OPGx-LCA5: Clinical Results Translated to Real Life Changes

Christine Kay, MD
Vitreo Retinal Associates
Affiliate Assistant Professor, University of South Florida

OPGx-LCA5 Gene Therapy is Designed to Restore Structure and Function in Photoreceptors of LCA5 Patients

- *LCA5* accounts for ~2% of all LCA patients; ~200 patients in the U.S.[1,2]
- Photoreceptor structure in *LCA5* is severely impaired due to a lack of functioning lebercilin[3]
- OPGx-LCA5 gene therapy is designed to address mutations in the *LCA5* gene, which encodes for lebercilin protein
  - AAV8 vector delivers a functional LCA5 gene directly to photoreceptor cells via subretinal injection
  - Same CMV enhancer and CβA promoter technology as voretigene

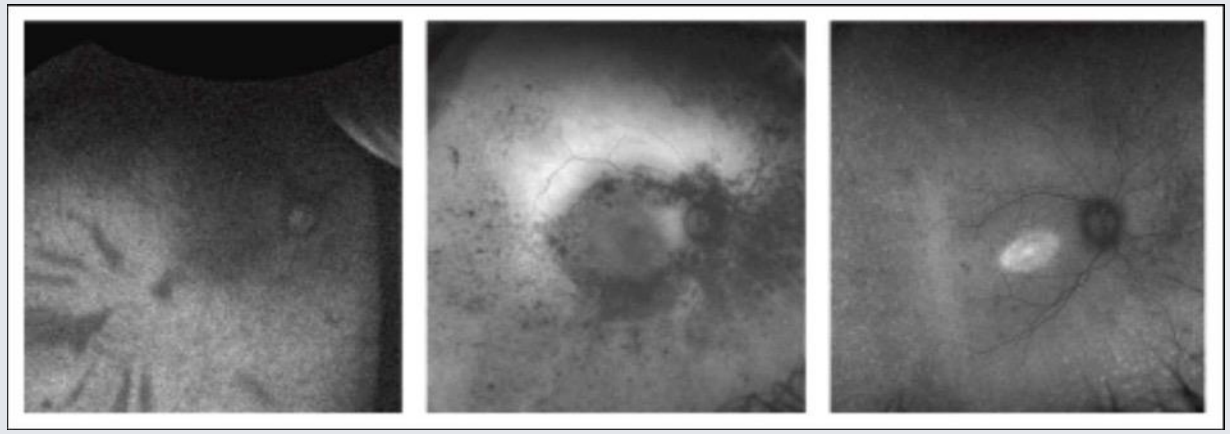
AAV, adeno-associated virus; CMV-CβA, chicken beta-actin; CMV, cytomegalovirus, LCA5, Leber congenital amaurosis 5.

1. Stone et al. *Ophthalmology.* 2017;124:1314-1331. **2.** Triangle Insights Group market research (compilation of prevalence studies), conducted August 2023 **3.** Uyhazi KE, et al. *Invest Ophthalmol Vis Sci*. 2020;61:30.

Phase 1/2 Study of OPGx-LCA5 Gene Therapy in LCA5 Patients

- First-in-human, open-label study of unilateral subretinal injection of OPGx-LCA5 gene therapy
- Nonrandomized, single ascending, dose escalation, with 3 patients treated at each dose level:
  - 1E10 vg/eye, 3E10 vg/eye, and 1E11 vg/eye
- One-year results in three low-dose (1E10 vg/eye) adult patients

