# Preliminary safety of ATSN-201 subretinal gene therapy in patients with X-linked retinoschisis

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# Financial Disclosure – Christine Kay, M.D.

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- Consultant
- Stock options

**Beacon Therapeutics:**

- Investigator

**Foundation Fighting Blindness:**

- Investigator

**Alkeus:**

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**Ascidian Therapeutics:**

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**Novartis:**

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**Biogen:**

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**4D Therapeutics:**

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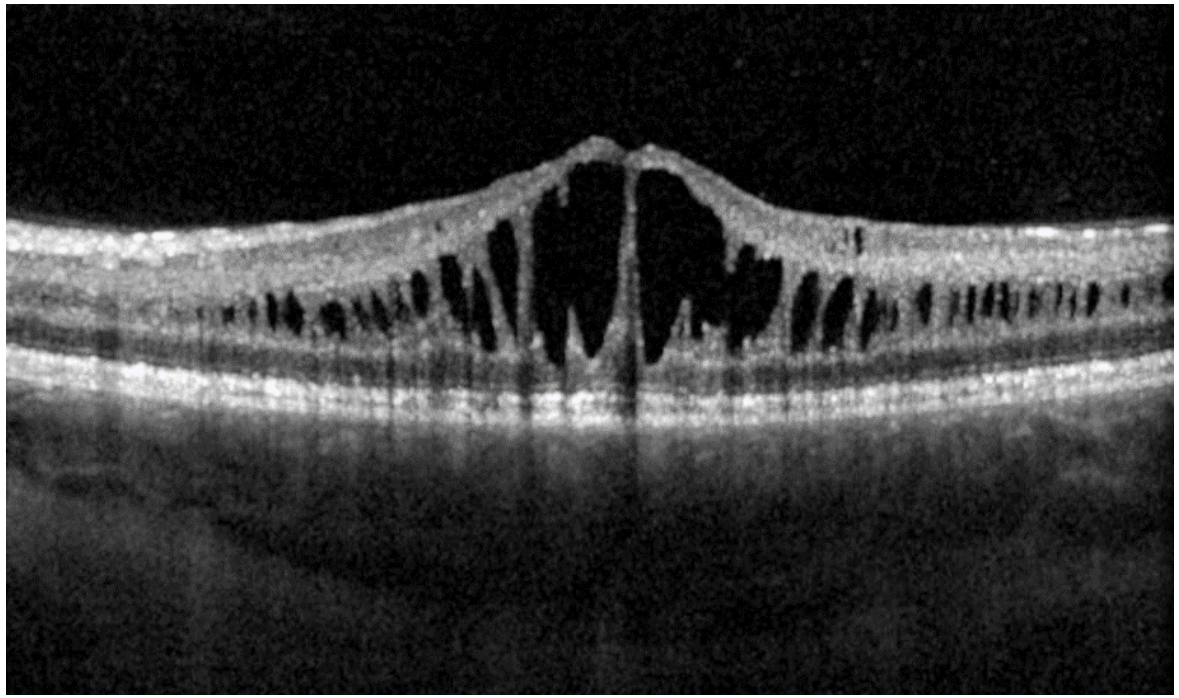
# X-Linked Retinoschisis (XLRS)

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

### XLRS is caused by mutations in *RS1* gene

- 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
- 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**

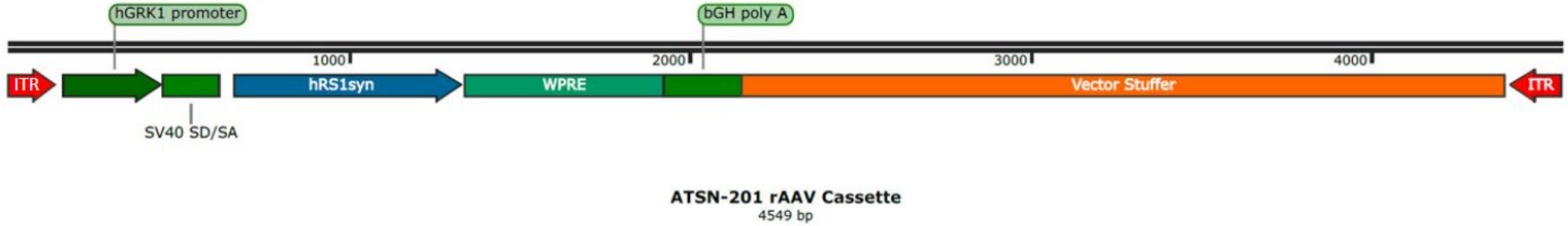
**FOVEAL SCHISIS IN XLRS**



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

# ATSN-201

- **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**
- Human rhodopsin kinase promoter
- Synthetic 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)

