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Wet AMD Symposium 3

1-Year Results of a Phase 2 Pharmacodynamic Study: Subretinal Delivery of Investigational Gene Therapy ABBV-RGX-314 for Neovascular AMD

- Robert Avery, MD

Objective: One Year Results of a Phase 2 Pharmacodynamic Study: Subretinal Delivery of Investigational Gene Therapy ABBV-RGX-314 for Neovascular AMD

Purpose: Many patients with nAMD do not achieve continuous control of neovascularization, and therefore lose vision. Chronic repeated intravitreal injections to treat nAMD can be burdensome and adherence can be challenging, leading to undertreatment. ABBV-RGX-314 is an investigational, single administration gene therapy designed to deliver a transgene for a soluble anti-VEGF Fab. A Phase 1/2a trial in previously treated nAMD participants provided evidence for sustained anti-VEGF levels after ABBV-RGX-314 subretinal delivery, and those participants are now enrolled in a long-term safety follow up study. The purpose of this Phase 2 pharmacodynamic study is to evaluate the clinical similarity between subretinally delivered ABBV-RGX-314 produced with REGENXBIO's NAVXpress bioreactor platform process and the initial adherent cell culture process. REGENXBIO's NAVXpress process is a commercial-ready, suspension cell (bioreactor) process supplying cGMP commercial-ready material to the ongoing ATMOSPHERE® and ASCENT™ pivotal trials. Investigational ABBV-RGX-314 may, if approved, be manufactured for the commercial market using REGENXBIO's NAVXpress process.

Methods: This study is a multi-center, open-label pharmacodynamic study to evaluate subretinal delivery of ABBV-RGX-314 produced by either the NAVXpress platform process (Bioreactor, BRX) or the adherent cell culture manufacturing process (Hyperstack®, HS), which was used in the Phase 1/2a trial of ABBV-RGX-314 for nAMD. Sixty participants with previously treated nAMD are assigned to one of two dose levels ($6.4x10^{10}$ GC/eye or $1.3x10^{11}$ GC/eye) with half of the participants receiving BRX and half receiving HS at each dose level (n=15 for each of the four cohorts). ABBV-RGX-314 transgene product concentration in the eye at Month 6 is the primary endpoint. Secondary endpoints include safety and tolerability, change from baseline in best corrected visual acuity (BCVA) and central retinal thickness (CRT), and the need for supplemental anti-VEGF injections post-ABBV-RGX-314 administration.

Results: All cohorts have fully enrolled. As of November 20, 2023, ABBV-RGX-314 was well tolerated in all cohorts. Six serious adverse events (AEs) were reported; none were considered related to ABBV-RGX-314. Common AEs in the study eye through 6 months included post-operative inflammation (30%), post-operative conjunctival hemorrhage (28%), and retinal pigmentary changes (17%). At six months, ABBV-RGX-314 transgene product concentrations in the study eye were similar. These cohorts demonstrated stable-to-improved BCVA and CRT and meaningful reductions in anti-VEGF injection burden, with many injection-free patients (range: 60% to 80%). One year results will be presented for the first time.

Conclusion: ABBV-RGX-314 produced by the NAVXpress platform process has been well-tolerated and demonstrated a similar clinical profile to the adherent cell culture process. Interim results support the dose levels and cGMP commercial-ready material evaluated in the ongoing ATMOSPHERE and ASCENT pivotal trials. This is a preliminary analysis performed by REGENXBIO for an ongoing trial.

