CHRD Center for Hereditary Retinal Degenerations

Safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic variants in *GUCY2D* (LCA1):

Durability through 3 years post-treatment

Artur V. Cideciyan, Tomas S. Aleman, Paul Yang, Allen C. Ho, Andreas K. Lauer, Shannon E. Boye, Sanford L. Boye, Alejandro J. Roman, Vivian Wu, Malgorzata Swider, Iryna Viarbitskaya, Alexandra V. Garafalo, Alexander Sumaroka, Laura Pardon, Dan Yoon, Christine N. Kay, Kenji P. Fujita

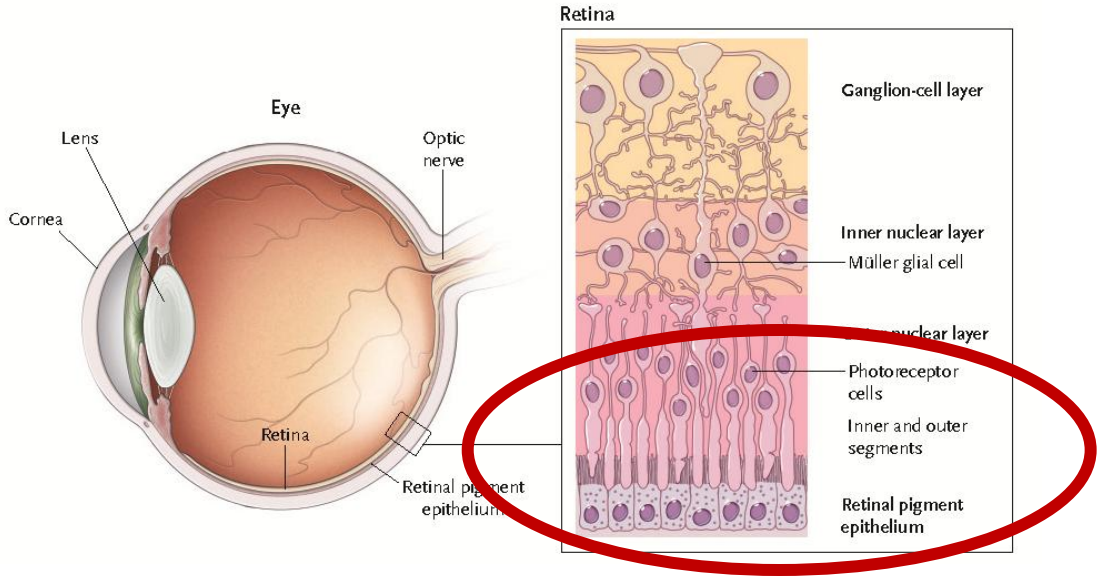
Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA
Casey Eye Institute, Oregon Health & Science University, Portland, OR
Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA
Department of Pediatrics, University of Florida, Gainesville, FL
Atsena Therapeutics, Durham, NC
Vitreoretinal Associates, Gainesville, FL

