Twelve-Month Safety and Efficacy of ATSN-101 in Patients with Leber Congenital Amaurosis Caused by Biallelic Mutations in *GUCY2D* (LCA1)

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Leber Congenital Amaurosis (LCA1)

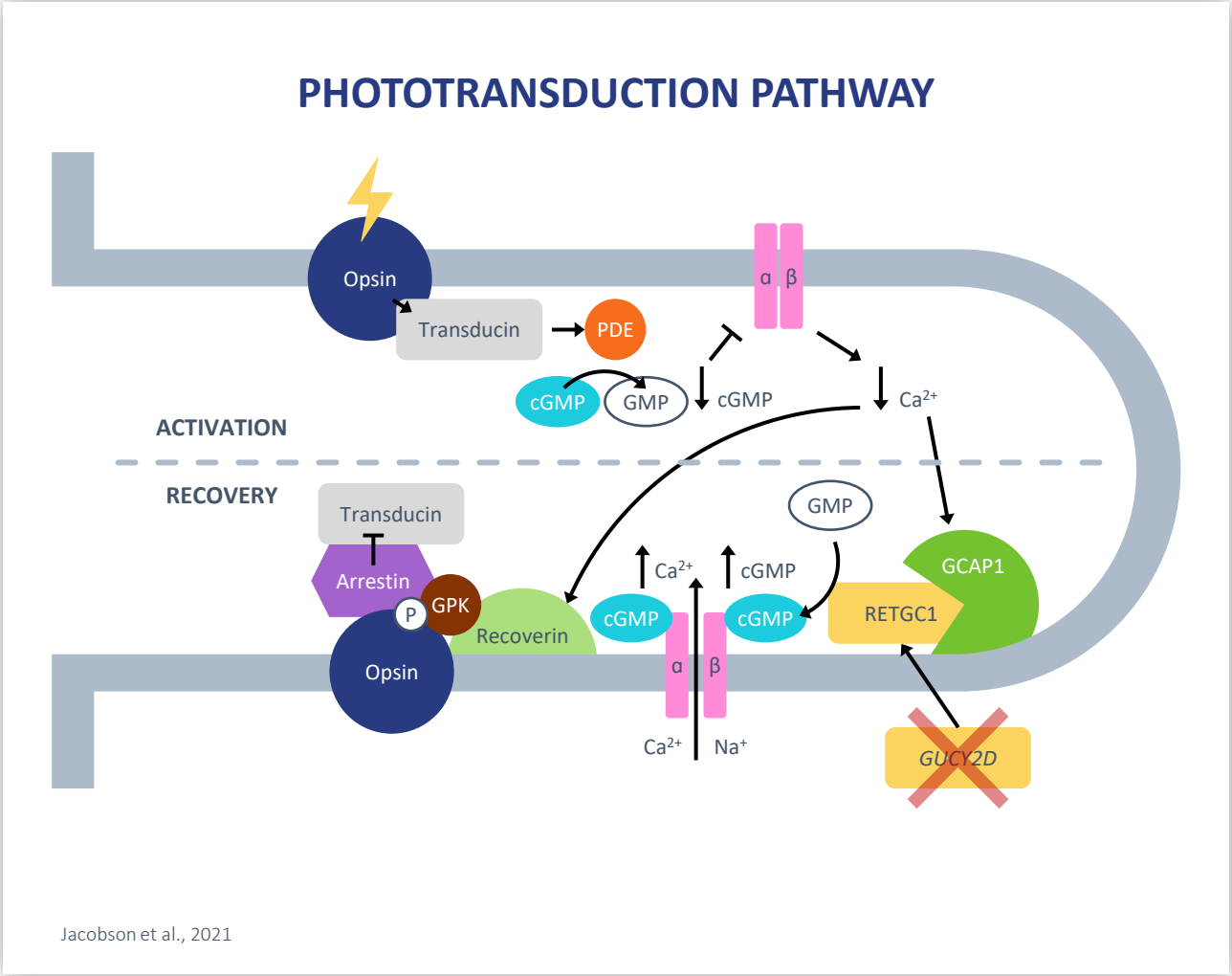
Leber Congenital Amaurosis Is a Group of Monogenic, Autosomal Recessive Diseases that Are the Leading Cause of Blindness in Children