3 adult patients: Same phenotype, diverse severity

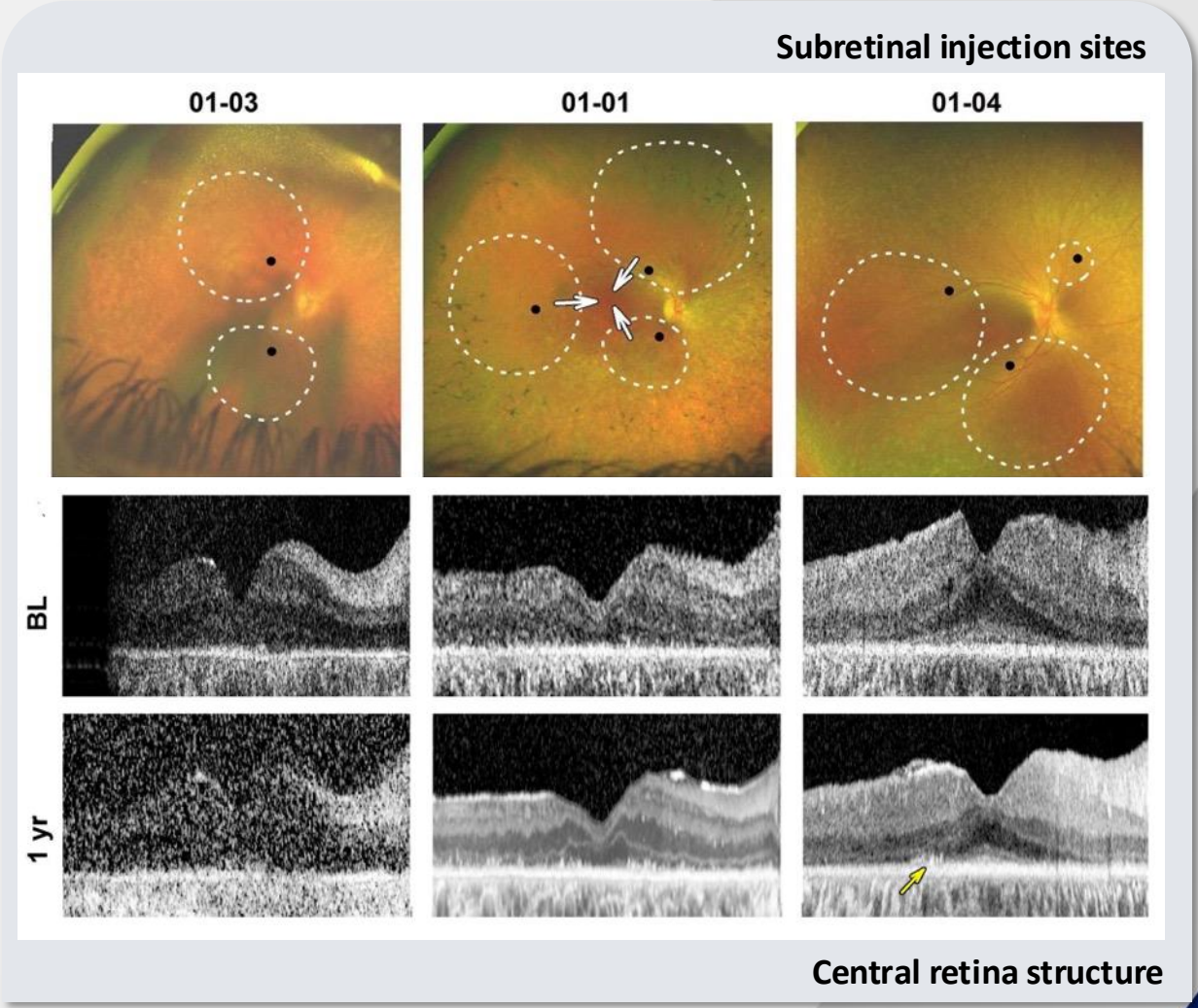


01-03	01-01	01-04
26 years, Male BL VA: HM (OU)	34 years, Female BL VA: 20/300 OD, 20/400 OS	34 years, Female BL VA: 20/200 OU

BL, baseline; LCA5, Leber congenital amaurosis 5; HM, hand motion; OD, right eye; OS, left eye; VA, visual acuity.

OPGx-LCA5 was Safe and Well-Tolerated Through One Year

- No observed dose-limiting toxicities
- Uneventful subretinal injections
  - 300 ml total volume
  - Multiple SR injections, shallow blebs that initially spare the fovea
  - Slow extension to fovea during fluid air exchange
  - Standard 1-month oral steroid taper regimen
- Central retinal structure
  - Retina reattached
  - No major changes post-treatment
- AEs were anticipated, mild, and unrelated to treatment
- All AEs resolved