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RO-104, a Novel Trispecific Antibody, Significantly Reduces Lesion Area and Vascular Leakage in a Laser-Induced Nonhuman Primate CNV Model

- Harit Bhatt, MD, MBA, FASRS, FACS
- Ramanath Bhandari, MD

Objective: This study assess the safety and efficacy of RO-104, a novel trispecific Fab targeting VEGF-A, VEGF-C and Ang-2, in reducing laser-induced choroidal neovascular lesions in non-human primates for therapeutic benefit in wet AMD

Purpose: Wet age-related macular degeneration (AMD) is a leading cause of blindness and vision loss in the world. Mainstay treatment of wet AMD for the past decade has been anti-VEGF-A monotherapy, yet a significant proportion of patients with wet AMD fail to achieve clinical improvement with VEGF-A monotherapy. RO-104 is a novel, trispecific Fab that targets VEGF-A, VEGF-C and Ang-2, three central pathways that mediate choroidal neovascularization. Previous in-vivo experiments have shown reduction lesion area in laser-induced rat CNV model. This study examines safety and efficacy of RO-104 in laser-induced CMV in non-human primates.

Methods: A laser-induced choroidal neovascularization (LCNV) model in Cynomolgus monkeys was developed and validated as an experimental model of wet AMD. Eight animals received LCNV centered on the macula. Neovascularization and leakiness were measured at day 14 via fluorescein angiography. Treatment was initiated by intravitreal (IVT) injection into both eyes on day 15 with low dose RO-104 (0.27 mg; n=3), high dose RO-104 (1.09 mg; n=3), and PBS vehicle control (n=2). Two weeks post-treatment (day 28), lesions were assessed via fluorescein angiography and blood, aqueous humor and vitreous humor were collected at time points up to 29 days. Pre-and post-treatment fluorescein angiograms were analyzed and lesions were scored on a clinical severity grading system from Grades 1-4 by a masked observer. Grade 1 denoted no hyperfluorescence, Grade 2 denoted hyperfluorescence without leakage, Grade 3 denoted hyperfluorescence in early or mid-transit with late leakage and Grade 4 denoted bright hyperfluorescence in early or mid-transit with lake leakage extending beyond the borders of the laser spot. Mid-phase fluorescein angiogram images were aligned with i2Kretina and ImageJ was used to quantify lesion size before and after treatment.

Results: LCNV and subsequent intravitreal injections were well tolerated in animals. One animal receiving low-dose RO-104 experienced mild intraocular inflammation in both eyes, that self resolved in one eye over the 2 week treatment period. Across both eyes in all animals, there were a total of 6 Grade 1 lesions, 43 Grade 2 lesions, 25 Grade 3 lesions, and 61 Grade 4 lesions. Lesion size prior to treatment did not differ significantly across groups within initially scored Grade 1, 2 or 3 lesions. Vehicle injections over the 2-week treatment period showed moderate increase in Grade 1 (1 to 4) and Grade 2 lesions (8 to 15) with decrease of Grade 3 (5 to 3) and Grade 4 (22 to 14) lesions. Treatment with low-dose RO-104 over 2 weeks resulted in no change in number of Grade 1 lesions (1 to 1), and reduction in Grade 4 (27 to 8)lesions with subsequent increase in Grade 2 (12 to 22) and Grade 3 (5 to 14) lesions. The increase in Grade 2 and 3 lesions are directly attributed to the Grade 4 lesion reductions. Treatment with high-dose RO-104 eliminated all Grade 3 (15 to 0) and Grade 4 lesions (12 to 0) into Grade 1 (4 to 30) and Grade 2 (23 to 24). The increase in Grade 1 and 2 lesions are directly attributed to the reduction in Grade and 4 lesions. Overall, treatment with high-dose RO-104 outperformed other treatments, with Grade 4 lesions having improved ~ 2.5 grades, Grade 3 lesions improved ~1.5 and Grade 2 lesions improved 1 grade. When treated with either dose of RO-104, lesion area of Grade 4 lesions significantly improved about twice that of vehicle.