LCA1 is caused by mutations in *GUCY2D* gene

- Result is early vision loss with relatively preserved retinal anatomy

Mechanism is clear

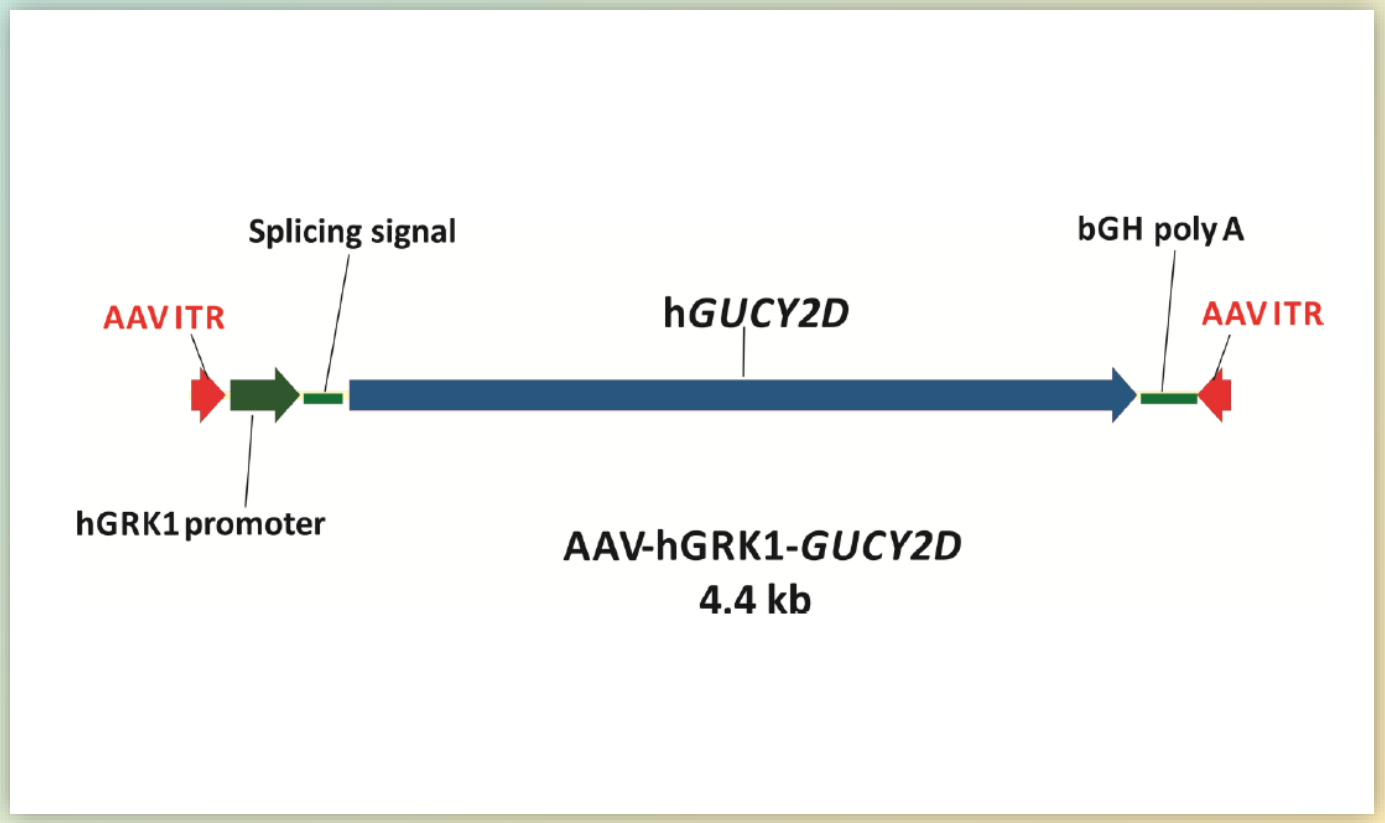
- *GUCY2D* encodes a protein "retinal Guanylate Cyclase 1" (retGC1) expressed in photoreceptor outer segments
- retGC1 is a key enzyme in the photo-transduction cascade responsible for the recycling of cGMP during the recovery phase
- Without functional retGC1, LCA1 patients' photoreceptors are 'stuck' and cannot recover from light stimulus