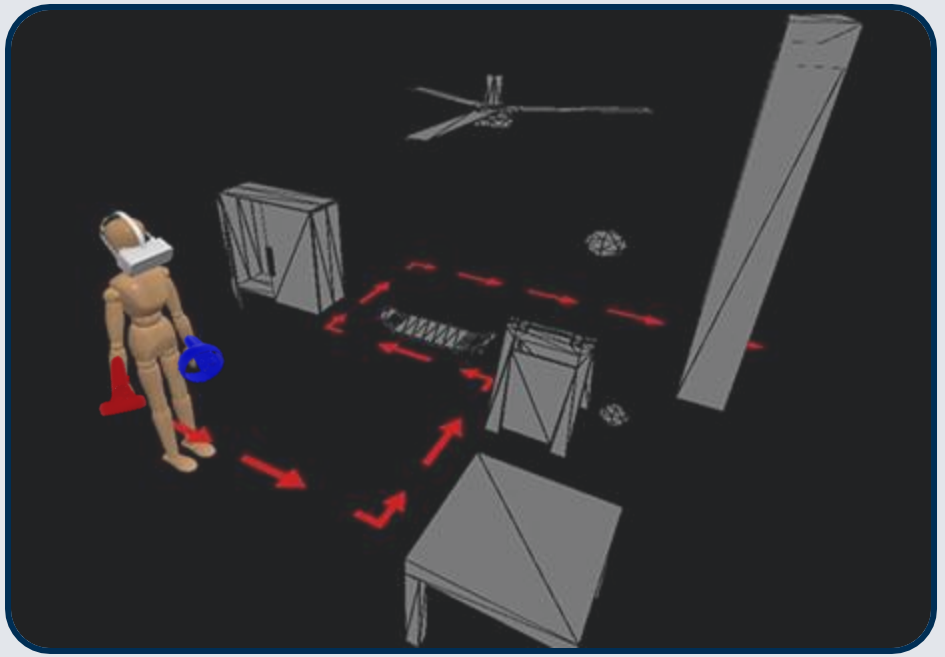


AE, adverse event; LCA5, Leber congenital amaurosis 5; SR, subretinal.

Overview of Efficacy Endpoints

- Multi-Luminance Orientation and Mobility Test (MLoMT)
- Full-field stimulus testing; dark and light-adapted
- BCVA
- Microperimetry
- Chromatic VA
- Transient pupillary light reflexes; dark-adapted
- Patient-reported outcomes

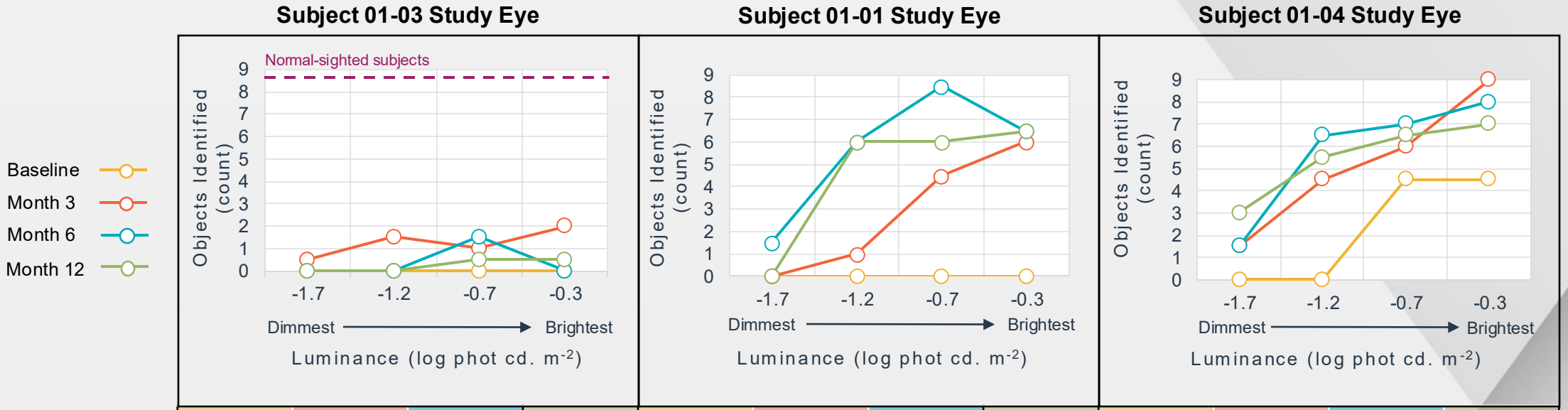
Functional Vision Testing with MLoMT



- VR headset with hand trackers to navigate a virtual course with obstacles and tag objects
- Score is total number of tagged objects per light level

BCVA, best-corrected visual acuity; VA, visual acuity; VR, virtual reality.

All Treated Subjects Identified More Objects Through 12 Months Compared to Baseline in the MLoMT