Data cut: 08 April 2024

| ENROLLED | COHORT | | |
|---|---|---|---|
| | | **PART A:** Dose Escalation | |
| ✓ | 1 | Low dose (N=3), ≥ 18 years | 1.5E10 vg/eye |
| | 2 | Mid dose (N=3), ≥ 18 years | 5.0E10 vg/eye |
| | 3 | High dose (N=3), ≥ 18 years | 1.7E11 vg/eye |
| | | **PART B:** Expansion | |
| | 4 | Control (N=3), ≥ 18 years | No intervention |
| | | Low volume (N=3), ≥ 18 years | TBD from Part A |
| | | High volume (N=3), ≥ 18 years | TBD from Part A |
| | 5 | (N=3), ≥ 6 and < 18 years | TBD from Part A |

Drug administered as a one-time subretinal injection (150 uL) ATSN-201 into study eye using 2 blebs and avoiding foveal detachment
Corticosteroid regimen: 6-week prednisone regimen starting at 1mg/kg/day, 20 mg triamcinalone acetonide periocular injection, 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:

- Best corrected visual acuity (BCVA)
- Optical coherence tomography (OCT)
- Microperimetry (MP)

# Demographics and Baseline Characteristics

| | Cohort 1<br>N=3 |
|---|---|
| **Age (Years)** | |
| Median | 21 |
| Range (Min, Max) | 18, 26 |
| **Race, N(%)** | |
| White | 2 |
| Unknown | 1 |
| **Study eye BCVA (ETDRS letters)** | |
| Median (Snellen equivalent) | 69 (20/50) |
| Range (Min, Max) | 37 (20/160), 71 (20/50) |
| **Study eye central 1mm retinal thickness (µm)** | |
| Median | 411.6 |
| Range (Min, Max) | 367.5, 417.4 |

# Safety Summary: Overview

**No serious adverse events (SAEs) or DLTs**

**No instances of macular hole formation or retinal detachment**

**Total of 24 TEAEs reported**

- All Grade 1 or 2 in severity
- 18 related to surgical procedure

**Ocular inflammation has been minimal and reversible with steroid treatment**

**BCVA has remained stable in all subjects**

**No subjects have discontinued from the study**

| | Cohort 1 N=3 |
|---|---|
| **# of Events** | |
| **Any TEAE** | 24 |
| **Any Serious TEAE** | 0 |
| **Severity** | |
| Grade 1 | 16 |
| Grade 2 | 8 |
| Grade 3-5 | 0 |
| **Related to ATSN-201** | |
| Possibly / Probably / Definitely Related | 3 |
| Not Related / Unlikely to be Related | 21 |
| **Related to Surgical Procedure** | |
| Possibly / Probably / Definitely Related | 18 |
| Not Related / Unlikely to be Related | 6 |

# Safety Summary: Adverse Events Related to ATSN-201

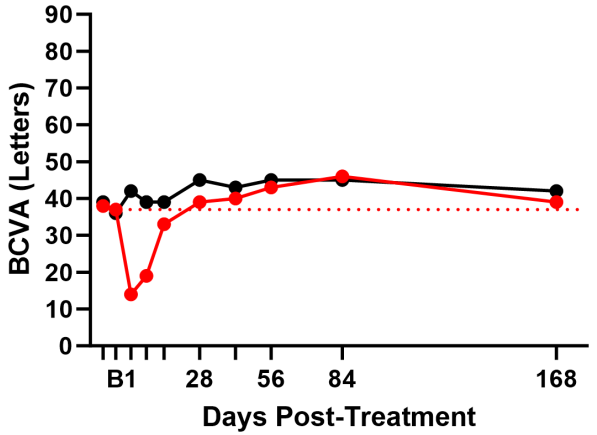
| TEAEs Related to Study Drug (1 event each, all in Subject #2) | Grade 1 | Grade 2 | Total |
|---|---|---|---|
| **# of Events** | 0 | 3 | 3 |
| Anterior uveitis | 0 | 1 | 1 |
| Intermediate uveitis | 0 | 1 | 1 |
| Papillitis | 0 | 1 | 1 |