Jacobson et al., 2021

ATSN-101: AAV5-*GUCY2D*

- ATSN-101 (AAV5-*GUCY2D*) is a subretinal gene therapy product being developed to introduce the functional human *GUCY2D* to photoreceptors.
- AAV5 Capsid
- Human rhodopsin kinase promoter
- Human *GUCY2D* coding sequence (accession # NM_000180.4)
- Poly-adenylation signal derived from bovine growth hormone, all flanked by AAV2 inverted terminal
- Subretinal Injection



AAV ITR= Adenoassociated virus type 2 inverted terminal repeat; hGRK1= human rhodopsin promoters; h*GUCY2D*= full coding region of human guanylate cyclase 1; bGH polyA= bovine growth hormone poly-adenylation signal (Jacobson *et al.*, 2021)

LCA1 Phase 1/2 Clinical Trial Design (NCT03920007)

Data cut: June 15, 2023

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	(N=3), >18 years	1.0E11 vg/eye
✓	5	(N=3), 6-18 years	1.0E11 vg/eye

Drug administered as a single subretinal injection (300 uL) ATSN-101 into study eye
Corticosteroid regimen: 21-day prednisone regimen starting at 1mg/kg/day, 20 mg triamcinalone acetonide periocular injection, and topical 1% prednisolone
Study eye = worse-seeing eye

Key inclusion criteria:

- Male or female with biallelic mutations of *GUCY2D*
- BCVA:
  - Cohort 1-3: 20/200 or worse
  - Cohort 4-5: 20/80 or worse
- Outer nuclear layer identifiable on central retina OCT

Primary endpoint:

- The incidence of adverse events (AEs, SAEs) over a 52-week period following a single subretinal dose of ATSN-101. (Safety follow-up will continue to 5 years)

Secondary endpoints:

- Best corrected visual acuity (BCVA)
- Full-field stimulus test (FST)
- Multi-luminance mobility test (MLMT)
- Visual function questionnaire (VFQ-25)

Safety Summary

No drug-related SAEs reported

- Three SAEs in two subjects have been reported overall, all related to surgical procedure.
  - Macular hole, Endophthalmitis/Retinal detachment

Ocular inflammation seen to date has been infrequent, minimal, and reversible with steroid treatment

- Eight events in 6 subjects of ocular inflammation (subretinal inflammation, vitritis, iridocyclitis) noted, all Grade 1 or 2 in severity and resolved/resolving with steroid.
- Four events in 4 subjects were related to IMP
- Subjects demonstrated improvements in FST despite inflammation.

