IND-enabling Studies to Support the Clinical Development of ATSN-201, a Subretinally Delivered, Laterally Spreading Gene Replacement Therapy For X-linked Retinoschisis (XLRS)

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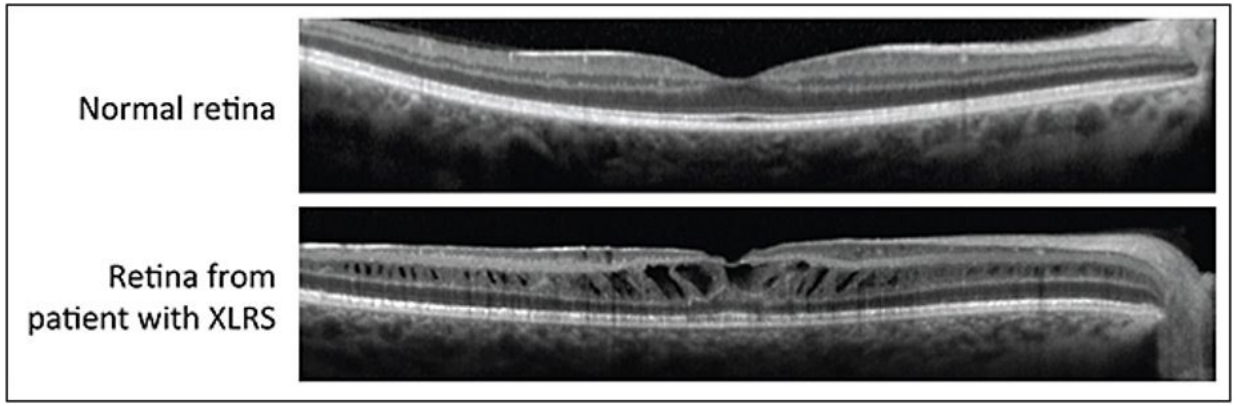
Disclosures

Income and equity

- Atsena Therapeutics (employee)

X-linked Retinoschisis (XLRS)

- Monogenic, X-linked recessive disorder caused by mutations in the gene Retinoschisin (RS1)
- Mutations in *RS1* leads to progressive vision loss that begins in early childhood, characterized by:
  - Abnormal splitting of the layers of the retina (schisis cavities) in the central retina
  - Abnormal electroretinogram (ERG)- diminished b-wave
  - Loss of photoreceptors in later stage disease (5th decade)
- RS1 plays a role in cell-cell adhesion, fluid balance and photoreceptors/bipolar cell synapse
- While RS1 is a secreted protein, expression of RS1 by photoreceptors provides more effective and long-lasting rescue (Byrne et al., 2014)