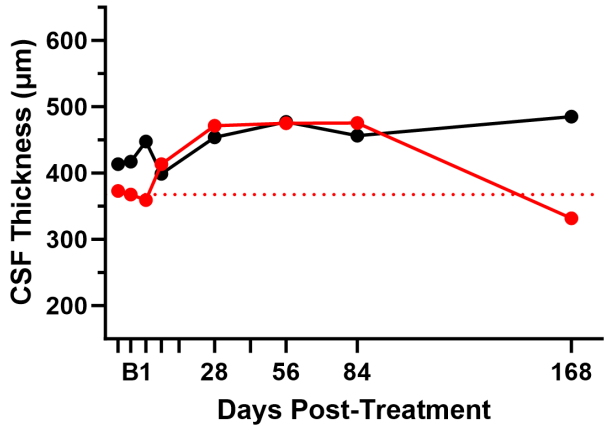
| Visit | AC Cells | Vitreous Cells | Optic Disc |
|---|---|---|---|
| Week 4 (Day 28) | Grade 1 (6-15 cells) | Trace (2-20 cells) | Subtle blurring of disc margin |
| Week 6 (Day 42) | Trace (1-5 cells) | Trace (2-20 cells) | Subtle blurring of disc margin |
| Month 2 (Day 56) | Grade 0 (no cells seen) | Trace (2-20 cells) | Subtle blurring of disc margin |
| Month 3 (Day 84) | Grade 0 (no cells seen) | Trace (2-20 cells) | Improvement in elevation of nerve rim |
| Month 6 (Day 168) | Grade 0 (no cells seen) | Grade 0 (0-1 cell per high powered field) | Within normal limits |

Subject #2 was treated with **oral prednisone** and **prednisolone acetate 1%** taper (Days 28-70) and subsequently treated with **difluprednate** taper (Days 71-126)

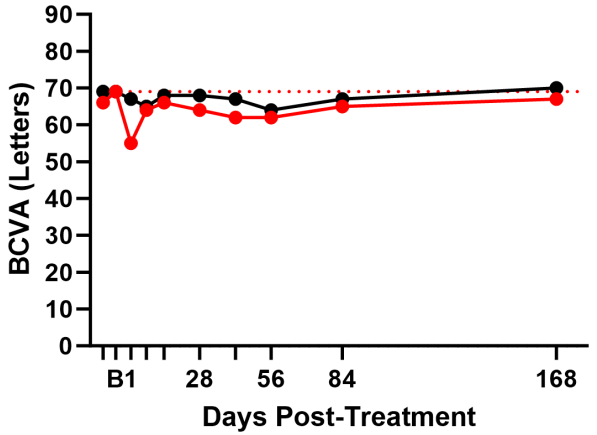
# BCVA and Central Retinal Thickness by Subject

