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

Charles Wykoff,[1,2] Sophie J. Bakri,[3] David R. Lally,[4] Catherine Egan,[5] and the MacTel Study Investigators

[1]Retina Consultants of Texas, Retina Consultants of America, Houston, TX; [2]Blanton Eye Institute, Houston Methodist Hospital, Houston, TX; [3]Mayo Clinic, Rochester, MN; [4]New England Retina Consultants, Springfield, MA; [5]Moorfields Eye Hospital, London, UK

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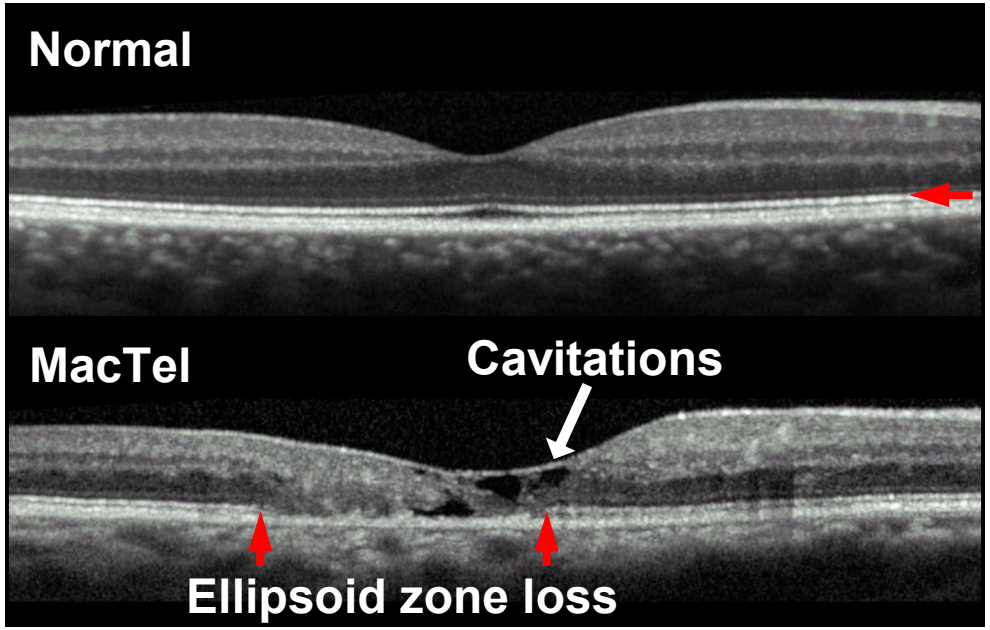
- This study includes research conducted on human subjects; institutional review board approval was obtained prior to study initiation

Macular Telangiectasia Type 2 (MacTel) Is a Neurodegenerative Disease That Leads to Vision Loss[1,2]

- MacTel is a bilateral, progressive, retinal neurodegenerative disease[1]
  - Associated with abnormalities in Müller glia, RPE, and photoreceptors in the central retina[2,3]
  - Progressive loss of the ellipsoid zone[2,4,5]
- Müller cells produce many neurotrophic factors, including ciliary neurotrophic factor (CNTF), which protects and preserves photoreceptors[4-6]
  - In preclinical models of retinal degeneration, photoreceptors can be rescued with intravitreal injection of CNTF[4,5]

