**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

**Retinal Gene Therapy Surgical Techniques**

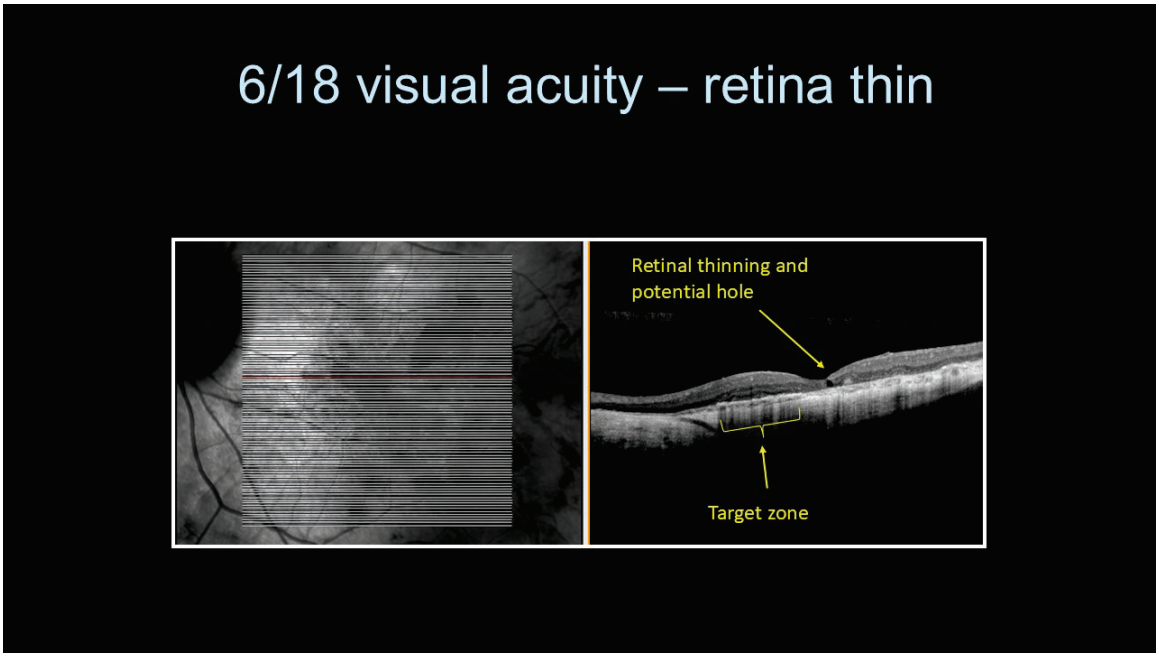



- Robert MacLaren, DSc DPhil FRCS FRCOphth FACS FMedSci

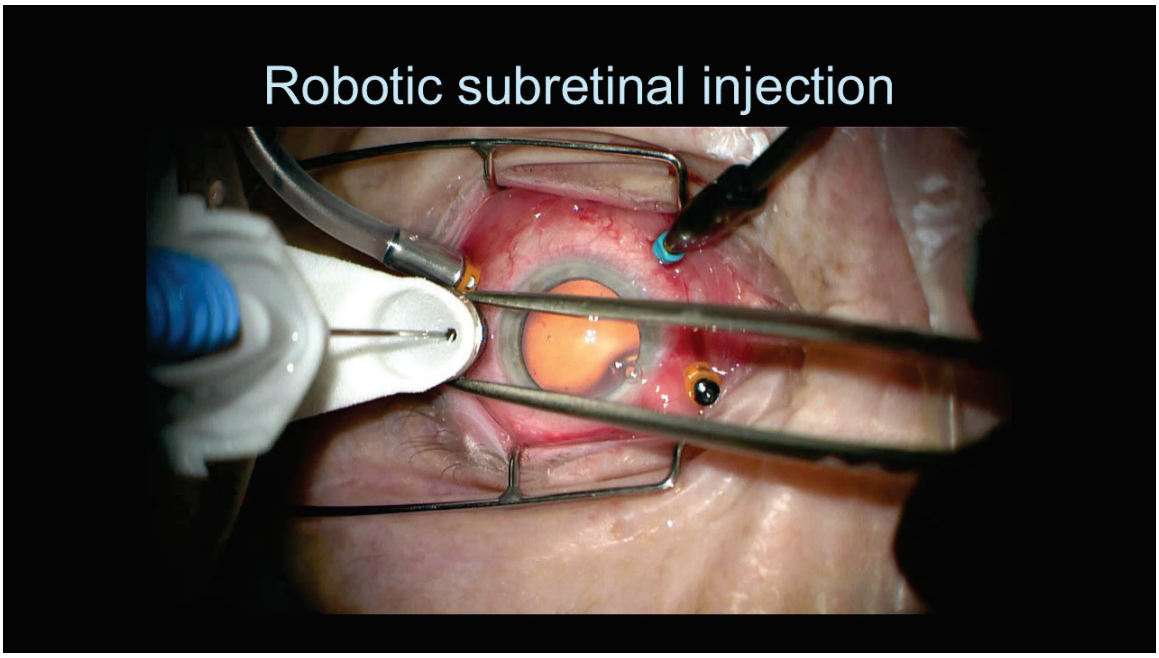


**Objective:** This paper describes different surgical techniques developed from over 100 cases of subretinal gene therapy.
**Purpose:** Subretinal gene therapy is technically challenging but more surgeons are performing it as retinal gene therapy treatments become more widespread. The technique of detaching the retina requires access to the subretinal space without hemorrhage as well as detaching the overlying retina without causing damage by excess stretch. In this paper I will explain key concepts in surgical videos to explain how subretinal gene therapy can be performed safely.
**Methods:** Surgical approaches in patients undergoing subretinal gene therapy for choroideremia, Leber congenital amaurosis (RPE65), retinitis pigmentosa and age-related macular degeneration will be presented. Techniques using heavy liquids and air-fluid exchange to detach the fovea will also be discussed. Use of a robot to perform a subretinal injection will also be shown.
