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Pooled Functionality Data of Revakinagene Taroretcel in Patients With Macular Telangiectasia Type 2

W. Lloyd Clark, MD,¹ Muna Bitar, PharmD,² Debora C. Manning, MPH,³ Thomas Aaberg, Jr, MD,^{2,4}
and the MacTel Study Investigators

¹Assistant Clinical Professor of Ophthalmology, University of South Carolina School of Medicine, Palmetto Retina Center, Retina Consultants of America, Columbia, SC; ²Neurotech Pharmaceuticals, Inc., Cumberland, RI; ³Veristat, Southborough, MA;

⁴Foundation for Vision Research, Grand Rapids, MI

Financial Disclosures

- W. Lloyd Clark has the following disclosures:
 - Consultant (Amgen, Bayer, Cardinal Health, Genentech/Roche, Neurotech, Ocular Therapeutix, Regeneron); Grant Support (Bayer, Eyepoint, Genentech/Roche, Kodiak, Notal Vision, Ocular Therapeutix, Oculis, Outlook, Regeneron); Speakers Bureau (Genentech/Roche, Regeneron)
- These trials were funded by Neurotech Pharmaceuticals
- This study includes research conducted on human subjects. Institutional Review Board approval was obtained prior to study initiation

Take Home Points

- NT-501 conferred both **anatomic and visual function benefits** across three randomized, sham-controlled studies
- Relative to sham, NT-501 demonstrated a:
 - preservation of anatomy
 - 36% reduction in photoreceptor loss
 - preservation of function
 - 68% reduction in reading speed loss
 - 35% reduction in retinal sensitivity loss^a

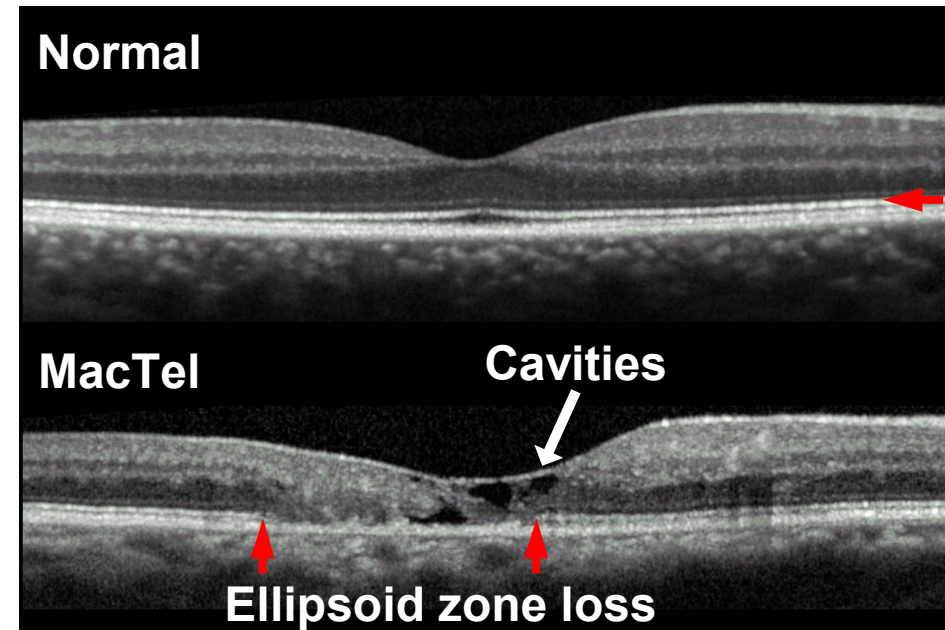
NT-501, revakinagene taroretcel.

^aResults per study in the respective per-protocol populations were weighted by the proportion of treated eyes with non-missing data in each study and combined descriptively.

Macular Telangiectasia Type 2 (MacTel) Is a Neurodegenerative Disease That Leads to Vision Loss^{1,2}

- MacTel is a bilateral, progressive retinal neurodegenerative disease
 - Leads to vision loss and functional impairment^{1,2}
 - Associated with abnormalities in Müller glia, retinal pigment epithelium, and photoreceptors in the central retina^{3,4}
 - Characterized by progressive loss of the ellipsoid zone on SD-OCT³

SD-OCT



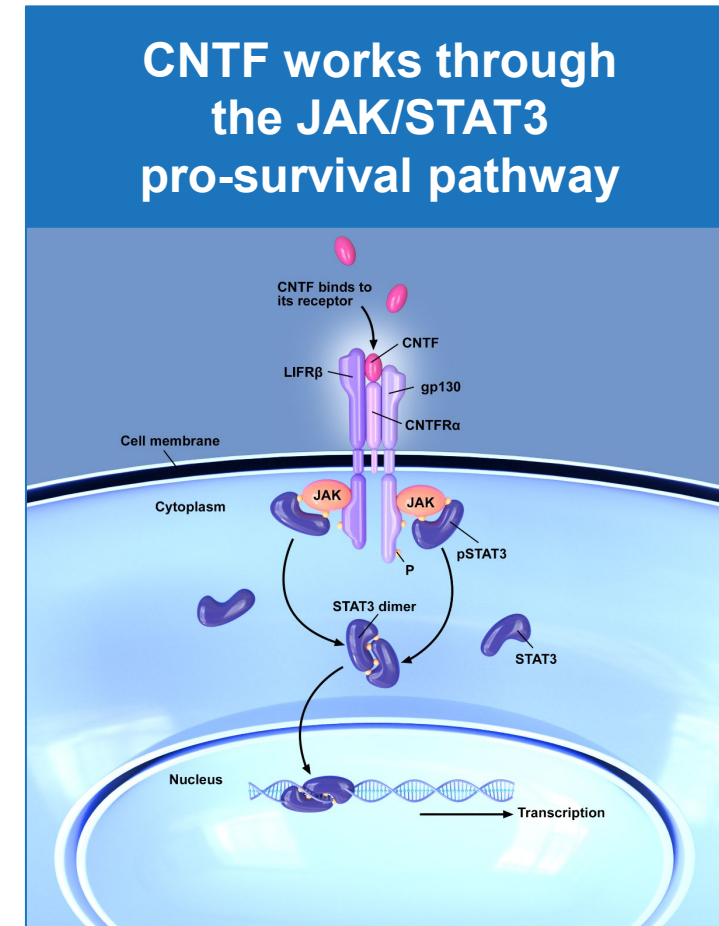
MacTel, macular telangiectasia; SD-OCT, spectral-domain optical coherence tomography.

1. Charbel Issa P, et al. *Prog Retin Eye Res*. 2013;34:49-77. 2. Heeren TFC, et al. *Ophthalmology*. 2020;127:1539-48. 3. Heeren TFC, et al. *Retina*. 2018;38(suppl 1):S20-S26.

