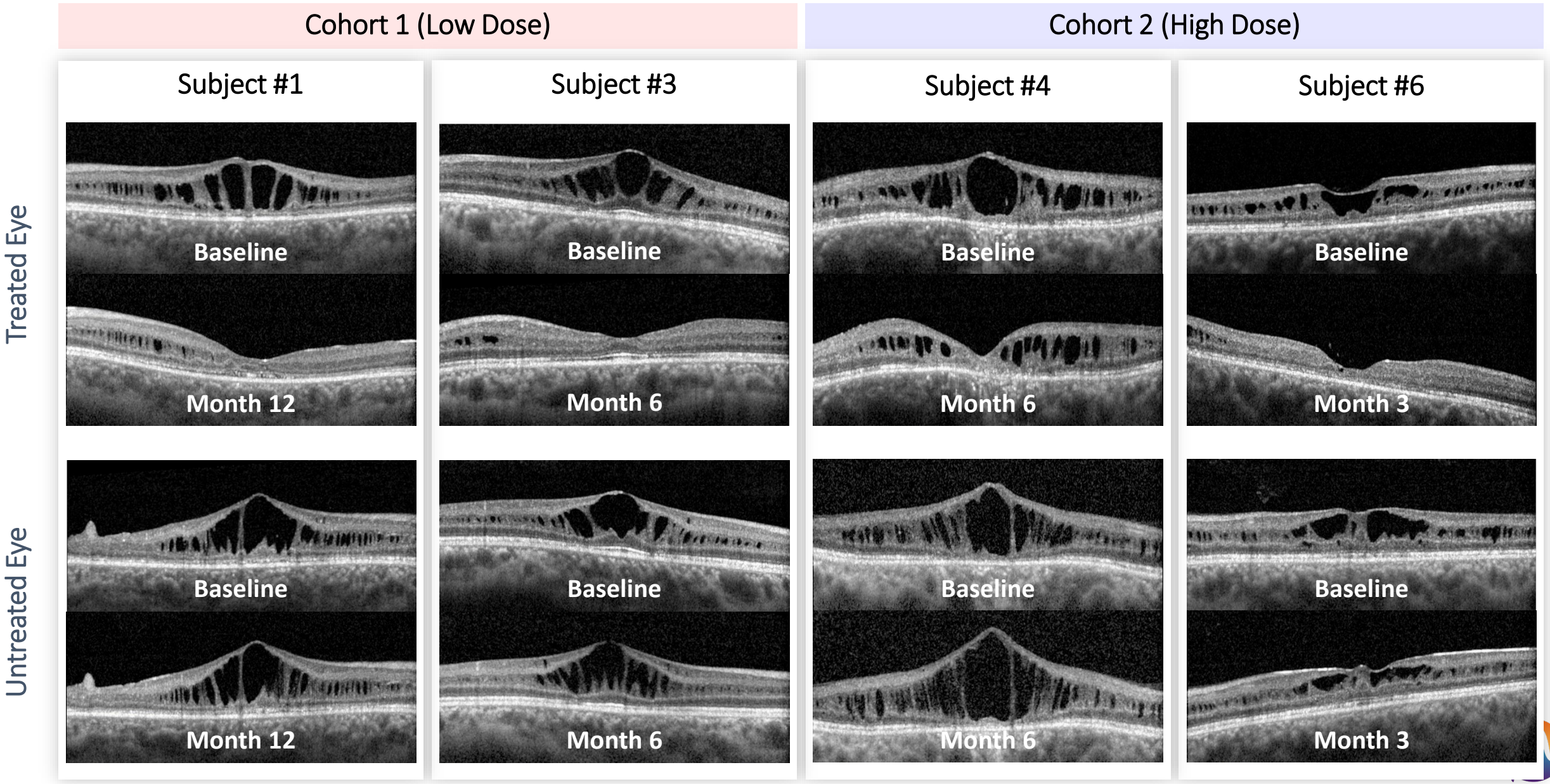
	Cohort 1 N=3	Cohort 2 N=3	Total N=6
# of Events			
Any TEAE	28	25	53
Any Serious TEAE	1	0	1
Any Severe TEAE	1	2	3
Severity			
Grade 1	19	12	31
Grade 2	8	11	19
Grade 3	1	2	3
Grade 4 or 5	0	0	0
Related to ATSN-201			
Possibly / Probably / Definitely Related	3	9	12
Not Related / Unlikely to be Related	25	16	41
Related to Surgical Procedure			
Possibly / Probably / Definitely Related	21	17	38
Not Related / Unlikely to be Related	7	8	15