CHRD Center for Hereditary Retinal Degenerations

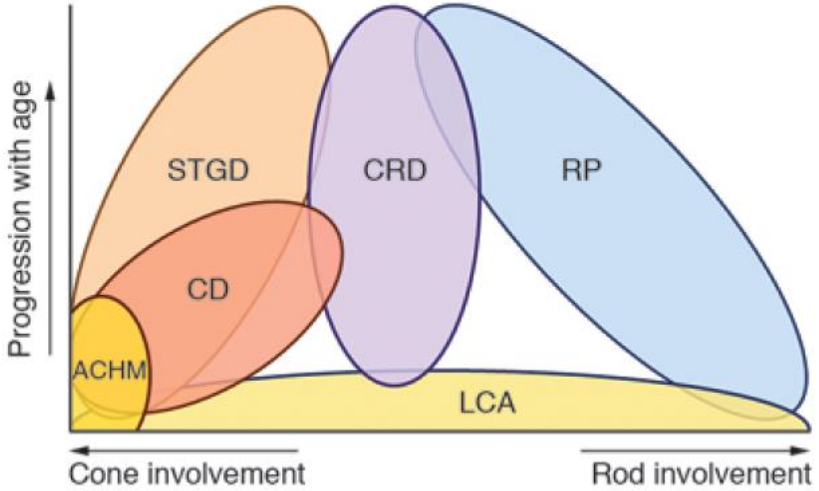
Financial Disclosures

Atsena Therapeutics: F
Opus Genetics: F, C
SepulBio: F, C
Alkeus: C

Leber congenital amaurosis (LCA)
Congenital loss of rod and cone function



From Jacobson & Cideciyan, *N. Eng. J. Med.* 2010



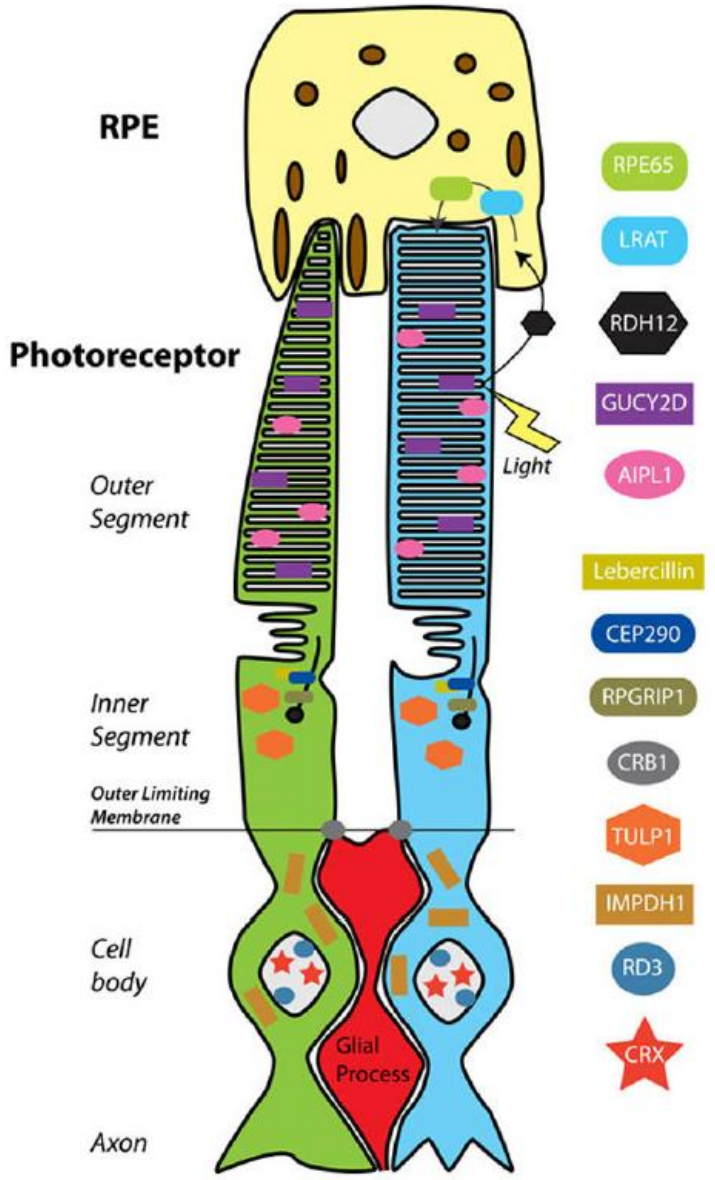
From den Hollander et al., 2010

CHRD Center for Hereditary Retinal Degenerations

Gene-targeted interventions in the clinic

AIPL1	*LCA5*
ALMS1	*LRAT*
CABP4	*MERTK*
CEP290	*NMNAT1*
CLUAP1	*OTX2*
CRB1	*PRPH2*
CRX	*RD3*
GUCY2D	*RDH12*
IFT140	*RPE65*
IMPDH1	*RPGRIP1*
IQCB1	*SPATA7*
KCNJ13	*TULP1*