4. Kedariseti KC, et al. *Clin Ophthalmol*. 2022;16:3297-309.

CNTF Is a Potent Neuroprotectant¹⁻³

- In response to injury, Müller glial cells release the neuroprotective factor CNTF¹
- **CNTF protects and preserves photoreceptors²⁻⁴**
- In preclinical models of retinal degeneration, photoreceptors can be rescued with intravitreal injection of CNTF^{2,4}

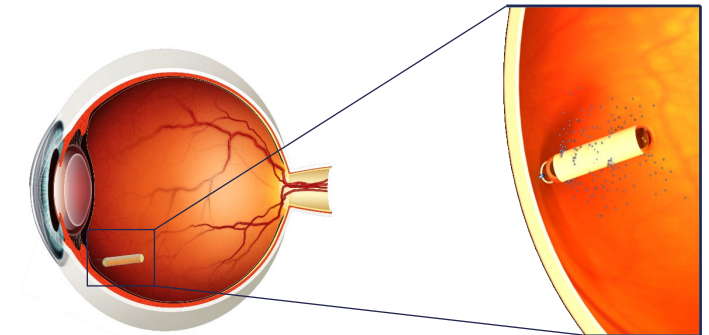
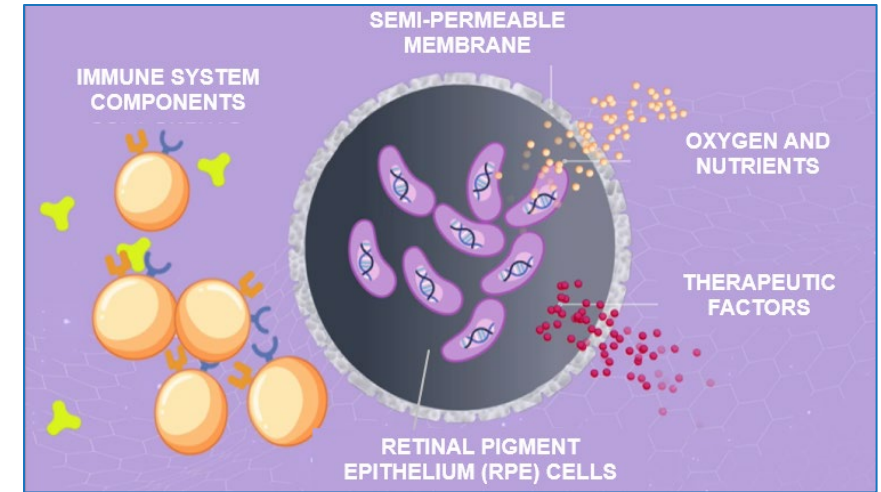


CNTF, ciliary neurotrophic factor; gp130, glycoprotein 130; JAK/STAT, Janus kinase/signal transducer and activator of transcription; LIFRβ, leukemia inhibitory factor β; P, phosphorous; STAT3, signal transducer and activator of transcription 3.

1. Bringmann A, et al. *Prog Retin Eye Res.* 2009;28:423-45. 2. Shen W, et al. *J Neurosci.* 2012;32(45):15715-27. 3. Sleeman MW, et al. *Pharm Acta Helv.* 2000;74(2-3):265-72. 4. Tao W, et al. *Invest Ophthalmol Vis Sci.* 2002;43(10):3292-8.

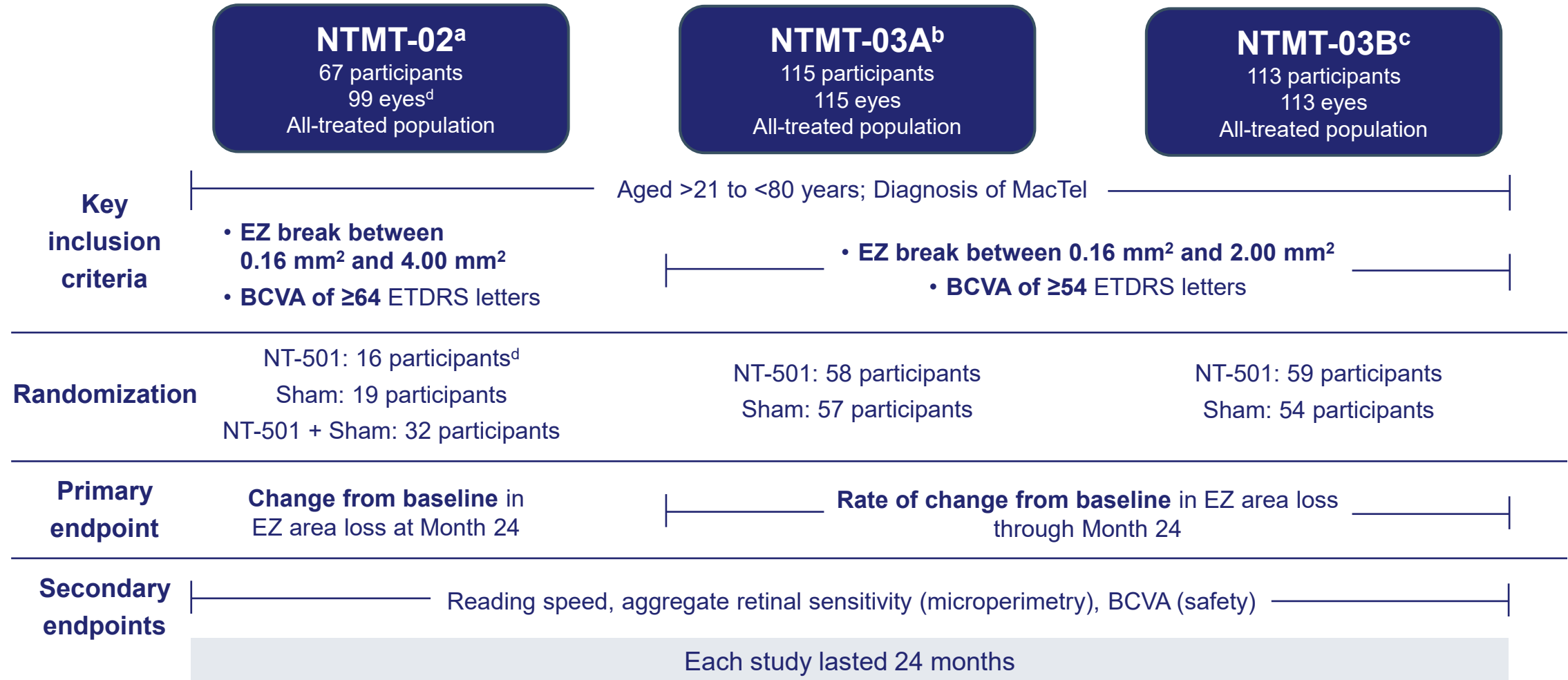
Encapsulated Cell Therapy Is Designed to Deliver Sustained Levels of CNTF