4 of 6 treated eyes had closure of foveal schisis at most recent visit

Treated Eye

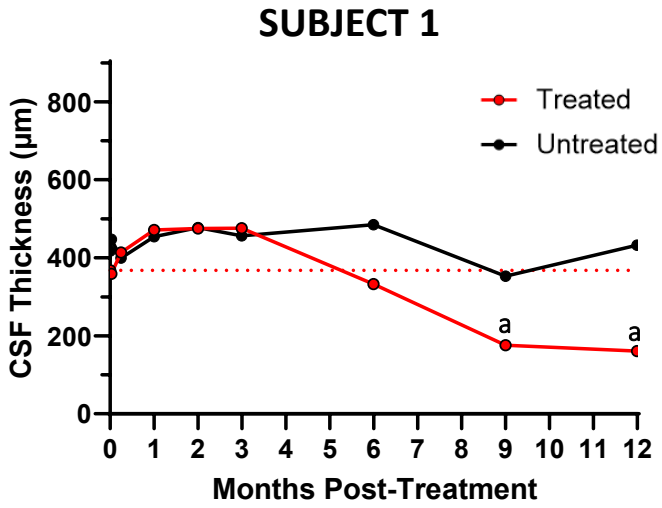
Cohort 1 (Low Dose)		Cohort 2 (High Dose)	
Subject #1	Subject #3	Subject #4	Subject #6
			

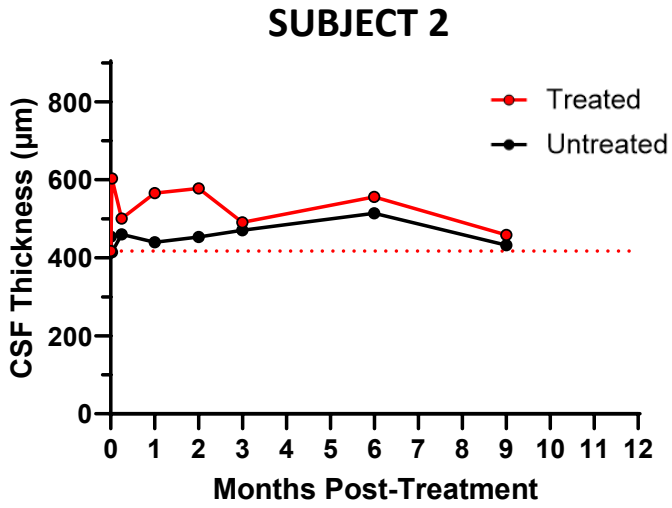
Untreated eyes did not demonstrate schisis closure

