Full-field Stimulus Test (FST) as a Clinical Endpoint in a Phase 1/2 Dose Escalation Study of ATSN-101

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Financial Disclosures

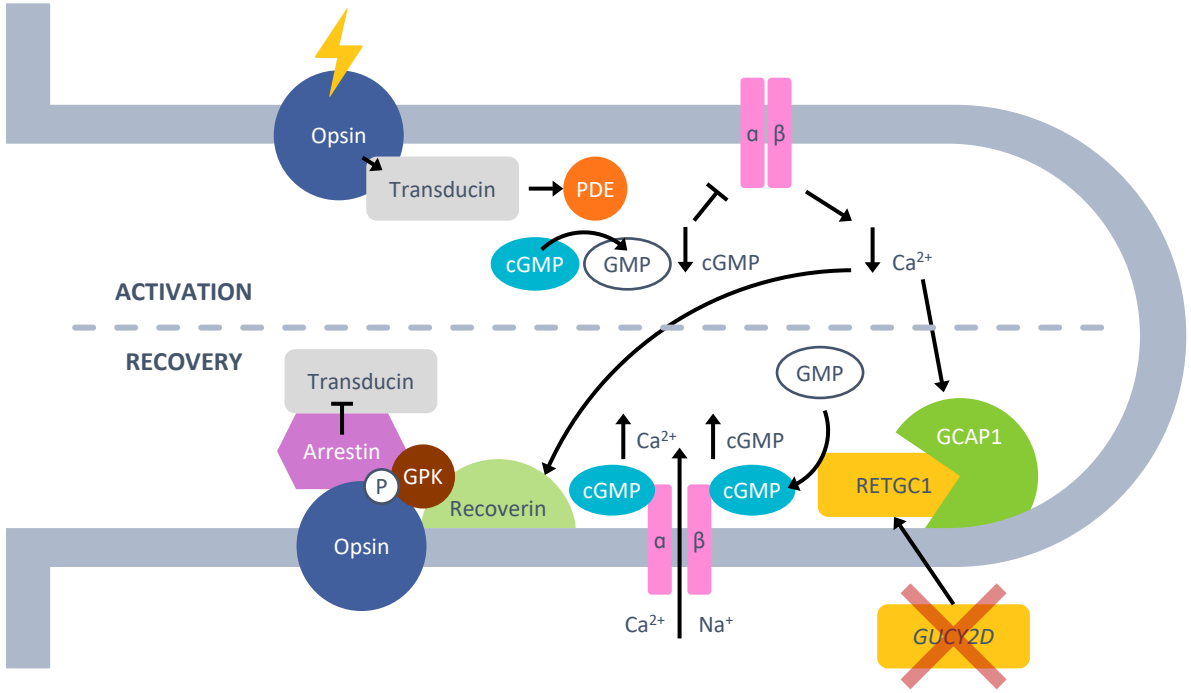
- Atsena Therapeutics

LCA1: Leber congenital amaurosis caused by mutations in *GUCY2D*

Leber congenital amaurosis (LCA) is a group of monogenic, autosomal recessive diseases that are the leading cause of blindness in children

- **LCA1 is caused by mutations in the *GUCY2D* gene**
  - Causes up to 20% of LCA cases
- ***GUCY2D* mechanism of action**
  - Encodes retinal guanylate cyclase-1 (**RetGC1**), a protein expressed in photoreceptor outer segments
  - RetGC1 is a **key enzyme in the phototransduction cascade** responsible for the recycling of cGMP during the recovery phase
  - Without functional RetGC1, photoreceptors are "stuck" and **cannot recover from a light stimulus**