- NT-501 is a first-in-class encapsulated cell therapy¹⁻³
 - Houses NTC-201-6A cells¹
 - Allogenic retinal pigment epithelial cells with a unique expression vector for CNTF release¹
 - Surgically implanted into the vitreous cavity² and stably anchored to the sclera⁴
 - Developed to produce long-term sustained levels of CNTF²
 - The FDA has set a PDUFA date of March 18, 2025



CNTF, ciliary neurotrophic factor; FDA, Food and Drug Administration; NT-501, revakinagene taroretsel; PDUFA, Prescription Drug User Fee Act
1. Plakkot S, et al. Poster presented at: Association for Research in Vision and Ophthalmology; April 23-27, 2023; New Orleans, LA. 2. Kauper K, et al. Poster presented at: Association for Research in Vision and Ophthalmology; April 23-27, 2023; New Orleans, LA. 3. Kauper K, et al. *Invest Ophthalmol Vis Sci*. 2023;64(8):3680. 4. Chew E, et al. *Ophthalmology*. 2019;126(4):540-9.

NT-501 Has Been Studied Across 3 Randomized, Sham-controlled Clinical Trials



BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; MacTel, macular telangiectasia type 2; NT-501, revakinagene tarorectel.

^aNCT01949324. ^bNCT03316300. ^cNCT03319849. ^dParticipants with one eligible eye (35 participants) received NT-501 (16 eyes) or sham (19 eyes). In participants with two eligible eyes (32 participants), one eye received NT-501 (32 eyes) and one eye received sham procedure (32 eyes). If both eyes were eligible, right eye was randomized 1:1 to sham or NT-501 and left eye received other surgery.

Rationale for a Pooled Functionality Analysis

- Rare disease
- Inherent variability of outcome measures¹⁻³
- Similar populations and study designs
- Increase the sample size

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ARVO Annual Meeting Abstract | June 2024

Reducing Test-Retest Variability of the E-ETDRS Test with Hierarchical Bayesian Modeling

Yukai Zhao, Luis A. Lesmes, Michael Dorri, Zhong-Yi

Investigative Ophthalmology & Visual Science June

3854

Abstract

Purpose: Visual acuity (VA) is the primary outcome in ophthalmic trials. However, the high test-retest variability of VA signals, we developed a hierarchical Bayesian model to reduce variability of E-ETDRS testing (the gold standard ETDRS chart).

Methods: We initiated post-hoc analysis of the generative model of trial-by-trial performance. The model comprises two parameters: the true VA and the test-retest variability. Size required to achieve a specific performance (e.g., 1%) is modeled. We developed two distinct procedures were developed to test (1) A Bayesian Inference Procedure (BIP) and (2) A Hierarchical Bayesian Procedure (HBM). The HBM model incorporates hierarchical Bayesian model (HBM) that parameters and hyperparameters from 2021a), and (3) A Hierarchical Bayesian procedure computes the joint distribution of the VA and test-retest variability. The HBM model was applied to a VA dataset obtained from each of 4 Bangertier foil conditions with We assessed TRV1.96 test-retest difference derived from the repeated E-ETDRS test.

Results: Figure 2 displays the Bland-Altman plot comparing the BIP and HBM results. The BIP for E-ETDRS, 0.19 for BIP, 0.14 for HBM. TRV for BIP is comparable to that of E-ETDRS by 22% and 30%, respectively.

Conclusions: By integrating information from the E-ETDRS tests, integrating information from the HBM exhibited the greatest test-retest procedures can be employed.

Clinical and Epidemiologic Research

Test-Retest Variability of Reading Performance Metrics Using MNREAD in Patients with Age-Related Macular Degeneration

Praveen J. Patel,¹ Fred K. Chen,^{1,2} Lyndon D.

Purpose: To determine the test-retest variability of reading ability using the MNREAD charts in patients with stable age-related macular degeneration (AMD).

Methods: In this prospective study, reading ability was measured at two visits in 124 nonretreated eyes of 124 patients with AMD, who were enrolled in an ongoing clinical trial using standardized MNREAD protocol. Only patients with stable AMD who could perform the reading test at 40 cm at both visits were included in the analysis. Different scoring rules were applied to calculate critical print size and maximum reading speed.

Results: Data from the 50 patients with a mean (SD) age of 71 (7.6) years who met the study criteria were analyzed as a mean (SD) interval of 43 (6) days between measurements. The 95% coefficient of repeatability (CR) was 0.30 logMAR for reading acuity. The CR for critical print size and maximum reading speed varied depending on the analysis method applied.

Conclusions: This is a report of estimates of the interession test-retest variability of reading performance metrics in patients with stable AMD. The results are helpful both in defining end points in clinical trials for AMD and in distinguishing clinical change from measurement variability in clinical practice. *Invest Ophthalmol Vis Sci.* 2011;52:3854-3859. DOI: 10.1167/jov.106601

Visual acuity is the most widely used measure of macula function in clinical trials and clinical practice. However, reading ability is an important component of vision function. Reading difficulty diminishes quality of life,^{1,2} and improvement in reading performance is one of the main objectives for elderly low-vision patients.³ The MNREAD charts, developed at the Minnesota Laboratory for Low-Vision Research, are a commonly used test in clinical trials and clinical practice to assess

Alibhai et al. *Int J Retina Vitreous* (2020) 6:16
<https://doi.org/10.1186/s40942-020-00217-0>

International Journal of Retina and Vitreous

ORIGINAL ARTICLE

Open Access

Test-retest variability of microperimetry in geographic atrophy

A. Yasin Alibhai^{1†}, Nihal Mehta^{1†}, Sheila Hickson-Curran², Carlos Moreira-Neto³, Emily S. Levine⁴, Elias Reichel¹, Jay S. Duker¹ and Nadia K. Waheed^{2*}

Abstract

Purpose: Microperimetry (MP) allows for measurement of retinal sensitivity at precise locations and is now commonly employed as a clinical trial endpoint. Test-retest reliability is important when evaluating treatment effects in patients with geographic atrophy (GA). This study aimed to determine the test-retest variability of MP in patients with moderate to severe GA using the MAIA MP device.

Methods: In this prospective study, patients with a confirmed diagnosis of foveal-involving GA were enrolled. Participants performed three MP assessments of a selected eye over two visits with the Macular Integrity Assessment (MAIA) 2 instrument (Centervue, Padova, Italy) utilizing a wide 30° grid, consisting of 93 stimuli (Goldmann III) using a 4-2 representation strategy, encompassing the entire area of GA and beyond. Mean retinal sensitivity (MS) was expressed as an average threshold value (dB) for the entire field tested. Coefficients of Repeatability at a 95% level (CoR₉₅) were calculated for Point Wise Sensitivity (PWS). Fixation stability (FS) was assessed by evaluating the area of an elliptical representation encompassing 95% of the cloud of fixation points (CFP) dataset generated by the MAIA MP, known as the bivariate contour ellipse area (BCEA).