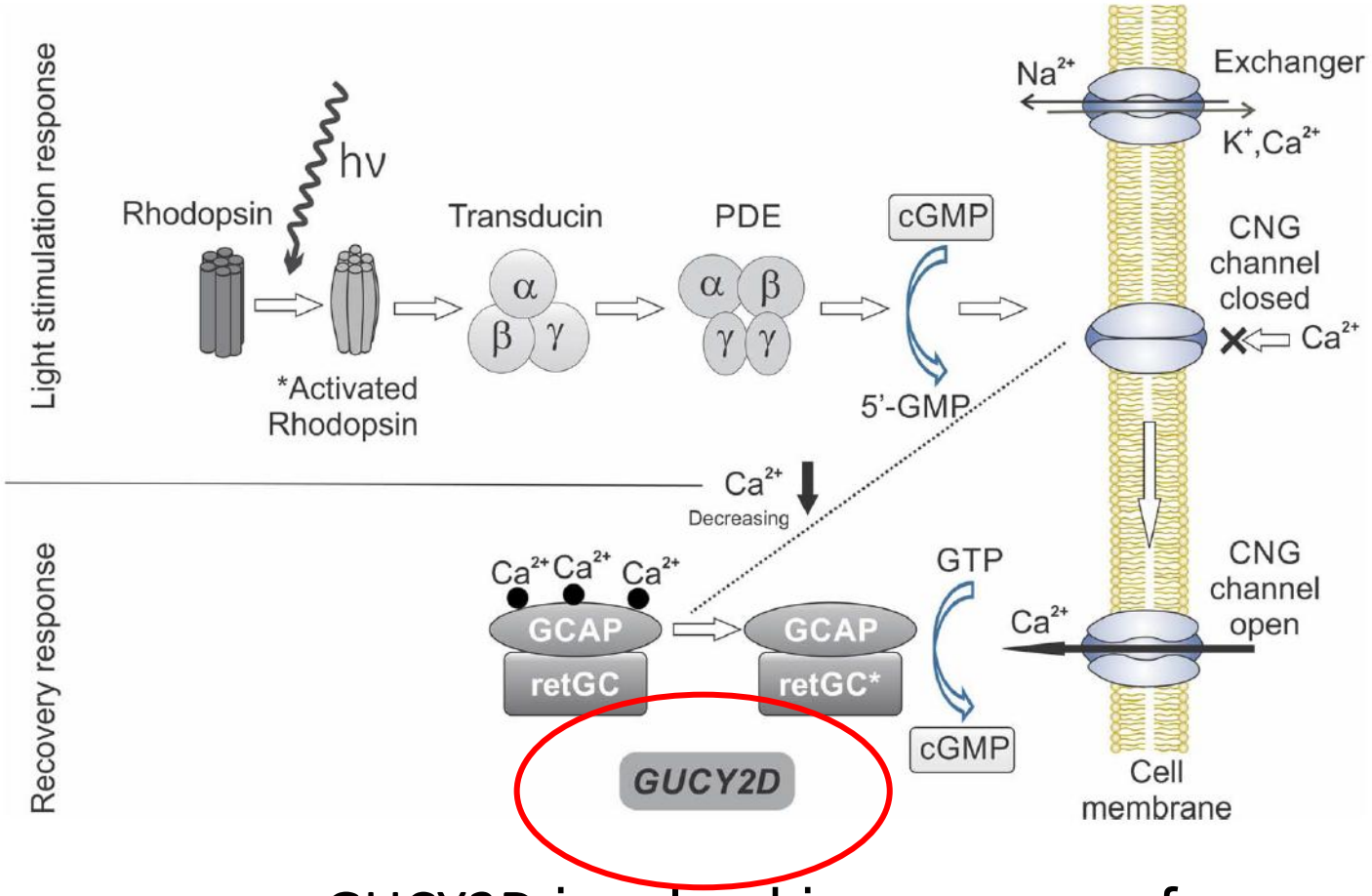
Distinct pathomechanisms



From Hufnagel et al, *Graefes Arch Clin ExpOphthalmol.* 2021

GUCY2D-LCA1

From Cideciyan & Jacobson, *Invest Ophthalmol Vis Sci.* 2019



GUCY2D involved in recovery of
both rod and cone phototransduction

CHRD Center for Hereditary Retinal Degenerations

GUCY2D-LCA human phenotype and natural history

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.
Jacobson et al, *Hum Mol Genet* 2013

Outcome measure for the treatment of cone photoreceptor diseases: Orientation to a scene with cone-only contrast.
Roman et al, *BMC Ophthalmol* 2015

Defining outcomes for clinical trials of Leber congenital amaurosis caused by *GUCY2D* mutations