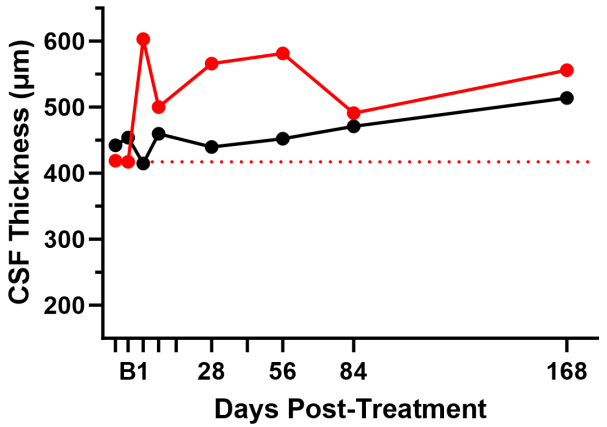

## Subject #1



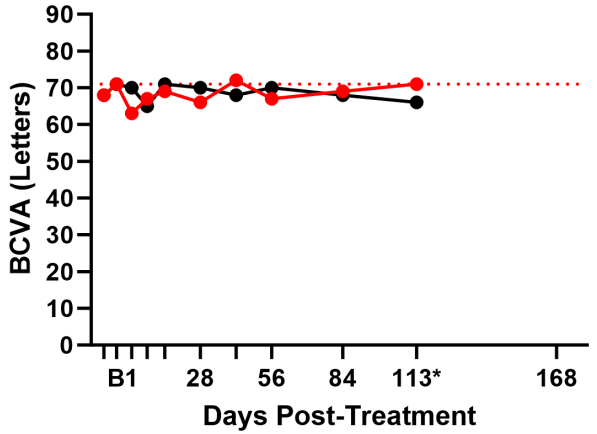



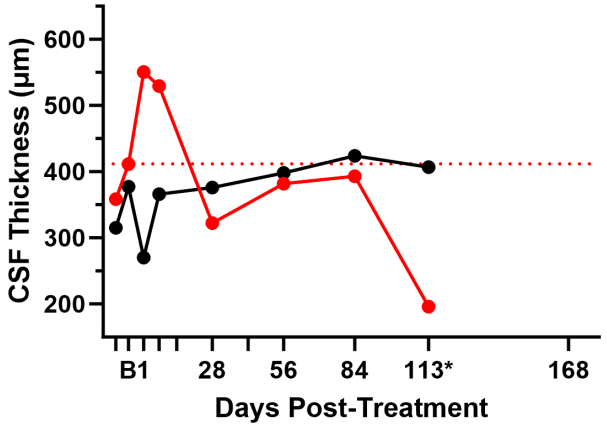