SD-OCT

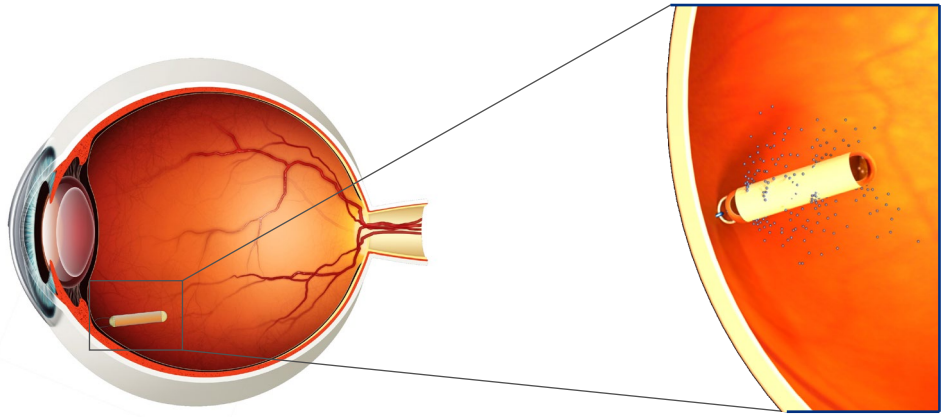


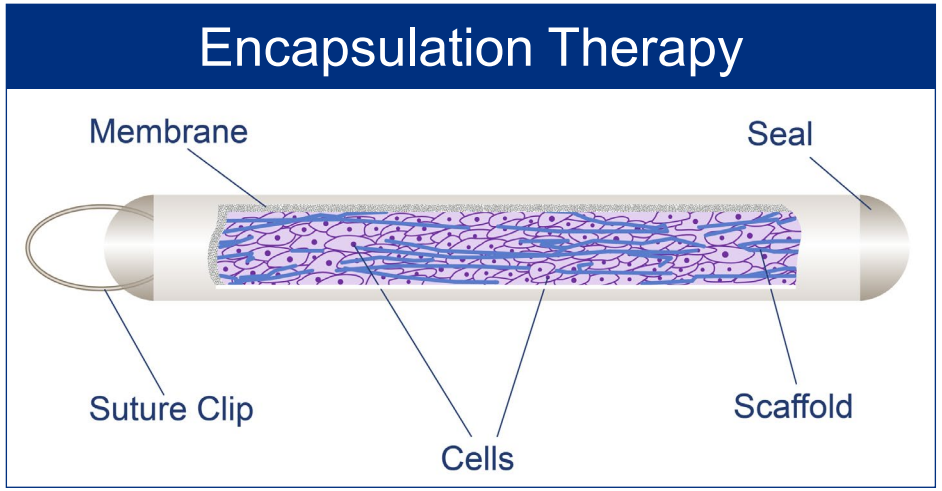
RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography.

1. Charbel Issa P, et al. *Prog Retin Eye Res*. 2013;34:49-77. **2.** Heeren TFC, et al. *Retina*. 2018;38(suppl 1):S20-S26. **3.** Kedarisetti KC, et al. *Clin Ophthalmol.* 2022;16:3297-3309.
4. Shen W, et al. *J Neurosci*. 2012;32(45):15715-15727. **5.** Tao W, et al. *Invest Ophthalmol Vis Sci.* 2002;43(10):3292-3298. **6.** Sleeman MW, et al. *Pharm Acta Helv*. 2000;74(2-3):265-272.

Encapsulated Cell Therapy (ECT): Intravitreal Sustained CNTF Delivery System

- Revakinagene taroretcel-lwey (NT-501) is a first-in-class ECT[1-3]
  - Houses NTC-201-6A cells[1]
    - Allogeneic RPE cells with an expression vector for CNTF release[1]
    - Cells remain alive and productive for many years[4]
    - Cells obtain oxygen and nutrients from vitreous[4]
    - Sequestered from the immune system[4]
  - Surgically implanted into the vitreous cavity[2] and attached to the sclera (for stability)[5]
  - Produces sustained long-term levels of CNTF[2]
- **NT-501 was approved by the FDA for the treatment of adults with MacTel on March 5, 2025**