Results: A total of 8 subjects were enrolled (21 tests), with six subjects completing 3 MP assessments. BCEA in these patients ranged from 20/100 to 20/800. The mean area of GA was 18.7 ± 12.3 mm². The average time to complete one MP assessment was 13 min 9 s and mean BCEA@95% was 38.5 ± 19.3°. The MS was 14.3 ± 4.5 dB. No significant increase in MS was noted between testing pairs 1&2 and 2&3. The preferred retinal locus was maintained in the same quadrant on successive tests. The mean CoR₉₅ for PWS were similar for testing pairs 1&2 (± 3.50 dB) and 2&3 (± 3.40).

Conclusion: Microperimetry using a wide grid can be reliably performed in a reasonable amount of time in patients with moderate and severe vision loss secondary to GA. There was no learning effect seen between sequential assessments when analyzing MS or PWS. A change of approximately 4 dB in PWS provides a threshold for considering a true change in this patient cohort.

Introduction

Microperimetry (MP) is a several-decades old technology designed to test retinal sensitivity at different points in the macula. First developed in the 1980s, MP was initially deployed as part of a scanning laser ophthalmoscope system. In its early forms, MP systems were relatively difficult to use. In the last two decades, however, there has been a resurgence in development of new microperimetry systems, beginning with the Nidek MP-1 and continuing more recently with the Nidek MP-3 and Macular Integrity Assessment (MAIA) 2 systems, which are more user friendly with the addition of features such as eye tracking.

With newer improvements, microperimetry (MP) has gained more widespread adoption as a means of

*Correspondence: nwaheed@uflmedicalcenter.org

[†]A. Yasin Alibhai and Nihal Mehta are co-first authors

¹Department of Ophthalmology, Tufts Medical Center, 800 Washington Street, Box 450, Boston, MA 02111, USA

Full list of author information is available at the end of the article

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1. Alibhai AY, et al. *Int J Retina Vitreous*. 2020 Apr 30;6:16. 2. Patel PJ, et al. *Invest Ophthalmol Vis Sci*. 2011 Jun 1;52(6):3854-9. 3. Zhao Y, et al. Poster presented at: Association for Research in Vision and Ophthalmology; May 5-9, 2024. Seattle, WA.

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Changes From Baseline in EZ Area Loss, Reading Speed, Retinal Sensitivity, and BCVA Were Assessed

Assessments

- Change from baseline assessments in the all-treated population in the Phase 3 and Phase 2 studies:
 - Anatomical:
 - Area of photoreceptor (ie, EZ area) loss (primary endpoint)
 - Functional:
 - Monocular reading speed
 - Aggregate retinal sensitivity (microperimetry)
 - Safety:
 - BCVA

Baseline Demographic Characteristics, by Participant^a

	Phase 2			Phase 3 (Study A)		Phase 3 (Study B)	
By participant	NT-501 (n=16)	Sham (n=19)	NT-501 + Sham (n=32)	NT-501 (n=58)	Sham (n=57)	NT-501 (n=59)	Sham (n=54)
Female , n (%)	9 (56)	11 (58)	21 (66)	39 (67)	40 (70)	46 (78)	36 (67)
Mean age , years (SD)	60.1 (10.7)	59.4 (7.6)	63.4 (8.4)	61.1 (8.0)	60.2 (8.4)	58.5 (7.6)	58.7 (8.9)
Race , n (%)							
White	12 (75)	16 (84)	30 (94)	50 (86)	48 (84)	55 (93)	47 (87)
Asian	0	1 (5)	0	2 (3)	3 (5)	3 (5)	1 (2)
Black or African American	0	0	1 (3)	1 (2)	2 (4)	0	0
American Indian or Alaska Native	0	0	0	0	1 (2)	0	0
Other	4 (25)	2 (11)	1 (3)	5 (9)	3 (5)	1 (2)	6 (11)
Ethnicity , n (%)							
Hispanic or Latino	1 (6)	0	1 (3)	1 (2)	5 (9)	4 (7)	4 (7)

Baseline demographic characteristics were well balanced across studies and treatment arms

NT-501, revakinagene tarorectel; SD, standard deviation.

^aResults reported for the all-treated population.

Baseline Ocular Characteristics, by Eye^a

By eye	Phase 2		Phase 3 (Study A)		Phase 3 (Study B)	
	NT-501 (n=48)	Sham (n=51)	NT-501 (n=58)	Sham (n=57)	NT-501 (n=59)	Sham (n=54)
EZ area loss (mm ²), n	48	51	58	57	59	54
Mean (SD)	0.70 (0.42)	0.77 (0.55)	0.51 (0.48)	0.49 (0.36)	0.52 (0.31)	0.48 (0.29)
EZ area category , n (%)						
<0.5 mm ²	18 (37.5)	20 (39.2)	41 (70.7)	40 (70.2)	31 (52.5)	33 (61.1)
≥0.5 mm ²	30 (62.5)	31 (60.8)	17 (29.3)	17 (29.8)	28 (47.5)	21 (38.9)
Mean BCVA , ETDRS letter (SD)	77.0 (5.6)	76.2 (6.9)	70.8 (9.11)	73.3 (8.64)	74.4 (7.76)	73.6 (9.23)
Snellen equivalent	20/32	20/32	20/40	20/40	20/32	20/32
Reading speed (wpm), n	47	49	57	56	59	53
Mean (SD)	94.29 (46.13)	107.26 (43.17)	92.09 (43.72)	96.01 (54.01)	96.49 (47.31)	94.09 (42.81)
Retinal sensitivity^b , n	40	45	53	54	52	49
Mean (SD)	89.15 (76.15)	107.96 (106.77)	62.14 (77.58)	59.02 (62.63)	57.92 (56.94)	50.48 (58.36)

Participants in the Phase 2 trial had greater baseline EZ area loss compared with the Phase 3 studies

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; NT-501, revakinagene tarorectel; SD, standard deviation; wpm, words per minute.

^aResults reported for the all-treated population, unless otherwise noted. Not available in full pool. ^bResults reported for the per-protocol population.

