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Six-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)

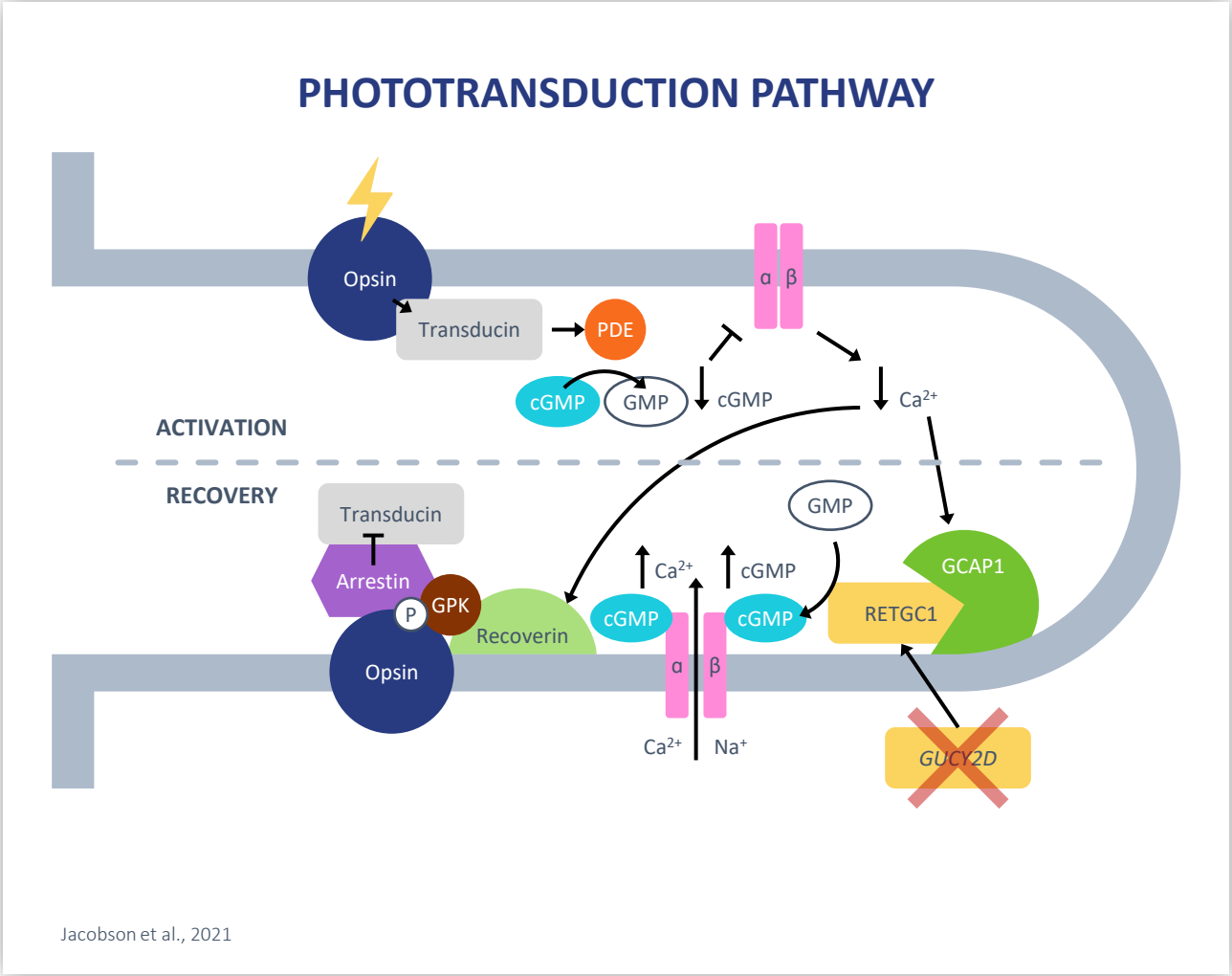
Leber Congenital Amaurosis Is a Group of Monogenic, Autosomal Recessive Diseases that Are the Leading Cause of Blindness in Children