**Results:** Subretinal gene therapy can be used safely to detach the retina without causing adverse effects on visual function when performed correctly. Statistically significant improvements in 2-lines of visual acuity and 3 lines of low luminance visual acuity were seen in two recent phase III clinical trials (choroideremia and X-linked retinitis pigmentosa) one year after subretinal injection in two recent publications (MacLaren et al., Nature Med 2023; Lam et al., Ophthalmol 2024). Whilst not meeting the primary endpoint, these data provide proof of the excellent safety profile of subretinal gene delivery,
**Conclusion:** Subretinal gene therapy requires knowledge of new techniques and concepts, but when performed correctly can be both safe and effective. The key advantage of subretinal injection relates to more efficient targeting of the outer retina and reduced inflammation compared with intravitreal injection.


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How to detach very thin retina to avoid creating a hole




Use of the robot to perform a subretinal injection

**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

# Subretinal Laru-zova Gene Therapy for XLRP: 24-Month Results of the Randomized, Controlled, Multicenter Phase 2 SKYLINE Trial




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- David Birch, MD
- Paul Yang, MD
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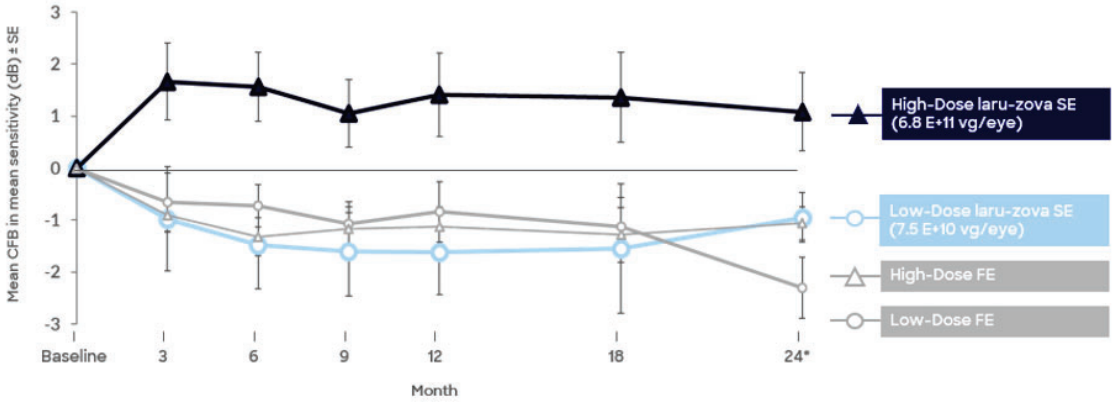


