

BLA Clinical Review Memorandum

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Priority Review (Yes/No)	Yes
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Applicant	Neurotech Pharmaceuticals Inc.
Established Name	NT-501
(Proposed) Trade Name	ENCELTO
Pharmacologic Class	Allogeneic encapsulated cell-based gene therapy product
Formulation	Sterile, pyrogenic combination product that delivers recombinant human ciliary neurotrophic factor (rhCNTF)
Dosage Form and Route of Administration	One NT-501 implant is a single-use encapsulated cell therapy (ECT) that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF (NTC-201-6A cell line), a neurotrophic factor, for surgical intravitreal administration. The recommended dosage delivered by NT-501 is (b) (4) of rhCNTF.
Dosing Regimen	Single dose
Indication and Intended Population	For treatment of adults with idiopathic macular telangiectasia type 2 (MacTel)
Orphan Designated (Yes/No)	Yes

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GLOSSARY

Ab	antibodies
AE	adverse event
AESI	adverse events of special interest
AMD	age-related macular degeneration
AR	adverse reaction
AREDS	Age-Related Eye Disease Study
BCVA	best-corrected visual acuity
BLA	Biologics License Application
CNTF	ciliary neurotrophic factor
CNV	choroidal neovascularization
dB	decibels
DHFR	dihydrofolate reductase
ECT	encapsulated cell therapy
ERG	electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	ellipsoid zone
FDA	Food and Drug Administration
GA	geographic atrophy
HF	human factor
IFU	instructions for use
IOP	intraocular pressure
IS/OS	inner segment/outer segment
ISE	integrated summary of efficacy
ISS	integrated summary of safety
MacTel	macular telangiectasia type 2
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
NAb	neutralizing antibodies
NEI-VFQ-25	National Eye Institute-Visual Function Questionnaire
PP	per protocol
PR	photoreceptor
PT	preferred term
rhCNTF	recombinant human ciliary neurotrophic factor
RP	retinitis pigmentosa
SAE	serious adverse event
SD-OCT	spectral domain optical coherence tomography
TEAE	treatment-emergent adverse event
URRA	Use-Related Risk Assessment
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
wpm	words per minute
YAG	Yttrium Aluminum Garnet

1. EXECUTIVE SUMMARY

On April 18, 2024, Neurotech Pharmaceuticals Inc. (the Applicant) submitted BLA 125798, seeking approval for ENCELTO (also known as NT-501 implant) as a single-dose, one-time implant for surgical intravitreal administration for treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

NT-501 is a single use, allogeneic encapsulated cell-based gene therapy product that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF (recombinant human ciliary neurotrophic factor). It is intended for surgical placement into the vitreous cavity of the eye via access through the sclera.

NT-501 received Orphan Drug Designation for the treatment of MacTel.

BLA 125798 is supported by safety and efficacy data from six studies: (i) Phase 1 study (NTMT-01), (ii) Phase 2 study (NTMT-02), (iii) a noninterventional long-term safety and efficacy Study NTMT-01/02E (main study), which included an interventional Substudy NTMT-01/02E-SS, (iv) Study NTMT-02-B, which evaluated bilateral administration of NT-501 implants, and two Phase 3 studies, (v) NTMT-03-A and (vi) NTMT-03-B.

Substantial evidence of effectiveness is established based on two adequate and well-controlled Phase 3 studies, NTMT-03-A and NTMT-03-B, which were identical in design (including efficacy endpoints, total duration, and enrolled population). These trials were multicenter, evaluator-masked, sham-controlled studies conducted in different study centers in the United States, Australia, and Europe. Both studies enrolled 21 to 80-year-old patients with non-neovascular MacTel, who had an inner segment/outer segment (IS/OS) photoreceptor (PR) break in ellipsoid zone (EZ) (area of IS/OS loss) between 0.16 and 2.00 mm², as measured by spectral domain optical coherence tomography (SD-OCT), and best-corrected visual acuity (BCVA) of 54-letter score or better (20/80 or better), as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at screening.

The primary efficacy endpoint in both studies was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline through Month 24, as assessed using SD-OCT in the study eye of patients with MacTel. The EZ, as depicted in ocular coherence tomography, is the portion of the inner segment of the photoreceptors that is immediately adjacent to the junction between photoreceptor inner and outer segments, and its integrity and intensity are important indicators of PR health. Significant thinning and break in EZ are seen with PR degeneration and loss. Secondary efficacy endpoints by order of hierarchical testing were: (i) the mean change in aggregate sensitivity loss of microperimetry within the EZ break area from baseline to Month 24, (ii) mean change in monocular reading speed from baseline at Month 24, and (iii) mean change in the National Eye Institute-Visual Function Questionnaire (NEI-VFQ-25) near activities subscale score from baseline at Month 24 (The near activities

subscale score was an average of the scores for items 5, 6, and 7 in the NEI-VFQ-25.).

The primary analysis population was a modified Intention to Treat (mITT) population that included all patients that received the product or sham procedure. A total of 115 patients were enrolled and underwent surgery under Study NTMT-03-A; 58 received NT-501 implant and 57 patients underwent a sham procedure. In Study NTMT-03-B, a total of 113 patients underwent surgery; 59 received NT-501 implant and 54 underwent a sham procedure.

Both studies met their primary endpoint and demonstrated that NT-501 slowed the rate of disease progression over 24 months. For study NTMT-03-A the mean rate of change in EZ area loss from baseline over 24 months was 0.075 (0.012) mm² / 24 months in the NT-501 group and 0.166 (0.013) mm² / 24 months in the sham group, with a statistically significant difference between groups (–0.091 [0.018] mm²; 95% CI: –0.125, –0.056; p<0.0001). For study NTMT-03-B the mean rate of change was 0.111 (0.0142) mm² / 24 months in the NT-501 group and 0.160 (0.0149) mm² / 24 months in the sham group, with a statistically significant difference between groups (–0.0486 [0.0206] mm²; 95% CI: –0.089, –0.0082; p =0.0186). The exhibited differences in both studies exceeded the measurement uncertainty, of 0.0132 mm² (SD =0.0114 mm²) of intra-grader variability and 0.018 mm² (SD =0.0343 mm²) of intergrader variability including an arbitrator, making the change clinically meaningful. These differences correspond to a 54.8% reduction in the rate of retinal degeneration through 24 months in Study NTMT-03-A and a 30.6% reduction in Study NTMT-03-B.

Study NTMT-03-A also met its first secondary efficacy endpoint, demonstrating that NT-501 slowed the aggregate retinal sensitivity loss from baseline through Month 24. Although there was a mean increase in aggregate retinal sensitivity loss from baseline to Month 24 in the NT-501 and sham groups, the magnitude of loss was significantly smaller in the NT-501 group compared to the sham group (25.3 versus 43 decibels (dB), respectively; p=0.02). For Study NTMT-03-B, the difference between NT-501 and sham in the change in aggregate retinal sensitivity loss from baseline to Month 24 was similar in the NT-501 and sham groups (40.02 versus 41.97 dB) and the difference was not statistically significant (p=0.83). For most of the remaining secondary endpoints, differences favored the NT-501 implant group.