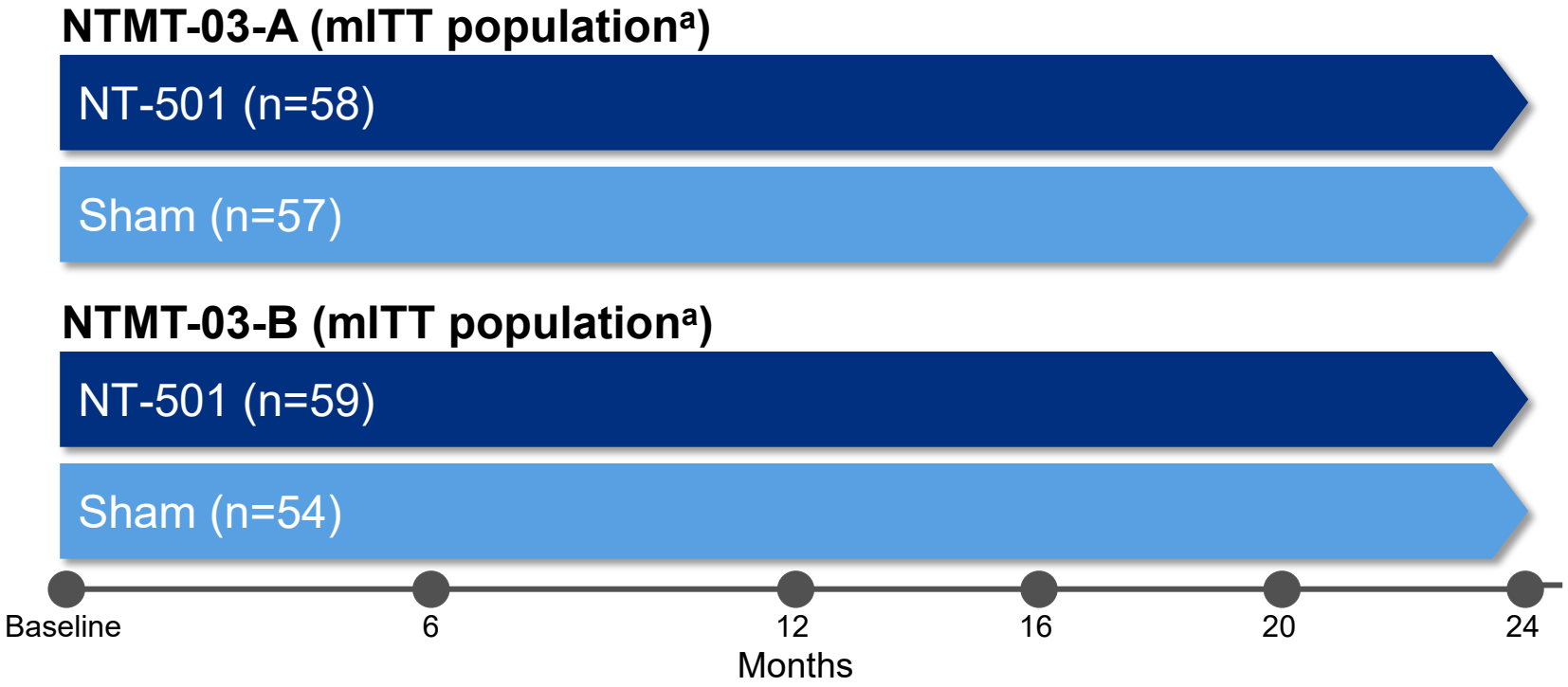
CNTF, ciliary neurotrophic factor; FDA, US Food and Drug Administration; MacTel, macular telangiectasia type 2; RPE, retinal pigment epithelium.

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.** Tao W. *Expert Opin Biol Ther.* 2006;6(7):717-726. **5.** Chew E, et al. *Ophthalmology.* 2019;126(4):540-549.

NT-501 Was Studied in Two Identical Phase 3 Trials Involving More Than 200 Participants

Key inclusion criteria

- Diagnosis of MacTel
- Aged >21 to <80 years
- EZ break between 0.16 and 2.00 mm^2
- BCVA of ≥54 ETDRS letters (Snellen 20/80 or better)



Primary endpoint: Rate of change in EZ area loss from baseline through Month 24

Secondary endpoints: Changes in retinal sensitivity and reading speed at Month 24

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; MacTel, macular telangiectasia type 2; mITT, modified intent-to-treat; NT-501, revakinagene taroretcel-lwey.
[a]The mITT population includes all randomized participants who underwent surgery (NT-501 or sham); this was the primary population for efficacy evaluations.

Baseline Characteristics Were Well Balanced Across Treatment Arms Within Each Study