**Objective:** The Phase 2 SKYLINE study seeks to evaluate the safety and efficacy of subretinal laru-zova gene therapy in participants with X-linked retinitis pigmentosa resulting from a mutation in the *RPGR* ORF15 gene.
**Purpose:** To assess the efficacy and safety of 2 dose levels of subretinal laru-zova in participants with X-linked retinitis pigmentosa (XLRP).
**Methods:** Males (N=14) with XLRP caused by *RPGR* mutations aged 8-50 were randomized to receive high (6.8 E+11 vg/eye) or low (7.5 E+10 vg/eye) dose subretinal laru-zova (AGTC-501). Participants had a baseline BCVA of 35-75 letters, a detectable EZ line on SD-OCT and mean macular sensitivity of 1-12 dB via microperimetery (MAIA). Safety, efficacy and tolerability of laru-zova were evaluated. Efficacy endpoints included proportion of responders via MAIA microperimetry and change from baseline (CFB) in mean sensitivity, BCVA, mobility course score, and EZ area. Response via MAIA microperimetry was defined as ≥7 dB improvement in ≥5 loci. Safety was assessed via adverse events (AEs) and functional, anatomical, and lab results.
**Results:** Eleven participants reached the M24 visit. In the high dose group, 4/7 participants (57%) were responders at M24 in the study eye (SE), compared to no responders seen in the untreated fellow eyes (FE). In the low dose group, 1/4 participants (25%) were responders at M24 in the SE, compared to no responders seen in the untreated FE. Mean sensitivity via MAIA microperimetry was improved in the high dose SE's and when compared to the low dose SE's or untreated fellow eyes at M24. The difference in mean CFB in mean sensitivity (whole grid) between the high and low doses in the SE was 2.03 dB (p=0.0490), and the difference between the high dose SE and FE was 2.30 (p=0.0156). The improvement in mean CFB in mean sensitivity (whole grid) seen at Month 3 in the high dose SE was sustained through Month 24. Positive trends were seen in the mobility maze for the high dose group, with 5/7 high dose SE's showing at least a one-level improvement, and 3/7 showing at least a two-level improvement in the maze test.

BCVA remained stable in the SE and untreated FE for the majority of participants. At M24, the difference in mean CFB between SE and FE in the high and low dose groups was 3.3 (p= 0.0653) and 5.0 (p=0.1228) letters, respectively. EZ Area remained stable or decreased in both the SE and untreated FE for participants. At M24, the difference in mean CFB between SE and FE in the high and low dose groups was -0.32 (p= 0.1521) and 1.02 (p=0.4086) $mm^2$, respectively. All p-values are nominal.

Ocular treatment-emergent adverse events (TEAEs) were mostly non-serious, mild or moderate in severity, and rates were similar between high dose and low dose groups. Three subjects in the low dose and two in the high dose groups had grade 1 or 2 non-serious ocular AEs related to laru-zova. Two ocular SAEs were reported (both in low dose participants), but neither was considered related to laru-zova (1 related to protocol required steroids, 1 related to surgical procedure).
**Conclusion:** The 24-month data in SKYLINE demonstrate that both dose levels of laru-zova were well-tolerated. Data show improvements in visual function via microperimetry with evidence of efficacy in study eyes of the high dose group when compared to study eyes in the low dose group and untreated fellow eyes. These favorable safety and efficacy results support continued development of laru-zova.


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*3 participants (1 high-, 2 low-dose) missed scheduled Month 24 visits.