Conclusion: IVT injection with RO-104 substantially reduced lesion severity, leakage area and lesion volume in a dose-dependent manner, with high-dose of RO-104 showing superior efficacy compared to low-dose and vehicle. Treatment with high-dose RO-104 delivered notable outcomes for severe lesions, completely resolving Grade 3 and 4 lesions into lower grades. Additionally, injections of RO-104 were well-tolerated, with only one case of intraocular inflammation occurring in the low-dose group. It is possible that the adverse event was due injection rather than the actual drug. In conclusion, RO-104 is a promising therapeutic for treatment of wet AMD and these finding support further investigation of RO-104 in clinical trials.

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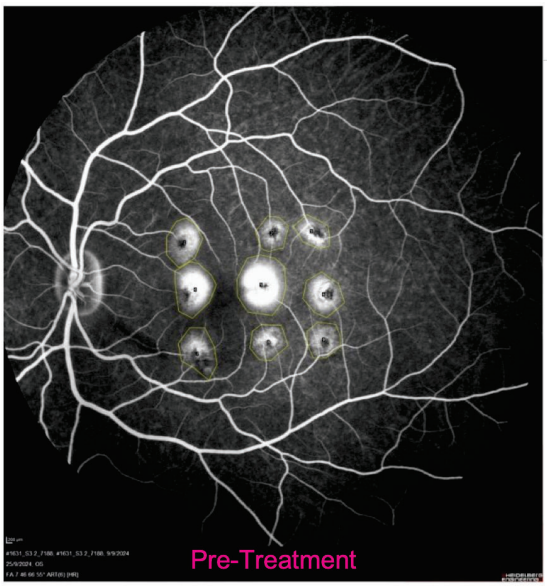
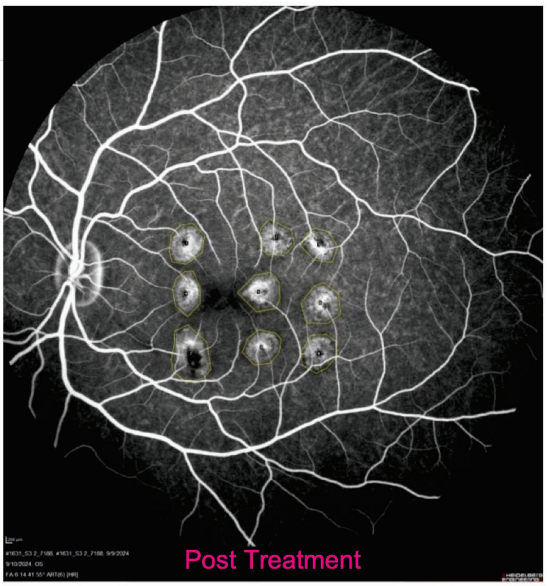
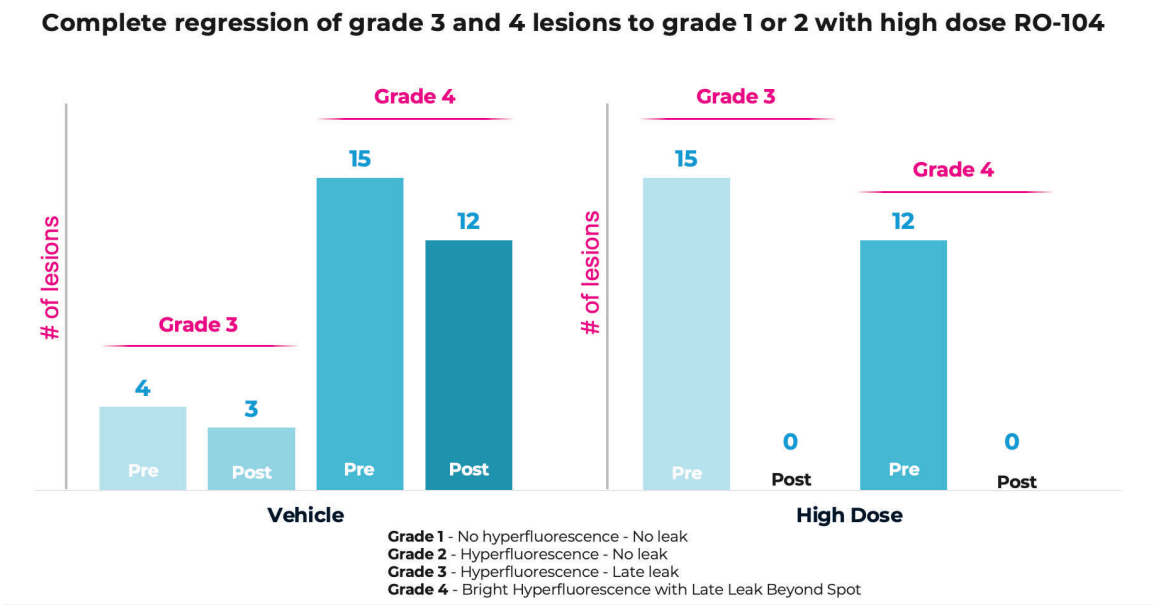