Jacobson et al, *Am J Ophthalmol* 2017

Postretinal structure and function in severe congenital photoreceptor blindness caused by mutations in the *GUCY2D* gene
Aguirre et al, *Invest Ophthalmol Vis Sci* 2017

Expanded retinal disease spectrum associated with autosomal recessive mutations in *GUCY2D*
Stunkel et al, *Am J Ophthalmol* 2018

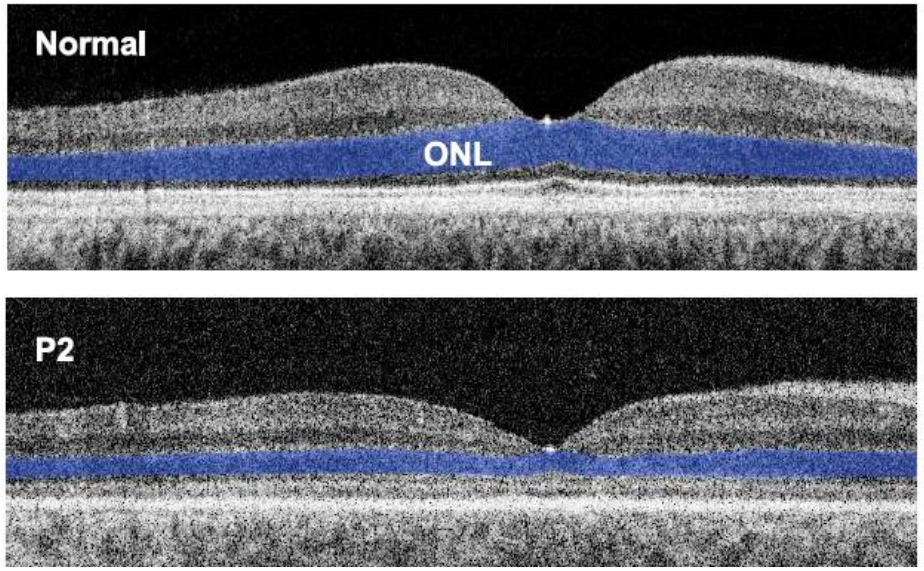
Proctor Lecture
Leber congenital amaurosis (LCA): Potential for improvement of vision
Cideciyan & Jacobson, *Invest Ophthalmol Vis Sci* 2019

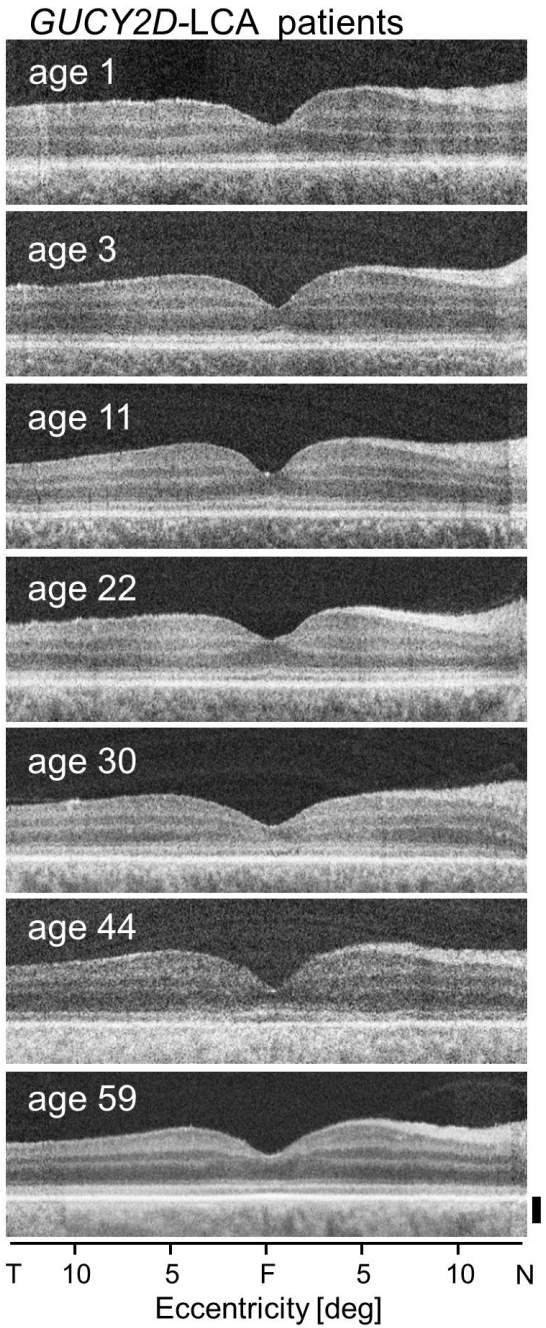
Leber congenital amaurosis due to *GUCY2D* mutations: Longitudinal analysis of retinal structure and visual function
Jacobson et al, *Intl J Mol Sci* 2021