CFB = change from baseline; FE = fellow eye (untreated); SE = study eye (treated); vg = vector genomes

Mean change from baseline in whole grid mean sensitivity via microperimetry

**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

# A Novel Modifier Gene Therapy for Retinitis Pigmentosa: 2-Year Results of a Phase 1/2, Multicenter, Dose-Escalation Study of Subretinal OCU400


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- Benjamin Bakall, MD, PhD
- Lejla Vajzovic, MD, FASRS
- Vinkata Chavali, PhD
- Alex Berezow
- Sahar Matloob, MD
- Arun Upadhyay, PhD
- Huma Qamar



**Objective:** Determine the long term safety, efficacy and tolerability of OCU400 (AAV5-h*NR2E3*)—a first-in-human novel modifier gene therapy—in subjects with retinitis pigmentosa (RP) due to autosomal dominant or recessive mutations in *NR2E3* or autosomal dominant mutations in *RHO*.
**Purpose:** Retinitis pigmentosa (RP), a group of rare genetic disorders caused by mutations in over 150 genes, is a leading cause of blindness among inherited retinal dystrophies, affecting approximately 1 in 4,000 individuals worldwide. The genetic heterogeneity of RP poses a significant challenge for gene-specific treatments. Modifier gene therapy provides a gene-independent approach, offering a potential treatment regardless of the underlying mutation. OCU400, a first-in-class gene-independent therapy, leverages the overexpression of NR2E3—a nuclear hormone receptor and transcription factor—to restore retinal homeostasis by modulating gene networks involved in cell survival, stress response, immunity, metabolism, and phototransduction. We present 24 months follow up data for Phase 1/2 trial of OCU400 (NCT05203939).
**Methods:** The trial enrolled 18 subjects aged 18 years and older with genetically confirmed RP due to autosomal dominant or recessive *NR2E3* or autosomal dominant mutations in *RHO* (AD-*RHO*). Patients were randomized to receive either a low ($1.66 \times 10^{10}$ vector genomes [vg]/mL), medium ($3.33 \times 10^{10}$ vg/mL), or high ($1.66 \times 10^{11}$ vg/mL) dose via a single subretinal injection in the worse-seeing eye (study eye). The primary outcome was safety, as determined by treatment-emergent (serious) adverse events (TE(S)AEs) over 12 months. Exploratory efficacy outcomes included change from baseline in best corrected visual acuity (BCVA), low luminance visual acuity (LLVA), and a mobility test (MT) under various lighting conditions. Patient were followed up for an additional 12 months for safety and change from baseline in BCVA and LLVA.
**Results:** No serious adverse events (AEs) related to OCU400 were reported (N=18). The efficacy population included 16 subjects (N=16), which excluded two subjects with surgery related AEs. At one year, 43.8% (7 of 16) subjects showed a gain of ≥5 letters with 12.5% (2 of 16) gaining ≥10 letters, compared to 6.3% (1/16) and 0% of untreated fellow eyes, respectively. Similarly, 43.8% (7 of 16) subjects gained ≥5 letters in 43.8% and 25% (4 of 16) subjects gained ≥10 letters on LLVA in study eyes, versus 18.8% (3 of 16) subjects and 0% in fellow eyes, respectively. For MT, 31.3% (5 of 16) and 18.8% (3 of 16) subjects on the study eyes improved by ≥1 and ≥2 lux levels, respectively, compared to 25% and 0% of fellow eyes.
Ten patients completed a two-year follow-up study, and no serious adverse events related to OCU400 were noted. Treated eyes showed a significant 2-line (10-letter) LLVA gain ($p < 0.01$) versus untreated fellow eyes. Subjects with RHO mutations (N=8) also demonstrated statistically significant LLVA improvement ($p < 0.01$).
**Conclusion:** OCU400 shows a favorable long-term safety and tolerability profile. An observed treatment effect in subjects with different mutations indicate a gene-independent mechanism of action. A Phase 3 trial (liMeliGhT) is ongoing (NCT06388200).


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**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

