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One Year Results from a Phase 1/2 Study of OPGx-LCA5 Subretinal Gene Therapy for the Treatment of *LCA5*-LCA in Adult Participants

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Purpose

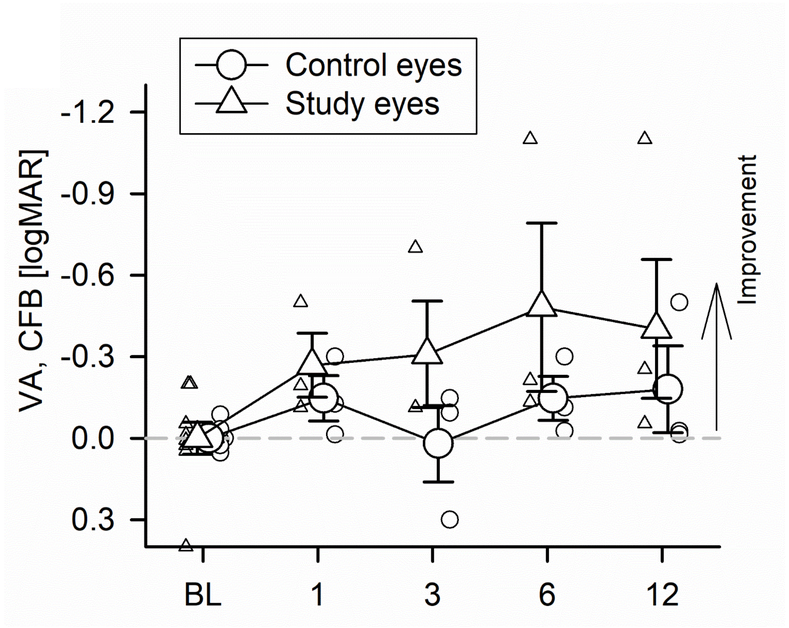
- Leber congenital amaurosis (LCA) is a rare inherited retinal disease (IRD) that leads to early-onset and severe vision loss or blindness within the first year of life.[1] LCA represents a heterogeneous group of conditions caused by variants in over twenty genes. A particularly severe form of LCA is caused by variants in the *LCA5* gene, for which there is currently no treatment.
- *LCA5* encodes Lebercilin, a protein that largely localizes to the bulge region at the base of the photoreceptor outer segment (POS), a critical region for intraflagellar transport and POS formation. Treating a defect in this specific location is promising since therapy could restore structure and function of the POS.
- Studies have shown that recombinant adeno-associated viral (AAV) vectors containing human *LCA5* delivered into the subretinal space of mice prevent photoreceptor degeneration in an *LCA5* model.
- OPGx-LCA5 gene therapy is designed to address mutations in the *LCA5* gene through the delivery of a functional *LCA5* gene directly to photoreceptor cells via subretinal injection.
- A Phase 1/2 first-in-human study of OPGx-LCA5 gene therapy is ongoing. To date, three adult participants and three adolescent participants with biallelic mutations in the *LCA5* gene have been treated. One-year results in three adult participants are presented here.

Methods

- Ongoing Phase 1b/2a non-randomized, dose-escalation, open-label study conducted at the University of Pennsylvania to assess safety and tolerability of OPGx-LCA5 gene therapy (NCT05616793)
- OPGx-LCA5 is a sterile suspension of adeno-associated virus 8 (AAV8) serotype vector containing single-stranded DNA encoding the unmodified human native LCA5 transgene (pAAV.Hnat.LCA5) driven by a cytomegalovirus immediate-early enhancer with a chicken beta-actin promoter
- Three adult participants (19, 26, and 34 years old) with diagnosed *LCA5*-LCA were enrolled and received a unilateral subretinal injection of OPGx-LCA5 at the vector dose of 1E10 vg/eye (low dose cohort); All participants had severe to profound vision loss diagnosed early in life
- Safety and tolerability were assessed by (1) number of drug-limiting toxicity events; (2) number of procedure-related adverse events (AEs); and (3) number and severity of AEs related to the study drug
- Efficacy was assessed by (1) visual acuity (VA); (2) full-field stimulus testing (FST); dark-adapted transient pupillary light reflex; (4) retina-tracking microperimetry and grating chromatic visual acuity; and (5) patient-reported outcomes using a modified National Eye Institute Visual Functioning Questionnaire-25; and a virtual reality Multi-luminance orientation and Mobility Test (MLoMT)