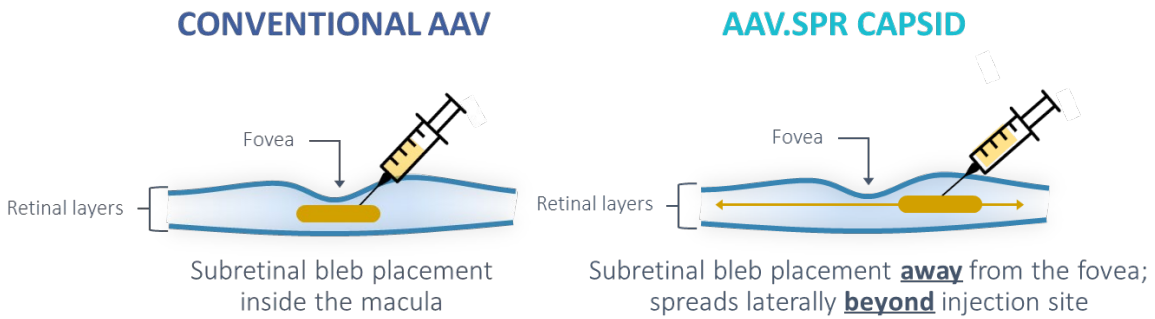


Lateral Spreading Capsid AAV.SPR Allows Subretinal Delivery of AAV-RS1 Vectors

Challenges

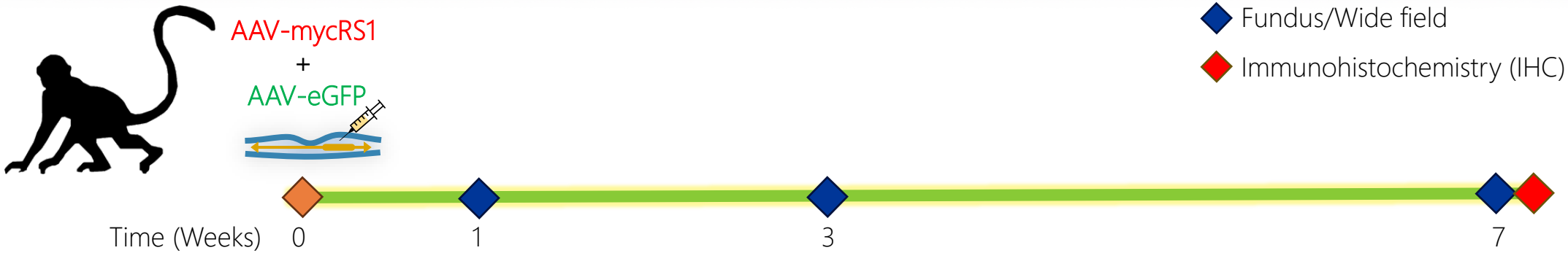
- The first two clinical trials utilized intravitreal delivery (IVT) due to the risk of detachment of XLRS retinas
- Failed to demonstrate efficacy likely related to:
  - Inefficient photoreceptor transduction by IVT delivery
  - Inflammation (XLRS patients have a pro-inflammatory phenotype)

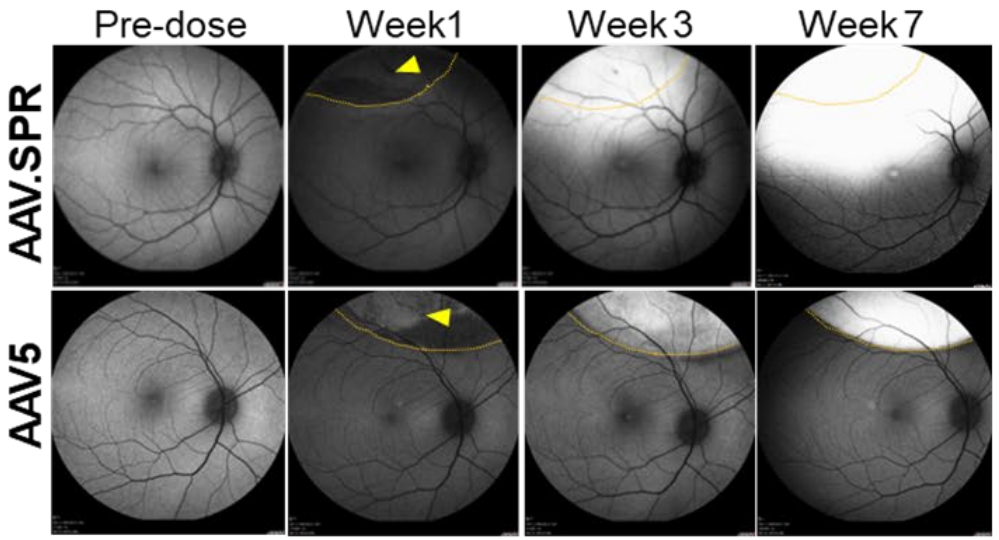
Delivery optimization: AAV.SPR (spread)



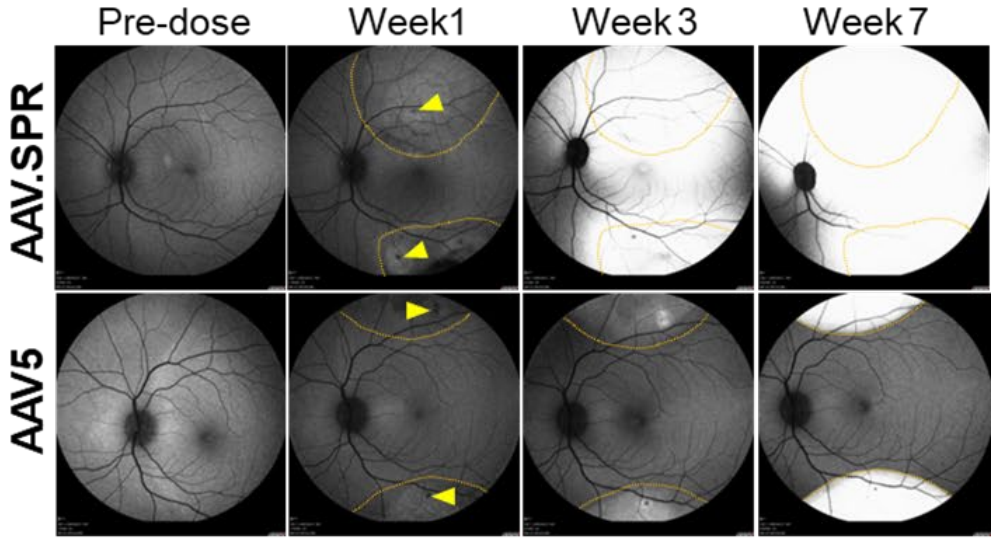
- Allows for subretinal injection in peripheral retina, avoiding foveal detachment and potential trauma
- Spreads to the fovea and efficiently transduces foveal photoreceptors
- Covers larger area resulting in wider area of retinal transduction