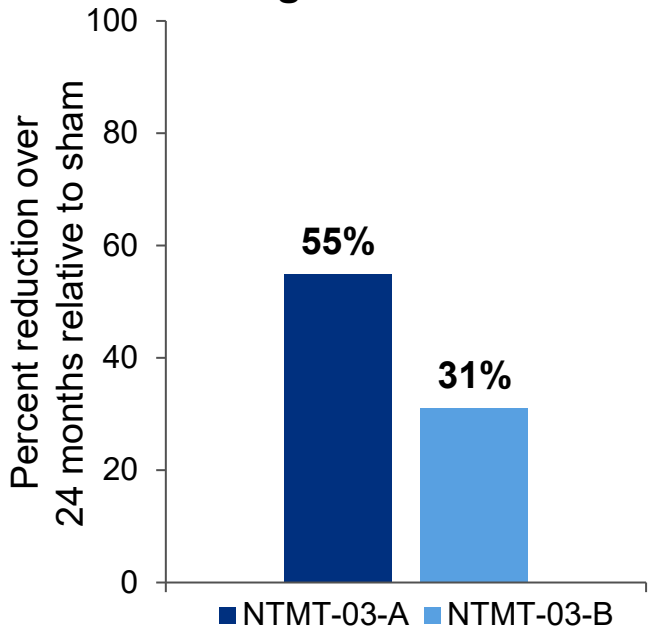
Characteristic in mITT population	NTMT-03-A		NTMT-03-B		Pooled	
	NT-501 (n=58)	Sham (n=57)	NT-501 (n=59)	Sham (n=54)	NT-501 (n=117)	Sham (n=111)
Female, n (%)	39 (67)	40 (70)	46 (78)	36 (67)	85 (73)	76 (68)
Mean (SD) age, years	61.1 (8.0)	60.2 (8.4)	58.5 (7.6)	58.7 (8.9)	59.8 (7.9)	59.5 (8.6)
Age category, n (%)						
<65 years	37 (64)	37 (65)	42 (71)	36 (67)	79 (68)	73 (66)
≥65 years	21 (36)	20 (35)	17 (29)	18 (33)	38 (32)	38 (34)
Race, n (%)						
White	50 (86)	48 (84)	55 (93)	47 (87)	105 (90)	95 (86)
Asian	2 (3)	3 (5)	3 (5)	1 (2)	5 (4)	4 (4)
Black or African American	1 (2)	2 (4)	0	0	1 (1)	2 (2)
American Indian or Alaska Native	0	1 (2)	0	0	0	1 (1)
Other	5 (9)	3 (5)	1 (2)	6 (11)	6 (5)	9 (8)
EZ area loss, mm^2						
Mean (SD)	0.51 (0.48)	0.49 (0.36)	0.52 (0.31)	0.48 (0.29)	0.52 (0.40)	0.48 (0.33)
Median (minimum, maximum)	0.35 (0.15, 1.99)	0.36 (0.16, 1.70)	0.48 (0.16, 1.63)	0.40 (0.16, 1.38)	0.42 (0.15, 1.99)	0.37 (0.16, 1.70)
Mean (SD) BCVA, ETDRS letters	70.8 (9.1)	73.3 (8.6)	74.4 (7.8)	73.6 (9.2)	72.6 (8.6)	73.4 (8.9)
Snellen equivalent	20/40	20/40	20/32	20/32	20/40	20/40
Foveal involvement, n (%)						
No	17 (29)	15 (26)	15 (25)	22 (41)	32 (27)	37 (33)
Unknown	1 (2)	0	0	0	1 (1)	0
Yes	40 (69)	42 (74)	44 (75)	32 (59)	84 (72)	74 (67)
History of diabetes, n (%)						
Yes	27 (47)	19 (33)	22 (37)	16 (30)	49 (42)	35 (32)
No	31 (53)	38 (67)	37 (63)	38 (70)	68 (58)	76 (68)

Participants were primarily White and female, had a mean age of approximately 60 years, and had a baseline visual acuity of approximately 20/40

BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; EZ, ellipsoid zone; mITT, modified intent-to-treat; NT-501, revakinagene taroretcel-lwey; SD, standard deviation.

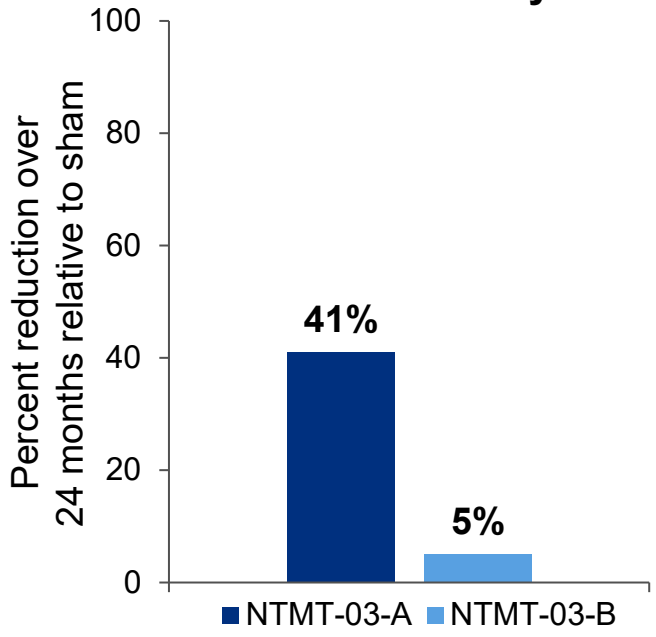
Key Efficacy Outcomes at 2 Years: NT-501 Led to Reductions in Loss of EZ Area, Retinal Sensitivity, and Reading Speed When Compared with Sham

Primary Endpoint: Reduction in Rate of Change in EZ Area Loss[a]