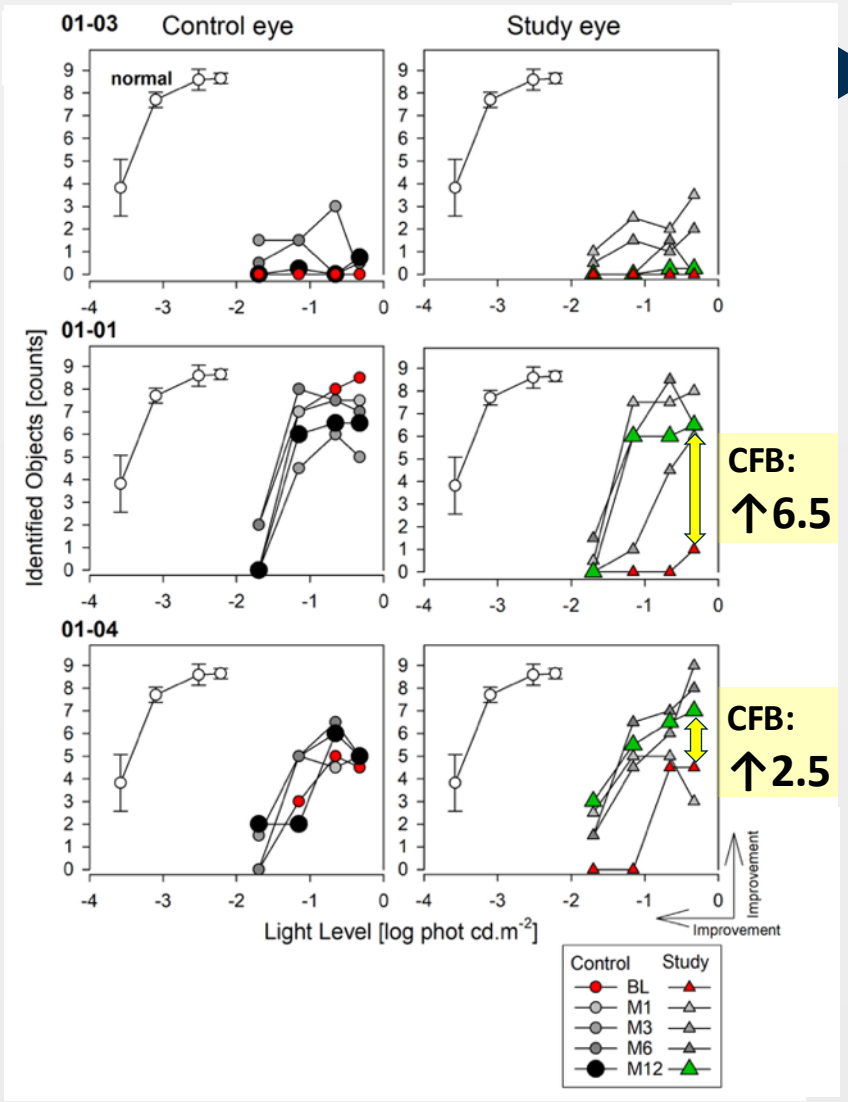


Luminance	BL	Month 3	Month 6	Month 12	BL	Month 3	Month 6	Month 12	BL	Month 3	Month 6	Month 12
-1.7 (dimmest)	0	0.5	0	0	0	0	1.5	0	0	1.5	1.5	3
-1.2	0	1.5	0	0	0	1	6	6	0	4.5	6.5	5.5
-0.7	0	1	1.5	0.5	0	4.5	8.5	6	4.5	6	7	6.5
-0.3 (brightest)	0	2	0	0.5	0	6	6.5	6.5	4.5	9	8	7

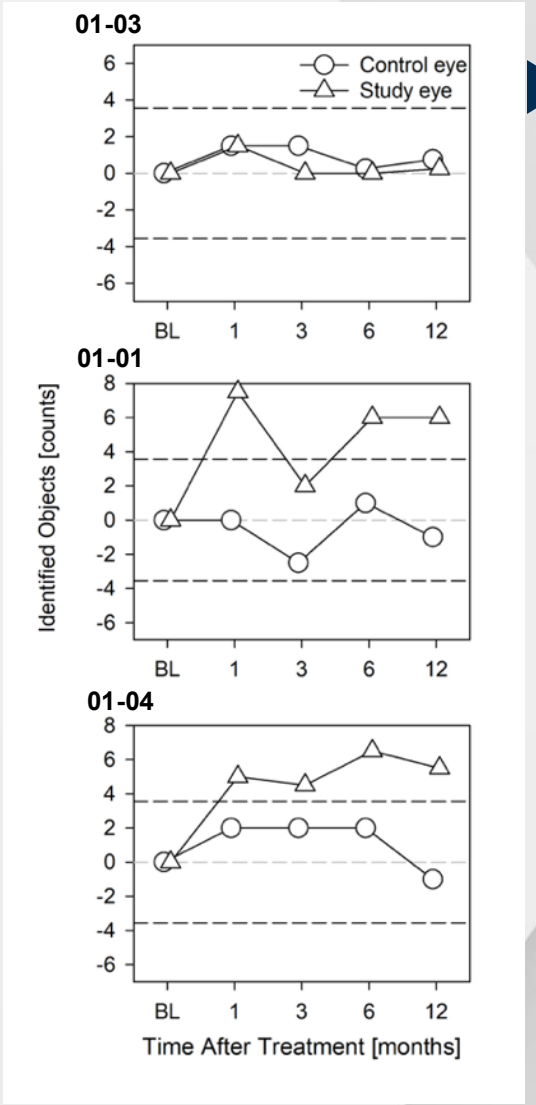
Count of Objects Identified (Max=9)

CFB, change from baseline; MLoMT, Multi-Luminance orientation and Mobility Test.