Safety of NT-501 was evaluated in three different pools. NTMT-03-A and NTMT-03-B were used to evaluate safety in Pool 1 and were used to provide the safety information in the United States Prescribing Information (USPI).

Pool 2 included Studies NTMT-01, NTMT-02, NTMT-01/02E, NTMT-02-B in addition to the two Phase 3 studies described above.

Study NTMT-01 was a Phase 1, open-label, nonrandomized, multicenter, pilot study that evaluated the safety and tolerability of NT-501 implants in seven study patients with MacTel.

Study NTMT-02 was a prospective, multicenter, partially assessor-masked, and sham-controlled study of patients with MacTel. A total of 67 patients were randomized; 15 received NT-501, 19 underwent sham surgery, and 32 underwent NT-501 and sham surgery.

NTMT-01/02E was a noninterventional study designed to provide long-term safety and efficacy follow-up for patients who had NT-501 implanted intraocularly and/or underwent sham surgery in the respective precursor study (NTMT-01 or NTMT-02). NTMT-01/02E also included Substudy NTMT-01/02E-SS, an open-label, single-dose study which offered to the patients in the sham group of Study NTMT-02, the option of receiving NT-501 in the same study eye that had undergone sham surgery. A total of 74 patients were followed under Study NTMT-01/02E and a total of 16 patients elected to have NT-501 implanted in the same study eye during the Substudy NTMT-01/02E-SS.

Study NTMT-02-B was a multicenter, open-label study to evaluate safety of bilateral NT-501 implants in study patients with MacTel. A total of 32 patients who had previously received NT-501 implant in 1 eye were enrolled and received the implant in the second eye.

Pool 3 consisted of all patients who received NT-501 implant across all indications (which also include retinitis pigmentosa [RP], geographic atrophy [GA] associated with age-related macular degeneration [AMD], and achromatopsia).

There were no deaths and no cases of infectious endophthalmitis. The rate of explantation was low across all studies (3 patients, 1.4%), with the earliest removal occurring 130 weeks (18.6 months) after implantation. The reasons for the explantation were vitreous hemorrhage, suture related complication and expulsion.

Across the MacTel studies, 13 study eyes (5.9%) experienced 1 ocular SAE each. The ocular SAEs occurring in more than one study eye were suture-related complication (5 eyes, 2.3%), device extrusion, (2 eyes, 0.9%), and vision blurred (2 eyes, 0.9%). The remaining events, all occurring in one study eye (0.5%) each in the NT-501 group, included visual impairment, noninfectious endophthalmitis, vitreous hemorrhage, and device expulsion.

Device expulsion was considered to be related to both NT-501 and surgery, noninfectious endophthalmitis was considered to be related to NT-501, and all other ocular SAEs were considered by the investigator to be related to the surgical procedure.

Suture-related complications was the most common adverse reaction due to the procedure encountered with higher frequency in the treatment group. Delayed dark adaptation and miosis were the only AEs related to NT-501 or ciliary neurotrophic factor (CNTF) and were reported in 20.9% and 18.2% of patients across all MacTel studies. These reports were consistently mild, did not progress, and did not lead to explantation. All delayed dark adaptation AEs were based on patient queries only and were not further investigated with

psychophysical or electrophysiologic testing by the Applicant. Cataract formation related to the product or procedure was reported in 4.1% of treated eyes, with no related cataract formation reported in sham eyes in the MacTel studies. The higher rate of cataract formation in eyes receiving NT-501 is possibly due to CNTF but might also be related to surgical trauma or malposition of the NT-501 during the surgical placement procedure.

In a 6-month study, NTMT-02-B, there was low reported occurrence of antidrug antibodies. Therefore, the effect of these antibodies on the safety, and/or effectiveness of NT-501 is unknown.

Severe vision loss, infectious endophthalmitis, retinal tears and/or detachment, vitreous hemorrhage, implant extrusion, cataract formation, suture related complications and delayed dark adaptation have been identified as potential risks associated with the implant. The applicant has added these risks in the “Warnings and Precautions” section of the USPI and plans to mitigate these risks with routine pharmacovigilance, a Phase 3 extension sham dosing study, and through an ongoing Natural History Observation Study questionnaire.

Overall, the efficacy and safety data in this BLA support a favorable benefit-risk profile for patients with MacTel. NT-501 is effective in slowing down the progression of disease in patients with MacTel, NT-501 was well-tolerated for a period of up to 9 years after intraocular implantation.

Based on the favorable benefit-risk profile and the lack of available treatment options for MacTel, the clinical review team recommends traditional approval of this BLA.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Key baseline demographic information for the modified intention-to-treat (mITT) and safety populations of the two pivotal phase 3 studies, NTMT-03-A and NTMT-03-B, combined is summarized in [Table 1](#). The mITT population included all randomized patients who underwent either NT-501 implantation surgery or sham surgery. The Safety population included all randomized patients who underwent either NT-501 implantation surgery or sham surgery and had at least one safety measurement.

Overall, baseline demographics of the two study arms (treatment and sham control) were balanced across the two pivotal studies. The average age of 228 patients enrolled in Studies NTMT-03-A and NTMT-03-B was 59.6 years (ranging from 40 to 78 years). The majority of patients were White (87.7%) and female (70.6%).

Table 1. Demographics, Modified Intention-to-Treat and Safety Populations, NTMT-03-A and NTMT-03-B

Demographic	NT-501 N=117	Sham N=111	Total N=228
Age (years)	-	-	-
Mean (standard deviation)	59.8 (7.9)	59.5 (8.6)	59.6 (8.2)
Median (min, max)	60 (40, 77)	59 (40, 78)	59.5 (40, 78)
Age group at randomization n (%)	-	-	-
<65 years	79 (67.5%)	73 (65.8%)	152 (66.7%)
≥65 years	38 (32.5%)	38 (34.2%)	76 (33.3%)
Sex	-	-	-
Female	85 (72.6%)	76 (68.5%)	161 (70.6%)
Male	32 (27.4%)	35 (31.5%)	67 (29.4%)
Race, n (%)	-	-	-
White	105 (89.7%)	95 (85.6%)	200 (87.7%)
Asian	5 (4.3%)	4 (3.6%)	9 (3.95%)
Black or African American	1 (0.9%)	2 (1.8%)	3 (1.32%)
Other	6 (5.1%)	8 (7.2%)	14 (6.1%)
Not collected	0 (0.0%)	1 (0.9%)	1 (0.4%)
American Indian or Alaska Native	0 (0.0%)	1 (0.9%)	1 (0.4%)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	5 (4.3%)	9 (8.1%)	14 (6.1%)
Not Hispanic or Latino	112 (95.7%)	101 (91%)	213 (93.4%)
Unknown	0 (0.0%)	1 (0.9%)	1 (0.4%)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewers

1.2 Patient Experience Data

N = population size

Please see Patient Experience Data reviewed in this BLA, summarized in [Table 2](#).