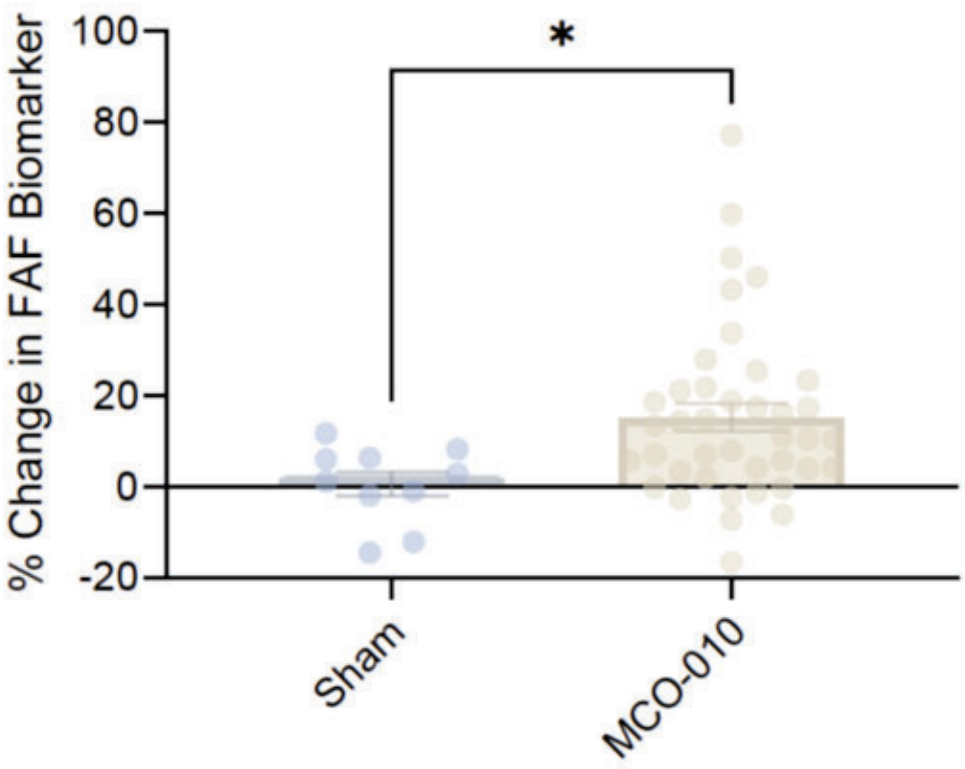
# Extended Efficacy and Safety of MCO-010 Optogenetic Therapy for RP: 126-Week Results From the RESTORE Follow-Up Study (REMAIN)


- David Liao, MD, PhD
- David Boyer, MD
- Charles Wykoff, MD, PhD, FASRS
- Vitaliy Zak, MD
- Lance Bergstrom, MD
- Andres Emanuelli, MD
- Sunil Gupta, MD
- Victor Gonzalez
- Michael Singer, MD
- Joanne Hu, OD
- Samuel Barone, MD
- Sai Chavala, MD
- Samarendra Mohanty, PhD



**Objective:** To evaluate the long-term efficacy and safety of MCO-010, a mutation-agnostic optogenetic therapy, in patients with severe vision loss due to retinitis pigmentosa (RP).
**Purpose:** RESTORE was a phase 2b/3 clinical trial assessing an AAV2-packaged multi-characteristic opsin (MCO) transgene delivered via intravitreal (IVT) injection. Long-term follow-up of patients who received MCO-010 optogenetic therapy continues in the REMAIN study. Efficacy and safety of MCO-010 up to 126 weeks post-injection is reported.
**Methods:** Patients received a single IVT injection of 0.9E11 gc/eye (low-dose; n=9) or 1.2E11 gc/eye (high-dose; n=9) MCO-010 or sham (n=9) in the study eye. At Week 100, unmasking occurred, and patients dosed with MCO-010 were invited to participate in the long-term follow-up study. Expression of MCO protein, which contains the mCherry biomarker, was quantified using fundus autofluorescence (FAF). Changes from baseline in best corrected visual acuity (BCVA) and corresponding area under the curve (AUC) profiles were evaluated through Week 126.
**Results:** Biomarker fluorescence at Week 52 was significantly higher in MCO-010 injected eyes (n=8) compared to sham-treated eyes (n=2, $P < 0.05$; Figure 1). Mean improvements in BCVA at Week 126 compared to baseline for the low- and high-dose groups were 0.310 ± 0.139 and 0.322 ± 0.114 LogMAR ($P = 0.038$ and 0.007), respectively. At Weeks 52, 76, 100, and 126, the AUC (LogMAR*weeks ± standard error of the mean) for the low-dose group were 16.121 ± 5.885 ($P$=0.035), 25.389 ± 8.547 ($P$=0.024), 31.586 ± 11.186 ($P$=0.027), and 38.294 ± 14.085 ($P$=0.039), respectively, compared to control. AUC values for the high-dose group were 10.908 ± 4.188 ($P$=0.091), 21.992 ± 6.040 ($P$=0.011), 31.486 ± 7.858 ($P$=0.003), and 38.866 ± 9.885 ($P$=0.004), respectively. MCO-010 was well tolerated and no drug-related serious adverse events were observed over the study period.
**Conclusion:** BCVA improved with MCO-010 in both low- and high-dose groups over a period of two and half years. Cumulative vision improvement over time demonstrates the durable efficacy of a single administration of MCO-010.