## Subject #2



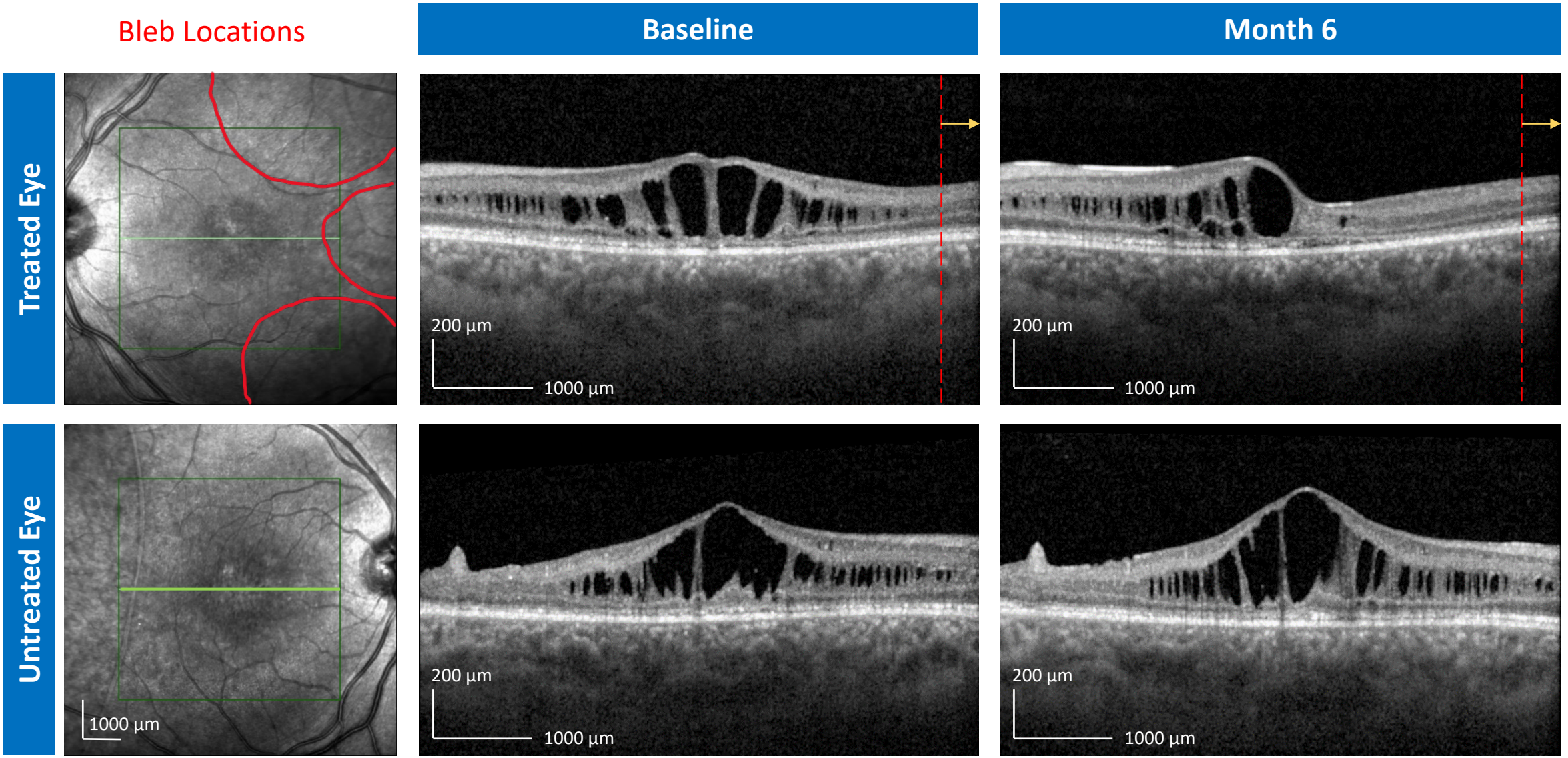

## Subject #3



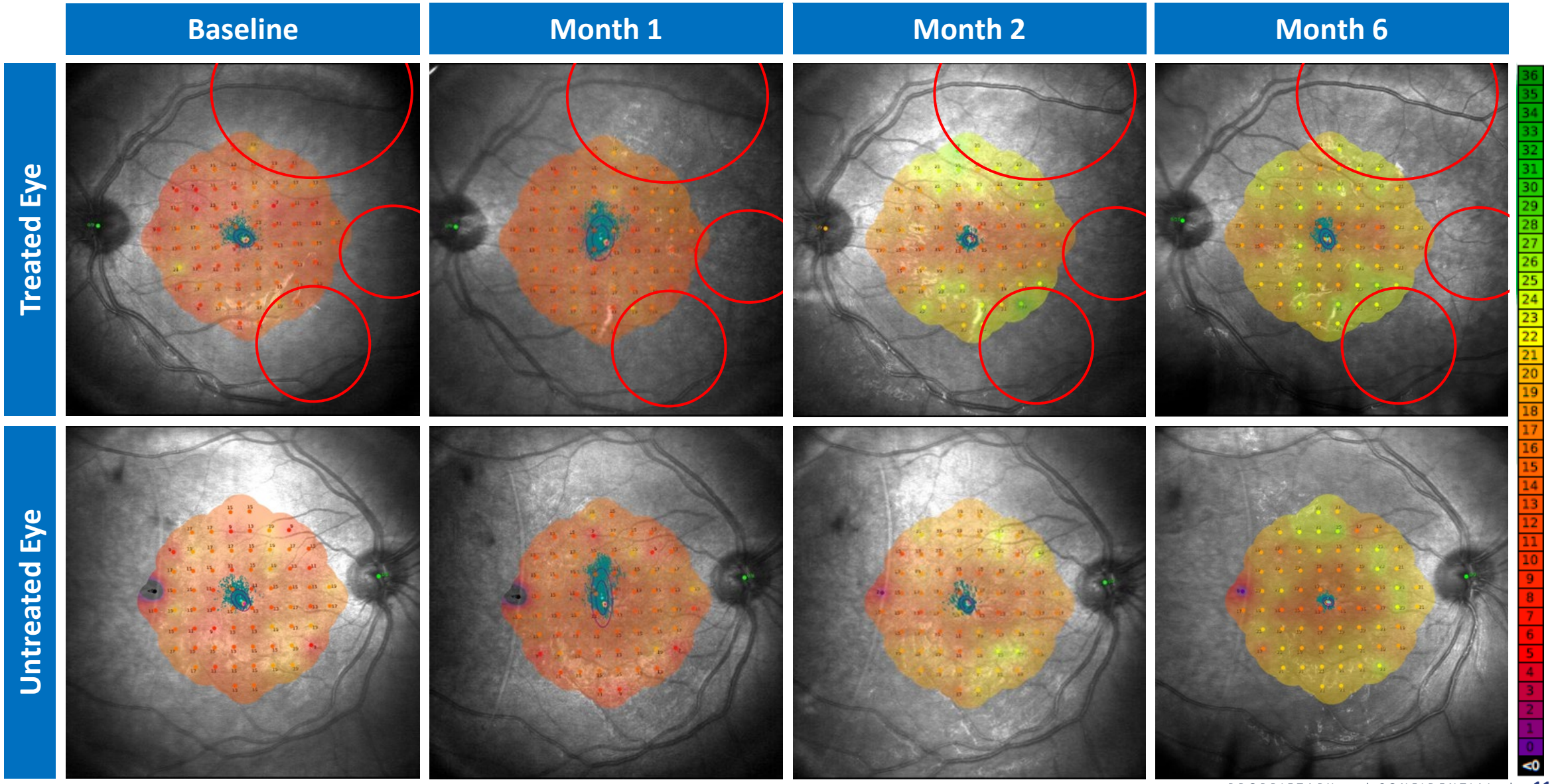




CSF = central subfield (central 1 mm of ETDRS grid)