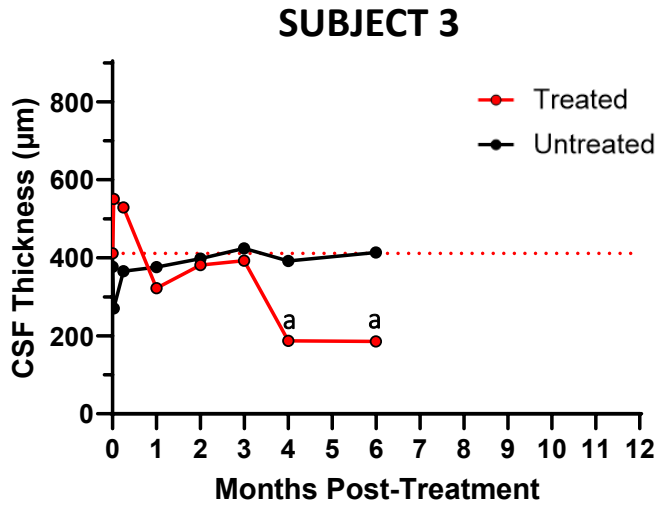


Majority of treated eyes show reduction in central retinal thickness

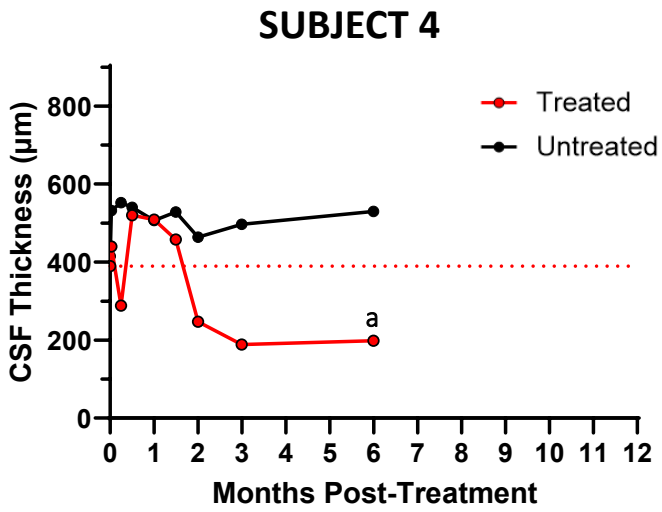
COHORT 1

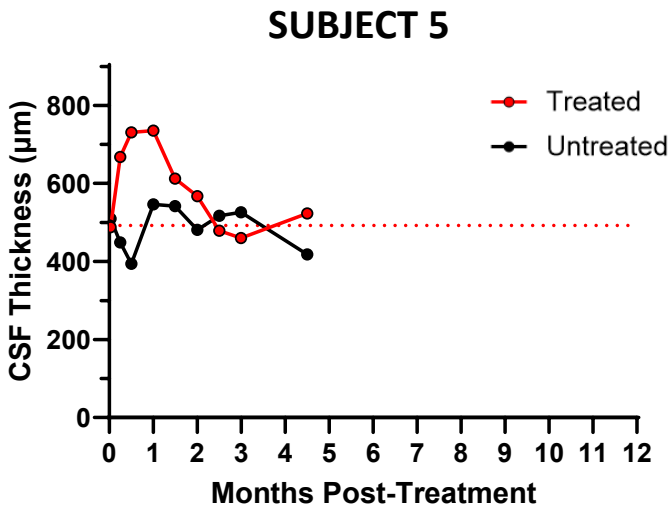


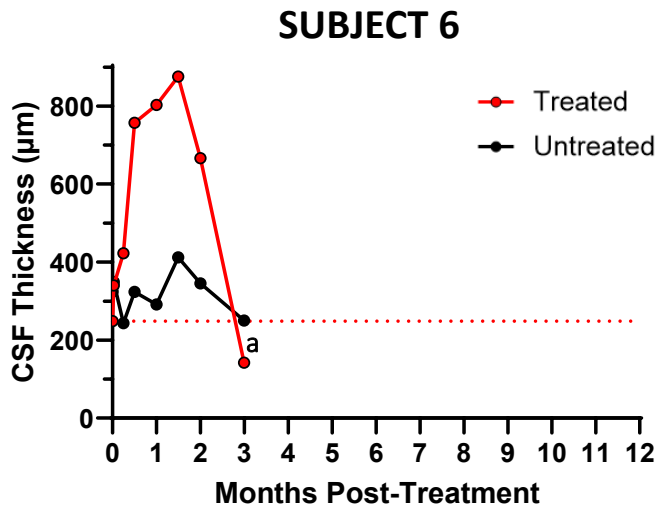




COHORT 2







[a] Closure of foveal schisis

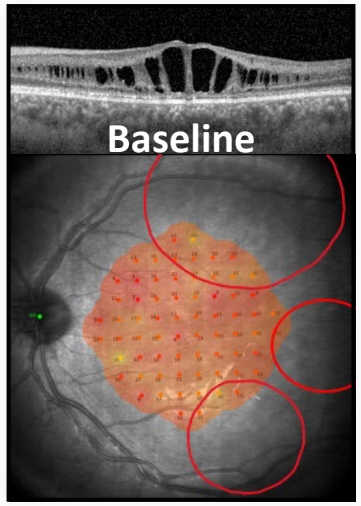
Eyes with structural improvements also show improvements in function