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Change in FAF biomarker from baseline at Week 52

**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

**Oral Gildeuretinol Slows Disease Progression in Early Stargardt Disease: Updates From the TEASE-3 Study**




- Kenneth Fan, MD, MBA
- Philip Ferrone, MD, FASRS
- Michael Gorin, MD, PhD
- Leonide Saad, PhD
- Gabrielle Bartolomeo
- Ilyas Washington
- Marc Mathias
- Christine Kay, MD



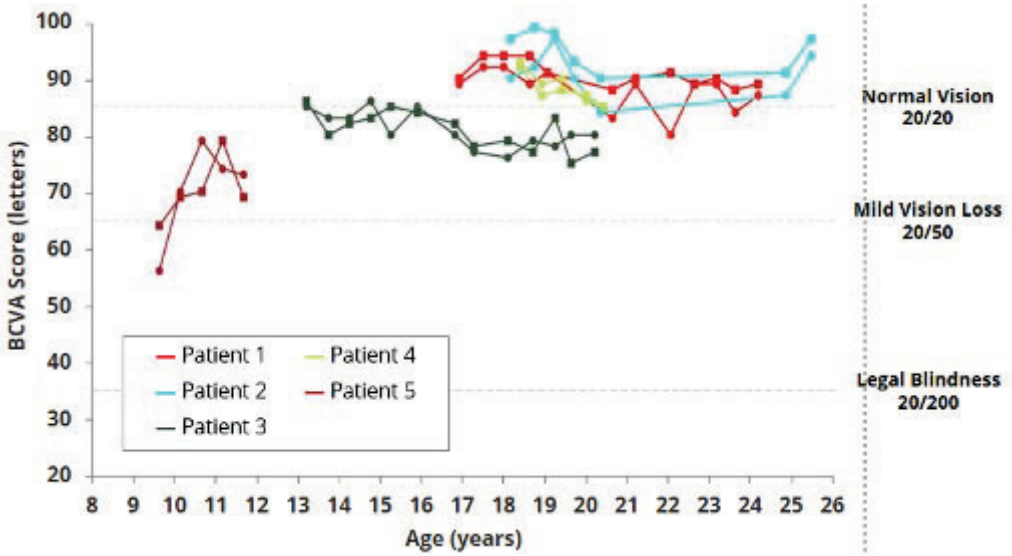
**Objective:** To evaluate whether gildeuretinol acetate slows disease progression of early-stage Stargardt disease
**Purpose:** Stargardt disease is the most common inherited juvenile macular dystrophy and has no approved treatment. The TEASE studies aim to evaluate gildeuretinol as a daily oral therapy for Stargardt disease. In previously presented TEASE-1 results, gildeuretinol was well tolerated and significantly reduced the atrophic lesion growth rate in people with Stargardt disease who had well-delineated atrophic lesions at baseline. The ongoing TEASE-3 study was designed to evaluate gildeuretinol safety and efficacy in Stargardt patients with less severe retinal phenotypes at baseline.

**Methods:** TEASE-3 (NCT02402660) is an open-label, 24-month study of daily oral gildeuretinol 14 mg/day. Target enrollment is approximately n=20. Eligible participants are ≥8 years old, have a Stargardt disease clinical diagnosis with genetic confirmation, and early signs of maculopathy on fundus autofluorescence (FAF) or optical coherence tomography (OCT) without well-delineated atrophic lesions. Efficacy endpoints included change from baseline in best corrected visual acuity (BCVA), FAF imaging, photoreceptor density by OCT, and retinal sensitivity by microperimetry. Participants who complete TEASE-3 are invited to enroll in TEASE-4 (NCT04239625), a 24-month open-label extension study.