Fluorescein Angiography of lesion response.



Complete regression of grade 3/4 lesions to grade 1/2 with high dose RO-104

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Ixoberogene Soroparvovec (Ixo-vec) Intravitreal Gene Therapy for Neovascular Age-Related Macular Degeneration (nAMD): Results From OPTIC and LUNA Trials

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- MD
- Carl Regillo, MD
- Dante Pieramici, Eduardo
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- Bakall, MD, PhD
- Dina Akasheh, PhD
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- Traci Clemons, PhD
- Adam Turpcu, PhD
- Rabia Ozden, MD
- Star Seyedkazemi, PharmD Arshad
- Khanani, MD, MA, FASRS Charles
- Wykoff, MD, PhD, FASRS

Objective: To evaluate efficacy and safety of Ixoberogene soroparvovec (Ixo-vec) for the treatment of neovascular age-related macular degeneration (nAMD) in patients who required frequent bolus intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF) therapy.
Purpose: Frequent bolus injections and vision decline limit long-term clinical outcomes in patients with nAMD. Ixo-vec is a gene therapy product that is comprised of the AAV.7m8 capsid, derived from *in vivo* directed evolution for enhanced transduction of retinal cells, and provides sustained levels of aflibercept (AFL) expression following a single IVT injection. The 5-year OPTIC trial (2 years plus a 3-year extension) evaluated the long-term safety and durability of Ixo-vec at doses of $6x10^{11}$ vg/eye (6E11) and $2x10^{11}$ vg/eye (2E11). LUNA is a Phase 2, multicenter, randomized, double-masked study, designed to evaluate the safety and efficacy of the low dose from OPTIC (2E11) and a new lower dose of 6x1010 vg/eye (6E10) with enhanced steroid prophylaxis. OPTIC and LUNA were conducted in previously treated patients with nAMD who demonstrated response to anti-VEGF therapy. Here, we present OPTIC 4-year data from the 2E11 dose and LUNA 52-week data from both dose groups.
Methods: In OPTIC (NCT04645212), patients with nAMD and a high anti-VEGF treatment burden received a single IVT injection of Ixo-vec at 2E11 with a short course of steroid prophylaxis (13 days of prednisone or 6 weeks of difluprednate). In LUNA (NCT05536973), patients with nAMD were randomized across two Ixo-vec doses, 6E10 and 2E11, with enhanced corticosteroid prophylactic regimens, including locally administered options of a 22-week regimen of difluprednate drops or IVT dexamethasone followed by difluprednate drops. We report injection burden reduction including injection freedom, best-corrected visual acuity (BCVA), change in central subfield thickness (CST), aqueous AFL levels, and safety and tolerability from these studies, along with LUNA pre-specified patient treatment preference survey.