PHOTOTRANSDUCTION PATHWAY

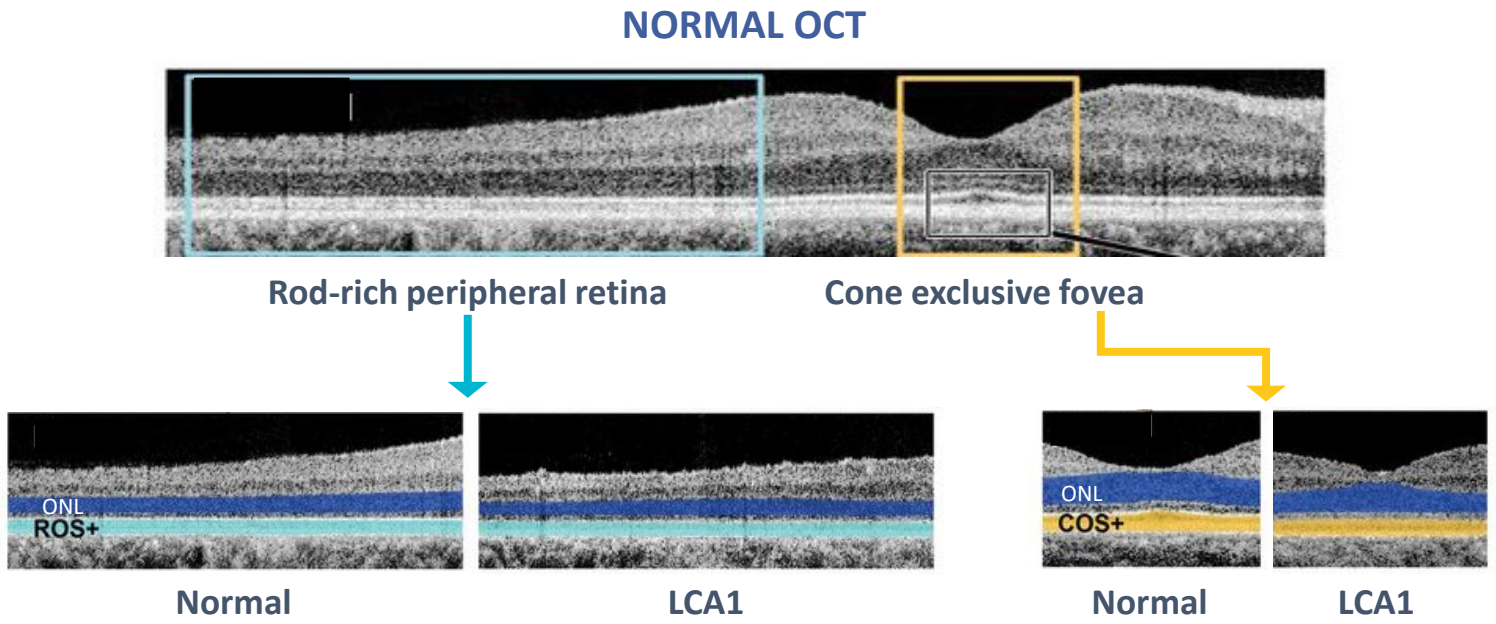


Modified from Jacobson et al., 2021

Kumaran N et al., *Br J Ophthalmol*. 2017
Jacobson SG et al., *iScience*. 2021.

LCA1: Clinical characteristics

- Severely reduced visual acuity from infancy
  - 20/80 to no light perception
- Reduced or non-recordable electroretinogram (ERG)
- **Nystagmus**
- Digito-ocular sign
- Normal fundus appearance
- **Relatively normal retinal thickness** on optical coherence tomography (OCT)



Modified from Jacobson et al., 2013

The majority of LCA1 patients retain retinal structure over their lifetime
High likelihood of successful outcomes with gene replacement therapy

Low vision and nystagmus make use of common clinical endpoints challenging
(eg, microperimetry, standard automated perimetry)

Jacobson SG et al., *Int J Mol Sci*. 2021
Jacobson SG et al., *iScience*. 2021.

Full-field stimulus test (FST)

- Specifically developed for patients with low vision and nystagmus
- Full-field stimuli presented to determine the dimmest light level perceived
- Chromatic FST (eg, red and blue stimuli) can assess whether thresholds are primarily rod- or cone-mediated
- Test-retest variability is approximately **±3 dB**
  - Similar for normal controls and patients with retinal degeneration