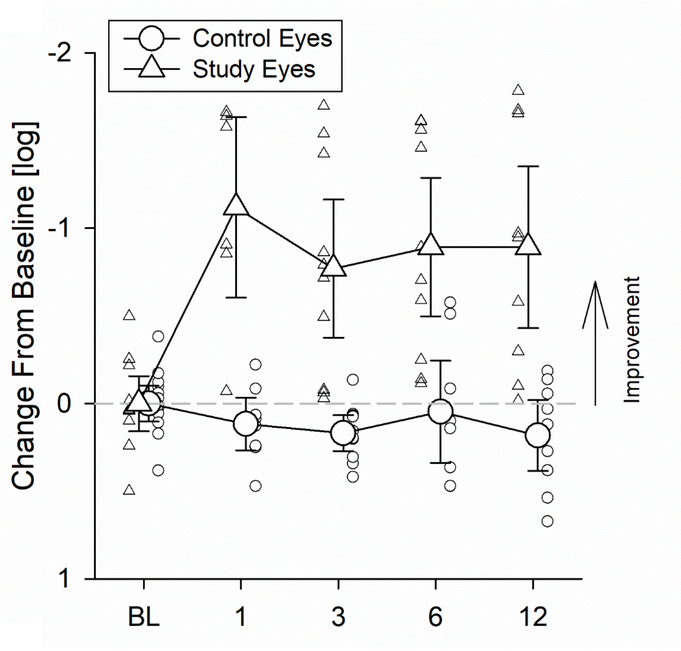
Results

Mean Change from Baseline in VA



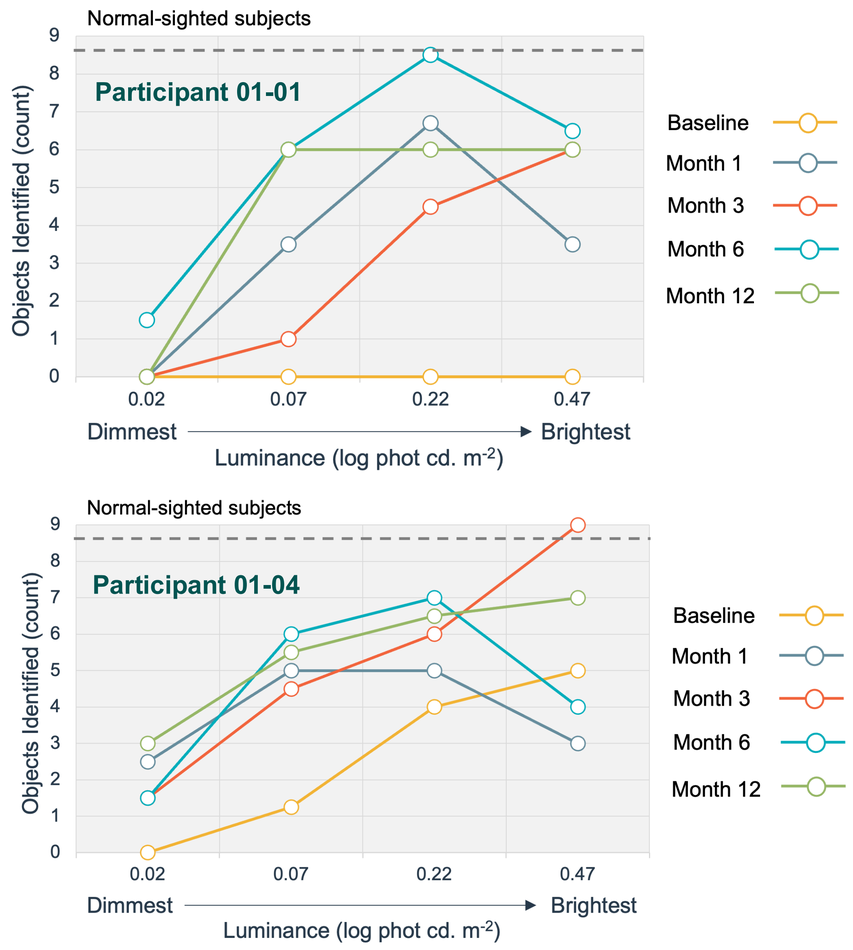
- On average, greater change from baseline (CFB) in study eyes, with 0.35 logMAR improvement (equivalent to 3.5 lines) by 12 months
- Formed vision possible for first time ever in most affected participant (hand motion at baseline)

Mean Change from Baseline in FST



- Study eyes showed lower thresholds after treatment indicating improved sensitivity
- At 12 months, 0.86 log improvement in study eyes vs. 0.16 log deterioration in control eyes

Virtual Reality MLoMT



- Two participants (01-01 and 01-04) had marked improvement in object recognition over a large range of luminances in the study eye
- One participant (01-03) went from not being able to navigate through the course to being able to complete it successfully

Safety & Tolerability

- No observed dose-limiting toxicities
- Uneventful subretinal injections; Retina reattached and no major changes post-treatment
- AEs were mild, resolved promptly and were unrelated to treatment

Conclusions

- OPGx-LCA5 was safe and well-tolerated, with robust efficacy signals at 12 months in 3 adult participants with severe to profound vision loss due to *LCA5*-LCA.
- Improvements in VA and FST suggest enhanced visual perception and clarity, and improvement in MLoMT translates to improved functional benefits.
- OPGx-LCA5 therapy offers hope for improved quality of life and greater independence for individuals affected by *LCA5.*

1. Aleman TS, Uyhazi KE, Roman AJ, et al. Recovery of cone-mediated vision in *Lebercilin* associated retinal ciliopathy after gene therapy: One-year results of a phase I/II trial. Mol Ther (2025), https://doi.org/10.1016/j.ymthe.2025.06.035.

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