Table 2. Data Considered in BLA 125798

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input checked="" type="checkbox"/>	Patient-reported outcome	6.1.8 , 6.1.11.2 , 6.2.8 , 6.2.11.2
<input type="checkbox"/>	Observer-reported outcome	-
<input type="checkbox"/>	Clinician-reported outcome	-
<input type="checkbox"/>	Performance outcome	-
<input type="checkbox"/>	Patient-focused drug development meeting summary	-
<input type="checkbox"/>	FDA Patient Listening Session	-

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	-
<input type="checkbox"/>	Observational survey studies	-
<input checked="" type="checkbox"/>	Natural history studies	7.1.4
<input type="checkbox"/>	Patient preference studies	-
	Other: (please specify)	-
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	-
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	-
<input type="checkbox"/>	Patient-focused drug development meeting summary report	-
<input type="checkbox"/>	FDA Patient Listening Session	-
<input type="checkbox"/>	Other stakeholder meeting summary report	-
<input type="checkbox"/>	Observational survey studies	-
<input type="checkbox"/>	Other: (please specify)	-

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

MacTel is a rare, retinal disease affecting the macula with variable prevalence reported among different studies. It is characterized by bilateral, asymmetric, slowly progressive, retinal neurodegeneration with characteristic alterations of the retinal vasculature and localized retinal degeneration. Although it was previously believed to be a vascular condition, recent evidence suggests a neurodegenerative etiology characterized by Müller glial cell dysfunction. Müller glial cells are the primary glial cell of the retina, providing structural and neurotrophic support to the retina. Müller glial cells express CNTF receptor and Müller cell protein expression is upregulated by CNTF. Müller glial cells are hypothesized to mediate CNTF protection of PRs and possibly ganglion cells.

Müller glial cell dysfunction and apoptosis impedes the production of neuroprotective factors, resulting in PR death. According to the Applicant, studies have demonstrated that exogenous CNTF initially targets Müller glia to trigger a cascade of signaling events that promote PR survival. CNTF binds to CNTF receptors on Müller glial cells, activating the Janus kinase/signal transducer and activator of transcription pathway. This pathway prompts Müller glial cells to produce growth factors and neuroprotective factors, including CNTF. Neuroprotective factors provide structural/neuroprotective support by activating cell survival pathways. Administration of intravitreal CNTF in a mouse model with conditionally ablated Müller glial cells significantly reduced the area of OS loss (PR layer).

MacTel is an adult-onset disease, and most patients are diagnosed in their 40s and 50s. Reports of familial clusters and affected monozygotic twins suggest that MacTel has a genetic component, although no hereditary pattern has yet been established. The Melbourne Collaborative Cohort (1) estimated the prevalence at 0.004 to 0.022% in 22,415 patients, but the Beaver Dam Eye Study (2) reported a prevalence of 0.1% in 4,790 individuals between the ages of 43 and 86 years. The lower prevalence in the Melbourne Collaborative Cohort study was possibly attributed to the fact that in that study only 17% of images that had 1 or more findings that might indicate the presence of MacTel were selected for grading, leading to missing eyes with retinal signs of MacTel in the 83% of the cohort not graded. Although the population in both studies was primarily White, it is thought that MacTel is equally prevalent throughout the world with no racial predilection.

The natural course of MacTel is that of gradual bilateral macular PR loss and consequent loss of vision, occasionally accompanied by the development of neovascularization and severe vision loss (3, 4). The disease affects visual function with initial paracentral scotomas and later loss of BCVA. In the early stages of MacTel, functional impairment may be mild, with no impairment or metamorphopsia (distorted vision), and only a slight reduction in binocular BCVA. Despite the presence of deep paracentral scotomata and reduced reading ability, distance Snellen visual acuity can be preserved due to eccentric fixation. As the disease progresses with further loss of macular PRs, there is a decrease in visual acuity which becomes more pronounced with time secondary to foveal PR atrophy. Development of neovascularization (neovascular MacTel) can further complicate the clinical picture with development of subretinal hemorrhages, fluid leakage and thickening of the macula.

Fluorescein angiography is the gold standard for diagnosing MacTel, and leakage on fluorescein angiography may precede any other visible changes. Typical structural changes include vascular abnormalities, such as telangiectatic capillaries, dilated and right-angled veins, loss of retinal transparency, and redistribution of macular pigment. In SD-OCT, morphological changes highly characteristic of the disease include thinning of the central retina, low-reflective spaces ("cavities") in the inner and outer retina, and focal loss of the EZ, also

known as IS/OS break, that typically starts temporal to the foveal center and later spreads to involve the fovea (5, 6).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Focal and grid laser photocoagulation, photodynamic therapy, intravitreal triamcinolone acetonide, and anti-vascular endothelial growth factor (anti-VEGF) drugs have been used to treat non-proliferative MacTel, but their success remains controversial (7-11). Anti-VEGF drugs have been reported to be associated with anatomical and functional improvement in most of studies of proliferative MacTel (11).

2.3 Safety and Efficacy of Pharmacologically Related Products

This is the first medication to be marketed in this class and there are no pharmacologically related products currently available.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

NT-501 has previously been tested in clinical trials in patients with RP, achromatopsia, and GA.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

[Table 3](#) summarizes the key regulatory history since IND submission.

Table 3. Key Regulatory History

Regulatory Milestones	Date
I. IND submission	02-14-2003
II. Fast Track designation granted	12-17-2018
III. Orphan Drug designation granted	03-29-2012
IV. Pre-BLA meeting	08-31-2023
V. BLA 125798/0 submission	04-18-2024
VI. BLA filed	06-17-2024
VII. Mid-Cycle communication	08-15-2024
VIII. Late-Cycle meeting	10-07-2024
IX. Major Amendment	10-16-2024

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was filed on April 18, 2024. The submission was adequately organized and integrated to enable conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices and Submission Integrity

All clinical studies were performed in compliance with Good Clinical Practice guidelines as outlined by the International Council for Harmonization and relevant regulatory authorities. All clinical studies were conducted under the supervision of an Institutional Review Board/Ethics Committee; informed consent procedures were implemented in accordance with Good Clinical Practice guidelines. All studies were conducted ethically and in accordance with the Declaration of Helsinki, and adhered to applicable regulatory requirements, including those set forth by FDA, European Medicines Agency, and other relevant regulatory authorities.

3.3 Financial Disclosures

Covered clinical study (name and/or number): NTMT-01, NTMT 02, NTMT-0102E, NTMT-02-B, NTMT-03-A and NTMT-03-B
Was a list of clinical investigators provided? X Yes <input type="checkbox"/> No (Request list from Applicant)
Total number of investigators identified: <u>70</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 1

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided?

X Yes ☐ No (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1

Is an attachment provided with the reason? X Yes ☐ No (Request explanation from Applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

For information about Chemistry, Manufacturing and Controls, please see CMC Review.

4.2 Assay Validation

For Assay validation considerations, please see CMC review.