All Treated Subjects Identified More Objects Through 12 Months Compared to Baseline in the MLoMT



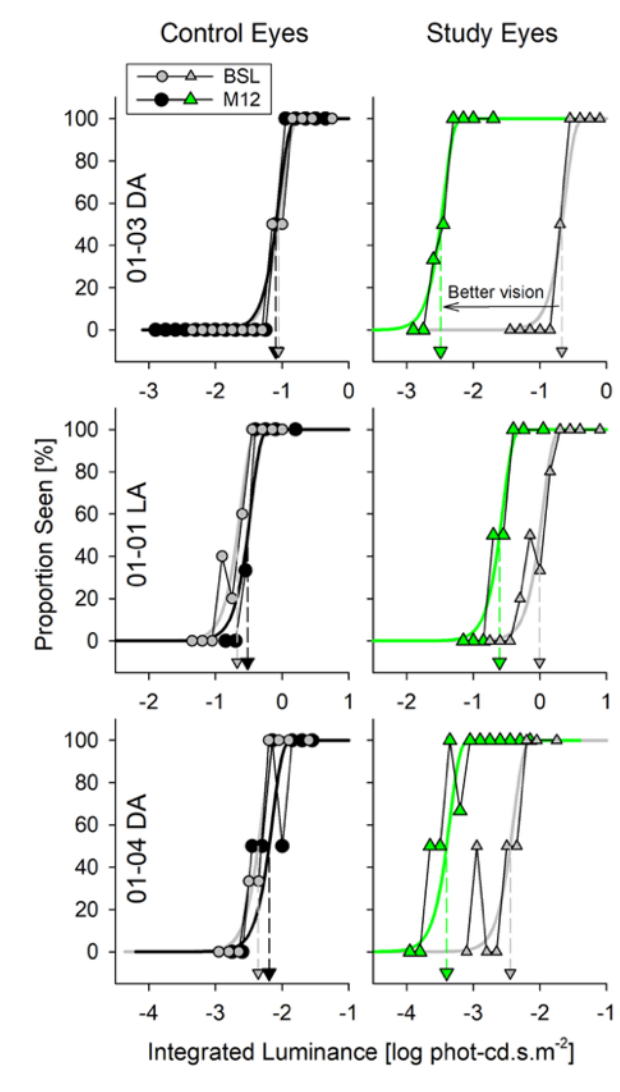
- Treated patients identified more objects at 12 months (green) compared to baseline (red)

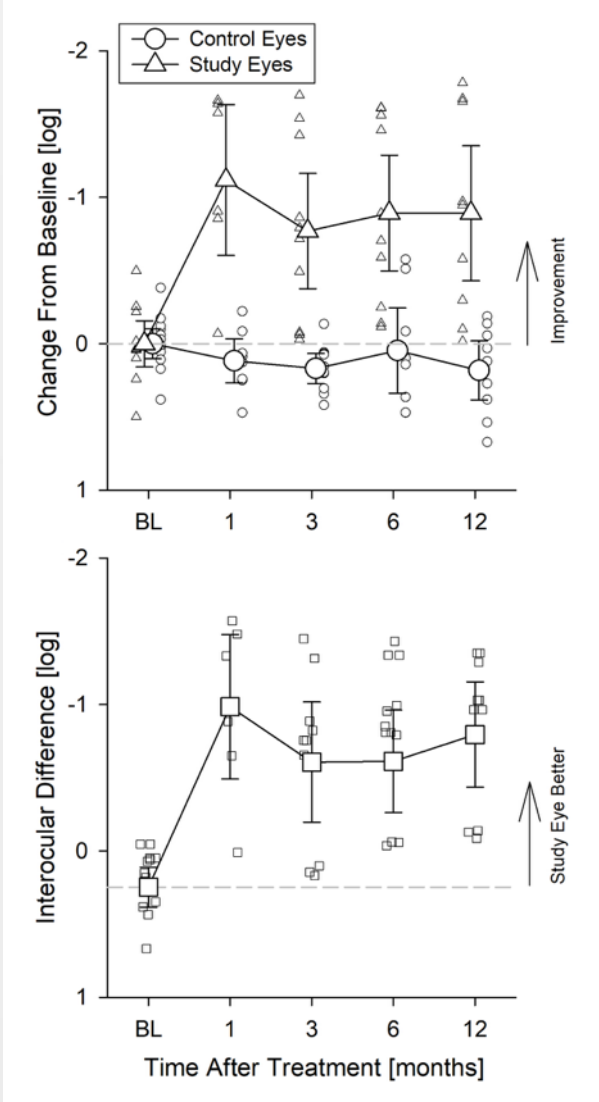


- Improvement in orientation and mobility (triangles) in two patients exceeded variability of the test up to 12 months post-treatment

BL, baseline; CFB, change from baseline; MLoMT, Multi-Luminance orientation and Mobility Test.