Baseline Demographic and Ocular Characteristics in Pooled Sample^a

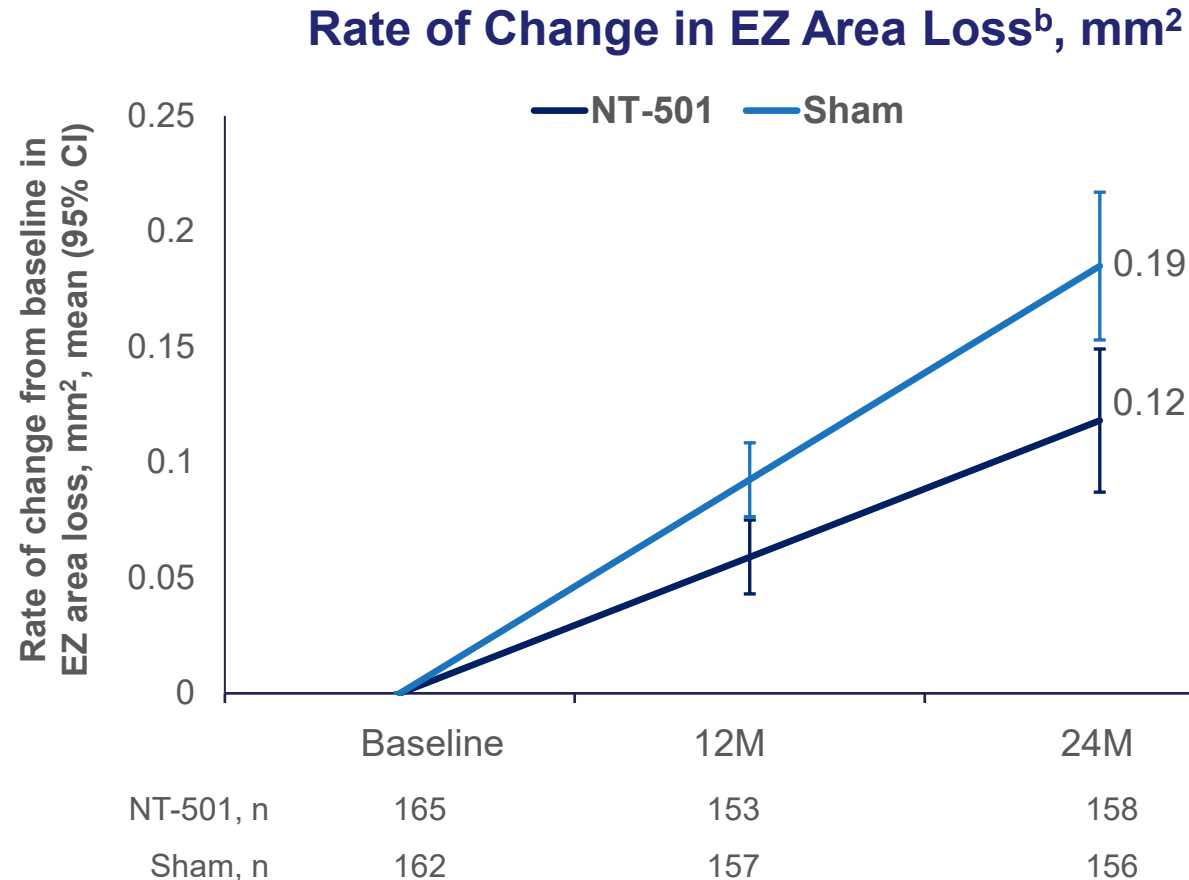
	Phase 2 and Phase 3 Pool ^b	
	NT-501 (n=165)	Sham (n=162)
Demographic characteristics (by participant)		
Female , n (%)	115 (69.7)	108 (66.7)
Mean age , years (SD)	60.5 (8.4)	60.3 (8.6)
Race , n (%)		
White	147 (89)	141 (87)
Asian	5 (3)	5 (3)
Black or African American	2 (1)	3 (2)
American Indian or Alaska Native	0	1 (1)
Other	11 (7)	12 (7)
Ethnicity , n (%)		
Hispanic or Latino	7 (4)	10 (6)
Ocular characteristics (by eye)		
EZ area loss (mm ²), n	165	162
Mean (SD)	0.57 (0.41)	0.57 (0.43)
EZ area category , n (%)		
<0.5 mm ²	90 (54.5)	93 (57.4)
≥0.5 mm ²	75 (45.5)	69 (42.6)
Mean BCVA , ETDRS letter (SD)	73.8 (8.2)	74.2 (8.5)
Snellen equivalent	20/40	20/32
Reading speed (wpm), n	163	158
Mean (SD)	94.32 (45.50)	98.86 (47.24)
Retinal sensitivity^c , n		
Mean (SD)	-	-

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; NT-501, revakinagene tarorectel; SD, standard deviation; wpm, words per minute.

^aResults reported for the all-treated population, unless otherwise noted. Not available in full pool. ^bPer the NTMT-02 study design, participants with two eligible study eyes received NT-501 in one eye and sham in the other eye. These 32 participants are included in both columns for the pooled summary. ^cResults reported for the per-protocol population.

NT-501 Demonstrated Greater Preservation of EZ Area Over 2 Years Compared With Sham in All Treated Participants^a

- A 19.3% reduction in photoreceptor loss with NT-501 compared with sham in Phase 2
- A 54.8% reduction in photoreceptor loss with NT-501 compared with sham in Phase 3, Study A
- A 30.6% reduction in photoreceptor loss with NT-501 compared with sham in Phase 3, Study B