4.3 Nonclinical Pharmacology/Toxicology

For information about Nonclinical Pharmacology/Toxicology please see Pharmacology/ Toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

NT-501 is a biologic-device combination product implanted intravitreally. The NT-501 implant contains allogeneic retinal pigment epithelial cells expressing human CNTF. The implant consists of a sealed, semipermeable, hollow fiber membrane capsule that surrounds a scaffold of six strands of polyethylene terephthalate yarn loaded with CNTF-secreting NTC-201.6A cells. NT-501 is surgically positioned into the vitreous cavity of the eye. NT-501 has been developed to deliver a continuous nominal CNTF dose. NT-501 was developed

to express several levels of CNTF and was categorized as NT-501-10.02 (low output) and NT-501-6A.02 (high output) based on the rate of CNTF expression and consequent vitreous steady-state levels. The 6.5-mm combination product was designed to deliver a high output of CNTF; NT-501-6A.02 was used in all MacTel clinical studies.

4.4.2 Human Pharmacodynamics

N/A.

4.4.3 Human Pharmacokinetics

Given the intraocular route of administration and the local action of NT-501, significant serum exposure to CNTF is not expected, and systemic exposure to CNTF is not relevant to the product's efficacy. In limited PK assessments completed in Studies NTMT-01 and NTMT-02-B, there were no measurable serum levels of CNTF at 12, 24, and 36 months after NT-501 implantation. Therefore, no pharmacokinetic or pharmacodynamic analyses were performed.

4.5 Statistical

Please see separate Statistical review for details of the statistical analyses.

4.6 Pharmacovigilance

Severe vision loss, infectious endophthalmitis, retinal tears and/or detachment, vitreous hemorrhage, implant extrusion, cataract formation, suture related complications and delayed dark adaptation have been identified as potential risks associated with the implant. The applicant has added these risks in the "Warnings and Precautions" section of the USPI and plans to mitigate these risks with routine pharmacovigilance, a Phase 3 extension sham dosing study, and through an ongoing Natural History Observation Study questionnaire.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The data constituting the evidence included in this BLA submission derives from six studies and one substudy, Studies NTMT-01, NTMT-02, NTMT-01/02E (that includes Substudy NTMT-01/02E-SS), NTMT-02-B, NTMT-03-A and NTMT-03-B.

For assessment of efficacy, and in the context of Applicant's proposed indication, the clinical review primarily focused on data from pivotal studies NTMT-03-A and NTMT-03-B.

For assessment of safety data from all six studies were analyzed. Safety analyses were particularly focused on treatment-emergent adverse events occurring through 24 months of follow-up, treatment-emergent ocular adverse reactions occurring through 24 months of follow-up, and serious adverse events leading to discontinuation. Additional analyses examined long-term safety events

occurring after the 24-month follow-up period. Analyses differentiated adverse events by event severity, eye type affected (investigational product, sham surgery or untreated fellow eye), and treatment relatedness (NT-501, surgery, CNTF).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The clinical review was based on review of the final clinical study reports, protocols, and other relevant submissions for Studies NTMT-01, NTMT-02, NTMT-01/02E (that includes Substudy NTMT-01/02E-SS), NTMT-02-B, NTMT-03-A and NTMT-03-B.

5.3 Table of Studies in the NT-501 Clinical Program

Table 4. Studies and Clinical Trials

Study Identifier (Phase) Country(ies)	Study Design	Follow-Up Duration	Study Endpoint	Patients Enrolled
NTMT-01 (Phase 1) US	Open-label, single arm, multicenter Control: Fellow untreated eye	60 months	Primary safety	7 patients (7 eyes)
NTMT-02 (Phase 2) US, AU	Prospective, multicenter, single-masked, sham controlled Control: Fellow untreated eye	48 months	Primary efficacy endpoint: Change in the EZ (area of IS/OS loss) (Month 24 – baseline) as measured by en-face imaging by SD-OCT in study eye(s) Secondary efficacy endpoints <ul style="list-style-type: none"> • Change in the EZ (area of IS/OS loss) from baseline to Month 12 • Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 12 and 24 	67 patients (99 eyes)

Study Identifier (Phase) Country(ies)	Study Design	Follow-Up Duration	Study Endpoint	Patients Enrolled
NTMT-01/02E/ NTMT-01/02E-SS (Phase 2) US, AU	Main Study: Prospective, multicenter, noninterventional SS: Single arm interventional study	Main Study: 108 months (Cohort 1) or 72 months (Cohort 2) SS: 48- months	Main study Cohorts 1 and 2: <ul style="list-style-type: none"> Change in the ellipsoid zone (area of IS/OS loss) from baseline to Months 72, 84, 96 and 108. Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 72, 84, 96 and 108. Study SS: Safety	Main Study: Cohort 1 – 6 patients/study eyes Cohort 2 – 64 patients/ 94 study eyes: 45 NT-501; 49 sham SS: 16 patients/eyes
NTMT-03-A (Phase 3) US, AU, DE, FR	Prospective, multicenter, evaluator- masked, sham-controlled Control: Sham surgery control group	24 months	Primary efficacy endpoint: Rate of change in the area of EZ loss (IS/OS; macular photoreceptor loss) from baseline through Month 24, as assessed using SD-OCT. Secondary efficacy endpoints: <ul style="list-style-type: none"> -Mean change in aggregate sensitivity of microperimetry within the EZ break area from baseline at Month 24 -Mean change in monocular reading speed from baseline at Month 24 	115 patients/eyes (58 NT-501; 57 sham)
NTMT-03-B (Phase 3) US, AU, DE	Prospective, multicenter, evaluator- masked, sham-controlled Control: Sham surgery control group	24 months	Primary efficacy endpoint: Rate of change in the area of EZ loss (IS/OS; macular photoreceptor loss) from baseline through Month 24, as assessed using SD-OCT. Secondary efficacy endpoints: <ul style="list-style-type: none"> -Mean change in aggregate sensitivity of microperimetry within the EZ break area from baseline at Month 24 -Mean change in monocular reading speed from baseline at Month 24 	113 patients/eyes (59 NT-501; 54 sham)

Study Identifier (Phase) Country(ies)	Study Design	Follow-Up Duration	Study Endpoint	Patients Enrolled
NTMT-02-B (Phase 2) US, AU	Multicenter, open-label in patients who received NT-501 in a single eye prior to or in the Phase 1/2 extension study (NTMT-01/02E) or in 1 of the Phase 3 studies	6 months	Primary safety	32 patients/eyes (32 NT-501)

Source: Reviewer table

5.4 Consultations

Consultative input was obtained from the Center for Devices and Radiologic Health. Arlesa Hubbard, Human Factors Engineer, Team Lead in the Division of Drug Delivery and General Hospital Devices and Human Factors, Center for Devices and Radiologic Health provided consultation regarding the Human Factor (HF) study and Use-Related Risk Assessment (URRA). Findings and recommendations are included in [Appendix 1](#).

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee was not convened for this application as no controversial issues were identified that would benefit from external expert advice.