FST Demonstrated Gains in Cone Mediated Sensitivities

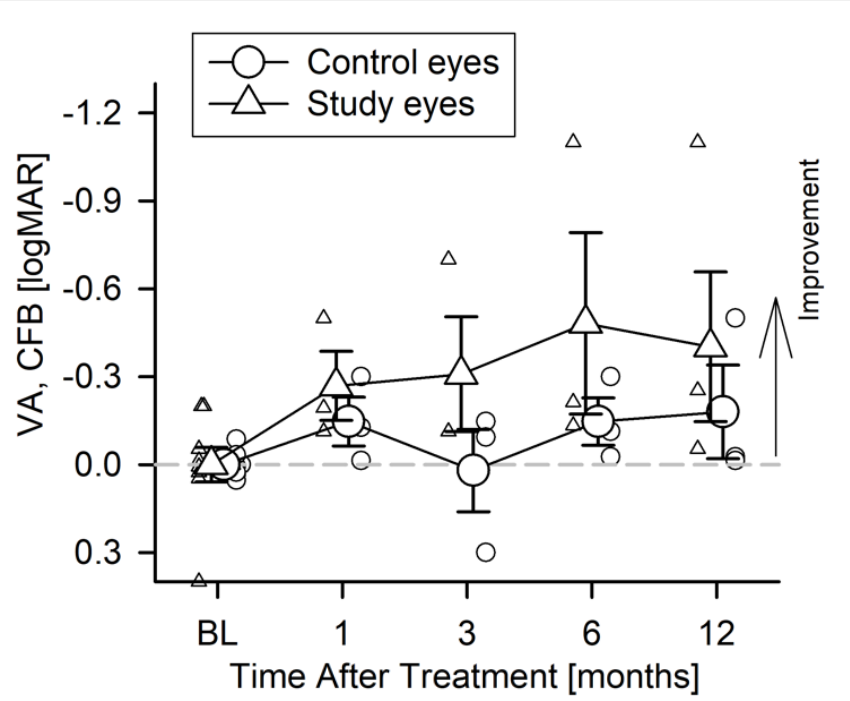


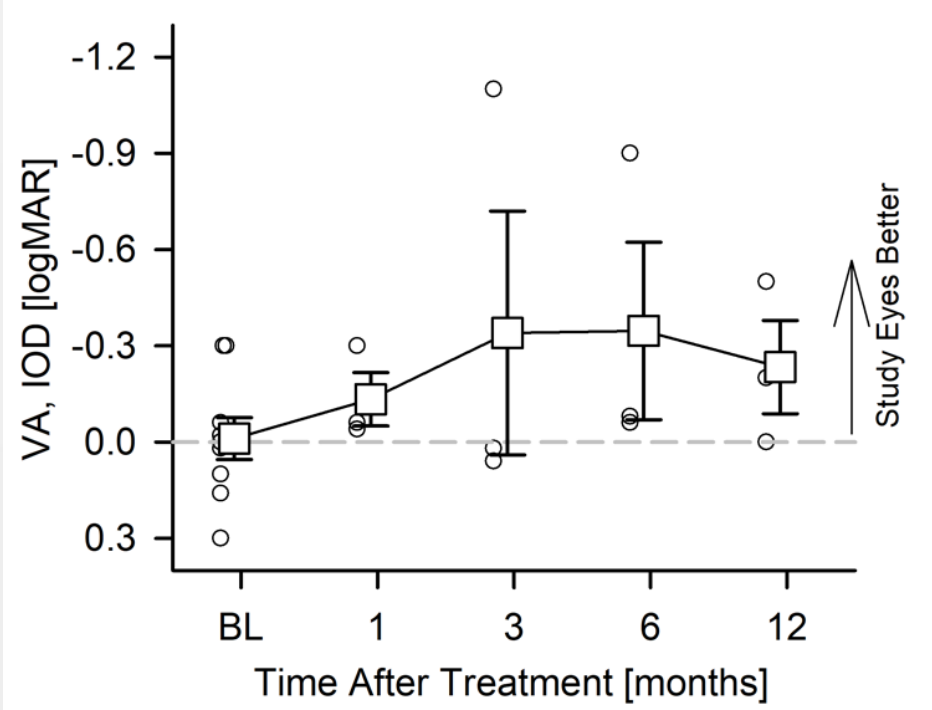


- Larger improvements from baseline were observed in treated eyes compared to control eyes at all time points
- At 12 months, 0.86 log mean improvement in treated eyes vs 0.16 log units in control eyes
- Interocular difference showed an average of 0.7 log units better sensitivity in treated eyes compared to control eyes at 12 months

Patients 01-03 and 01-04 were measured under dark-adapted conditions; Patient 01-01 was measured in light-adapted conditions.
BL, baseline; DA, dark-adapted; FST, full-field sensitivity testing; LA, light-adapted.