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



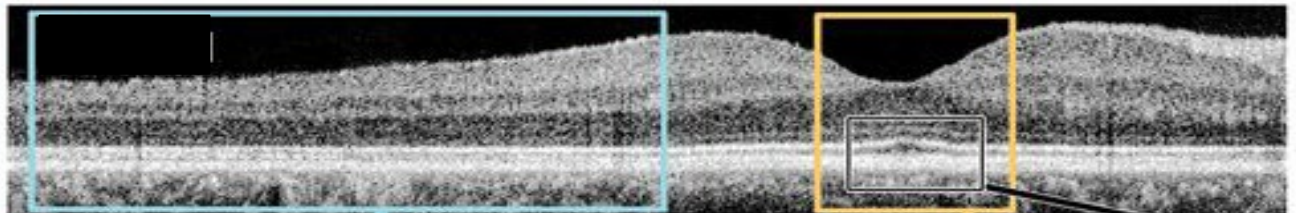
Jacobson et al., 2021

LCA1 Patients' Retinal Thickness/Structure

Majority of LCA1 Patients Have Relatively Normal Retinal Thickness

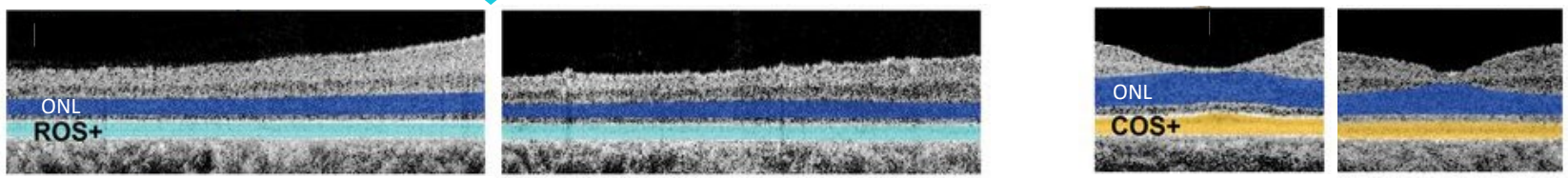
Preserved photoreceptor structure increases odds of successful gene therapy

NORMAL PATIENT'S OCT SCAN



Rod-rich peripheral retina

Cone exclusive fovea



Normal LCA1 Normal LCA1

THE MAJORITY OF LCA1 PATIENTS RETAIN RETINAL STRUCTURE OVER THEIR LIFETIME

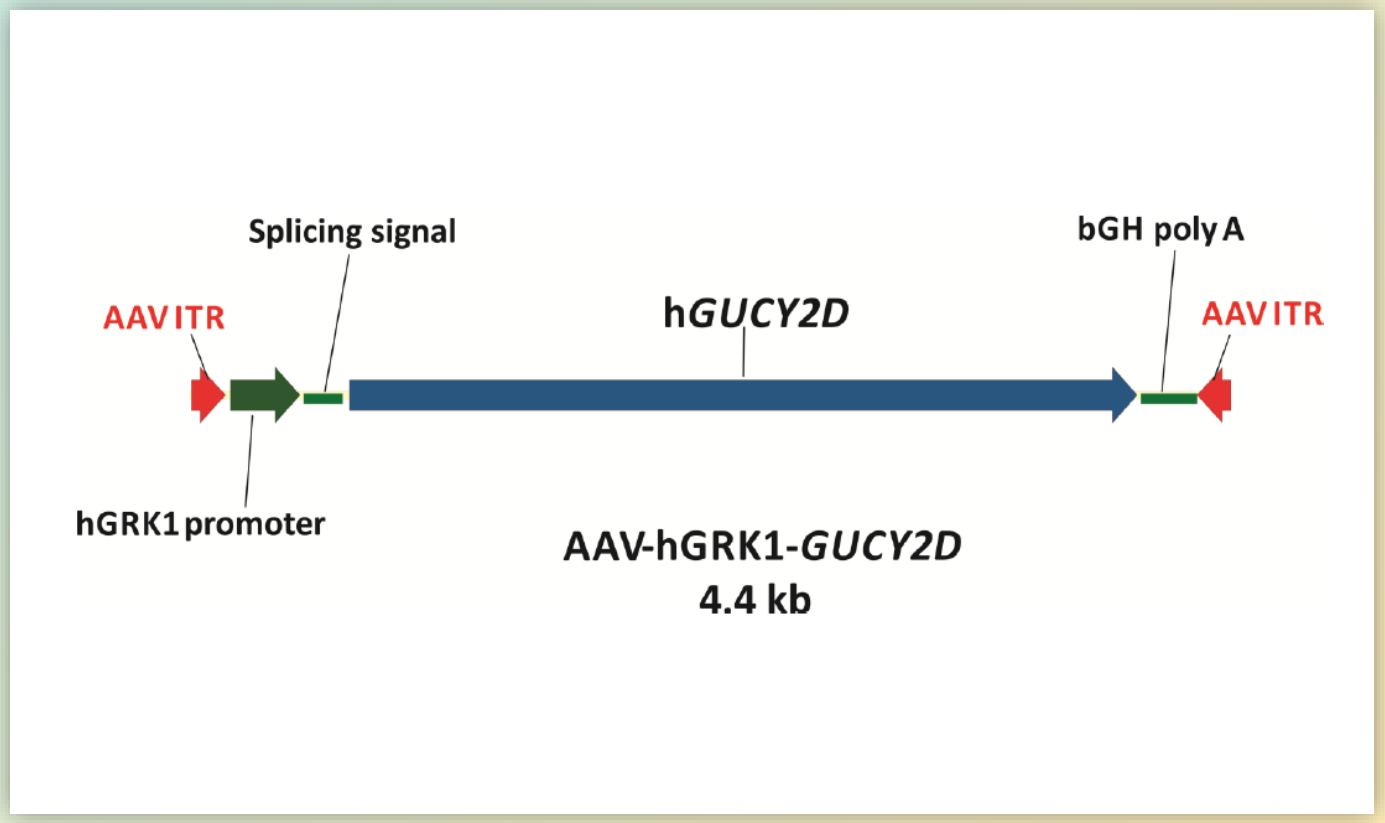
High likelihood of successful outcomes with gene replacement therapy