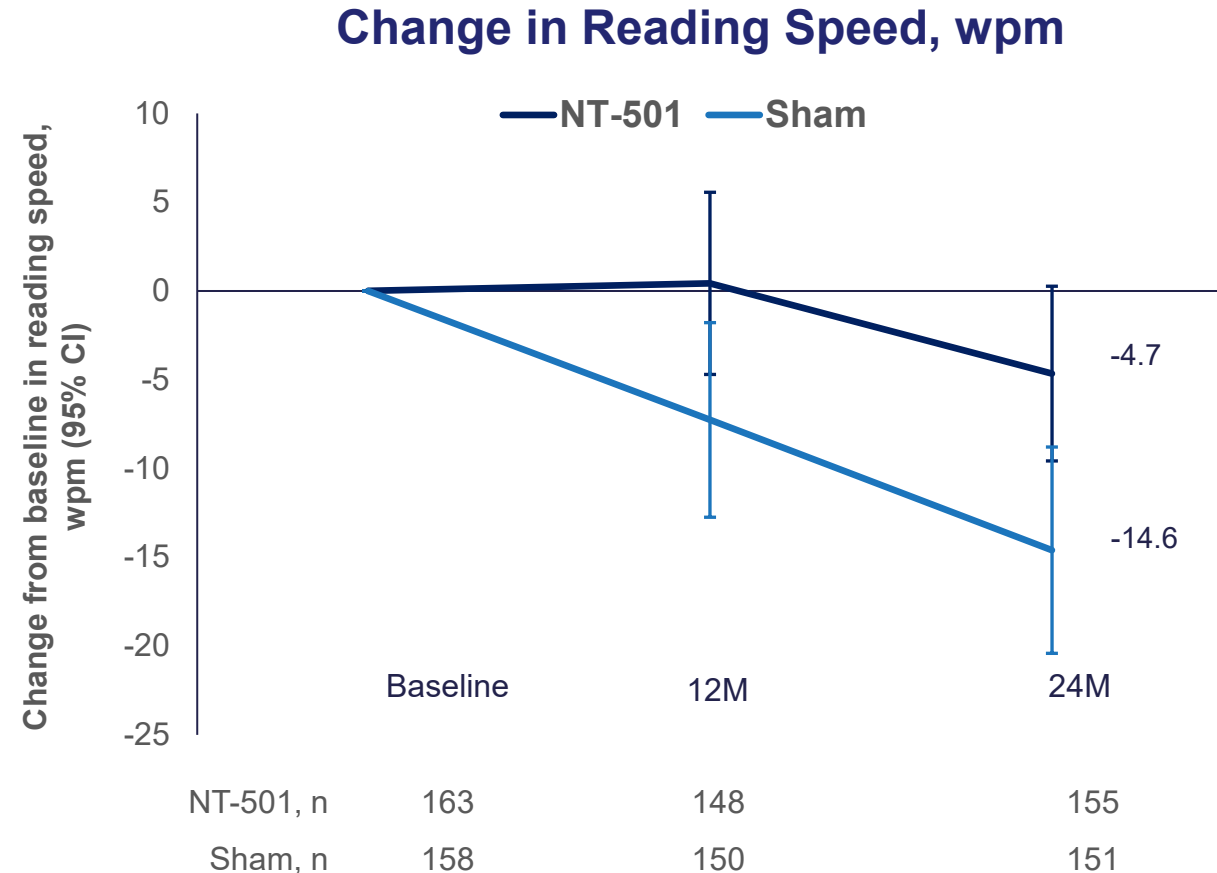
36.2%
Reduction in
Photoreceptor
Loss
(p=0.003)

CI, confidence interval; EZ, ellipsoid zone; M, month; NT-501, revakinagene tarorectel.

^aPer the NTMT-02 study design, participants with two eligible study eyes received NT-501 in one eye and sham in the other eye. These 32 participants are included in both groups for the pooled analysis, by study eye. ^bRate of EZ change, difference, and CIs from a repeated measures model. The outcome variable is EZ area assessed longitudinally at baseline, Months 12, 16 (Phase 3 only), 18 (Phase 2 only), 20 (Phase 3 only), and 24. At baseline, EZ area is calculated as the mean area across two independent readers. The model includes treatment group, time (continuous), treatment*time interaction, and participant-specific random intercepts. The difference between treatment groups in rate of EZ change is estimated at Month 12 and Month 24 based on the treatment*time interaction term.

NT-501 Preserved Reading Speed Over 2 Years Compared With Sham in All Treated Participants^a

- A 90.7% reduction in reading speed loss with NT-501 compared with sham in Phase 2
- A 49.3% reduction in reading speed loss with NT-501 compared with sham in Phase 3, Study A
- A 69.1% reduction in reading speed loss with NT-501 compared with sham in Phase 3, Study B

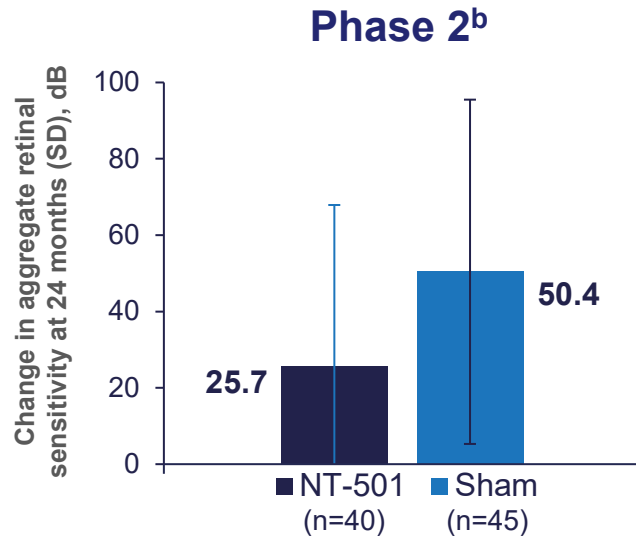


68.1%
Reduction in
Reading
Speed Loss
($p=0.0104$)

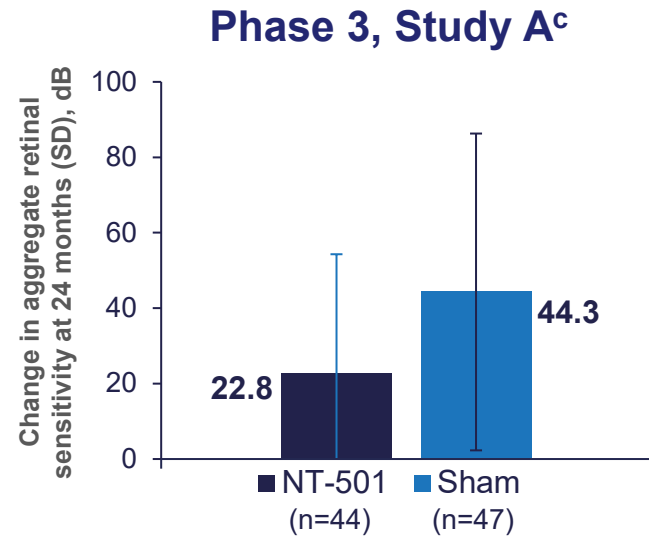
CI, confidence interval; M, month; NT-501, revakinagene tarorectel; SD, standard deviation; wpm, words per minute.

^aPer the NTMT-02 study design, participants with two eligible study eyes received NT-501 in one eye and sham in the other eye. These 32 participants are included in both groups for the pooled analysis, by study eye.