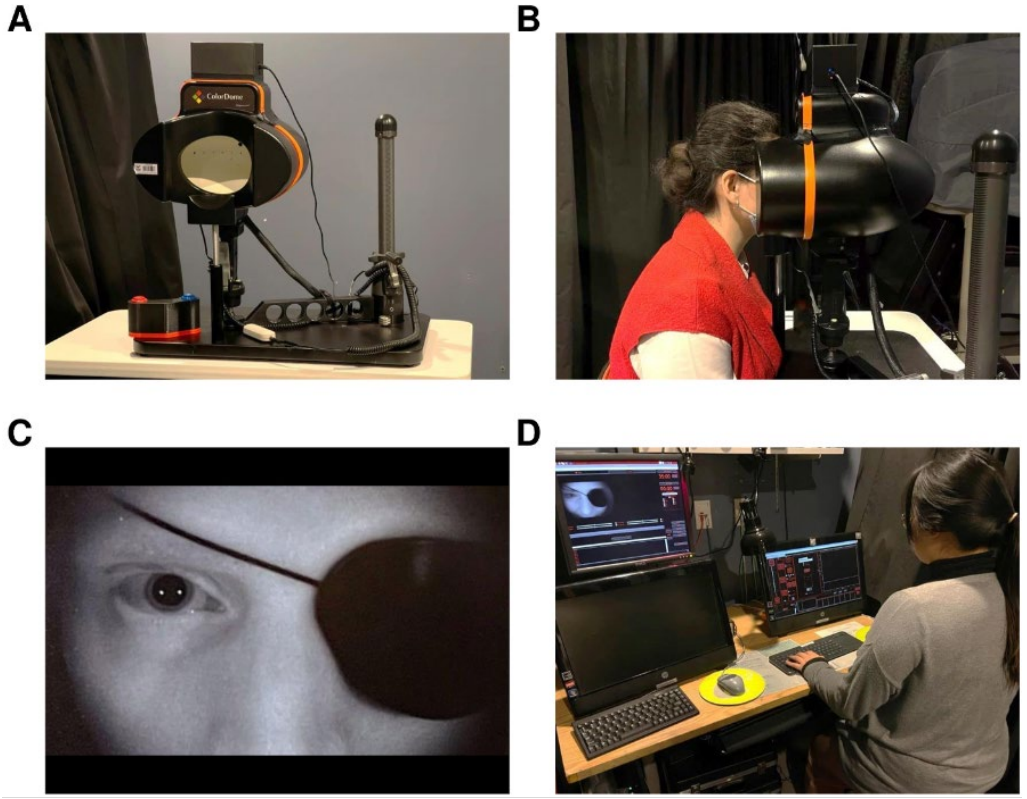


Image from Roman AJ et al., Prog Retin Eye Res. 2022

Roman AJ et al., *Exp Eye Res*. 2005
Roman AJ et al., *Physiol Meas.* 2007
Klein M and Birch DG. *Doc Ophthalmol*. 2009
Roman AJ et al., *Prog Retin Eye Res*. 2022
Shi LF et al., *Eye (Lond)*. 2024

LCA1 Phase 1/2 Clinical Trial Design (NCT03920007)

ATSN-101 (AAV5-hGRK1-*GUCY2D*) is a gene therapy developed to introduce the functional human *GUCY2D* to photoreceptors *(administered as a single 300 µL subretinal injection)*

ENROLLED	COHORT		
		PART A: Dose Escalation	
✓	1	Low dose (N=3), >18 years	1.0E10 vg/eye
✓	2	Mid dose (N=3), >18 years	3.0E10 vg/eye
✓	3	High dose (N=3), >18 years	1.0E11 vg/eye
		PART B: Expansion	
✓	4	High dose (N=3), >18 years	1.0E11 vg/eye
✓	5	High dose (N=3), 6-18 years	1.0E11 vg/eye

Key inclusion criteria:

- Male or female with biallelic mutations of *GUCY2D*
- Best-corrected visual acuity (BCVA):
  - Cohorts 1-3: 20/200 or worse
  - Cohorts 4-5: 20/80 or worse
- Outer nuclear layer identifiable on macular OCT

Primary endpoint:

- The incidence of adverse events (AEs, SAEs) over a 12-month period

Secondary endpoints:

- BCVA
- FST
- Multi-luminance mobility test (MLMT)
- Visual Function Questionnaire (VFQ-25)