Results: In OPTIC, 15 patients received Ixo-vec 2E11 with a mean (SD) age of 78.4 (7.4) years and time (SD) since diagnosis of 3.6 (2.5) years. At baseline, patients had received a mean (SD) of 9.9 (1.3) annualized anti-VEGF injections in the year prior to Ixo-vec and had a mean (SD) BCVA and CST of 65.4 (7.4) ETDRS letters and 407.1 (172.5) µm, respectively. Patients experienced an 87% reduction in annualized injection burden, with 47% of patients remaining anti-VEGF injection-free over 4 years. Ixo-vec maintained a mean BCVA change of -2.9 ETDRS letters and mean CST improvement of -117.7µm from baseline through 4 years. Early aqueous AFL levels were associated with sustained long-term protein expression. There was no new onset of inflammation (≥ 1+ anterior chamber [AC]/vitreous [V] cells) after week 28. 100% of patients were inflammation free at 1 year. Except for one patient (who had inflammation following a complex cataract surgery), all remained without inflammation through 4 years. In LUNA, 60 enrolled patients [mean age (SD), 76.6 (7.8) years, time since diagnosis 3.0 (2.9) years] received 10.1 (2.6) annualized anti-VEGF injections in the year prior to receiving Ixo-vec. Baseline mean (SD) BCVA and CST were 72.3 (7.7) ETDRS letters and 350.6 (115.2) µm, respectively. These previously treated patients showed a substantial reduction in treatment burden with 54% (6E10) and 69% (2E11) of patients remaining injection free at week 52. 75% (6E10) and 79% (2E11) needed ≤1 supplemental aflibercept injection. 89% (6E10) and 90% (2E11) needed ≤2 supplemental aflibercept injections. 75% (6E10) and 67% (2E11) of patients with ≤6 injections in the year prior remained injection-free, while 100% (6E10) and 89% (2E11) needed ≤1 supplemental aflibercept. BCVA and CST remained stable with least-squares-mean change of -2.1 (6E10) and -1.8 (2E11) ETDRS letters and -10.2µm (6E10) and -21.9µm (2E11), respectively. Aqueous humor AFL levels were similar to the OPTIC trial. In LUNA, there were no Ixo-vec-related serious adverse events (AEs); all AEs were mild or moderate in severity. Of 34 patients in the locally administered corticosteroid cohorts, none had inflammation at week 52. 93% of patients in the LUNA trial preferred Ixo-vec over their prior anti-VEGF therapy.
Conclusion: In OPTIC and LUNA, Ixo-vec was well tolerated and maintained visual and anatomic endpoints in patients with nAMD. Injection burden was meaningfully reduced in patients who previously needed frequent anti-VEGF treatment. The enhanced prophylactic regimen of difluprednate drops in LUNA was as effective as IVT dexamethasone plus difluprednate and more effective than the 6-week difluprednate course used in OPTIC in minimizing inflammation and was preferred by patients. Based on these results, the ARTEMIS Phase 3 trial has been designed to evaluate the efficacy and safety of a single IVT injection of Ixo-vec at 6E10 vs. on-label aflibercept 2 mg in patients with nAMD.

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Longitudinal Validation of the Performance of an AI-Based Algorithm in a Home OCT Pivotal Study of Age-Related Macular Degeneration

- S. Krishna Mukkamala, MD, FASRS
- Theodore Leng, MD, MS, FASRS
- Ella Leung, MD
- Michael Elman, MD