CHRD Center for Hereditary Retinal Degenerations

GUCY2D-LCA1 patients uniformly retain relatively good OCT lamination

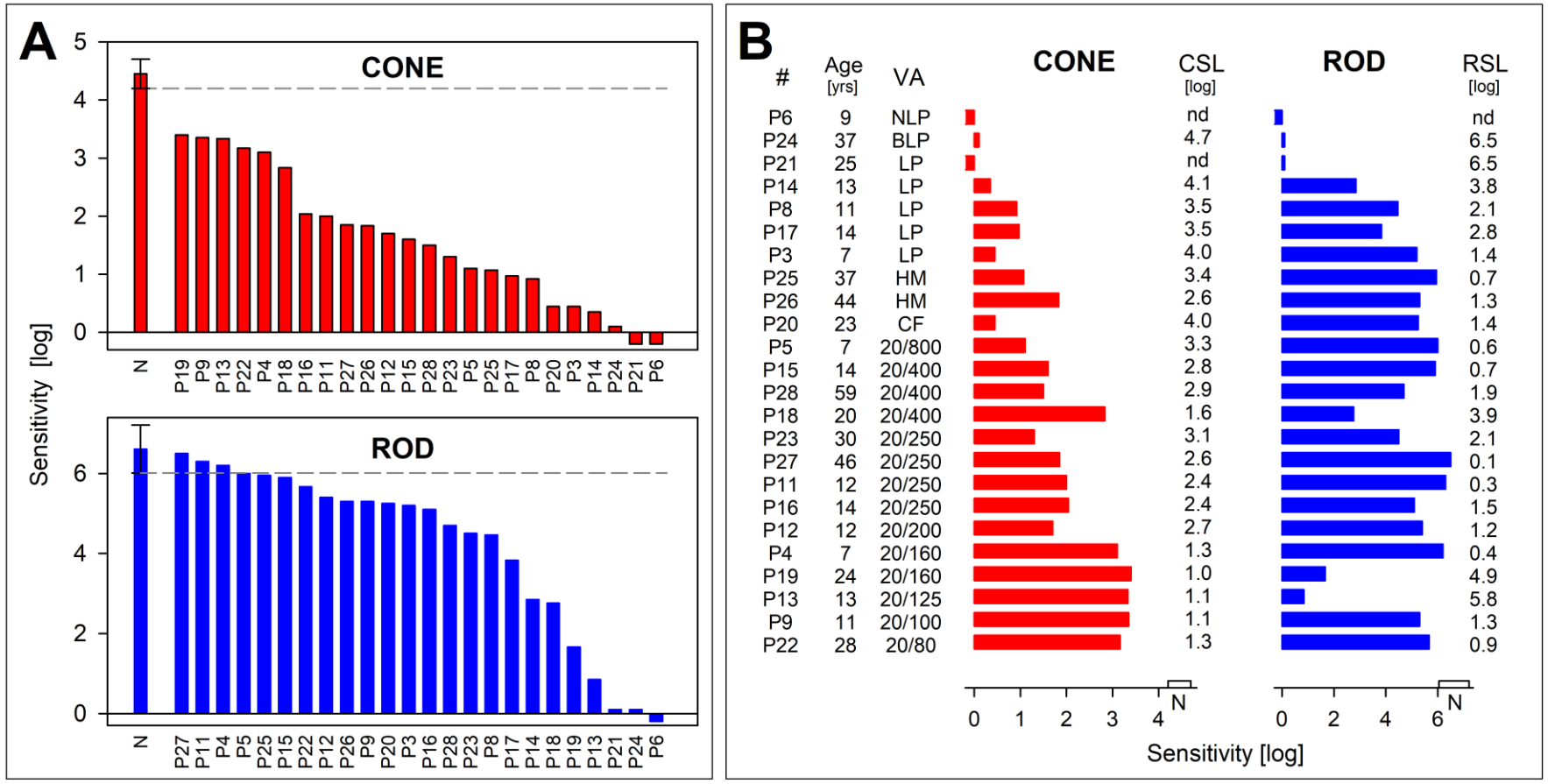
BCVA
20/400





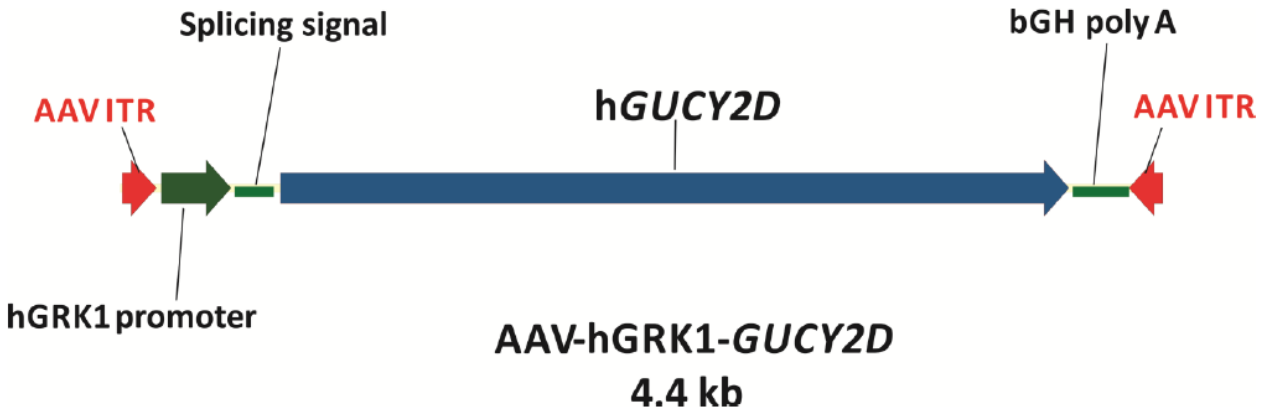
CHRD Center for Hereditary Retinal Degenerations

GUCY2D-LCA patients have an incomparably wide spectrum of visual function

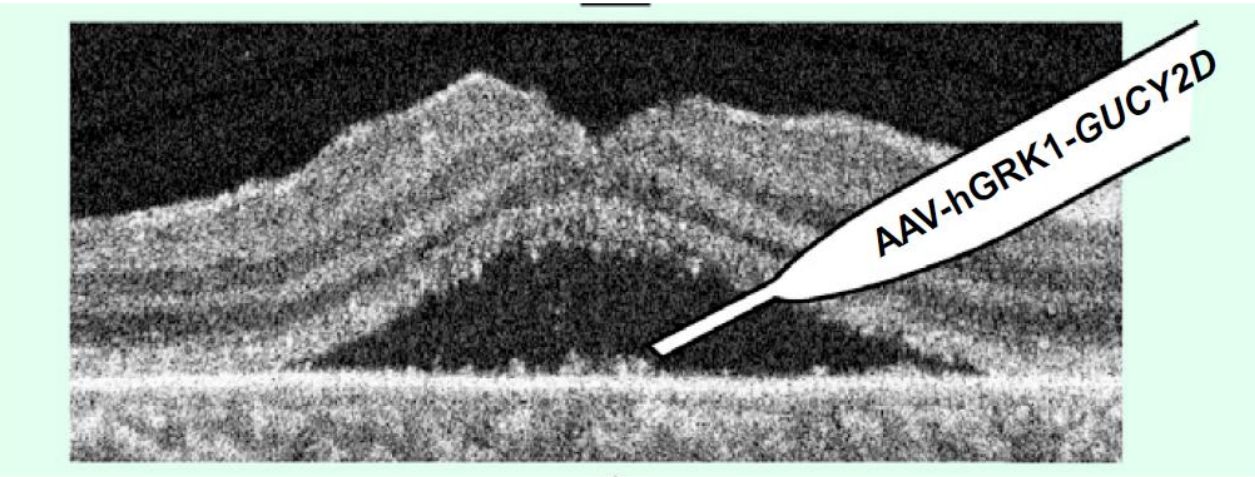


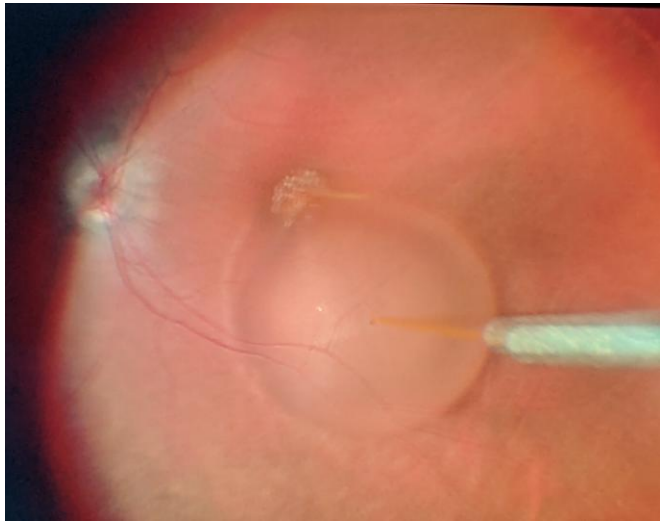
CHRD Center for Hereditary Retinal Degenerations

AAV5 vector with GRK1 promoter



Subretinal gene augmentation therapy





CHRD Center for Hereditary Retinal Degenerations

LCA1 Phase 1/2 Clinical Trial Design (NCT03920007)

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 following a single subretinal dose of ATSN-101 (safety follow-up will continue to 5 yrs)

Secondary endpoints:

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

CHRD Center for Hereditary Retinal Degenerations

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)**

CHRD Center for Hereditary Retinal Degenerations

Safety Summary

Data cut: August 6, 2025

No drug-related SAEs reported

- Three SAEs in two subjects have been reported overall, all related to surgical procedure and within 1st year.
  - Macular hole, Endophthalmitis/Retinal detachment

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

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

Total of 84 TEAEs reported (56 related to surgical procedure)

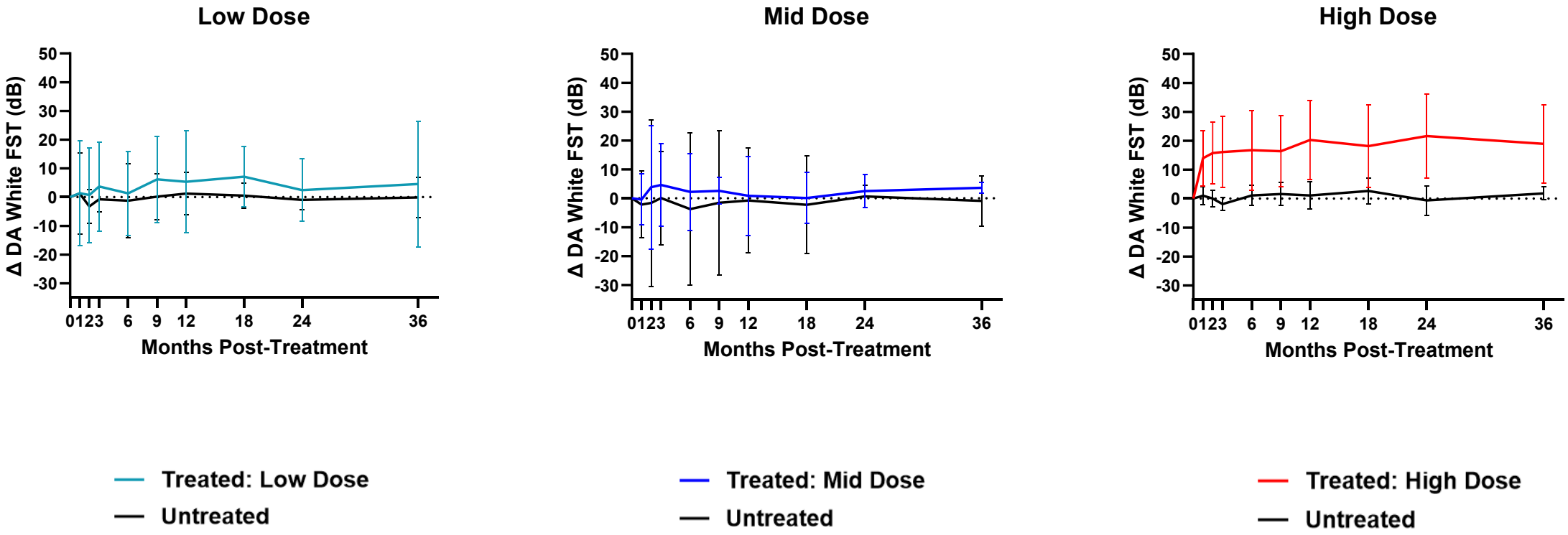
None have discontinued from the study due to AE

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	16	11	15	21	21	**84**
Any Serious TEAE	0	1	0	0	2	**3**
Severity						
Grade 1	16	11	13	17	19	**76**
Grade 2	0	0	2	4	2	**8**
Grade 3-5	0	0	0	0	0	**0**
Related to ATSN-101						
Related	0	0	2	3	0	**5**
Not Related	16	11	13	18	21	**79**
Related to Surgical Procedure						
Related	11	9	9	12	15	**56**
Not Related	5	2	6	9	6	**28**

CHRD Center for Hereditary Retinal Degenerations

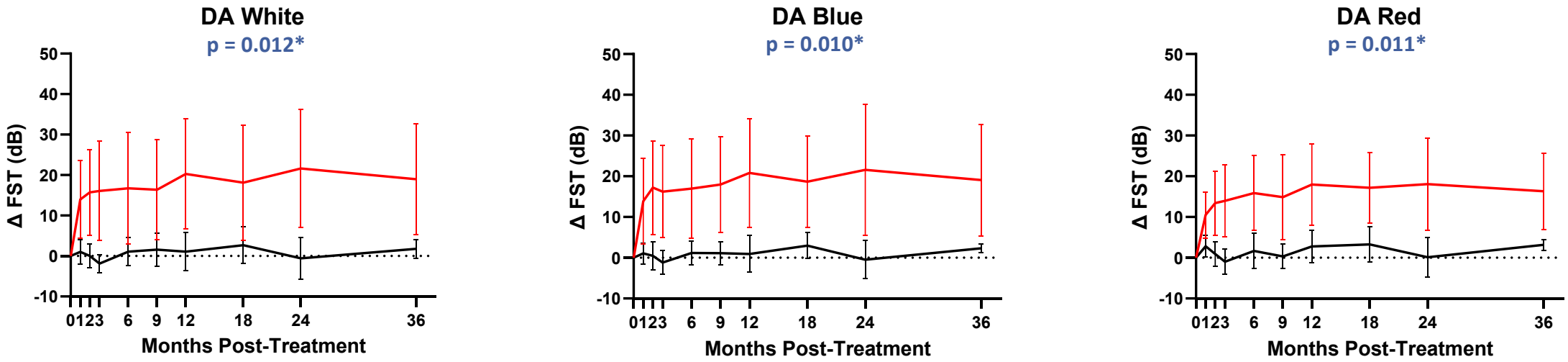
FST: High dose is more efficacious than low or mid doses