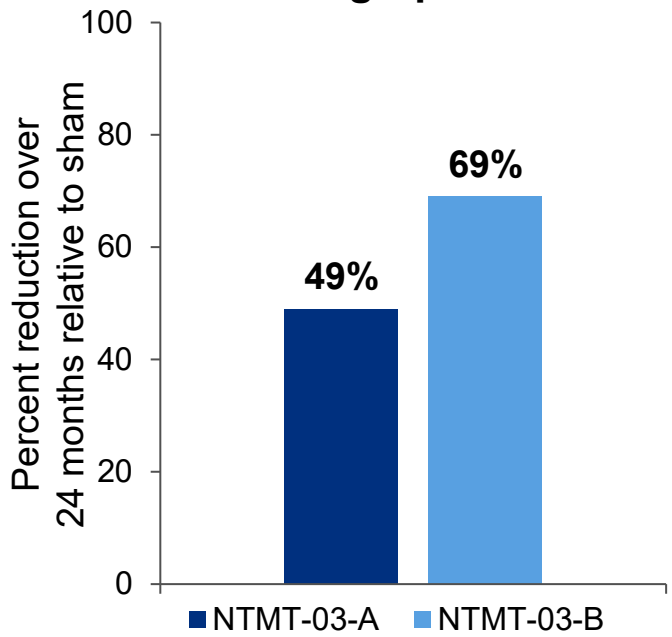
NT-501 reduced the rate of change in **EZ area loss** by **55%** in NTMT-03-A ($P<0.001^{b,c}$) and **31%** in NTMT-03-B ($P=0.0186^{b,c}$), relative to sham treatment

Secondary Endpoint: Reduction in Retinal Sensitivity Loss[a]



NT-501 reduced **retinal sensitivity** loss by **41%** in NTMT-03-A ($P=0.020^{b,d}$) and **5%** in NTMT-03-B ($P=0.835^{b,d}$), relative to sham treatment

Secondary Endpoint: Reduction in Reading Speed Loss[a]



NT-501 reduced **reading speed** loss by **49%** in NTMT-03-A ($P=0.385^{b,d}$) and **69%** in NTMT-03-B ($P=0.033^{b,d,e}$), relative to sham treatment

EZ, ellipsoid zone; mITT, modified intent-to-treat; NT-501, revakinagene taroretcel-lwey.
[a]Analyzed in the mITT population. [b]*P* values based on difference in measures of NT-501 versus sham through 24 months. [c]Based on a repeated-measures model that included baseline and Months 12, 16, 20, and 24, adjusting for study group, time (continuous), treatment × time interaction, and participant-specific random intercepts. The difference in rates of change in EZ area loss over 2 years between study groups was based on the treatment × time interaction term. [d]Two-sample *t* test comparing change from baseline to Month 24 in NT-501 versus sham. [e]Nominal *P* value.

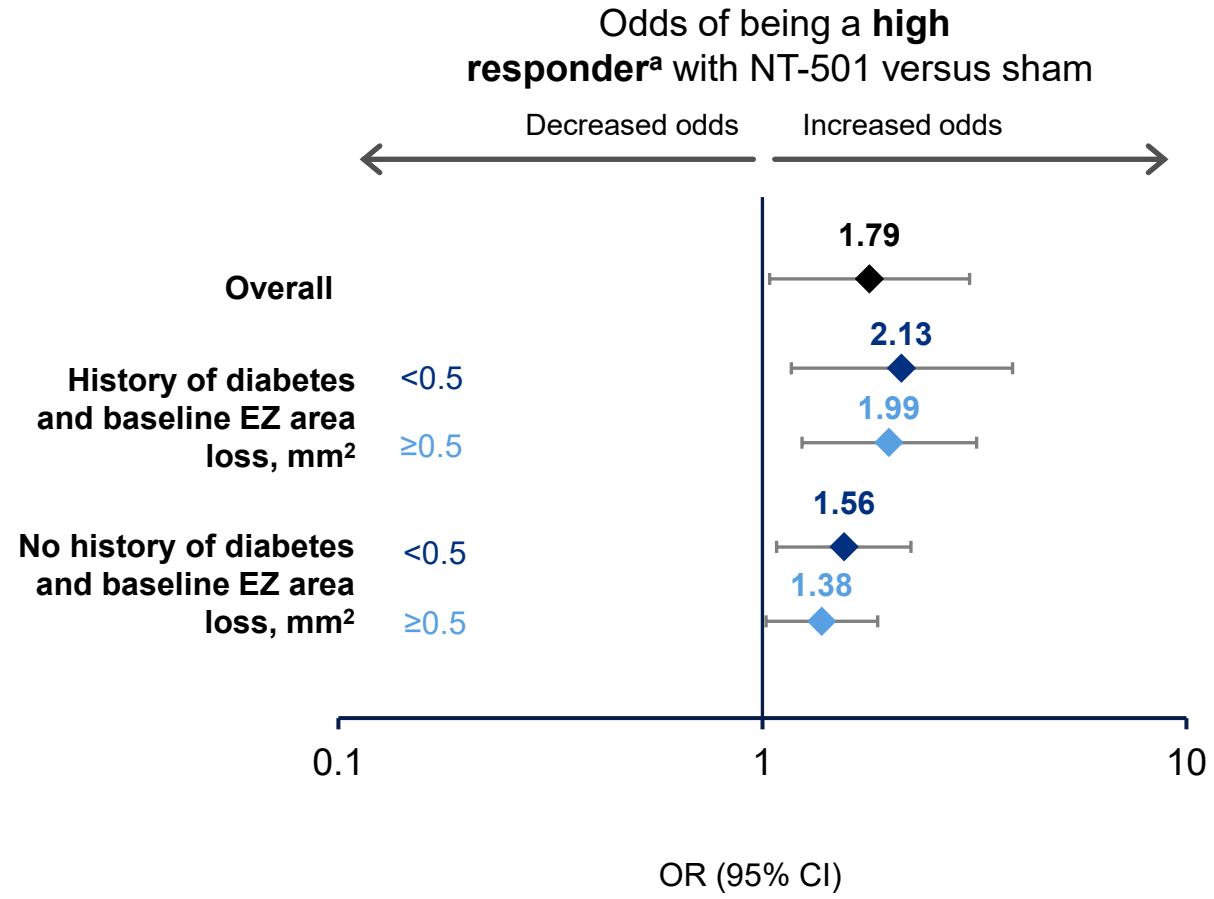
Post Hoc Analysis to Explore Differences in Trials A and B