Yang P et al., *Lancet*, 2024

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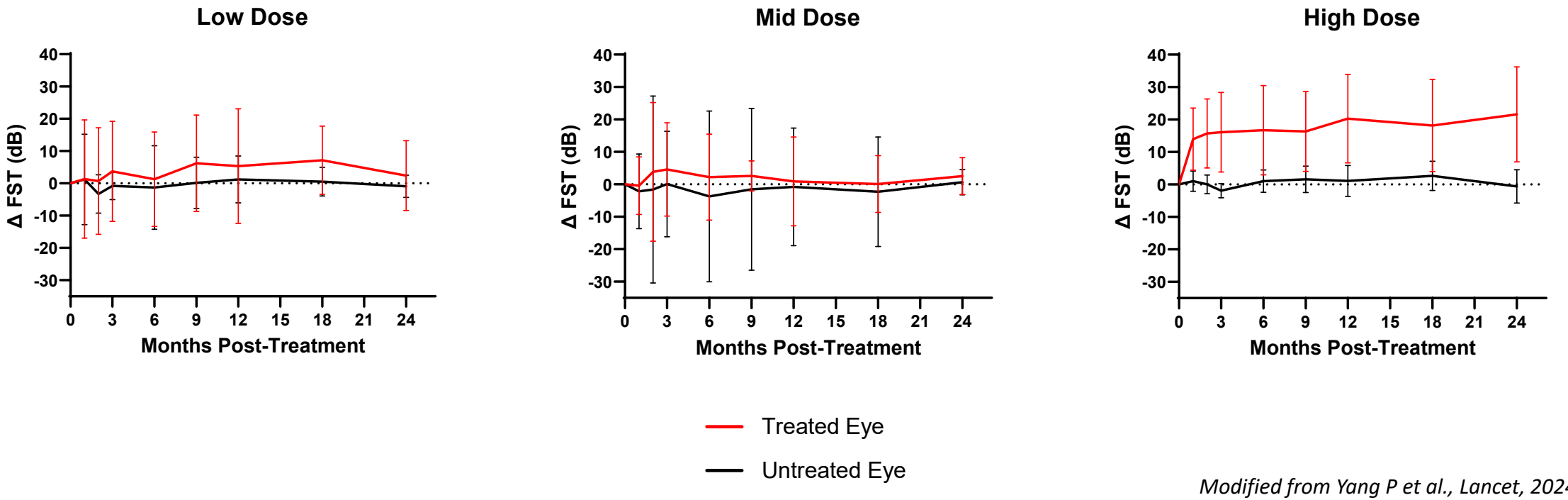
High-dose cohorts demonstrate improvement in dark-adapted FST

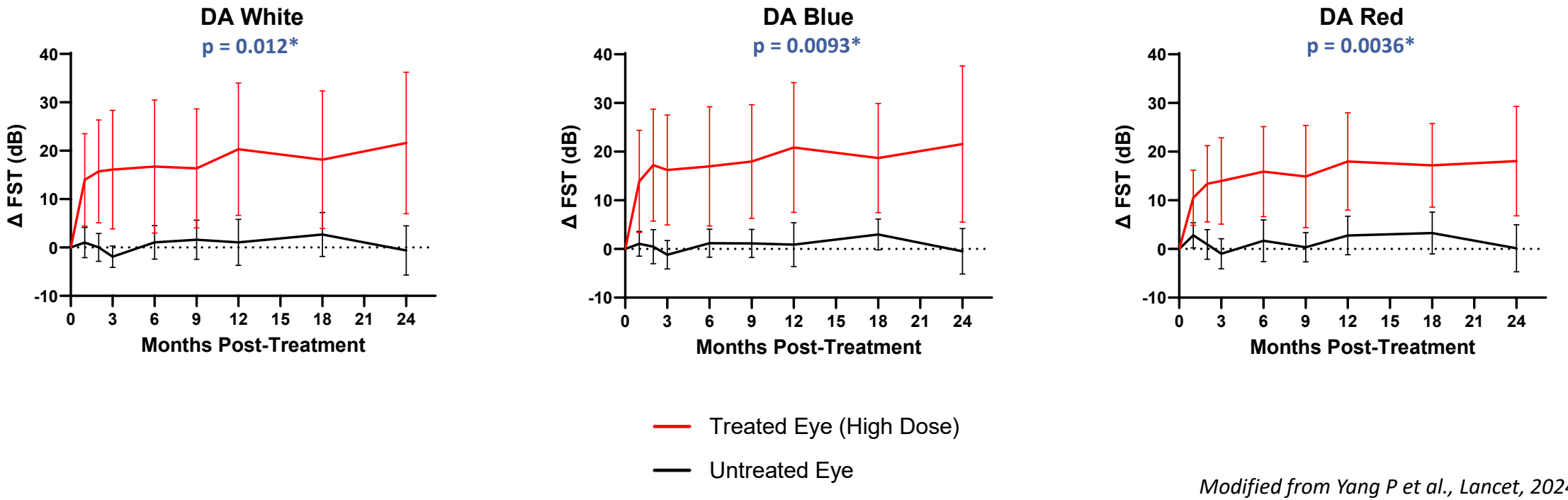
Dark-adapted (DA) White FST



Modified from Yang P et al., Lancet, 2024

High-dose cohorts demonstrate improvement in dark-adapted FST

Significant differences between treated and untreated eyes were observed for **both white and chromatic stimuli**



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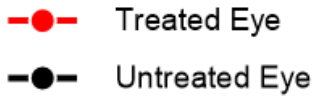
***Based on area under the curve (AUC) analysis comparing treated and untreated eyes**