Data represented as mean change from Baseline with 95% CI

CHRD Center for Hereditary Retinal Degenerations

High-dose cohorts demonstrate durable improvement in FST



***Derived from paired t-test comparing the AUC from baseline to Year 3 between treated and untreated eyes**

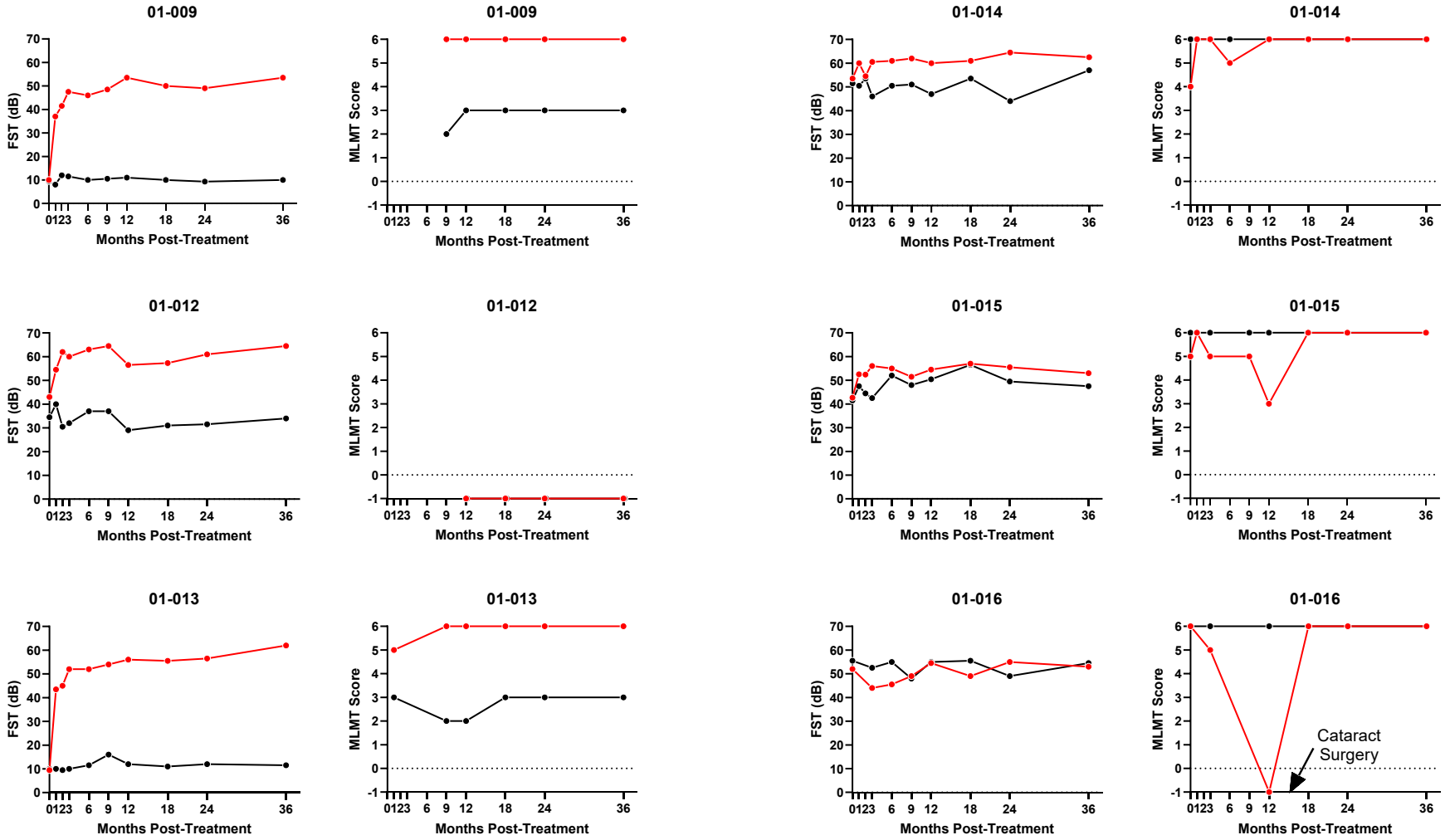
Data represented as mean change from Baseline with 95% CI