- Evaluated the impact of baseline characteristics on treatment responses to better understand these observed differences in the efficacy outcomes
- Treatment response was examined as *responder status*
  - Participants were considered high responders if they had a ≥50% reduction in disease progression (based on EZ area loss) compared with the sham treatment
- Eight baseline variables were assessed using a **multivariate approach**; the following two were found to be associated with response:
  - **EZ area loss** (<0.5 mm^2 or ≥0.5 mm^2 based on the mean baseline loss in both studies [0.5 mm^2])
  - History of diabetes (yes or no based on medical history)

EZ, ellipsoid zone.

Both Baseline EZ Area Loss and Diabetes Were Associated With Higher Odds of Treatment Response

- In the multivariate analysis, **smaller baseline EZ area loss** and a **history of diabetes** were both associated with greater odds of achieving high responder status[a]
  - Participants with diabetes had higher odds of response than those without, regardless of baseline EZ area loss
  - Participants with smaller baseline EZ area loss had higher odds of treatment response than those with larger lesion size, regardless of diabetes status

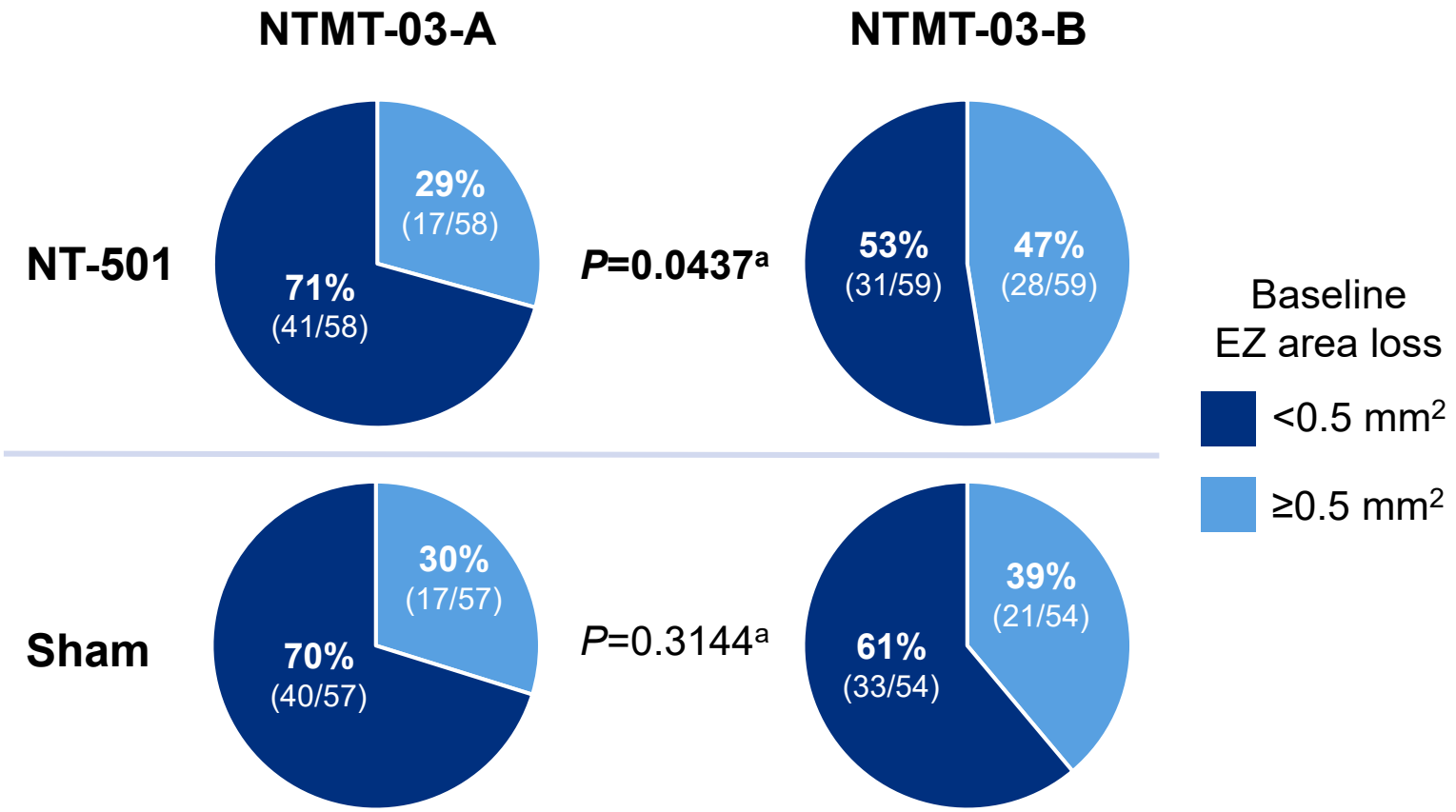


CI, confidence interval; EZ, ellipsoid zone; NT-501, revakinagene taroretcel-lwey; OR, odds ratio.
Results are pooled data from both Phase 3 clinical studies. [a]Defined as mean rate of change in EZ area ≥50% relative to mean rate of change in sham-treated group.

Distribution of Baseline Factors in the Phase 3 Trials: More Participants Treated With NT-501 in Trial A Had Smaller Baseline Lesions Versus Trial B

- Significant difference in the distribution of baseline lesion sizes in the NT-501 groups between studies
  - No significant differences between studies in sham groups
- A greater proportion of participants who received NT-501 in trial A had smaller baseline lesions compared to the NT-501 group in trial B

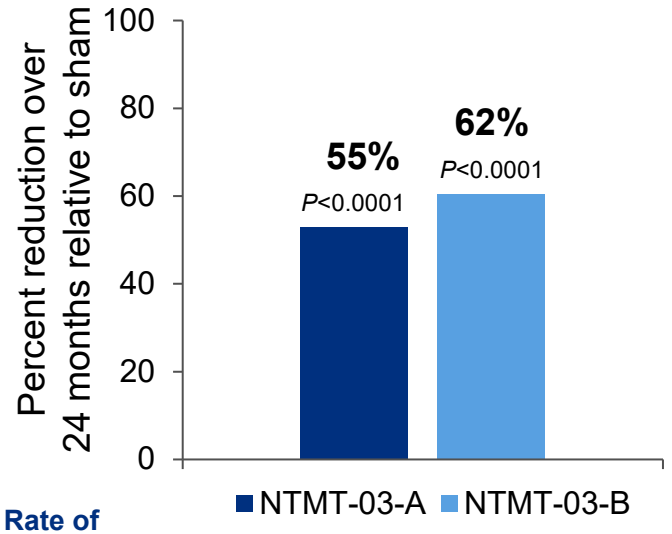
Baseline Lesion Size Between the Phase 3 Clinical Studies



EZ, ellipsoid zone; NT-501, revakinagene taroretcel-lwey.
[a]Nominal chi-square *P* value; bolded value is statistically significant.