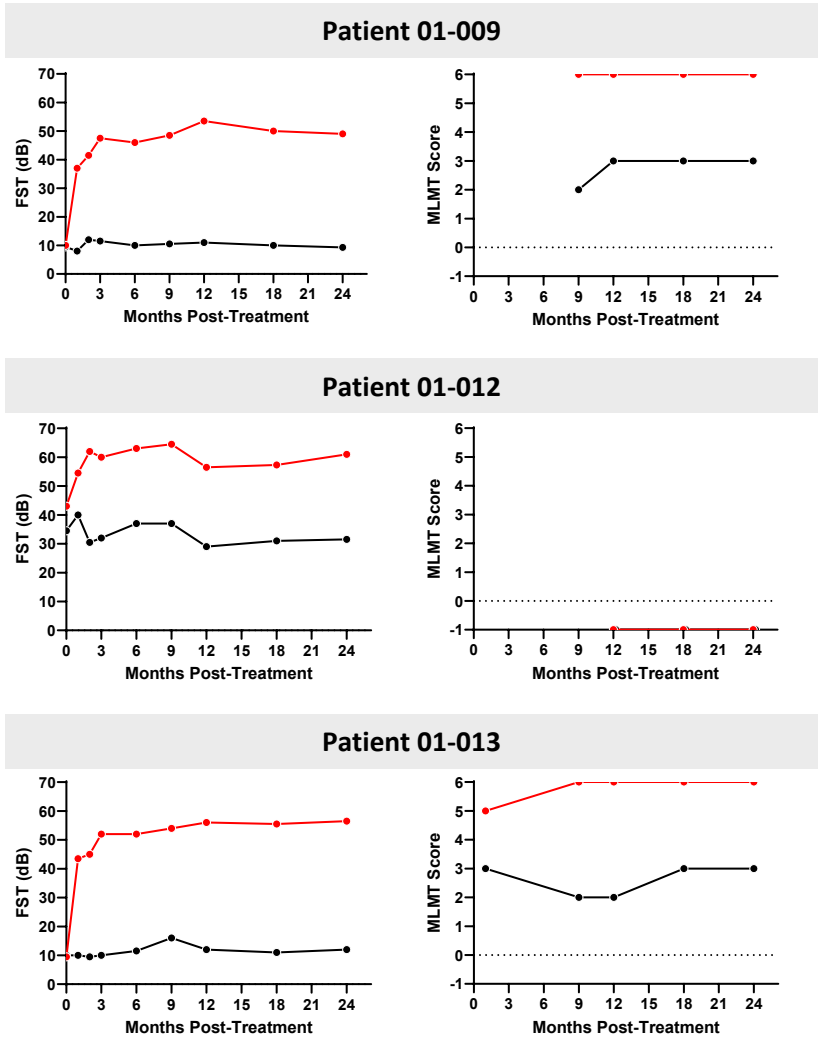
Statistical analysis performed from Baseline through Month 12 (end of Main Study Period)

FST is consistent with performance on a multi-luminance mobility test (MLMT)

MLMT was added as an exploratory endpoint midway through the trial

Six high-dose patients performed both FST and MLMT





Modified from Yang P et al., Lancet, 2024

Conclusions

- ATSN-101 subretinal gene therapy leads to improvements in retinal sensitivity
- Greatest effect observed in patients receiving high-dose ATSN-101 (1.0E11 vg/eye)
  - On average, **~20 dB (100-fold)** improvement
  - 2 patients improved by **> 40 dB (10,000-fold)**
  - Similar magnitude of improvement observed in Phase 3 trial of voretigene neparvovec
- Treatment effect is durable
  - Improvements were maintained over the 12-month Main Study Period
  - Effect persists through **at least 24 months post-treatment**
- Retinal sensitivity measured with FST is consistent with performance on a standardized mobility test

Considerations for a Future Phase 3 Trial

- FST is a clinically meaningful endpoint
  - Results consistent with mobility test used as a primary endpoint for an approved retinal gene therapy
  - Improvements observed far exceed test-retest variability
- FST is a commercially available test, and methodology can be easily standardized
- Real life mazes (ie, MLMT) are logistically more challenging to implement in a global Phase 3 trial
  - Requires a large footprint and staff who are experienced running the maze
  - More difficult to standardize across sites
  - May not be practical to set up a maze at every clinical site
  - If traveling to a centralized location, jet lag is a consideration

Thank You!

Atsena Therapeutics

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