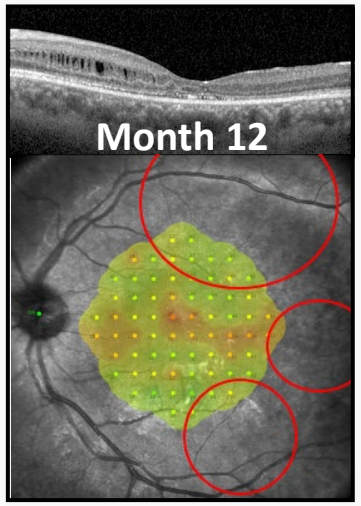
Cohort 1 (Low Dose)

Cohort 2 (High Dose)

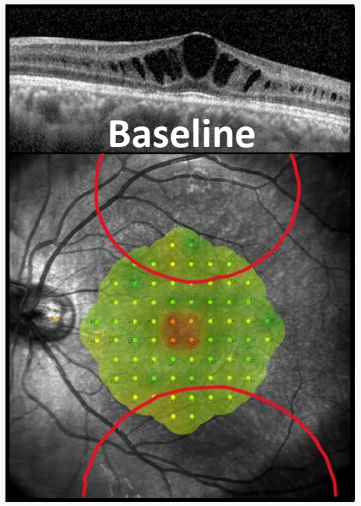
Treated Eye

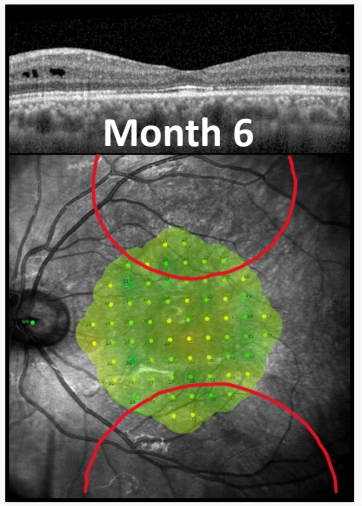
Subject #1



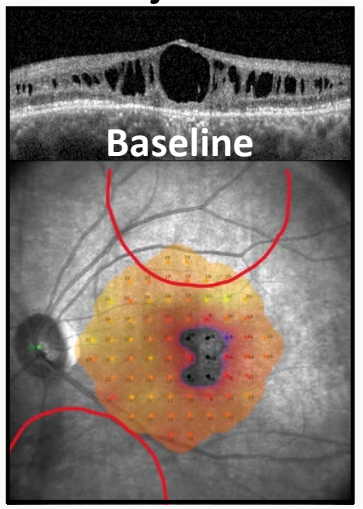


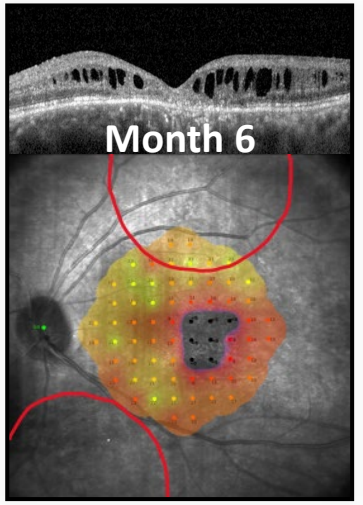
Subject #3



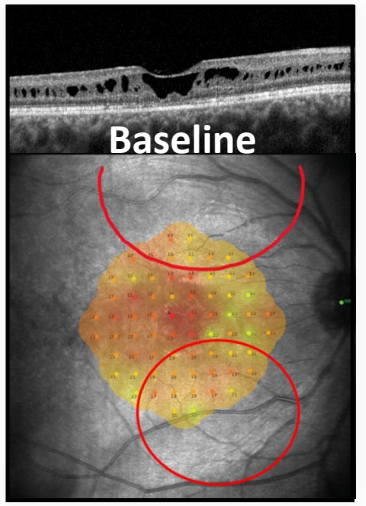


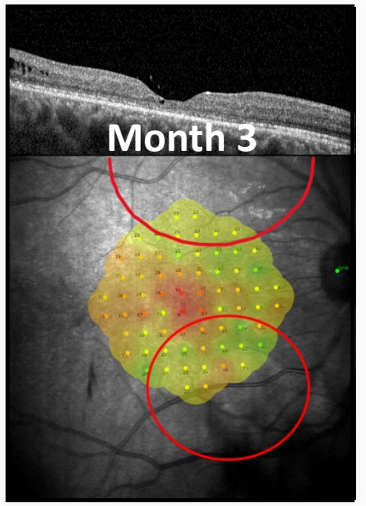
Subject #4





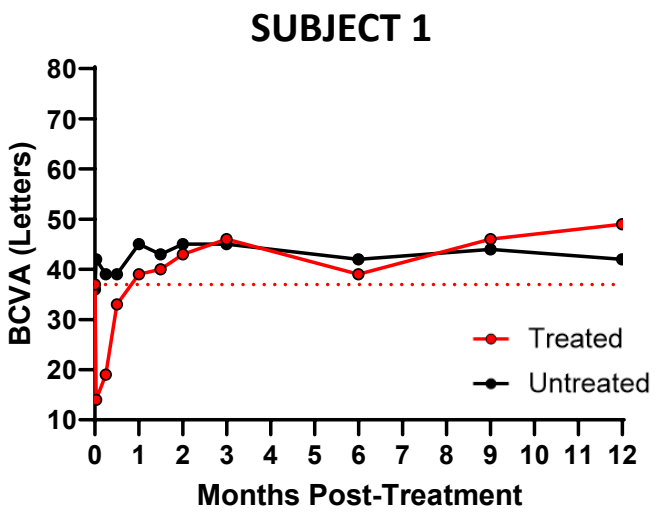
Subject #6

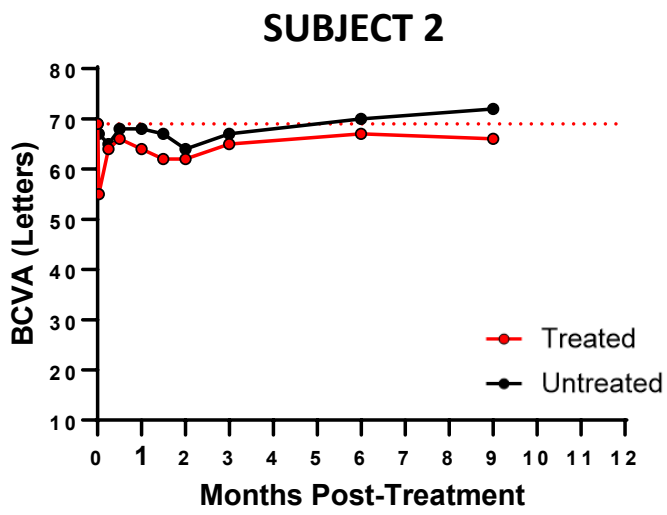