ONL-outer nuclear layer
ROS- rod outer segments
COS- cone outer segments

Jacobson et al., 2013

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: December 7, 2022

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% prenidsolone
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:

- BCVA – best corrected visual acuity
- FST – full-field stimulus testing
- Mobility testing (MLMT)
- Visual Function Questionnaire (VFQ-25)

Demographics and Baseline Characteristics

	Cohort 1 N=3	Cohort 2 N=3	Cohort 3 N=3	Cohort 4 N=3	Cohort 5 N=3	Total N=15
Age (Years)						
Median	35	20	21	22	15	**21**
Range (Min, Max)	(22,44)	(18,32)	(18,32)	(19,76)	(12,15)	**(12,76)**
Gender, N(%)						
Female	2	1	3	2	2	**10 (67%)**
Male	1	2	0	1	1	**5 (33%)**
Race, N(%)						
Asian	1	0	1	1	0	**3 (20%)**
White	2	3	2	2	1	**10 (67%)**
Not Reported	0	0	0	0	2	**2 (13%)**
Study Eye BCVA (logMAR)						
Median (Snellen equivalent)	1.2 (20/320)	1.28 (20/380)	1.34 (20/440)	1.58 (20/760)	1.32 (20/420)	**1.32 (20/420)**
Range (Min, Max)	(1.16, 2.9)	(1.06, 4)	(1.16, 3)	(0.72, 3)	(1.22, 1.62)	**(0.72, 4)**

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 of ocular inflammation (subretinal inflammation, vitritis, iridocyclitis) noted, all Grade 1 or 2 in severity and resolved/resolving with steroid.
- Subjects demonstrated improvements in FST despite inflammation.

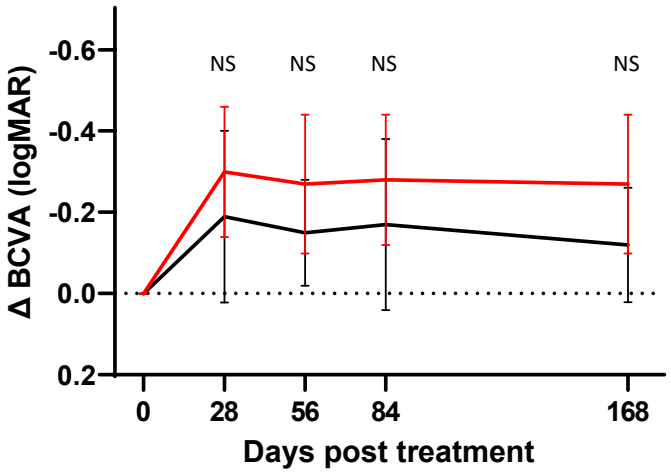
Total of 63 TEAEs reported (55 related to surgical procedure)