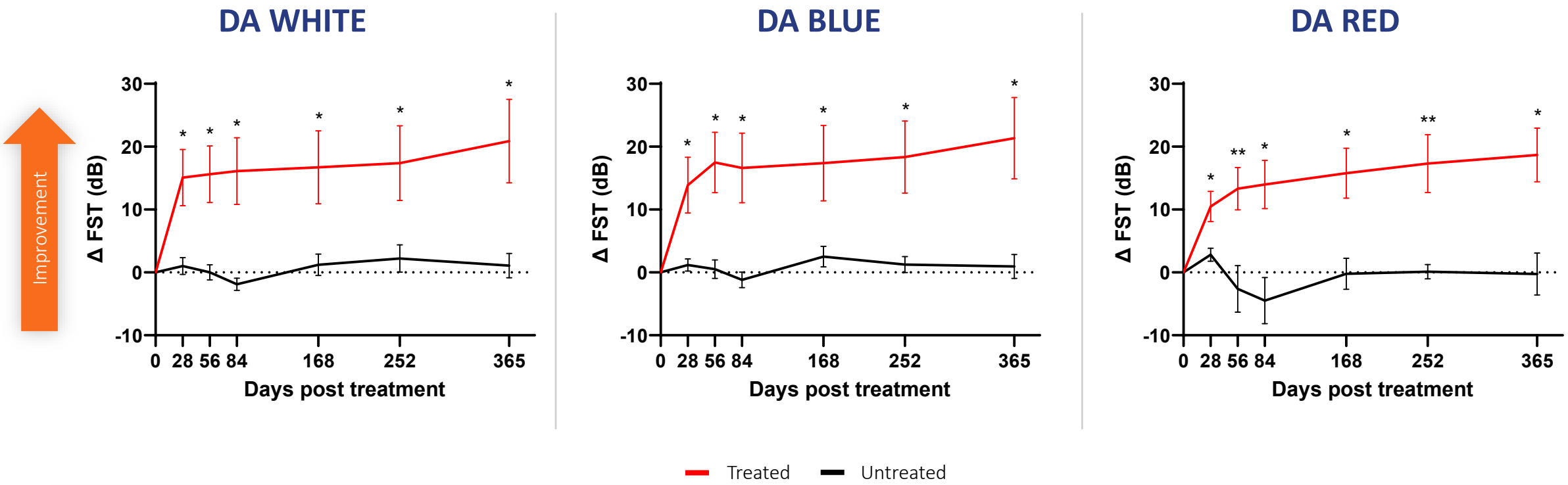
Total of 68 TEAEs reported (56 related to surgical procedure)

None have discontinued from the study due to AE

BCVA improved or remained stable in all but 1 patient who lost 0.16 logMAR at Week 52 (endophthalmitis/cataract)

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
# of Events						
Any TEAE	11	11	11	15	20	**68**
Any Serious TEAE	0	1	0	0	2	**3**
Severity						
Grade 1	11	11	9	13	18	**62**
Grade 2	0	0	2	2	2	**6**
Grade 3-5	0	0	0	0	0	**0**
Related to ATSN-101						
Related	0	0	2	2	0	**4**
Not Related	11	11	9	13	20	**64**
Related to Surgical Procedure						
Related	11	9	9	12	15	**56**
Not Related	0	2	2	3	5	**12**

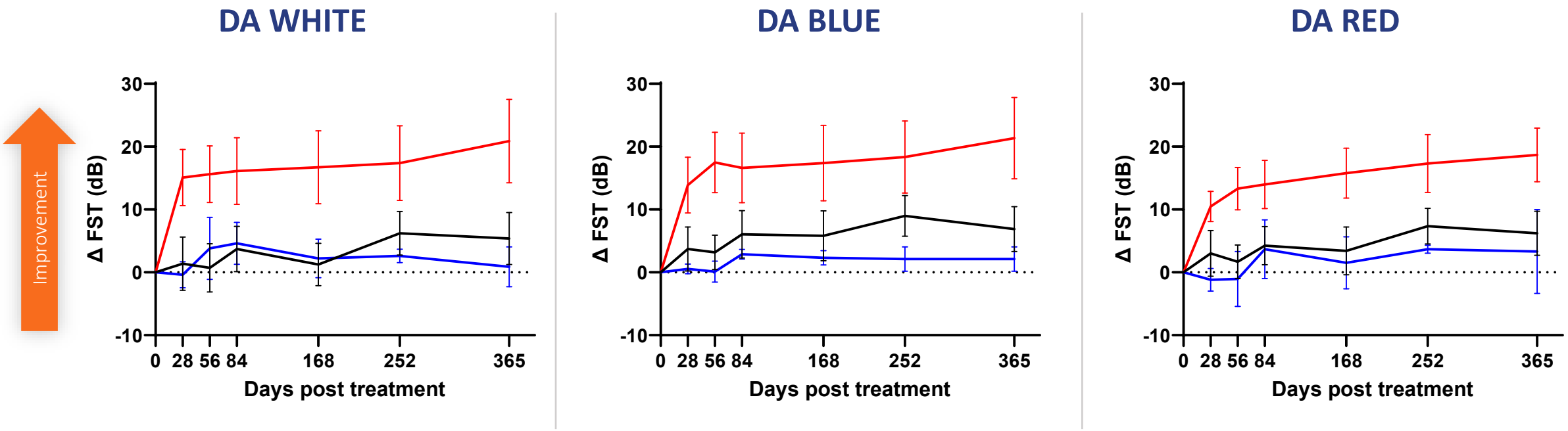
FST High Dose (Cohort 3, 4, and 5) Results