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed (if applicable)

During the review of this BLA, the reviewer consulted FDA regulatory guidance documents and academic literature for background and context regarding the targeted disease and mechanism of action of the product. A list of the literature is provided in [Section 12, References](#).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

There are six studies that support this BLA. These studies include a Phase 1 study (NTMT-01), a Phase 2 study (NTMT-02), a noninterventional long-term safety and efficacy study (NTMT-01/02E, main study, which also included an interventional Substudy NTMT-01/02E-SS), a bilateral administration study (NTMT-02-B), and two Phase 3 studies (NTMT-03-A and NTMT-03-B). Both Phase 3 studies provide the primary evidence of effectiveness for NT-501. All six

studies contribute to the safety database. This section describes the design and the conduct of all six studies in order of significance.

6.1 Trial #1: Study NTMT-03-A

Title: A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia Type 2.

National Clinical Trial #: NCT03316300

6.1.1 Objectives (Primary and Secondary)

The primary objective of the study was to assess the efficacy of NT-501 in patients with MacTel by determining the rate of change in the area of EZ loss (PR IS/OS loss) over 24 months, as measured by SD-OCT in the study eye of patients with MacTel.

The secondary objective was to evaluate the safety of NT-501 in patients with MacTel.

6.1.2 Design Overview

This was a prospective, multicenter, evaluator-masked, sham-controlled study of patients with MacTel. The study planned to enroll a total of 112 patients (56 per arm).

To confirm eligibility, the study included a screening period of up to 30 days. All patients underwent the following assessments to define eligibility: manifest refraction, BCVA testing, intraocular pressure (IOP) measurement, undilated pupil diameter measurements, slit-lamp biomicroscopy, dilated fundus examinations, microperimetry, SD-OCT imaging of the central macula, fundus autofluorescence imaging, color digital fundus photography, monocular reading speed, and NEI-VFQ-25 (12, 13).

The EZ area was measured using SD-OCT. Once obtained, the SD-OCT scans were transferred electronically to a central reading center and evaluated by masked readers. The EZ line break area and the area of EZ loss were determined by the central reading center. As part of the screening process (baseline measurements), two independent masked readers determined the lesion area from a single acceptable SD-OCT volume scan. If the 2 estimates of area were within 10% and at least 1 measure was ≥ 0.16 and ≤ 2.0 mm², the MacTel lesion was deemed eligible. If the 2 readings differed by more than 10%, an arbitrating reader estimated the area. If the third reading was within 10% of either of the first 2 estimates, then the third and selected primary readings were used to establish eligibility. The baseline area of EZ loss was the mean of the two qualifying estimates.

For postbaseline assessments, a single, central masked reader determined the lesion area from a single, acceptable OCT volume scan. The same central reader conducted reviews for all postbaseline assessments across both Phase 3

studies (Studies NTMT-03A and NTMT-03B), demonstrating consistency and reproducibility.

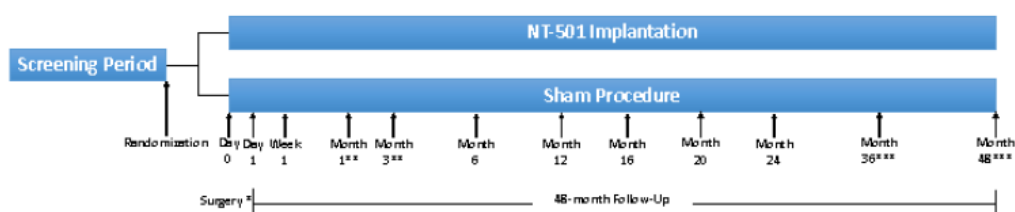
Retinal sensitivity (reported in dB) was measured in all studies using macular integrity assessment microperimetry. The measurements were generally taken when study eyes were undilated. Microperimetry results were transferred electronically to a central reading center and evaluated by masked readers.

Monocular reading speed was measured using the International Reading Speed Texts Worksheets developed by the International Reading Speed Texts Study Group (14). The worksheets use standardized paragraphs of text for measuring reading speed, with the aim to measure reading speed under natural conditions, a requirement of everyday life. Reading speed for each eye was calculated as the number of words read per minute.

Eligible patients were randomized 1:1 in two different arms, a treatment arm and a sham control arm, and received the implant/sham procedure in a single eye designated as the study eye. If both eyes were eligible, then the study eye was selected by a centralized randomization process or by patient preference if they elected to exclude a study eye from consideration. Implant or sham surgery on Day 0 was to have occurred within 30 days after randomization and/or within 58 days after screening. A pre-surgery BCVA measurement was obtained (both eyes) within 1 week prior to the day of the surgery. On Day 0, prior to surgery, patients had their medical ophthalmic histories and concomitant medications updated; their eligibility criteria were also re-evaluated.

All patients were to be followed through Month 24 post-product administration while a subset enrolled early into the study was to be followed through Month 36 or 48.

Figure 1. Study Schematic, NTMT-03-A



Source: Applicant's submission, NTMT-03-A Appendix 5.3.5.1.16.1.1 Protocol and Amendments, Protocol version 7.0.

6.1.3 Population

Key Inclusion Criteria

1. At least one study eye with a positive diagnosis of MacTel with evidence of fluorescein leakage typical of MacTel and at least one of the other features

that include hyperpigmentation that is outside of a 500-micron radius from the center of the fovea, retinal opacification, crystalline deposits, right-angle vessels, or inner/outer lamellar cavities

2. An IS/OS EZ break (area of IS/OS loss) as measured by SD-OCT between 0.16 and 2.00 mm²
3. BCVA of 54-letter score or better (20/80 or better) as measured by the ETDRS chart at screening
4. Steady fixation in the foveal or parafoveal area and sufficiently clear media for good quality photographs
5. Age, >21 years of age or <80 years of age at screening

Key Exclusion Criteria

The ocular exclusion criteria were related to the study eye only (unless indicated for either eye):

1. Intravitreal steroid therapy for non-neovascular MacTel within the last 3 months
2. Intravitreal anti-VEGF at any time in the study eye OR intravitreal anti-VEGF therapy in the fellow eye within the past 3 months, at randomization
3. Evidence of ocular disease other than MacTel that, in the judgment of the examining physician, could confound the diagnosis, procedures, or outcome of the study (e.g., glaucoma, severe non-proliferative or proliferative diabetic retinopathy, uveitis)
4. Chronic requirement (e.g., >4 weeks at a time) for ocular medications and/or a diagnosed disease that, in the judgment of the examining physician, was vision-threatening or could affect the primary outcome (artificial tears are permitted)
5. Evidence of intraretinal neovascularization or subretinal neovascularization, as evidenced by hemorrhage, hard exudate, subretinal fluid, or intraretinal fluid in either eye
6. Evidence of central serous chorio-retinopathy in either eye
7. Evidence of pathologic myopia in either eye
8. Significant corneal or media opacities in either eye
9. History of vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
10. Any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the Age-Related Eye Disease Study (AREDS) clinical lens grading system

11. Cataract surgery in the previous 3 months or Yttrium Aluminum Garnet (YAG) laser within 4 weeks
12. Participation in any other clinical trial of an intervention (drug or device) within the last 6 months
13. Chemotherapy
14. Pregnancy or breastfeeding
15. History of malignancy that would compromise the 24-month study survival
16. History of ocular herpes virus in either eye
17. Evidence of intraretinal hyperreflectivity by ocular coherence tomography

6.1.4 Study Treatments or Agents Mandated by the Protocol

Patients enrolled in the treatment arm received the high-output encapsulated device NT501.6A.02, delivering a nominal CNTF dose of 20 ng/device/day while patients in the control arm underwent a sham procedure. There was no comparator product used in the control arm.