Visual Acuity Gains



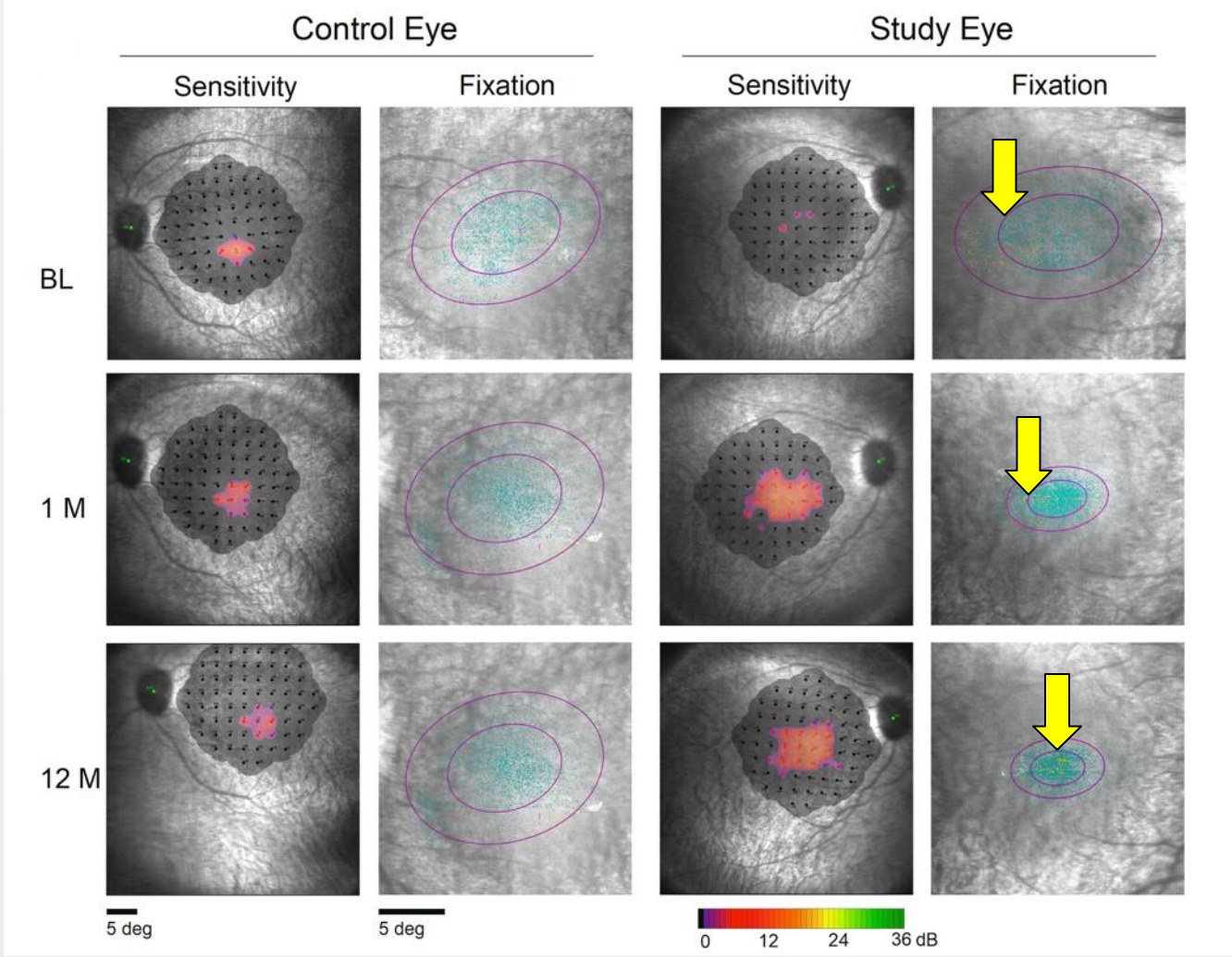


- Formed vision possible for the first time ever in the most affected patient (per patient records, he never had better vision than hand motion)
- On average, better VAs in treated eyes compared to baseline and untreated eyes
- Average improvement of 0.35 logMAR; equivalent to 3.5-line improvement across 3 participants

BL, baseline; CFB, change from baseline; IOD, intraocular difference; VA, visual acuity.