None have discontinued from the study due to AE

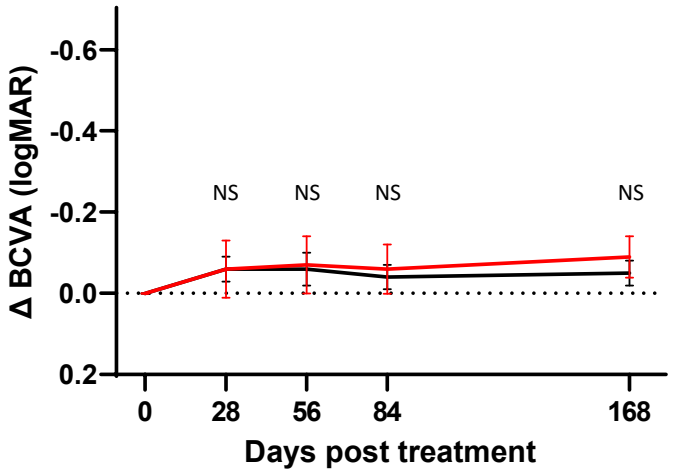
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
# of Events						
Any TEAE	11	11	10	15	16	**63**
Any Serious TEAE	0	1	0	0	2	**3**
Severity						
Grade 1	11	11	8	13	14	**57**
Grade 2	0	0	2	2	2	**6**
Grade 3-5	0	0	0	0	0	**0**
Related to ATSN-101						
Related	0	0	2	2	0	**4**
Not Related	11	11	8	13	16	**59**
Related to Surgical Procedure						
Related	11	9	9	12	14	**55**
Not Related	0	2	1	3	2	**8**