Significant improvement in FST is seen across all three colors tested with dark-adapted (DA) FST

*: p<0.05, **: p<0.01 from paired t-test
Error bars represent mean +/- standard error

FST Dose Comparison



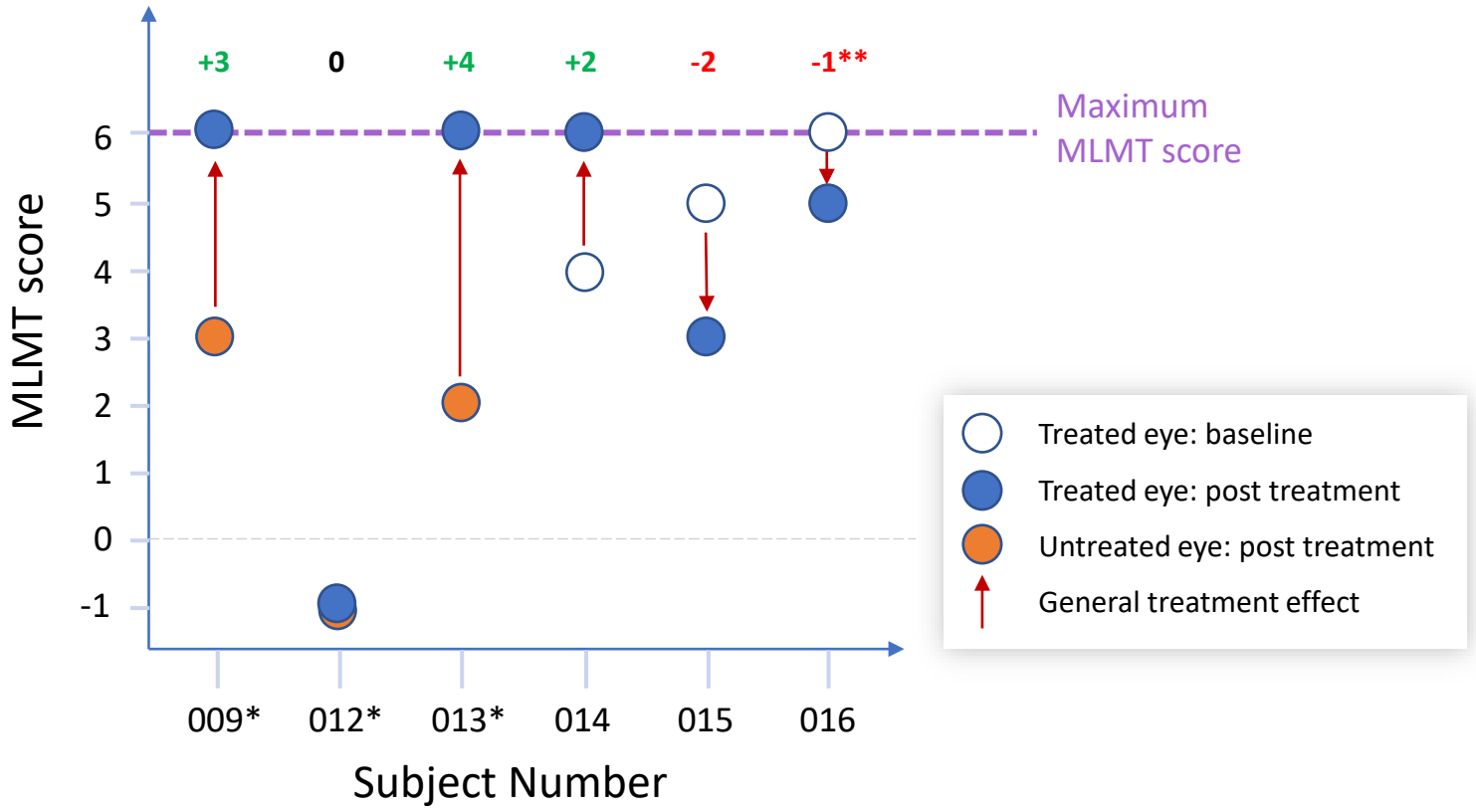
High dose is more efficacious than low dose, mid dose