Greater than 18-fold Improvement in Macular Sensitivity in Subject 01-04

Control eye: Small area of severely reduced sensitivities at 5 points with no change through 12 months



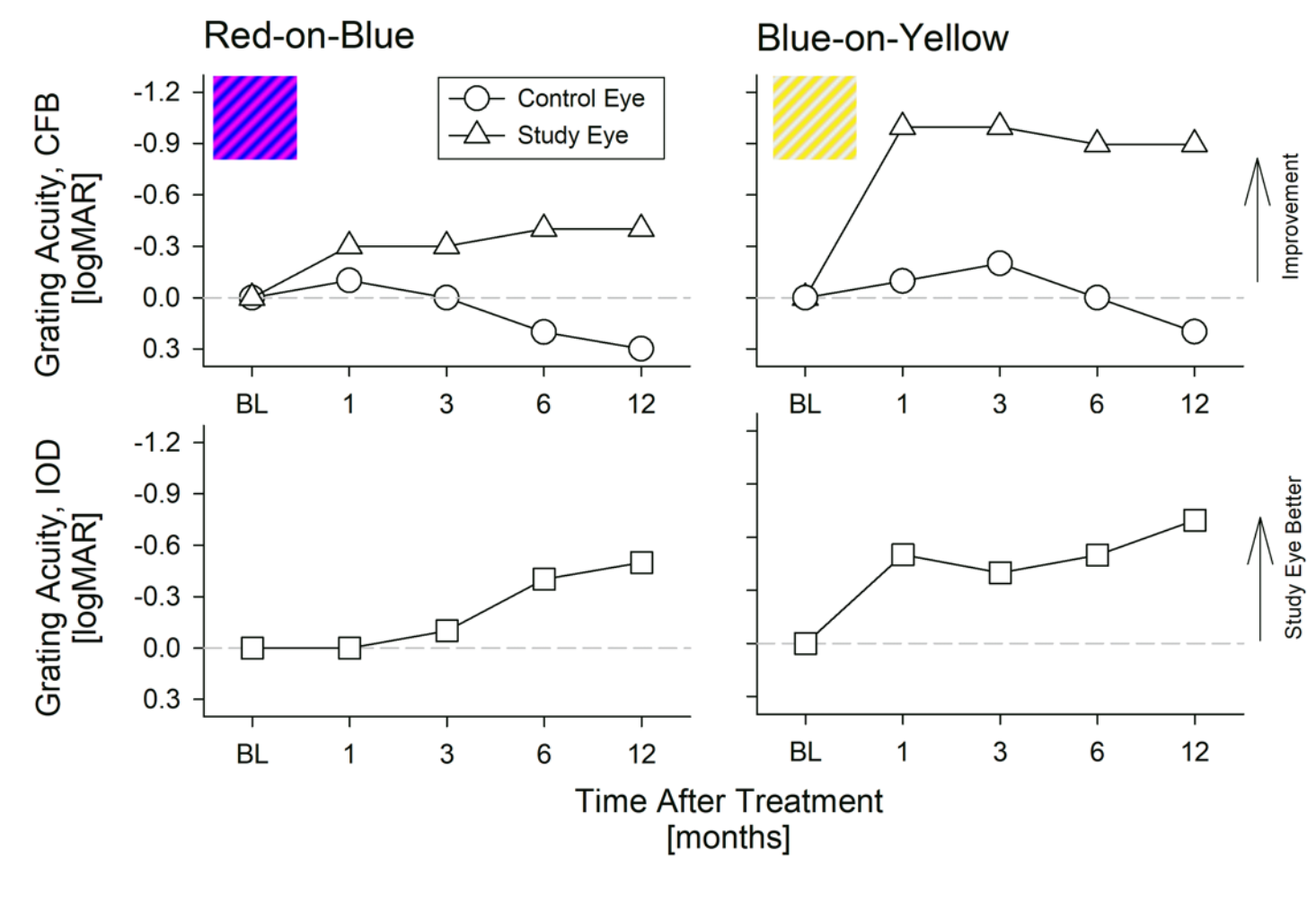
Study Eye:

- **Baseline:** Measurable only in scattered points of barely detectable sensitivity; Fixation unsteady, over area of ~10 degrees
- **1 Month:** Improved with detectable sensitivities in 19 points over area of ~15 degrees
- **12 Months:** Similar results observed
- Movement to a more stable fixation to foveal center

Standard 10-2 test pattern was used to present white stimuli on a mesopic white background

Note: Microperimetry only possible in one subject; Two subjects could not fixate at baseline.

Chromatic Visual Acuity in Subject 01-04



- Improvements in cone-specific resolution between 0.3 and 1 logMAR

Note: Chromatic grating only tested in subject 01-04 to better understand foveal function.

BL, baseline; CFB, change from baseline; IOD, intraocular difference.

Conclusions

- OPGx-LCA5 was safe/well-tolerated and demonstrated robust biologic efficacy at 12 months in three adult patients
- Efficacy was corroborated through multiple functional outcomes:
  - Improvement in MLoMT translates to improved ability to navigate the environment and perform daily activities
  - VA and FST improvements suggest enhanced visual perception and clarity
- Phase 1/2 study is ongoing with 2 additional pediatric patients treated (low dose, 1E10 vg/eye)
- Overall, OPGx-LCA5 therapy offers hope for improved quality of life and greater independence for individuals affected by LCA5

FST, full-field sensitivity testing; LCA5, Leber congenital amaurosis 5; VA, visual acuity.