Objective: To longitudinally validate the clinical utility of an AI-based home OCT retinal hypo-reflective spaces volume trajectories in the management of neovascular age-related macular degeneration.
Purpose: To test the hypothesis that trajectories of the AI-based algorithm allow the reviewing physician to identify clinically relevant trends in the volume of total hypo-reflective spaces (TRO) with high level of accuracy; hence providing additional validation to the value of implementing this new technology in clinical research, drug development and routine retinal care.
Methods: Ad-hoc analysis of TRO trajectories during a 5-week at-home prospective, longitudinal study. 296 eyes of 169 adults aged 55 years or older with a diagnosis of nAMD in at least one eye and best-corrected visual acuity of 20/320 or better were enrolled. The presence of confounding pathologies was not exclusionary. The participants received a home OCT device to their home, self-installed it and performed a tutorial and a calibration session. Participants were instructed to self-image both eyes at home every day for five consecutive weeks. The output of each daily test was automatically uploaded to the cloud. Volume scans consisting of up to 88 B-scans were reconstructed. As a reference dataset, an expert grader reviewed the raw B-scans and classified the eyes as stable or with a change during the study. The AI-based algorithm analyzed the data, calculated TRO and generated trajectories. A dedicated method was used to plot a TRO fit curve for each trajectory while avoiding over or under fit (Figure 1) and used to evaluate the change, i.e. the fit curve amplitude (Signal) and the within-subject measurement variations (Noise). To validate the algorithm performance, the trajectories were scored by the Signal to Noise ratio (SNR). A Receiver Operating Characteristic curve (ROC) of the SNR vs. the reference provided an optimal threshold for identification of TRO change which was compared to a Reference Change Value acceptable in laboratory medicine. A different ROC was plotted for population-based absolute change thresholds and compared to the commonly used value of 10 VU TRO threshold. Main outcome measures were Area Under the Curve, sensitivity, specificity and accuracy at the optimal threshold for the 2 methods.
Results: A total of 8, 242 tests with a mean (SD) of 27.8 (7.0) tests per eye during a total of 9,563 monitoring days, a mean (SD) of 32.3 (6.2) days per eye were performed, to generate 296 trajectories that were analyzed. An expert grader classified 110 (37.2%) trajectories with a change and 186 (62.8%) as stable. The SNR ROC had an AUC of 0.981; optimal threshold of 2.78, sensitivity of 98.2%, specifically of 90.9% and accuracy of 94.5%. The Population-based ROC had AUC of 0.968, optimal threshold of 4 VU, sensitivity of 93.6%, specificity of 90.3% and accuracy of 92.0%. A 10 VU change had sensitivity of 74.5%, specificity of 94.6% and accuracy of 84.6% (Figure 2).
Conclusion: The identification of an optimal SNR with acceptable performance validates NOA based segmentation and its utility in longitudinal clinical use. In the presence of a reactivation or response to treatment, the noise was observed to be insignificant compared to the true change. Nearly all activations and responses are detectable using SNR criterion widely used in clinical applications. The population-based approach showed lower sensitivity. By the quality standards of laboratory medicine, the AI-based segmentation is validated, and the derived trajectories are a reliable tool for identifying clinically relevant changes.