Error bars represent mean +/- standard error

Change in MLMT score at Week 52

Six high-dose subjects were tested with Spark Therapeutics' MLMT

- FDA considers **2-step improvement** on MLMT to be clinically meaningful
- **3 subjects demonstrated a ≥ 2 level improvement at Week 52**
  - All 3 achieved the max score of 6
  - Improvement: compared to baseline or untreated fellow eye (when baseline unavailable)
- Individual patient response limited by floor or ceiling effect

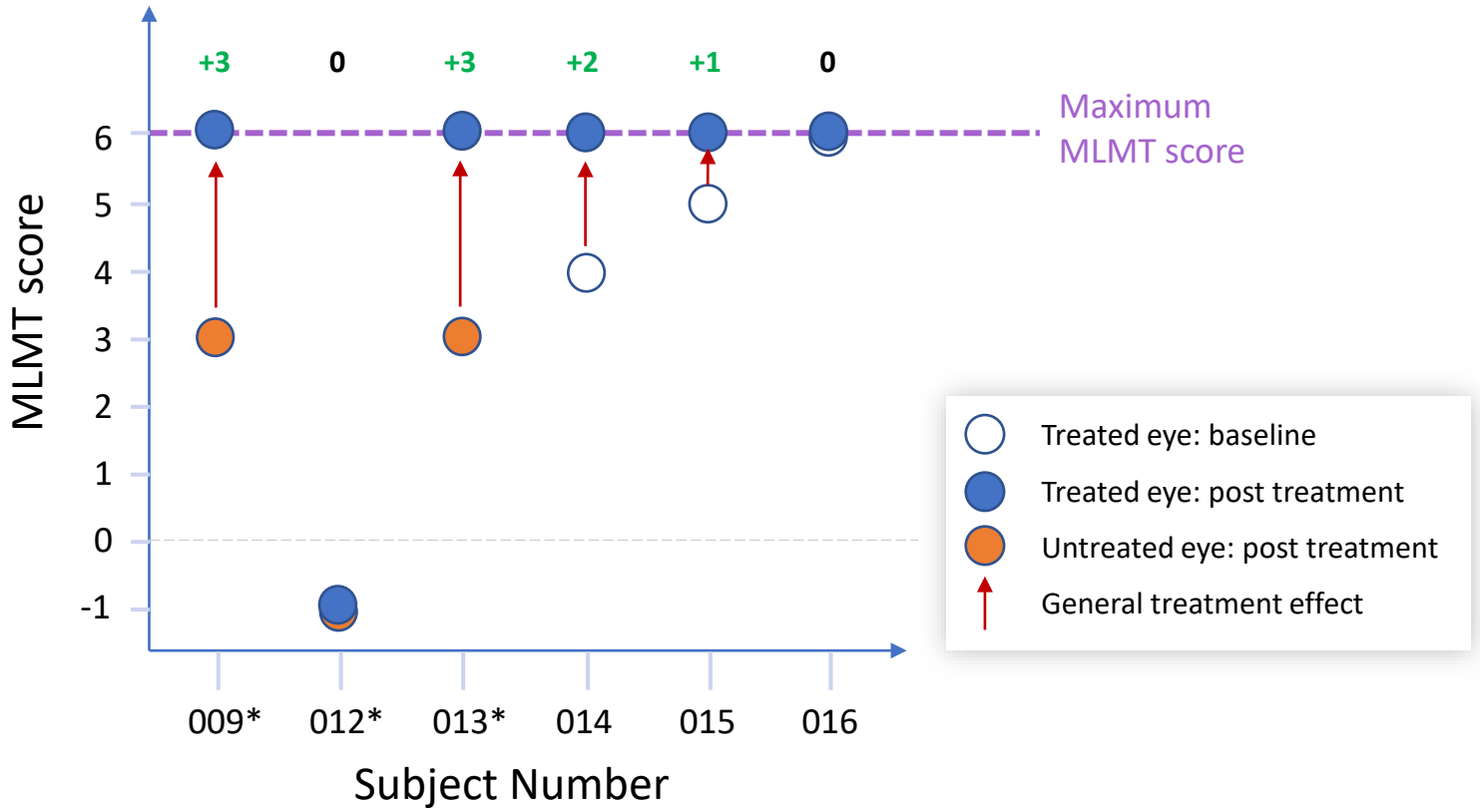


*For patients 009, 012, and 013, MLMT test at baseline was not performed; the score of the untreated eye at follow-up was used at the baseline for the treated eye
**Score shown for 016 is from Week 70, following cataract surgery and silicone oil removal (score was reduced to -1 at Week 52 due to a significant cataract)

Change in MLMT score at Week 78

Six high-dose subjects were tested with Spark Therapeutics' MLMT

- FDA considers **2-step improvement** on MLMT to be clinically meaningful
- **3 subjects demonstrated a ≥ 2 level improvement at Week 52**
  - All 3 achieved the max score of 6
  - Improvement: compared to baseline or untreated fellow eye (when baseline unavailable)
- Individual patient response limited by floor or ceiling effect



*For patients 009, 012, and 013, MLMT test at baseline was not performed; the score of the untreated eye at follow-up was used at the baseline for the treated eye

ATSN-101 (AAV5-*GUCY2D*)
is a subretinal gene therapy product being developed to introduce the functional human *GUCY2D* to photoreceptors for the treatment of LCA1

SAFETY