*Unscheduled visit

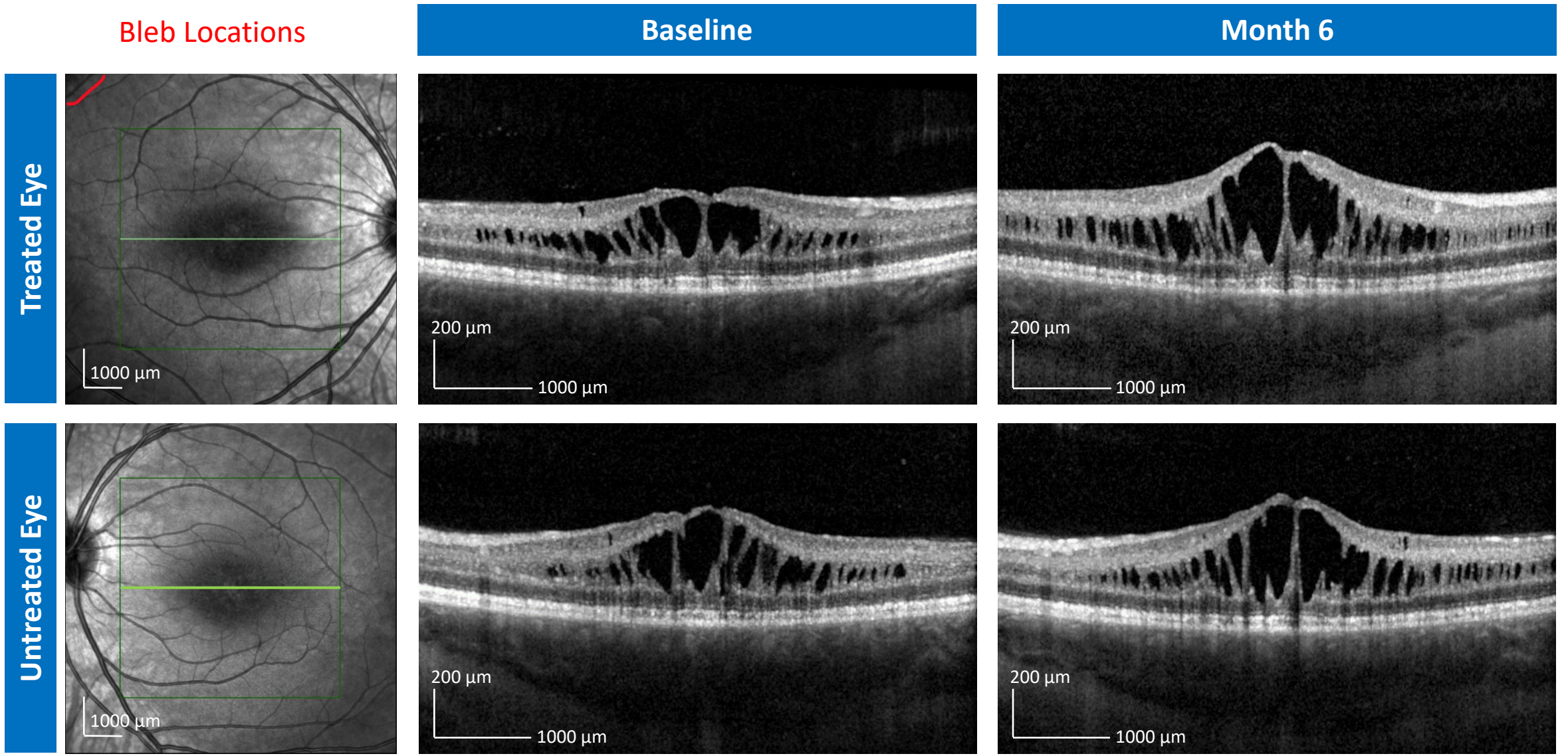
# Subject #1: Foveal schisis is reduced in the treated eye at Month 6