Patients in both arms received topical antibiotic drops (ofloxacin or equivalent) four times per day for 4 weeks (starting immediately following the surgical procedure) and topical steroid tapering dose over 4 weeks (starting on the day after the procedure). In addition, a subconjunctival steroid injection was administered in the NT-501 arm (only at the end of the procedure).

6.1.5 Description of Procedure

The product was inserted via sclerotomy into the vitreous cavity under a sterile technique by a qualified ophthalmologist in the NT-501 arm.

Patients in the sham arm followed the same pre-operative procedures as the NT-501 arm but only underwent a small conjunctival peritomy, pressure over the sham scleral “incision” site to simulate a sclerotomy, and closure of the conjunctival incision with a suture.

6.1.6 Sites and Centers

This was a multicenter study conducted at 20 study centers across the United States, Australia, France, and the United Kingdom.

6.1.7 Surveillance/Monitoring

All patients returned to the study center for postsurgical assessments on Day 1, Week 1, and at Months 6, 12, 16, 20, and 24. Additional in-clinic visits were scheduled at Months 1 and 3 for patients enrolled at study centers in France, whereas patients in other countries had telephone check-ins at these time points. A subset of patients enrolled early into the study were to have been followed through a Month 36 and/or a Month 48 visit, based on the date of the surgical

procedure; patients were required to provide additional informed consent for these visits. Patients who completed the Month 24 visit and had a Month 36 and/or Month 48 study visit scheduled to occur on or before December 1, 2021 exited from the study after completing the scheduled visit(s). Patients who had already completed the Month 24 study visit and had a Month 36 and/or Month 48 visit scheduled after December 1, 2021 did not complete these visits; instead, patients completed a safety check-in telephone call and exited the study by December 1, 2021.

Table 5. Schedule of Events, NTMT-03-A

SCHEDULE OF EVENTS													
Assessment/Procedure	Screening/ Baseline ^f	Surgery D 0	1 D Post- surgery	W 1 (= 2 D)	M 1 (= 7 D) Phone Call	M 3 (= 14 D) Phone Call	M 6 (= 30 D)	M 12 (=30 D)	M 16 (=30 D)	M 20 (=30 D)	M 24* (=30 D)	M 36* (=30 D)	M 48* (=30 D)
General Assessments													
Informed consent, demographics	X												
Informed consent addendum for visits at Months 36 and 48								X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Inclusion/exclusion criteria confirmed	X	X											
Medical evaluation	X ^a	X ^a											
Medical and ophthalmic history	X	X											
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X
Record current concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Implant/sham surgery/reconfirm inclusion/exclusion criteria		X											
Implant/sham site clinical examination			X	X	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Visual functioning questionnaire	X							X			X	X	X
Reading speed	X							X			X	X	X
Visual System Examination: Undilated													
Manifest refraction (each eye)	X			X ^b	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Best-corrected visual acuity (each eye)	X	X ^c		X	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Goldmann applanation tonometry (may be undilated)	X		X	X	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Measurement of pupil diameter	X			X ^d	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Visual System Examination: Dilated													
Microperimetry (macular integrity assessment)	X						X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X		X ^d	X ^d	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Dilated fundus examination	X		X ^d	X ^d	(X ^g)	(X ^g)	X	X	X	X	X	X	X
Spectral-domain optical coherence tomography (SD-OCT)	X						X	X	X	X	X	X	X
Fundus autofluorescence imaging (FAF)	X										X		
Color digital fundus photography (FP)	X										X		
Fluorescein angiography (FA)	X												
Laboratory Tests													
Urine pregnancy test	X ^e												

D = day; M = month (defined as 30 days); W = week

^a The medical evaluation may be performed during screening or on the day of surgery; the evaluation is standard for any surgical procedure or anesthesia (the tests performed will be site-specific)

^b Refraction is only required if there is a deterioration of 10 or more letters from baseline

^c Best-corrected visual acuity must be performed within 1 week prior to the day of surgery

^d There is no necessity to dilate the fellow eye for these examinations on Day 1 and Day 7

^e Urine pregnancy tests are required for premenopausal female participants only

^f In the event that a participant is rescreened and the rescreening occurs within 6 months of the initial screening, FA, FAF, and FP do not have to be repeated

^g In France, participants will attend in-clinic visits at Months 1 and 3 and undergo the assessments as indicated by (X) in the table.

^h The consent addendum for visits at M36 and M48 for applicable participants may be signed at any visit.

ⁱ Participants who have a M36 or M48 study visit scheduled to occur on or before 01DEC2021 will complete those visits as scheduled. Participants will exit from the study at that visit (complete Study Exit Form in Advantage eClinical). Participants who have not yet completed a Month-24 (M24) study visit, will complete the visit and exit from the study during the scheduled M24 visit (complete Study Exit Form in Advantage eClinical). All other participants who have already completed the M24 study visit and have a M36 or M48 visit scheduled after 01 December 2021, will complete a safety check-in call and exit the study on or before 01 December 2021 (complete Study Exit Form in Advantage eClinical).

Source: Applicant's submission, NTMT-03-A Appendix 16.1.1 Protocol and Amendments, Protocol version 7.0, page 7 of 48.

6.1.8 Endpoints and Criteria for Study Success

Efficacy

The primary efficacy endpoint was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline to Month 24, as assessed using SD-OCT in the study eye of patients with MacTel.

Reviewer's comment

Anatomic endpoints associated with the rate of photoreceptor loss, determined by measures such as optical coherence tomography are acceptable endpoints for traditional approval in retinal diseases. The comparison should be made between the baseline and at least two subsequent area images, with intervals of 6 months or more between images. The best curve fit analyses demonstrating

reduction in the rate of photoreceptor loss exceeding measurement uncertainty are considered clinically meaningful.

The EZ, as depicted in OCT, corresponds to the portion of the inner segment of the photoreceptors, that is immediately adjacent to the junction between photoreceptor inner and outer segments and its integrity and intensity are important indicators of photoreceptor health. Significant thinning and break in EZ are seen with photoreceptor degeneration and loss. This is an appropriate efficacy endpoint for the MacTel population. Previous published studies have shown that EZ loss is an important structural component reflecting visual function in patients with MacTel and have supported EZ loss as a measure for visual function (15-18). Slowing of the rate of EZ loss reflects photoreceptor preservation and clinical benefit through preserving retinal health and visual function. Therefore, slowing of the rate of EZ area loss is an acceptable surrogate endpoint of visual function and represents clinical benefit on vision.