CHRD Center for Hereditary Retinal Degenerations

Multi-luminance mobility test (MLMT) is mostly consistent with FST

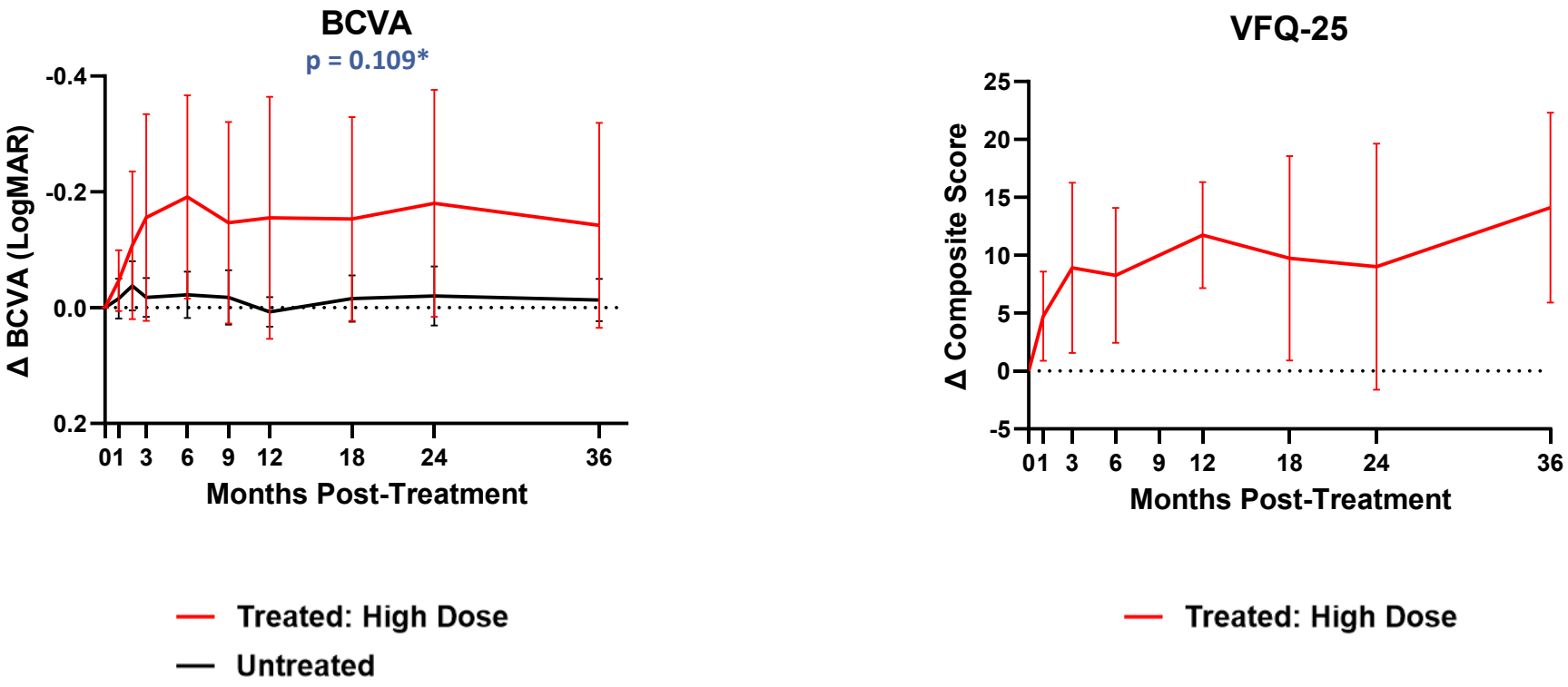
- MLMT was added as an exploratory endpoint midway through the trial.
- FDA considers 2-step improvement to be meaningful.

At the Year 3 visit, 5 of 6 eyes treated with high dose had the maximum score of 6



CHRD Center for Hereditary Retinal Degenerations

BCVA and VFQ-25 show modest improvements at the high dose



***Derived from paired t-test comparing the AUC from baseline to Year 3 between treated and untreated eyes**

Data represented as mean change from Baseline with 95% CI

CHRD Center for Hereditary Retinal Degenerations

Summary

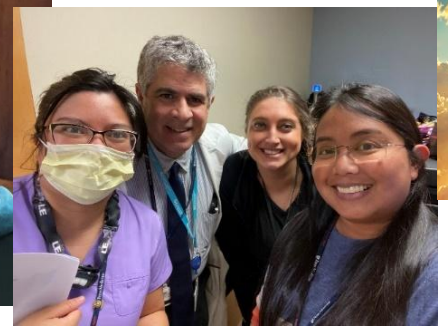
SAFETY

- To date, no drug-related SAEs reported
- Ocular inflammation has been infrequent, minimal, and reversible with steroid treatment
- Will continue to follow safety through 5 years post-treatment

EFFICACY

- Subjects treated at the high dose demonstrate significant improvements in dark-adapted FST
  - 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
  - **Durable through at least Year 3**
- MLMT is mostly consistent with FST improvements
- Modest improvements in BCVA and VFQ-25

CHRD Center for Hereditary Retinal Degenerations



Atsena Therapeutics

- Dan Yoon, MD
- Laura P. Pardon, OD, PhD
- Kenji P. Fujita, MD
- Shannon E. Boye, PhD
- Sanford L. Boye, MSc
- Christine N. Kay, MD
- Rachel Smith, PhD

Collaborators

- Allen C. Ho, MD – Wills Eye Hospital
- Paul Yang, MD, PhD – OHSU
- Andreas K. Lauer, MD – OHSU
- Sarah McCague, MS – CHOP
- Mark E. Pennesi, MD, PhD – OHSU/RFSW
- Lee McDaniel, PhD – JCHR

Colleagues

Alejandro J. Roman, Alexander Sumaroka, Alexandra V. Garafalo, Malgorzata Swider, Vivian Wu, Robert Russell, Iryna Viarbitskaya, Shivani Rawat, Rebecca Kim, Arlene Joy Santos, Kelsey Parchinski, Mariejel Weber, Samuel G. Jacobson and Tomas S. Aleman

Sanofi Genzyme

The following Sanofi employees were responsible for the successful implementation and design of the ongoing Ph1/2 LCA1 trial, interactions with health authorities, writing and preparation of the IND, and the generation of the critical GMP vector lot used to dose patients in the Ph1/2 trial.

- Beel-Lin Cheang, PhD
- Catherine R. O'Riordan, PhD
- Vanessa Davidson