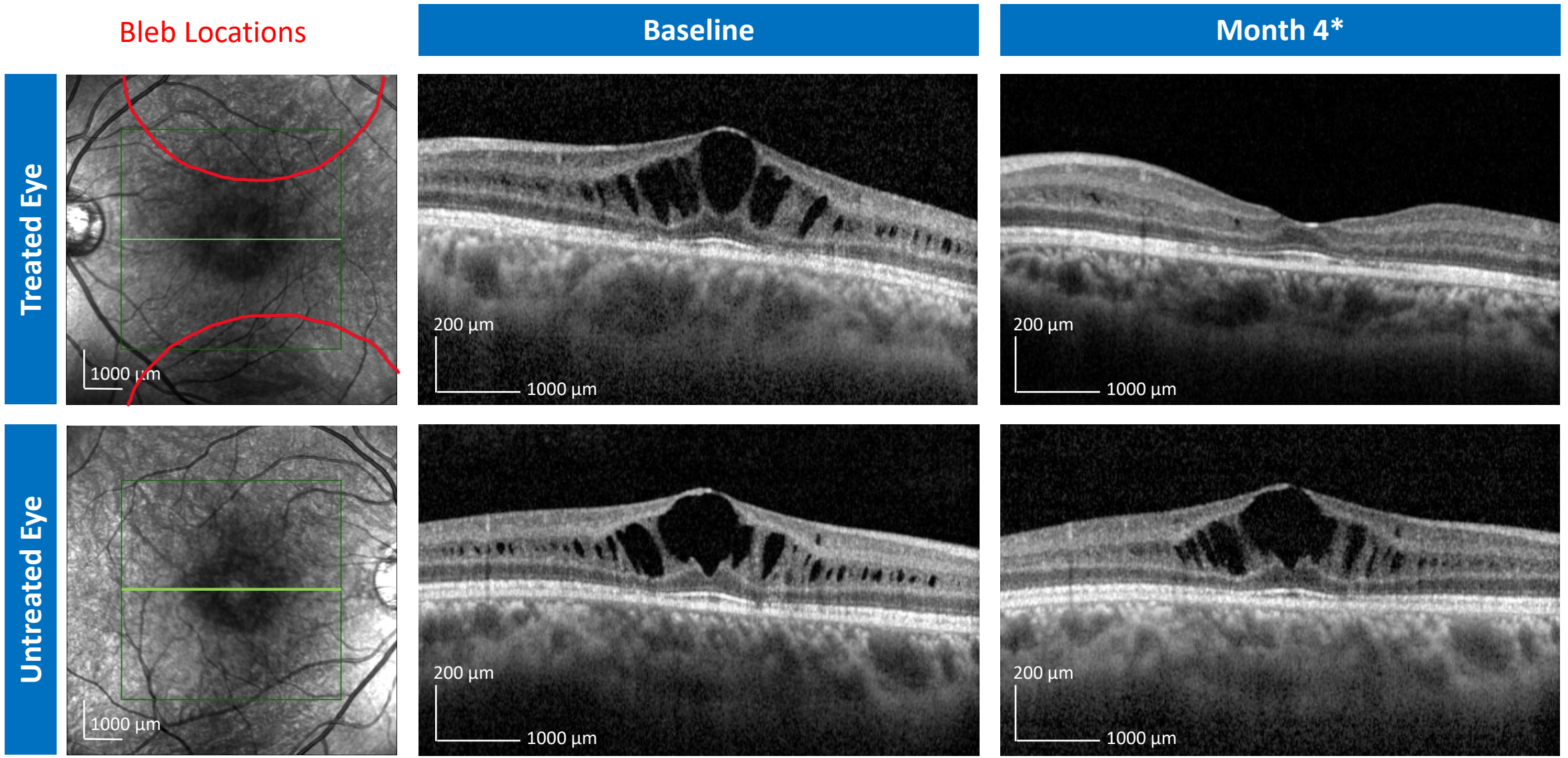
# Subject #1: Microperimetry



# Subject #2: No improvement in foveal retinoschisis at Month 6



# Subject #3: Foveal schisis is resolved in the treated eye at Month 4




*Unscheduled visit

**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

- Well-tolerated at the lowest dose up to 6 months post-treatment
- To date, no SAEs or DLTs reported
- Ocular inflammation has been minimal and reversible with steroid treatment
- Subretinal gene augmentation that avoids foveal detachment can be safely performed in patients with XLRS

## EFFICACY

- BCVA stable in all subjects
- Improvements in retinoschisis observed in 2/3 subjects treated with low dose ATSN-201