AAV.SPR Spreads Laterally from the Subretinal Bleb in NHP



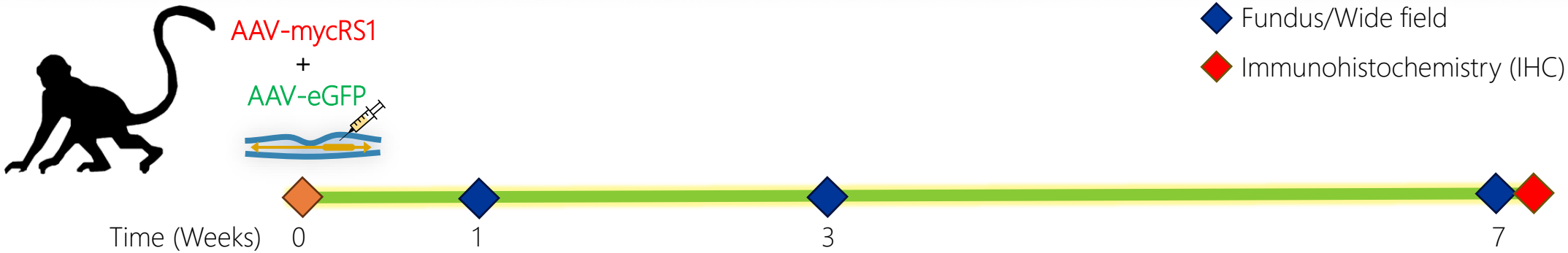


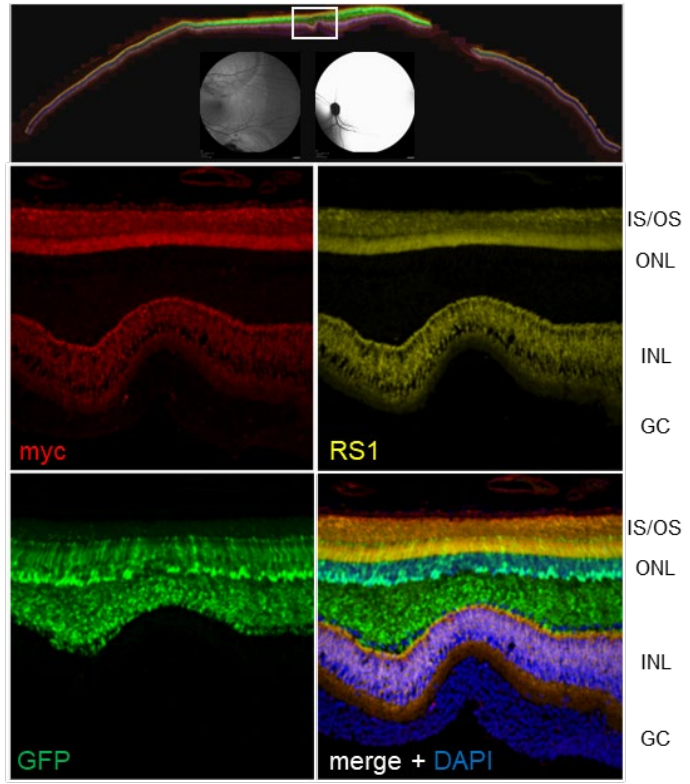
Single, 100 µL extrafoveal injection



Two, 50 µL extrafoveal injections

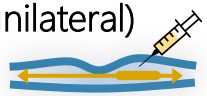
AAV.SPR Spreads Laterally from the Subretinal Bleb in NHP