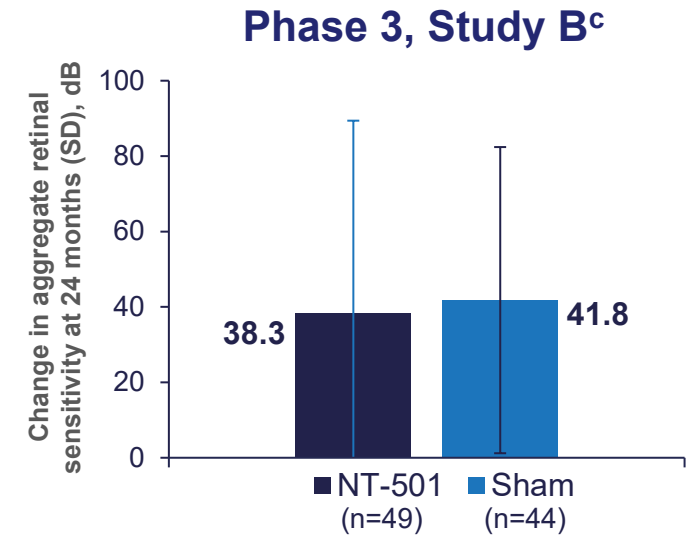
NT-501 Preserved Aggregate Retinal Sensitivity (Microperimetry) Over 2 Years Compared With Sham^a



A **49.0%** reduction in aggregate retinal sensitivity loss with NT-501 compared with sham in Phase 2



A **48.5%** reduction in aggregate retinal sensitivity loss with NT-501 compared with sham in Phase 3, Study A



An **8.4%** reduction in aggregate retinal sensitivity loss with NT-501 compared with sham in Phase 3, Study B

34.8% Reduction in Aggregate Retinal Sensitivity Loss Across the 3 Studies^d

dB, decibel; MAIA, Macular Integrity Assessment; NT-501, revakinagene tarorectel; SD, standard deviation.

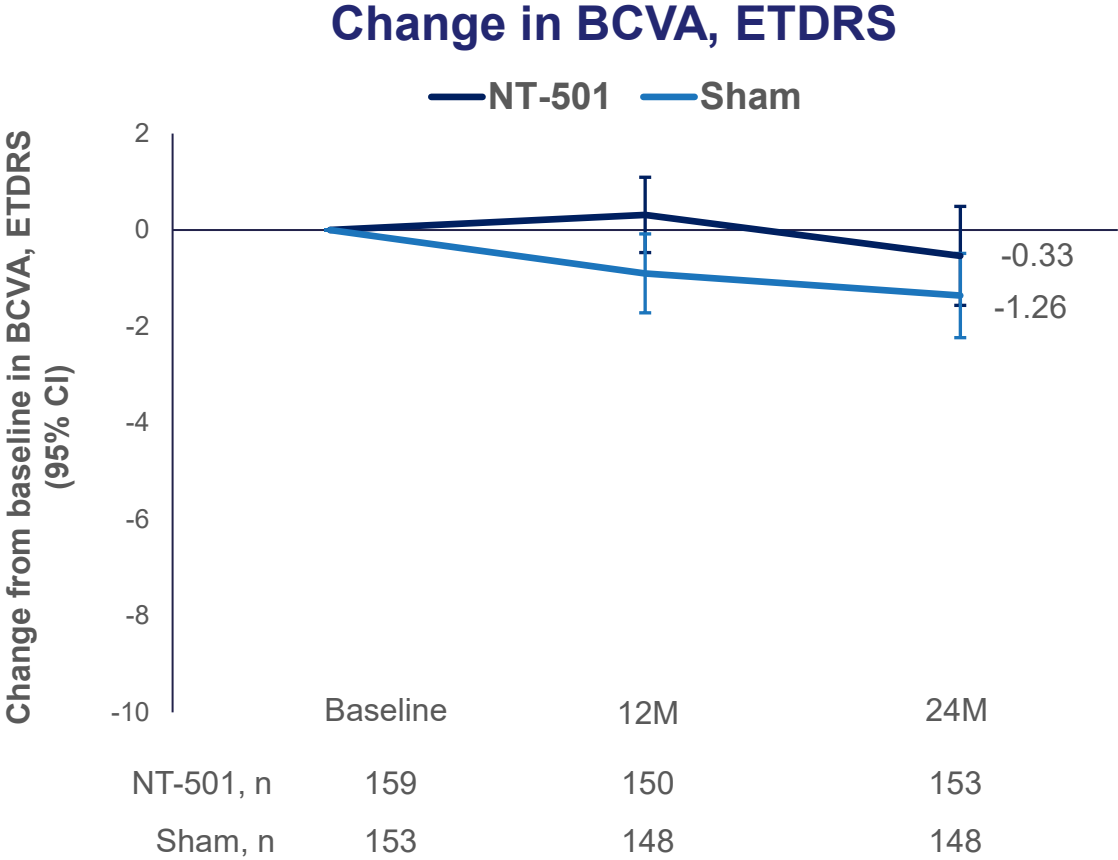
^aRetinal sensitivity was measured via MAIA microperimetry. ^bIn the Phase 2 study, retinal sensitivity is reported for the per-protocol population, which included all treated subjects who had no major protocol infractions (defined prior to unmasking of the study). Per the NTMT-02 study design, participants with two eligible study eyes received NT-501 in one eye and sham in the other eye. These 32 participants are included in both groups for the pooled analysis by study eye. ^cIn the Phase 3 studies, the retinal sensitivity per-protocol population is reported, including all treated subjects who had a baseline and Month 24 microperimetry collected according to study protocol. ^dResults per study in the respective per-protocol populations were weighted by the proportion of treated eyes with non-missing data in each study and combined descriptively.

BCVA Remained Stable for NT-501 and Sham Treatment Arms

Mean Change in BCVA, (SD) ^a		
Phase 2	NT-501	Sham
Baseline	77.0 (5.61)	76.2 (6.85)
12M	-0.9 (4.87)	-1.6 (3.81)
24M	-1.9 (5.85)	-2.0 (4.28)

Mean Change in BCVA, (SD)		
Phase 3, Study A	NT-501	Sham
Baseline	70.8 (9.11)	73.3 (8.64)
12M	1.0 (4.68)	-0.3 (5.36)
24M	0.2 (7.55)	-0.6 (6.30)

Mean Change in BCVA, (SD)		
Phase 3, Study B	NT-501	Sham
Baseline	74.4 (7.76)	73.6 (9.23)
12M	0.6 (5.12)	-0.9 (5.81)
24M	-0.3 (6.01)	-1.7 (4.99)



BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; NT-501, revakinagene tarorectel.
^aPer the NTMT-02 study design, participants with two eligible study eyes received NT-501 in one eye and sham in the other eye. These 32 participants are included in both groups by study eye.

Take Home Points

- NT-501 conferred both **anatomic and visual function benefits** across three randomized, sham-controlled studies
- Relative to sham, NT-501 demonstrated a:
 - preservation of anatomy
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 - 35% reduction in retinal sensitivity loss^a

NT-501, revakinagene taroretcel

^aResults per study in the respective per-protocol populations were weighted by the proportion of treated eyes with non-missing data in each study and combined descriptively.