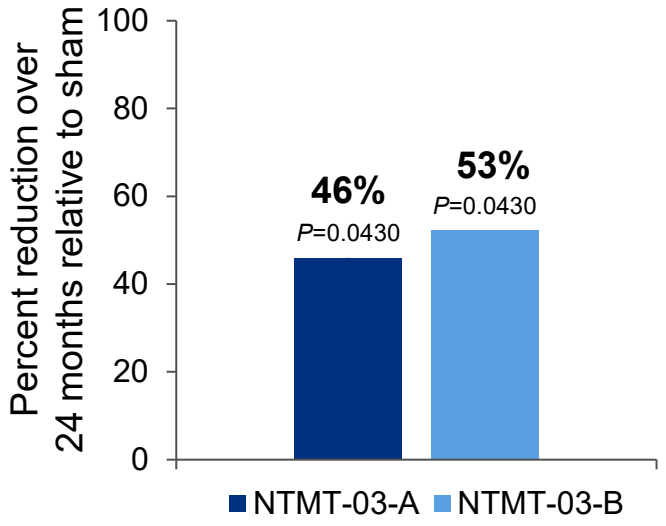
Subgroup of Participants with Smaller Baseline Lesions (<0.5 mm²)[a] in Trials A and B: Efficacy Outcomes

Reduction in Rate of Change in EZ Area Loss[b]



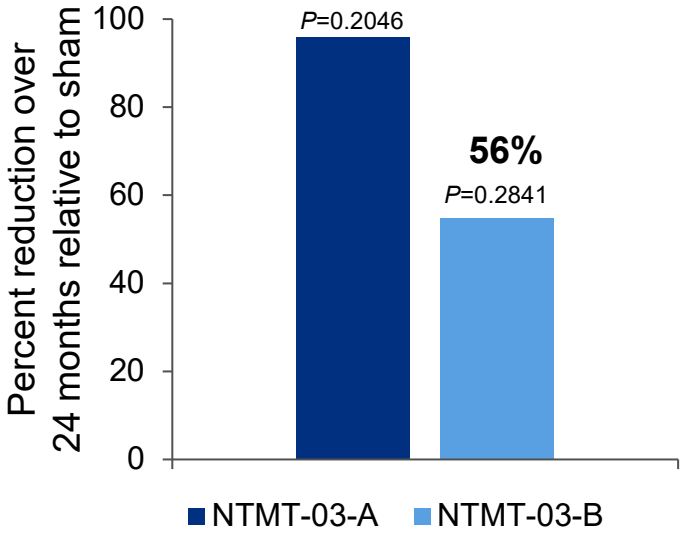
Rate of change in EZ area loss from baseline over 24 months		NTMT-03-A	NTMT-03-B
	NT-501	0.066 mm²	0.059 mm²
	Sham	0.146 mm²	0.155 mm²

Reduction in Retinal Sensitivity Loss[b]



Mean reduction in aggregate retinal sensitivity from baseline		NTMT-03-A	NTMT-03-B
	NT-501	17.04 dB	16.73 dB
	Sham	31.59 dB	35.37 dB

Reduction in Reading Speed Loss[b]



Mean reduction in reading speed from baseline		NTMT-03-A	NTMT-03-B
	NT-501	6.18 wpm	5.46 wpm
	Sham	12.20 wpm	18.88 wpm

Magnitude of reductions in EZ area loss, retinal sensitivity loss, and reading speed loss were more consistent between the studies with NT-501 treatment

dB, decibles; EZ, ellipsoid zone; mITT, modified intent-to-treat; NT-501, revakinagene taroretcel-lwey; wpm, words per minute.
All *P* values are nominal. [a]For participants with baseline lesion size <0.5 mm² in NTMT-03-A, 51% (n=41) had NT-501 and 49% (n=40) had sham; in NTMT-03-B: 48% (n=31) had NT-501 and 53% (n=33) had sham.
[b]Among participants with baseline lesion size <0.5 mm² in the mITT population.

Take-Home Points

- Treatment with NT-501 versus sham **led to reductions in the rate of EZ area loss** in participants with MacTel, meeting the primary endpoint, and the implant is now FDA approved
- **Within the current post hoc analysis, smaller baseline EZ area loss and a history of diabetes appeared to independently confer greater odds of being a high responder** with NT-501 versus sham
- The treatment response difference between NTMT-03-A and NTMT-03-B appears to be **related to baseline lesion size differences**
- Among participants with **smaller baseline lesions, consistent reductions** were found in **EZ area loss, retinal sensitivity, and reading speed**
- Though the entire Phase 3 cohort had a **treatment benefit**, participants treated **earlier in the disease process** had the greatest **anatomic and functional treatment benefit**, with increased likelihood of **reducing further disease progression**

EZ, ellipsoid zone; MacTel, macular telangiectasia type 2; NT-501, revakinagene taroretcel-lwey.

Thank You

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MacTel, macular telangiectasia type 2.