BCVA Results

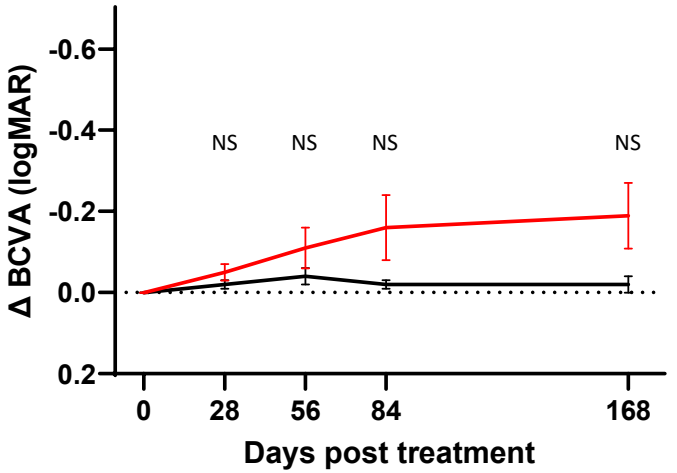
COHORT 1



COHORT 2



COHORT 3, 4, and 5



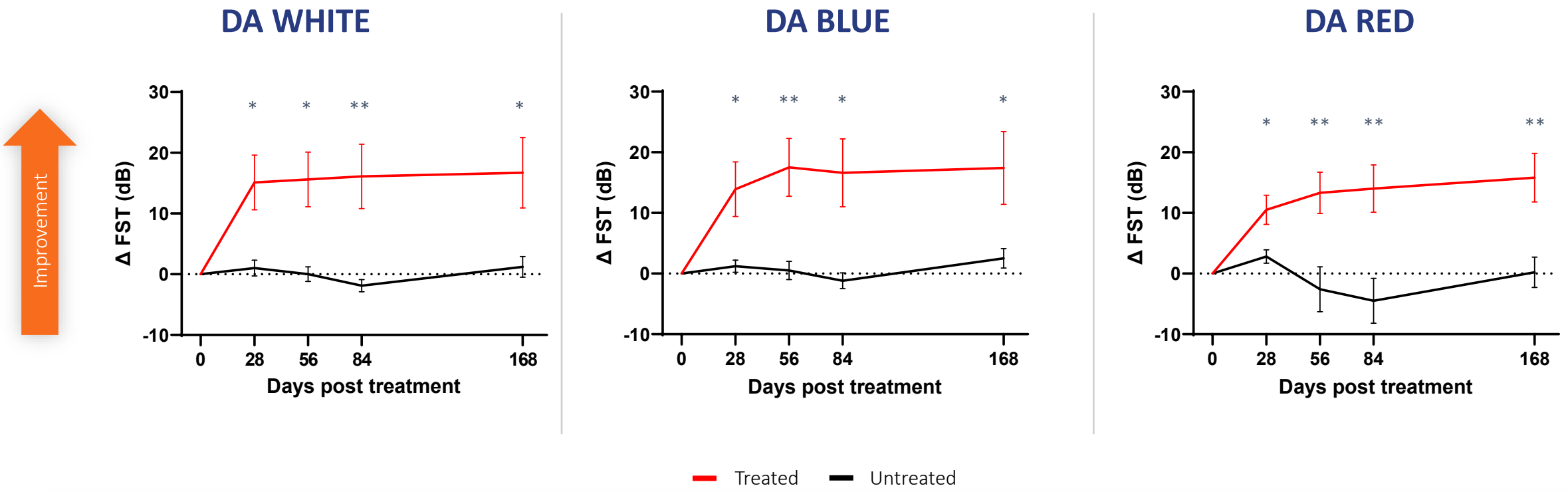
Treated Untreated

Two high-dose patients demonstrated BCVA improvement greater than 0.3 logMAR

No treated eyes had a decrease in BCVA

NS: p >0.05 from paired t-test
Error bars represent mean +/- standard error

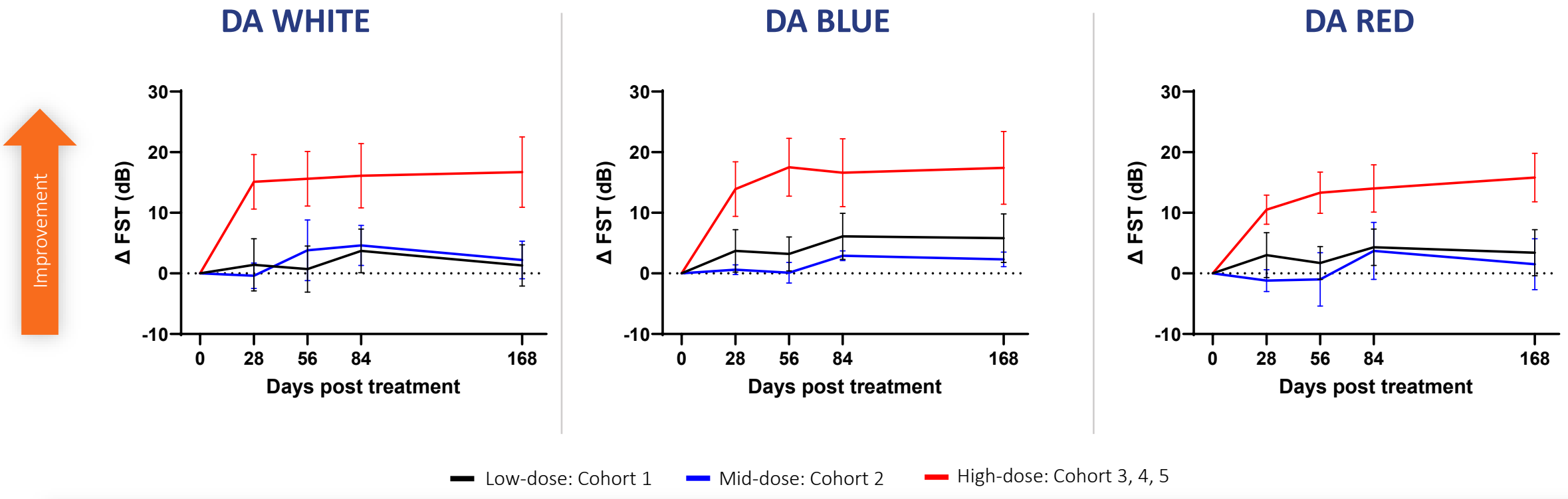
FST: High Dose (Cohort 3, 4, and 5) Results