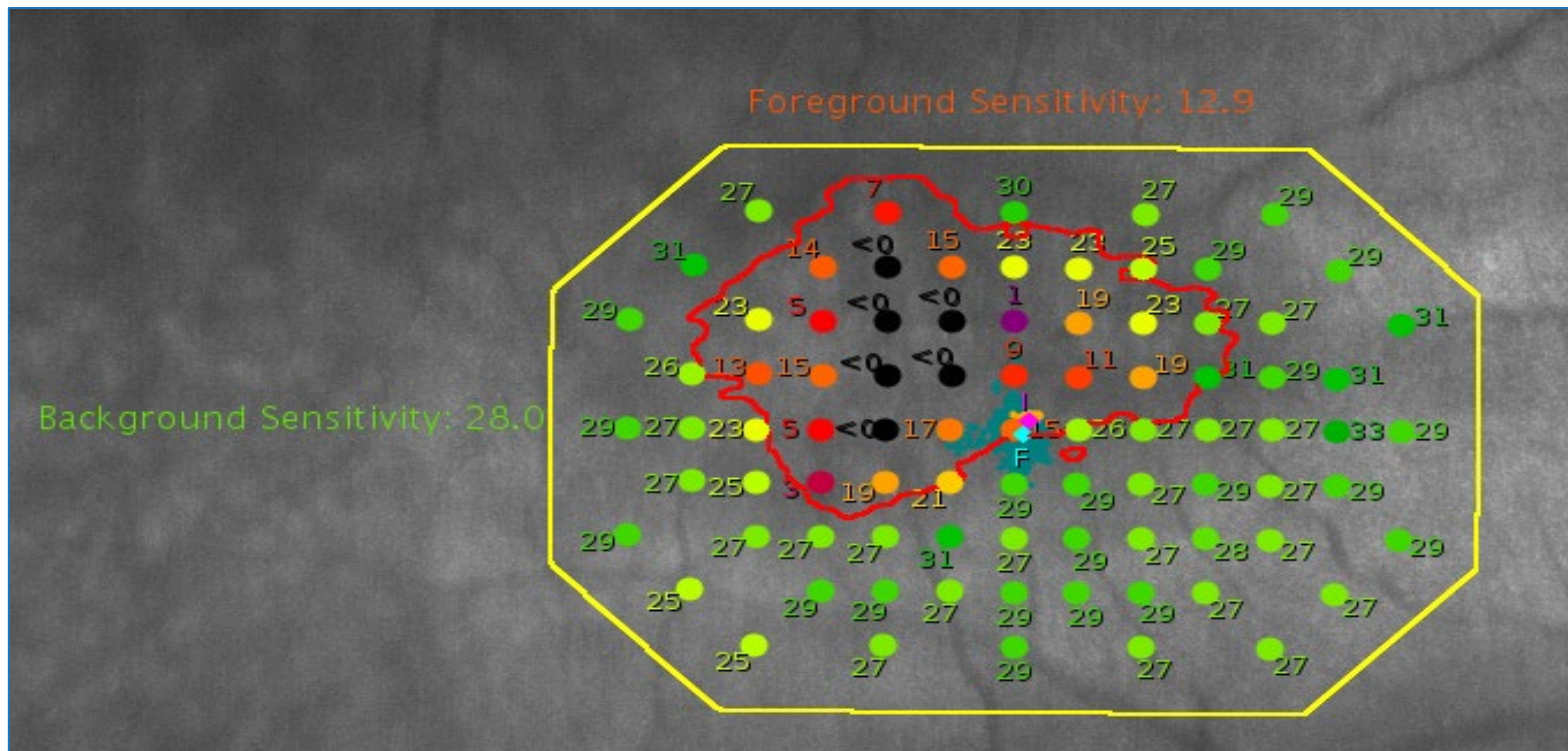
Acknowledgements

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Appendix

Aggregate Retinal Sensitivity Explained

The boundary in **yellow** denotes the FOV of the Microperimetry sensitivity map. All calculations are limited to the FOV only, since any extrapolation outside FOV may be subject to error¹



Calculation Overview²

1. Aggregate retinal sensitivity is calculated by summing and averaging test point values on microperimetry outside of the scotoma (considered the background retinal sensitivity)
2. Levels of retinal sensitivity within the scotoma are subtracted from this mean
3. The sum of these differences results in the value known as aggregate sensitivity

FOV, field of view.

Sources: 1. Data on file (includes image). 2. Chew EY, et al. *Ophthalmology*. 2019;126(4):540-549.

MacTel Patient Impact

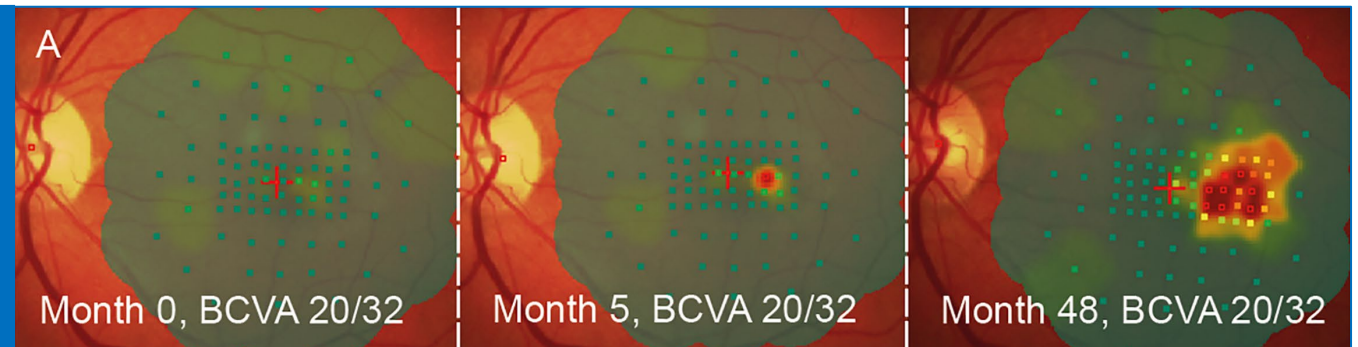
Visual Symptoms^{1,2}

- Patients can experience¹:
 - Blurred vision
 - Distorted vision
 - Expanding Paracentral blind spots
 - Loss of central vision
- Late disease stage defined by a BCVA of 20/200 or worse³
- Visual acuity is a suboptimal measure of disease burden

Impact on Activities of Daily Living²⁻⁶

- Reduced reading capabilities
 - Baseline reading speed for Phase 3 studies was reduced by 50% of normal
- Limitations on driving
- Loss of depth perception impacting mobility

These microperimetry images demonstrate progression of a new scotoma in a MacTel patient over 4 years



1. Finger RP, et al. *Investigative Ophthalmology & Visual Science*. 2009;50(3):1366-70. 2. Neurotech data on file. 3. Bronstad PM, et al. *JAMA Ophthalmol*. 2013;131(3):303-9. 4. Heeren TFC, et al. *Ophthalmology*. 2020;127(11):1539-48. 5. Lee AG, et al. AAO. Driving Restrictions per State. 2023. 6. Issa PC, et al. *Doc Ophthalmol*. 2009;119(2):133-40.



Thank you!