Durable Correction of Retinal Structure and Function Mediated by AAV.SPR-hRS1 in RS1KO Mice

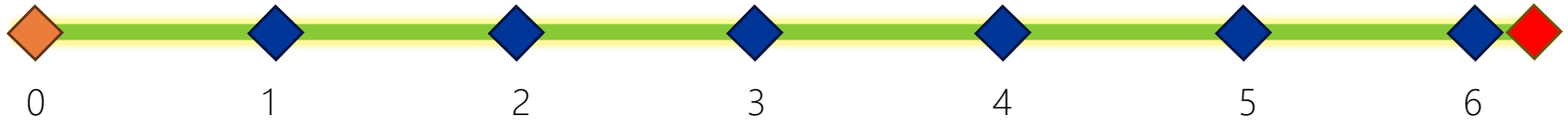
AAV.SPR-hRS1-X001
(unilateral)

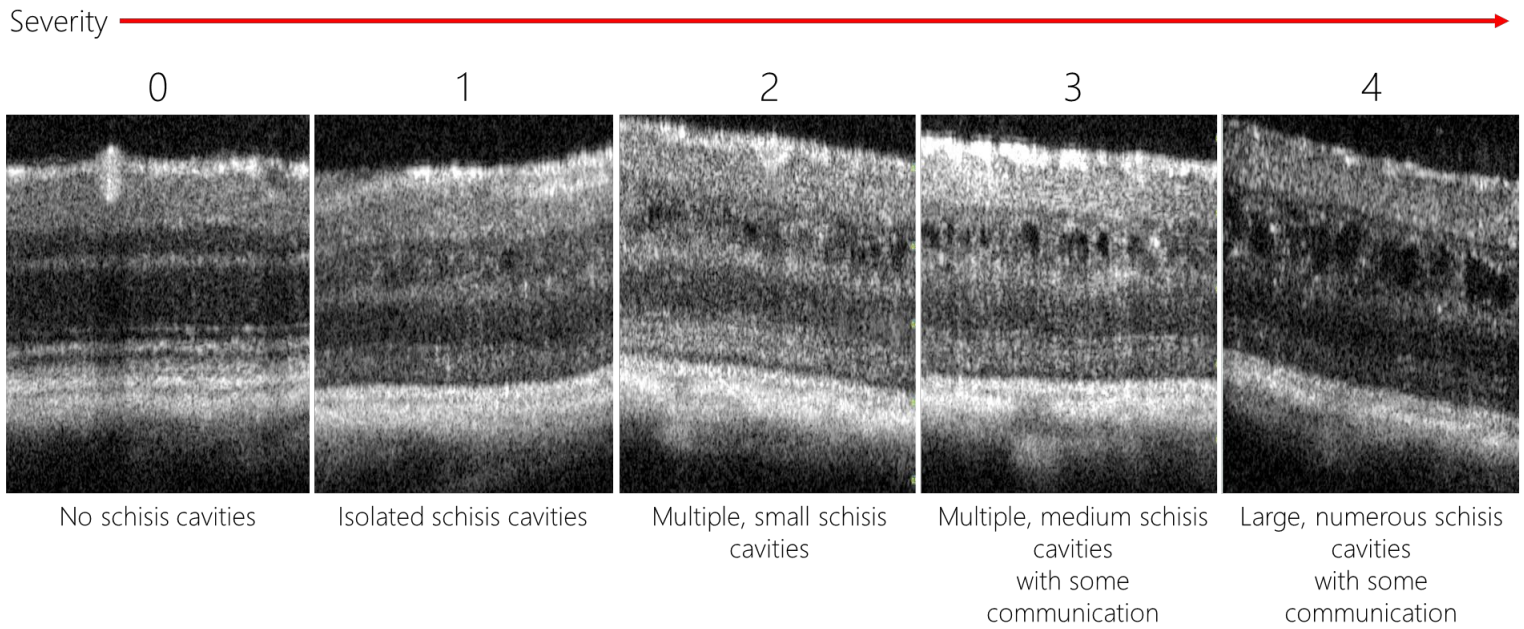


- Vehicle
- Low 3.3 x 10^8 vg/eye
- Mid 1.0 x 10^9 vg/eye
- High 3.0 x 10^9 vg/eye