The Applicant has provided a test to retest intra-grader variability of 0.0132 mm² (SD =0.0114 mm²) and intergrader variability of 0.018 mm² (SD =0.0343 mm²) when an arbitrator is included as measurement uncertainties. We note the magnitude of treatment effect observed in Study NTMT-03-A, demonstrated as the difference in mean rate of change (in mm²) in EZ area loss from baseline to 24 months between NT-501-Sham arms [0.091 mm² (95% CI: -0.13, -0.06)] exceeds the test measurement uncertainty ([Table 10](#)). For Study NTMT-03-B, although the point estimate of difference between NT-501-Sham arms (0.049 mm²) is beyond the measurement uncertainty, the upper bound of the 95% CI (-0.089, -0.008) fell within the test-retest variability ([Table 22](#)). Overall, this test is considered a reliable test for evaluation of the proposed endpoint.

The secondary efficacy endpoints, analyzed in the order listed, were as follows:

- Mean change in aggregate sensitivity of microperimetry within the EZ break area from baseline to Month 24
- Mean change in monocular reading speed from baseline at Month 24
- Mean change in the NEI-VFQ-25 near activities subscale score from baseline at Month 24 (The near activities subscale score was an average of the scores for items 5, 6, and 7 in the NEI-VFQ-25.)

Reviewer's comment

The degree of changes in aggregate retinal sensitivity loss and monocular reading speed that are clinically meaningful is unknown. However, a correlation of the anatomic changes seen with the decrease of the rate of change of EZ break with measures of visual function, (e.g., aggregate sensitivity loss in microperimetry and monocular reading speed), make the anatomic changes clinically relevant. Changes in visual function measures reflect the changes seen in the ocular anatomy to changes in the way the patient feels and functions.

Safety

The safety endpoints were as follows:

- Number and proportion of patients with a loss in BCVA of ≥ 15 letters from baseline in the study eye using the ETDRS distance chart
- Number and proportion of patients with at least one treatment-emergent SAE

6.1.9 Statistical Considerations & Statistical Analysis Plan

See separate statistical review for details of statistical analysis plan and analyses.

Analyses Populations

- mITT population: Included all randomized patients who underwent either NT-501 implantation surgery or sham surgery.
- Per protocol (PP) population: Included all patients in the mITT population who had no important protocol deviations (deviations that may have had a substantial impact on the primary efficacy endpoint).
- Safety population: Included all randomized patients who underwent either NT-501 implantation surgery or sham surgery and had at least one safety measurement.

Determination of Sample Size

The sample size calculation was based on the comparison of the two study groups over 24 months (720 days), incorporating a longitudinal mixed-effects model. The calculation was based on estimates from an analysis of Study NTMT-02 assuming that variance of EZ area is 0.0256, correlation between patient observations is 0.6 and within-patient variance is 0.47. With a type 1 error rate of 0.05 (2-sided) there was 80% power with a sample size of 50 patients per treatment group to detect a difference in rate of change 0.037 mm²/year in the EZ area in the NT-501 group versus the sham group. The sample size was increased to 56 patients per treatment group (112 total patients) to provide adequate power in the analysis of the population evaluable for efficacy.

Reviewer's comment

The assumed treatment effect of 0.037 mm²/year was derived from the NTMT-02 study results. The NTMT-02 (Phase 2) study allowed for the inclusion of both eligible eyes from a patient. For patients with two eligible eyes, one eye was randomized to the NT-501 implantation surgical arm and the other to the sham surgery arm, effectively creating a matched-pairs design for this subset of the sample. The analysis of the primary efficacy endpoint in Study NTMT-02 accounted for inpatient correlation, yielding an observed difference in the change of EZ area between the treatment and sham arms of 0.052 mm² over 24 months. In contrast, pivotal studies NTMT-03-A and NTMT-03-B studies were

designed to limit enrollment to one eye per patient, resulting in a sample with potentially greater baseline diversity and potentially higher variability in EZ area changes. To account for these design differences, the Applicant analyzed NTMT-02 data to estimate the treatment effect at 12 months. This analysis was conducted using the NTMT-02 per protocol population 12-month data, calculating the difference in least-squared means between NT-501 and sham arms while adjusting for the between eye correlation in patients who had both eyes included in the study. The resulting estimated 12-month treatment effect of 0.037 mm²/year informed the sample size calculations for NTMT-03A and NTMT-03B. We note that in a natural history follow up of 134 eyes in 70 patients with MacTel (mean duration of 4.7 years follow up), EZ loss progressed at a mean annual increment of 0.057mm². Although, EZ loss in MacTel has a non-linear progression, there is a correlation between the linear and area measures of EZ loss (19). Therefore, the observed treatment effect of 0.037 mm²/year was selected as a conservative estimate to reflect the anticipated increased variability in the Phase 3 population and ensure there was adequate power to detect a clinically meaningful treatment effect.

Analysis Method for Primary Endpoint

The primary efficacy variable is the rate of macular PR loss as determined by the EZ area loss values measured using SD-OCT. The area of EZ loss was defined as the mean of two independent readings of the single eligible SD-OCT enface image taken at baseline. For post-baseline assessments, a single, central masked reader determined the lesion area from a single, acceptable OCT volume scan. It is important to note that the same central reader conducted reviews for all post-baseline assessments across both Phase 3 studies (Studies NTMT- 03A and NTMT-03B), demonstrating consistency and reproducibility. The between group difference in the rate of EZ area loss (macular PR loss) over 24 months was assessed using a longitudinal mixed model including EZ area loss as the dependent variable, a random intercept term to account for within-patient variability, study group, time as a continuous variable, and the interaction between treatment and time. The visits at baseline and months 12, 16, 20, and 24 were included. The rate of EZ area loss and the corresponding 95% CI, SE, test statistic, and 2-sided p-value of the difference between study groups was computed from the parameter estimate for the treatment by time interaction term. The primary analysis of the primary efficacy endpoint was performed using the full mITT population without restriction due to missing visits.

The following sensitivity analyses of the primary efficacy endpoint were performed to assess the robustness of the primary analysis:

- The primary efficacy endpoint was analyzed using the mITT and PP populations restricted to only those patients with at least three visits recorded: baseline, Month 24, and at least one visit at Month 12, 16, or 20.

- Categorical time model: The mixed model was repeated with a categorical measure of time. In this model, a stochastic-adjusted EZ area loss was computed for measured timepoints.
- Covariate-adjusted model: An analysis as noted above was conducted but was adjusted for continuous baseline EZ area loss and continuous age at surgery. The difference in rate of change was defined as the parameter estimate for the treatment by time interaction term from a random intercept model.
- Exclusion of out-of-window visits: An analysis was performed excluding any out-of-window visits occurring more than ± 30 days outside of the planned time points.
- Inclusion of all data: An analysis was conducted with all observed efficacy assessments, regardless of timing (i.e., including visits outside the window for the primary analysis).