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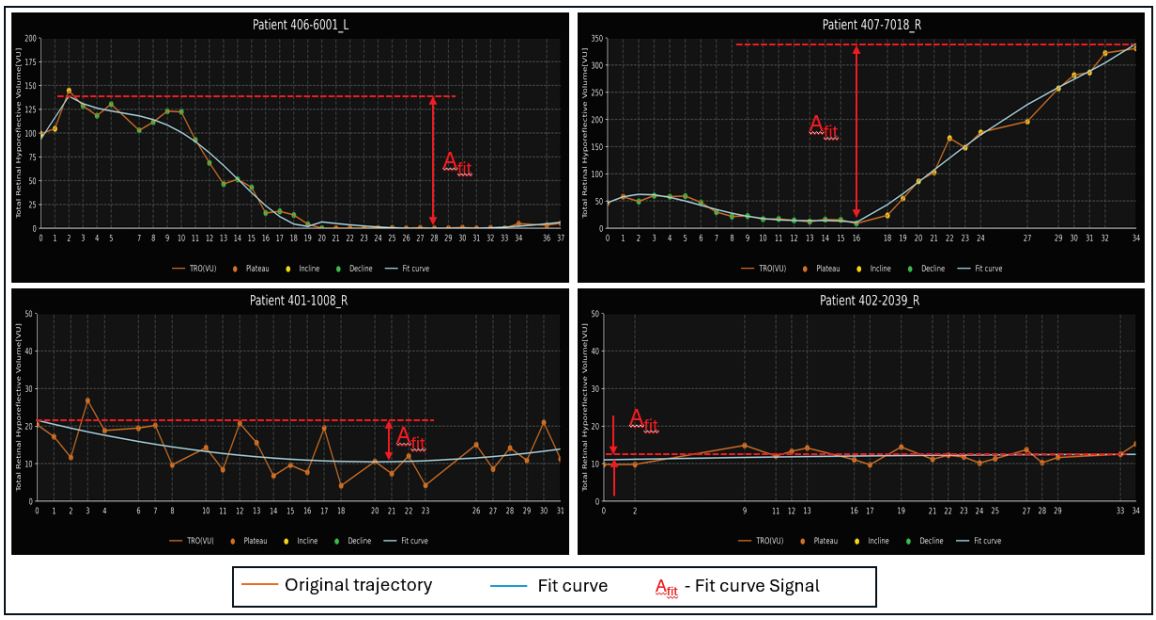
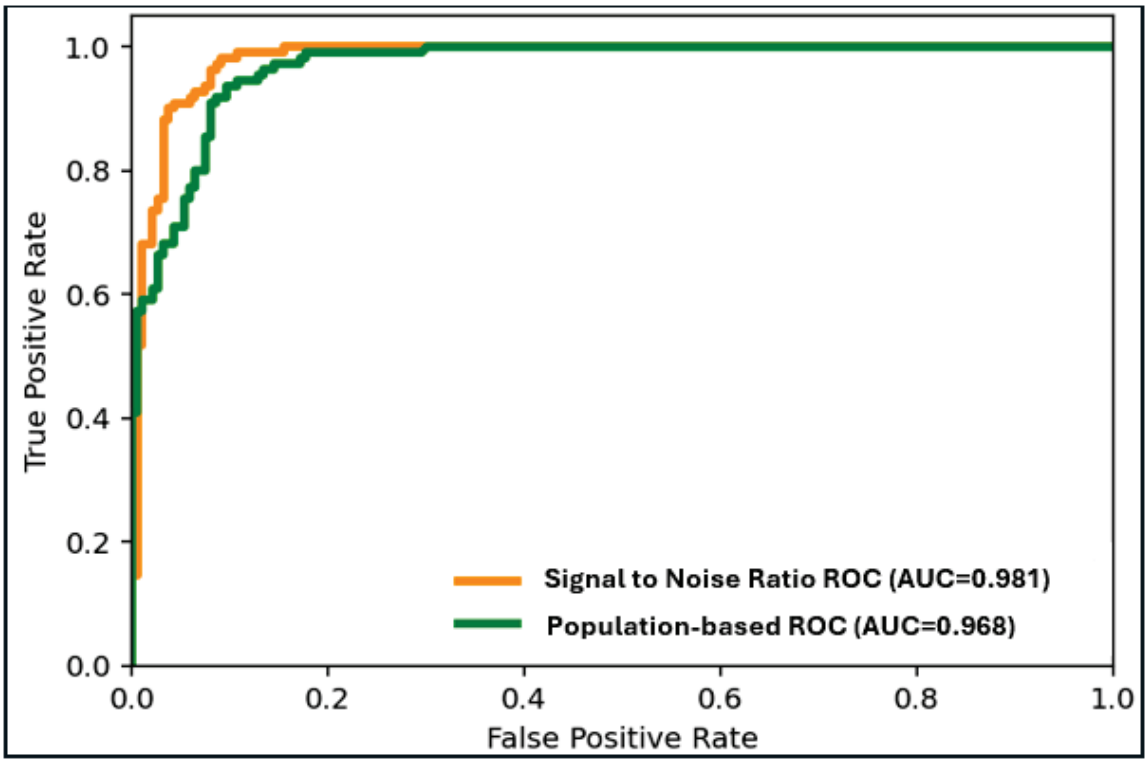