◆ Scotopic and photopic ERG
Optical coherence tomography (OCT) and schisis scoring

◆ IHC





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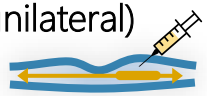

- Vehicle
- Low 3.3 x 10^8 vg/eye
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- High 3.0 x 10^9 vg/eye

- Scotopic and photopic ERG
  Optical coherence tomography (OCT) and schisis scoring
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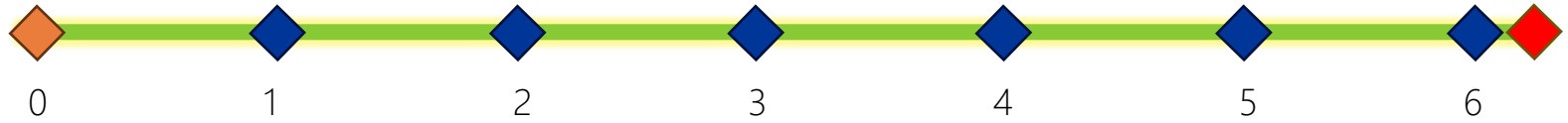
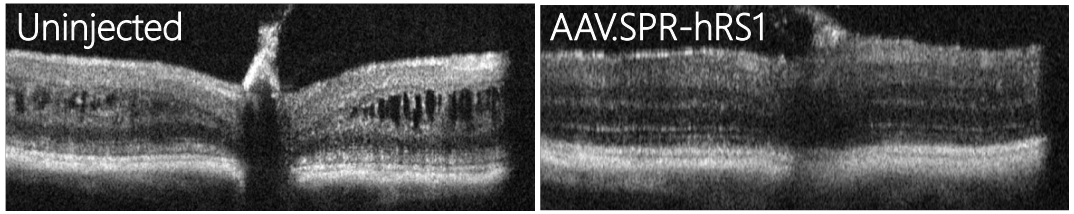
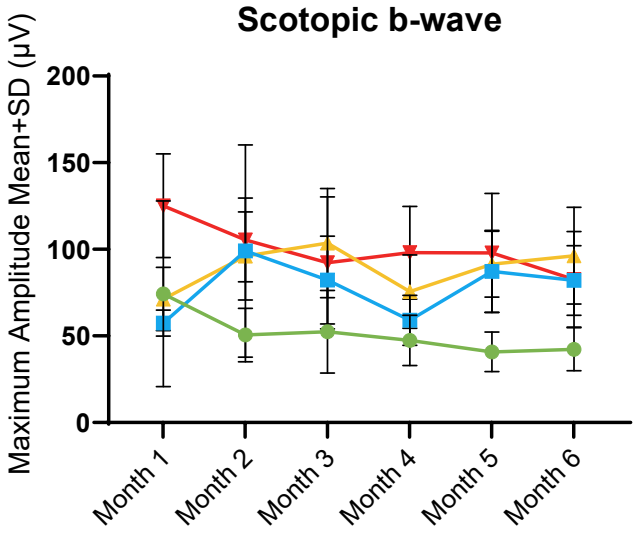
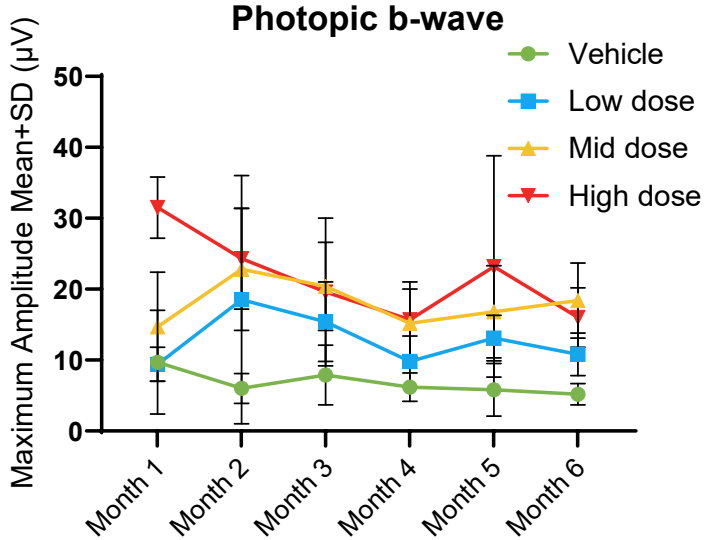
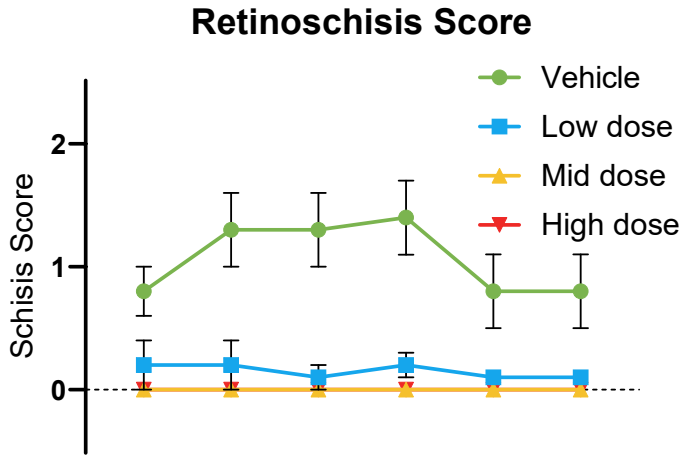