**Results:** As of January 2025, seven participants have enrolled in TEASE-3 (n=5, completed, n=2, ongoing), with time on treatment as long as ~7 years. Results from participants who have completed TEASE-3 are presented here. The ages at the time of enrollment were 13, 17, 18, 18, and 9 years. BCVA in ETDRS letters demonstrated little to no decline in BCVA in any of the five participants. Gildeuretinol was well-tolerated, and treatment emergent adverse events (TEAEs) were mostly mild or moderate. One serious TEAE was reported, a case of pelvic inflammatory disease considered unrelated to study drug. No study discontinuations occurred.

**Conclusion:** Oral daily gildeuretinol 14 mg was well-tolerated for up ~7 years in these five participants with early-stage Stargardt disease. BCVA demonstrated little to no decline, supporting the potential for gildeuretinol in reducing the rate of disease progression.


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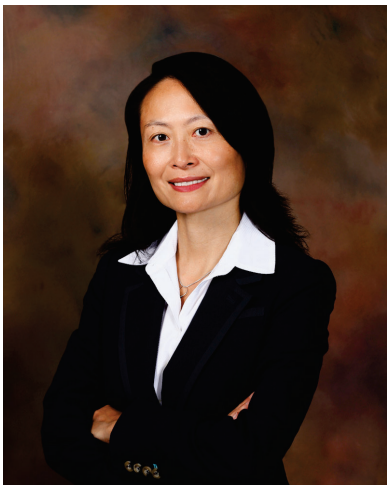



Best Corrected Visual Acuity (BCVA) Over Time. BCVA (ETDRS letters) by time

**8/01/2025**

**Hereditary Retinal Disease & Genetics Symposium 1**

**Secretion of Ciliary Neurotrophic Factor by NT-501 Encapsulated Cell Technology in Patients With Retinal Degenerative Disorders**




- Jiong Yan, MD
- Thomas Albini, MD
- Konrad Kauper
- Lisa Orecchio
- Arne Nystuen
- Alice Lee
- Eugene Gonzalez-Lopez
- Jacque Duncan, MD
- Jay Stewart, MD
- Thomas Aaberg, MD



**Objective:** The objective of this study was to examine drug-release levels and long-term function of cohort-explanted revakinagene taroretcel (NT-501) devices after implant durations of 0.5 to 14.5 years in people with retinal degenerative disease.

**Purpose:** Retinal diseases constitute a significant portion of eye disorders and have a profound impact on vision. Despite this, there are few effective treatments for chronic neurodegenerative conditions of the retina. Encapsulated cell technology (ECT) was developed to overcome the challenge of long-term therapeutic delivery to the retina. NT-501 consists of an encapsulated cell line that has been genetically engineered to produce a novel secreted form of human ciliary neurotrophic factor (CNTF). CNTF protects photoreceptors from degeneration and has shown promise in clinical studies when delivered via ECT. Given their chronic nature, long-term delivery of CNTF will be an important factor in the treatment of retinal diseases.

**Methods:** Samples from multiple clinical trials were collected from participants who underwent NT-501 explantation after various durations following study completion. Explants from participants with retinitis pigmentosa, atrophic macular degeneration, and macular telangiectasia type 2 were evaluated for NT-501–produced CNTF rate and potency, as well as encapsulated cell histomorphology. Serum samples from select participants were evaluated for CNTF as well as anti-CNTF and anti-encapsulated cell antibodies. All trials were approved by the relevant institutional review board/ethics committee, and all studies adhered to the tenets of the Declaration of Helsinki.

**Results:** Data from explanted participants demonstrated that NT-501 implants produced steady bioactive CNTF over 14.5 years at a mean rate of 1.75 ng/day. Explanted NT-501 devices ranging from 0.5 to 14.5 years had similar cellular distribution and gross morphology compared to pre-implant NT-501 devices. Neither CNTF nor anti-CNTF or anti-encapsulated cell antibodies were detected in any participant's serum.

**Conclusion:** Data from this retrospective analysis support intraocular NT-501 as a promising long-term treatment option for retinal degenerative diseases.


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