Examples of fit to the original trajectory



ROC of the Signal to Noise Ratio and Population-based methods

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The Effect of Baseline Ellipsoid Zone-Area Loss on Treatment Response of Revakinagene Taroretcel (NT-501) in Macular Telangiectasia Type 2

- Sophie Bakri, MD
- David Lally, MD
- Charles Wykoff, MD, PhD
- Catherine Eagan

Objective: The objective of this post hoc analysis was to examine the effect of smaller baseline ellipsoid zone (EZ) area loss on treatment effect across two phase 3 studies of ciliary neurotrophic factor–producing revakinagene taroretcel (NT-501) in macular telangiectasia type 2 (MacTel).
Purpose: MacTel is a bilateral, progressive, retinal, neurodegenerative disease with no current FDA-approved treatment. The efficacy of NT-501, a first-in-class encapsulated cell therapy that produces ciliary neurotrophic factor, has been evaluated in two phase 3 clinical trials. The treatment effect of NT-501 on study endpoints of EZ area loss, retinal sensitivity, and reading speed in participants was analyzed with respect to baseline characteristics. By exploring the effect of NT-501 on different stages of disease and baseline characteristics, we hope to provide insight into how best to treat patients with MacTel.
Methods: NT-501 was studied in identical phase 3, multicenter, prospective, masked, randomized, sham-controlled trials (NTMT-03-A and NTMT-03-B). Eligible adults had a diagnosis of MacTel in the study eye, an inner segment/outer segment photoreceptor break, an area of EZ loss between 0.16 and 2.00 mm^2, and a best corrected visual acuity (BCVA) score of 54 letters or better (Snellen equivalent of 20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Participants were randomized (1:1) to receive the NT-501 implant or to undergo the sham procedure. Total participants/eyes were 115 (NT-501, N=58; sham, N=57) in NTMT-03-A and 113 (NT-501, N=59; sham, N=54) in NTMT-03-B. The primary endpoint was rate of change in EZ area loss over 24 months; secondary functional endpoints included change in aggregate retinal sensitivity loss via microperimetry and reading speed. In this post hoc analysis, endpoints were evaluated from baseline through Month 24 in subgroups stratified by baseline EZ area loss (stratification based on mean baseline EZ area loss of 0.5 mm^2, <0.5 mm^2, or ≥0.5 mm^2).
Results: Treatment with NT-501 led to significant reductions in the rate of EZ area loss in both NTMT-03-A and NTMT-03-B (55% [p<0.0001)] and 31% [p=0.019], respectively) compared with sham, meeting the primary endpoint of the study. A significant reduction in aggregate retinal sensitivity loss was observed in NTMT-03-A but not in NTMT-03-B. An overall reduction in reading speed loss was seen with NT-501 treatment in both studies, with a greater difference in NTMT-03-B. To explore differences between the two studies that may explain the disparate results, baseline characteristic subgroups were explored. A greater response to treatment was observed in the subgroups with smaller lesion size (<0.5 mm^2; NTMT-03-A: n=41 NT-501, n=40 sham; NTMT-03-B: n=31 NT-501, n=33 sham). Notably, a higher proportion of participants who received NT-501 in NTMT-03-A had smaller baseline lesion sizes compared with the similar group in NTMT-03-B (71% vs. 53%; p=0.04). In the subgroup of participants with smaller baseline lesion size, relative to sham, participants receiving NT-501 had a 55% (p<0.0001) and 62% reduction (p<0.0001) in disease progression (rate of EZ area loss), 46% (p=0.0431) and 53% (p=0.0430) reduction in aggregate retinal sensitivity loss, and 96% (p=0.2046) and 56% (p=0.2841) reduction in reading speed loss (NTMT-03-A and NTMT-03-B, respectively).
Conclusion: In the phase 3 trials for MacTel, participants demonstrated a consistent anatomic and functional benefit when treated with NT-501 at an earlier stage of the disease.

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