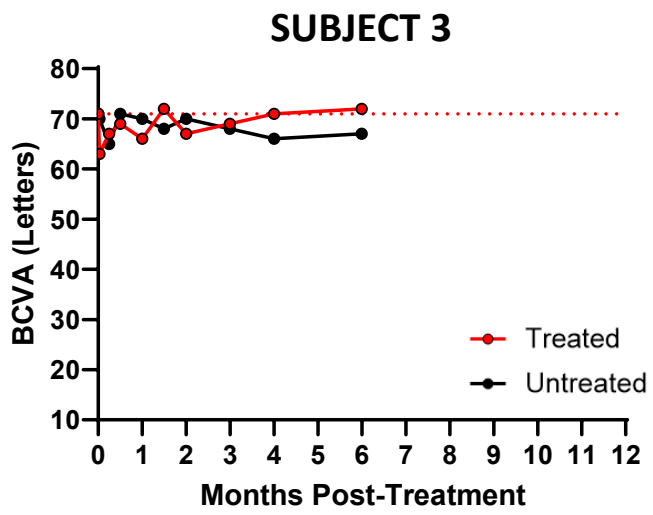


Majority of eyes show stable visual acuity

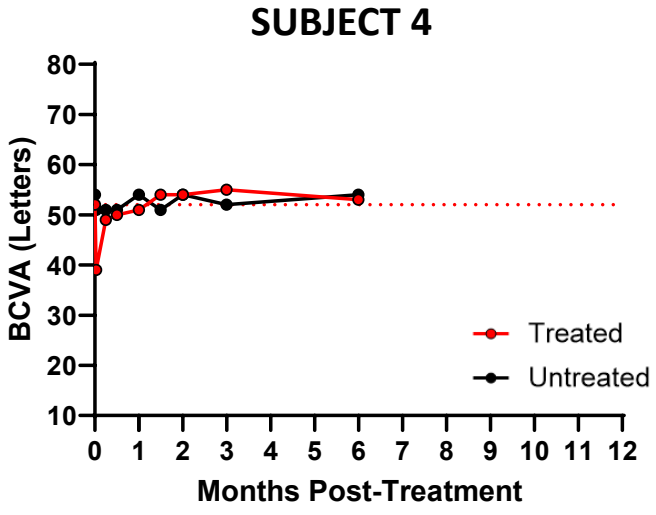
COHORT 1

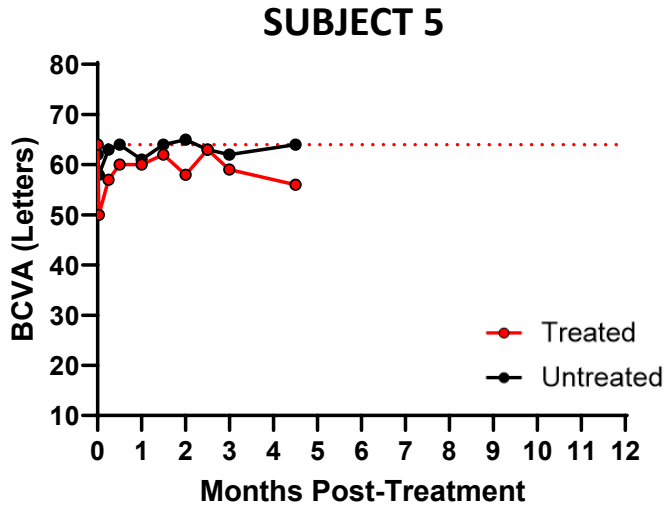


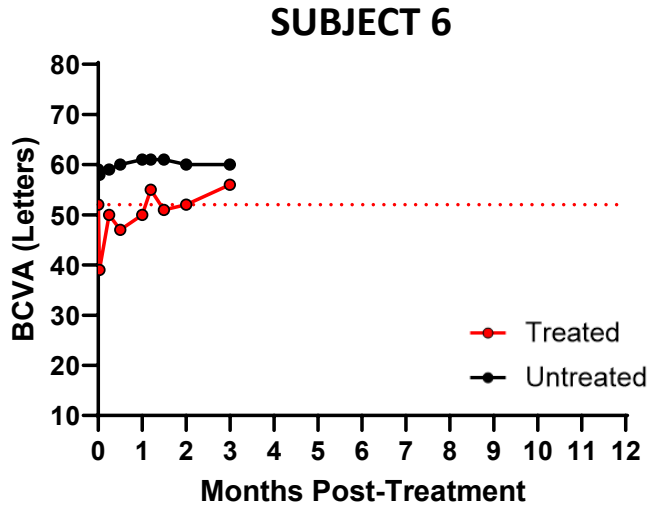




COHORT 2







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** up to 1 year post-treatment
- A **high dose** of 5.0 x 10^{10} vg/eye revealed 3 of 3 subjects developed subretinal deposits and retinal thickening
- **Dose will be de-escalated** to an intermediate dose of 3.0 x 10^{10} vg/eye in Cohort 3
- **One serious adverse event** to date
  - Unrelated to study drug or procedures
- **No dose-limiting toxicities**

EFFICACY

- Preliminary evidence of efficacy in both low and high dose cohorts
- **Majority of treated eyes** demonstrated a **reduction in central retinal thickness**
- Of the 2 subjects without a substantial decrease in 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 retinal sensitivity** observed in eyes demonstrating closure of foveal schisis