- As of month 12, no drug-related SAEs reported
- Ocular inflammation has been infrequent, minimal, and reversible with steroid treatment

EFFICACY

- FST: Significant improvement in FST is seen across all three colors tested with dark adapted FST
- MLMT: Clear improvement in MLMT is seen, with 3 high dose subjects improving by ≥ 2 levels to the maximum possible score (others limited by floor/ceiling effect)

References

- Jacobson SG, Cideciyan AV, Peshenko IV, Sumaroka A, Olshevskaya EV, Cao L, Schwartz SB, Roman AJ, Olivares MB, Sadigh S, Yau KW, Heon E, Stone EM, Dizhoor AM. Determining consequences of retinal membrane guanylyl cyclase (RetGC1) deficiency in human Leber congenital amaurosis en route to therapy: residual cone-photoreceptor vision correlates with biochemical properties of the mutants. Hum Mol Genet. 2013 Jan 1;22(1):168-83. doi: 10.1093/hmg/dds421. Epub 2012 Oct 3. PMID: 23035049; PMCID: PMC3606011.

- Jacobson SG, Cideciyan AV, Sumaroka A, Roman AJ, Charng J, Lu M, Choudhury S, Schwartz SB, Heon E, Fishman GA, Boye SE. Defining Outcomes for Clinical Trials of Leber Congenital Amaurosis Caused by *GUCY2D* Mutations. Am J Ophthalmol. 2017 May;177:44-57. doi: 10.1016/j.ajo.2017.02.003. Epub 2017 Feb 16. PMID: 28212877.

- Jacobson SG, Cideciyan AV, Ho AC, Peshenko IV, Garafalo AV, Roman AJ, Sumaroka A, Wu V, Krishnan AK, Sheplock R, Boye SL, Dizhoor AM, Boye SE. Safety and improved efficacy signals following gene therapy in childhood blindness caused by *GUCY2D* mutations. iScience. 2021 Apr 11;24(5):102409. doi: 10.1016/j.isci.2021.102409. PMID: 33997691; PMCID: PMC8099775.