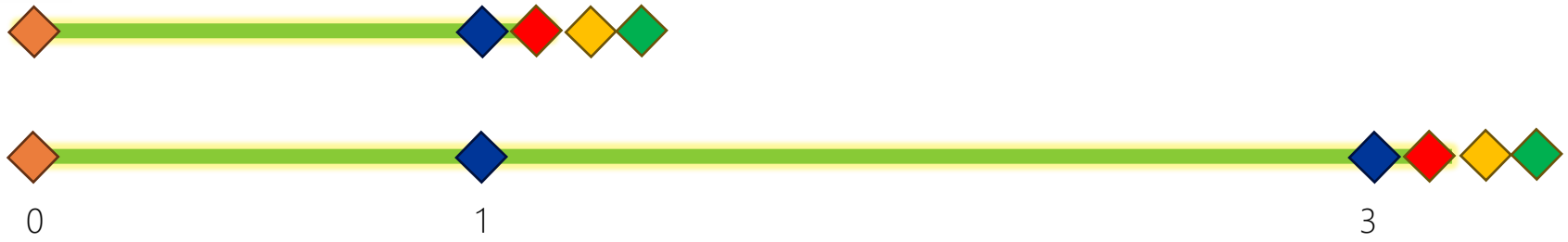


ATSN-201 Efficacy and Tolerability was Evaluated in a Hybrid Toxicology/Pharmacology Study in RS1KO mice

AAV.SPR-hGRK1-hRS1syn (ATSN-201)
(unilateral)

- Vehicle (n=20 RS1KO and 10 WT)
- Low 3.0 x 10^7 vg/eye (n=20)
- Mid 1.3 x 10^8 vg/eye (n=20)
- High 5.3 x 10^8 vg/eye (n=20)
- Max 2.1 x 10^9 vg/eye (n=20)

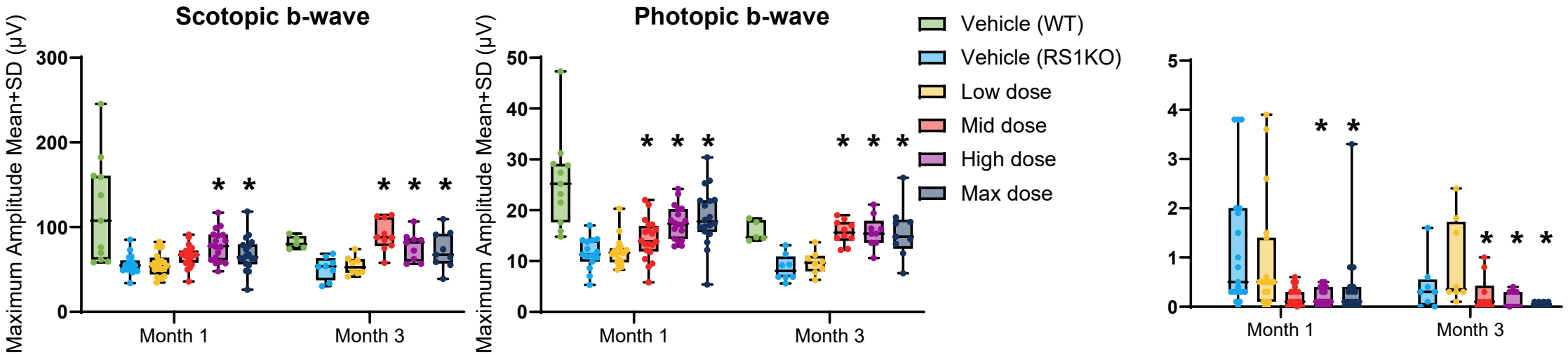
- Scotopic and photopic ERG, OCT and schisis scoring
  Clinical and ophthalmic evaluations
- Pathology (eye and main organs)
- Clinical pathology
- Biodistribution (target and non-target tissues)
  Gene expression (target and non-target tissues)