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



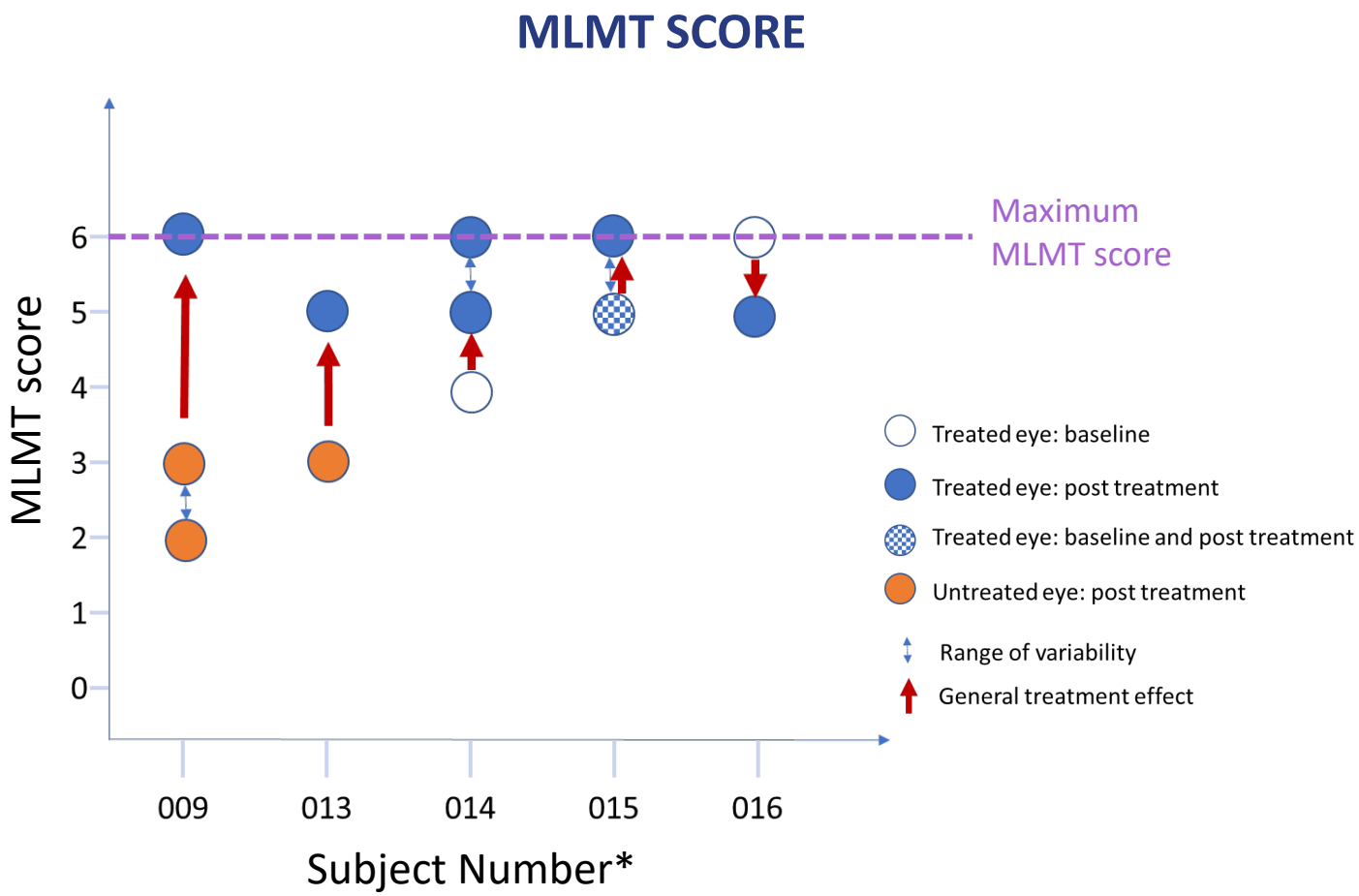
High dose is more efficacious than low dose, mid dose

Error bars represent mean +/- standard error

MLMT

Five subjects were tested with Spark Therapeutics' MLMT in high-dose (Cohort 3, 4, and 5)

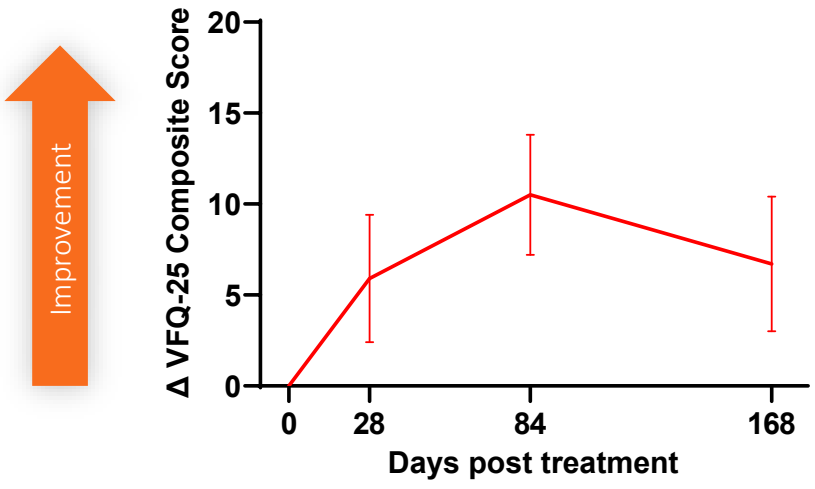
- FDA considers 2-step improvement on MLMT to be clinically meaningful
- Four subjects demonstrated either a maximum MLMT score of 6 or >= 2 level improvement at one or more post treatment visits
  - 3 out of 4 demonstrated >= 2 level improvement
  - Improvement: compared to baseline or untreated fellow eye (when baseline unavailable)
- Individual patient response limited by ceiling effect.



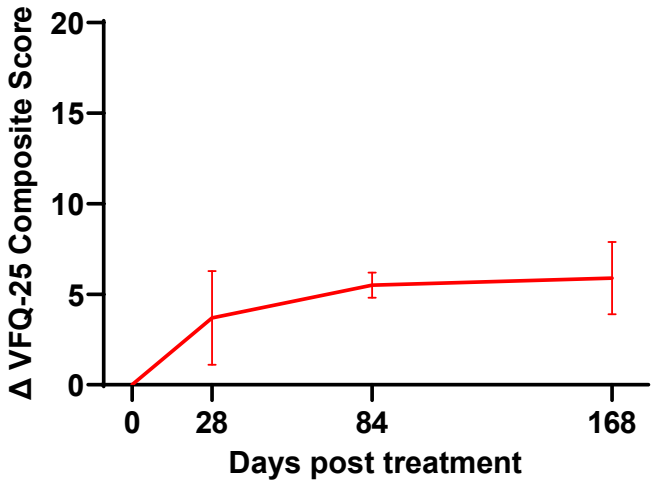
* For patients 009 and 013, MLMT test at baseline was not performed, the MLMT score at the untreated eye at follow-up was used at the baseline for the treated eye .

Patient Reported Outcomes

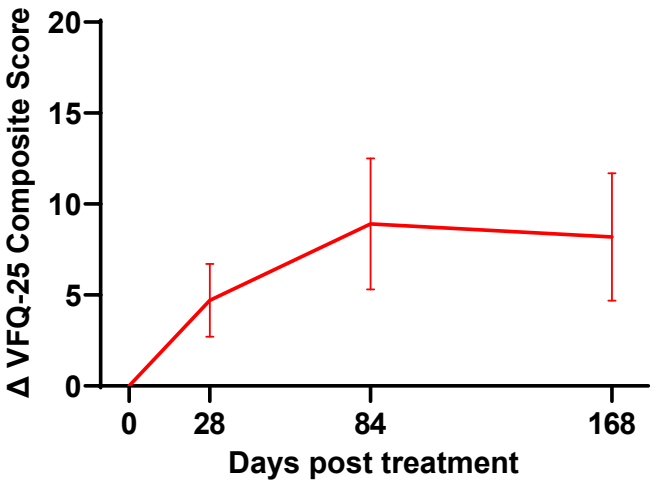
COHORT 1



COHORT 2



COHORT 3 and 4



Improvements in visual function were seen on VFQ-25

Error bars represent mean +/- standard error

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

- To date, no drug-related SAEs reported
- Ocular inflammation has been infrequent, minimal, and reversible with steroid treatment

EFFICACY

- BCVA response is variable
- FST: Significant improvement in FST is seen across all three colors tested with dark adapted FST
  - High dose (1.0E11 vg/eye) is more efficacious than low dose, mid dose
- MLMT: Clear improvement in MLMT is seen, 3 out of 4 subjects showing clinically meaningful improvement

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.

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