ATSN-201, No Observed Adverse Effect Level (NOAEL) in RS1KO Mice was the Highest Dose Evaluated

- ATSN-201 was well tolerated at all dose levels in RS1KO mice. There were no ATSN-201-related adverse effects on clinical and ophthalmic exams, clinical pathology, and systemic or ophthalmic pathology
- Minimal or no detectable vector genome sequences were detected in systemic tissues, but vector genome persistence and sustained expression of *hRS1* mRNA was observed in the eye following ATSN-201 administration
- The NOAEL was identified as the highest dose tested, a concentration of 2.1×10^{12} vg/mL
- At Month 3, significant dose-dependent improvements in scotopic and photopic b-waves, and retinoschisis scores were observed in RS1KO mice injected with the Mid, High and Max dose

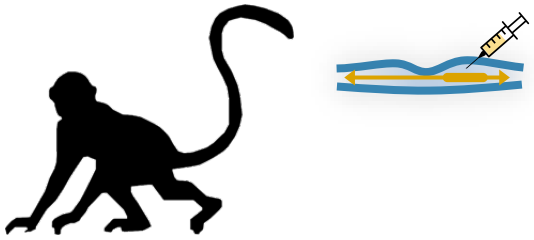
ATSN-201 Provided Significant Dose-dependent Improvements in Retinal Function and Structure in RS1KO Mice



ATSN-201 Safety and Biodistribution Profile was Evaluated in a GLP Toxicology Study in Cynomolgus Macaque

ATSN-201 (bilateral, 2 blebs of 75 µL)

- Vehicle (n=2)
- Low 2.0 x 10^{70} vg/eye (n=3)
- Mid 7.9 x 10^{10} vg/eye (n=3)
- High 3.2 x 10^{11} vg/eye (n=3)



- Ophthalmic evaluations (uveitis scoring), IOP
- Clinical pathology, clinical evaluations
- Immunogenicity (humoral and cellular responses)
- ERG, OCT, Fundus
- Pathology (eye and main organs)
- Biodistribution (target and non-target tissues)
  Gene expression (target and non-target tissues)

Time (Months) 0 1 2 3

ATSN-201, No Observed Adverse Effect Level (NOAEL) in NHPs was the Highest Dose Evaluated

- There were no ATSN-201-related systemic effects
- No ophthalmic exams findings or changes in IOP related with the treatment were identified. Fundus, ERG and OCT revealed no changes correlated with the treatment or timepoints
- No humoral responses against RS1 or cellular immune responses to the capsid or RS1 were detected. Several animals developed antibodies against AAV.SPR
- There were no ATSN-201 microscopic findings. Procedure related findings were observed in all the animals (including control group)
- The biodistribution analysis showed a dose dependent persistence of ATSN-201 in retinal tissues. Accordingly, high levels of *hRS1* mRNA expression were detected in the injected eyes. Minimal or no detectable vector genomes were detected in systemic tissues
- The NOAEL was identified as the highest dose tested, a concentration of 2.1×10^{12} vg/mL

Conclusions

- ATSN-201 (AAV.SPR-hGRK1-hRS1syn) was efficacious and well tolerated following subretinal administration
- Biodistribution and gene expression analysis demonstrated vector genome persistence and sustained expression *hRS1* mRNA in the retina
- Minimal systemic biodistribution was observed in both species
- The hybrid and GLP toxicology study did not reveal any ATSN-201-related adverse effects, the NOAEL was identified as the highest dose tested
- **Thus, these studies support the clinical use of ATSN-201 for the treatment of XLRS**

Clinical Trial Information

ATSN-201 Gene Therapy in *RS1*-Associated X-linked Retinoschisis (LIGHTHOUSE)

ClinicalTrials.gov ID NCT05878860

Email: clinicaltrials@atsenatx.com