The impact of missing data on the primary efficacy endpoint was assessed by a control-based imputation method.

Analysis Methods for Secondary Endpoints

Method of Assessment of Aggregate Sensitivity Loss

Software was developed (Duke Reading Center) to register SD-OCT to Macular Integrity Assessment scanning laser ophthalmoscopy images and to overlay EZ defect areas on the microperimetry maps generated from microperimetry sensitivity values at specific points (16). This method resulted Sensitivity thresholds measured within the EZ defect areas were compared with those measured external to the lesion. Background sensitivity was defined as the average of retinal sensitivity values measured at all test points located outside the area of the EZ defect in each eye. To obtain the aggregate retinal sensitivity loss, the absolute difference relative to the background sensitivity was calculated at each test point within the area of the EZ defect and these differences were summed. Aggregate retinal sensitivity loss (expressed in dB) thus reflected the EZ defect area and scotoma depth in a single variable.

For the secondary efficacy endpoints, the observed changes from baseline at Month 24 between groups were compared using t-tests. The estimated mean treatment effect, a 95% CI, and a 2-sided p-value were provided. A hierarchical testing procedure was applied to the secondary efficacy analyses to control the overall type I error rate. In the event that the primary efficacy endpoint was statistically significant, the secondary efficacy endpoints were tested at a 2-sided type I error rate of 0.05 in the order listed. If any of the secondary endpoints were found to be not statistically significant at the 2-sided 0.05 level, the hypothesis testing was stopped and the subsequent endpoint(s) were summarized descriptively; p-values, when produced, were for descriptive purposes only.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Overall, 120 patients with MacTel were enrolled and randomized to either have NT-501 implanted or to undergo the sham procedure. A total of five patients (three in the NT-501 group and two in the sham group) were randomized but did not undergo surgery. Of these patients, four withdrew consent prior to the surgery and one did not undergo the surgery due to COVID-19. One hundred fifteen patients underwent surgery (58 patients had NT-501 implanted and 57 patients underwent sham surgery). The mITT population includes all randomized patients who underwent NT-501 implantation or sham surgery. The safety population is identical to the mITT population.

Table 6. Analysis Populations, NTMT-03-A

Population	NT-501 Surgery N=58 N (%)	Sham Procedure N=57 N (%)	Total N=115 N (%)
Modified intent-to-treat population	58 (100.0)	57 (100.0)	115 (100.0)
Safety population	58 (100.0)	57 (100.0)	115 (100.0)
Per protocol population	55 (94.8)	56 (98.2)	111 (96.5)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst

N = number of patients

6.1.10.1.1 Demographics

The demographics of the mITT/safety population are shown in [Table 7](#).

Table 7. Baseline Demographics, mITT Population, Study NTMT-03-A

Demographic	NT-501 Arm N=58	Sham Control Arm N=57	All N=115
Age (years)	-	-	-
Mean (standard deviation)	61.1 (8.0)	60.2 (8.4)	60.7 (8.2)
Median (min, max)	61 (40, 77)	59.9 (47, 78)	60 (40, 78)
Age group at randomization N (%)	-	-	-
<65 years	37 (63.8)	37 (64.9)	74 (64.3)
≥65 years	21 (36.2)	20 (35.1)	41 (35.7)
Sex, N (%)	-	-	-
Female	39 (67.2)	40 (70.2)	79 (68.4)
Male	19 (32.8)	17 (29.8)	36 (31.3)
Race, N (%)	-	-	-
White	50 (86.2)	48 (84.2)	98 (85.2)
Asian	2 (3.4)	3 (5.3)	5 (4.3)
Black or African American	1 (1.7)	2 (3.5)	3 (2.6)
American Indian or Alaskan	0 (0.0)	1 (1.7)	1 (0.9)
Other	5 (8.6)	3 (5.3)	8 (7.0)

Demographic	NT-501 Arm N=58	Sham Control Arm N=57	All N=115
Ethnicity, N (%)	-	-	-
Hispanic or Latino	1 (1.7)	5 (8.8)	6 (5.2)
Not Hispanic or Latino	57 (98.3)	52 (91.2)	109 (94.8)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

N = number of patients

The baseline characteristics of the mITT population are shown in [Table 8](#).

Table 8. Baseline Characteristics, mITT Population, Study NTMT-03-A

Characteristic	NT-501 Implant Arm N=58	Sham Control Arm N=57	All N=115
Best corrected visual acuity (letters)	-	-	-
Number (n)	58	57	115
Mean (standard deviation)	70.8 (9.1)	73.3 (8.6)	72 (8.9)
Median (min, max)	71.5 (41, 89)	74 (51, 89)	73 (41, 89)
EZ area loss (mm ²)	-	-	-
Number (n)	58	57	115
Mean (standard deviation)	0.51 (0.477)	0.49 (0.358)	0.501 (0.421)
Median (min, max)	0.35 (0.15, 1.99)	0.36 (0.16, 1.7)	0.35 (0.15, 1.99)
Aggregate sensitivity of microperimetry within the EZ break area	-	-	-
Number (n)	56	55	111
Mean (standard deviation)	63.9 (80.6)	58.3 (62.3)	61.1 (71.9)
Median (min, max)	35.2 (0.75, 398.8)	35.5 (2, 281.3)	35.5 (0.75, 398.8)
Reading speed (words per minute)	-	-	-
Number (n)	57	56	113
Mean (standard deviation)	92.1 (43.71)	96 (54)	94 (48.90)
Median (min, max)	87.64 (1-200.42)	100.0 (0-238.19)	94.3 (0-238.19)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

N = number of patients

6.1.10.1.3 Patient Disposition

Table 9. Patient Disposition, Study NTMT-03-A

Disposition	NT-501 Surgery N=61 n (%)	Sham Procedure N=59 n (%)	Total N=120 n (%)
Randomized	61 (100.0)	59 (100.0)	120 (100.0)
Received surgery	58 (95.1)	57 (96.6)	115 (95.8)
Retained implant throughout the study	57 (93.4)	0 (0.0)	57 (47.5)
Discontinued during the treatment period	5 (8.2)	5 (8.5)	10 (8.3)

Disposition	NT-501 Surgery N=61 n (%)	Sham Procedure N=59 n (%)	Total N=120 n (%)
Reason for discontinuation	-	-	-
Adverse event related to study	1 (1.7)	0 (0.0)	1 (0.9)
Eligible and did not enroll in amendment (Month 36 and Month 48)	4 (6.9)	4 (7.0)	8 (7.0)
Withdrawal of consent	0 (0.0)	1 (1.8)	1 (0.9)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = number of patients

6.1.11 Efficacy Analyses

The mITT population was the primary population for the analysis of the efficacy endpoints; the PP population was used to perform supportive analyses of the primary and secondary efficacy endpoints.

6.1.11.1 Analyses of Primary Endpoint

The primary endpoint was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline through Month 24, as assessed using SD-OCT in the study eye of patients with MacTel.

The study met its primary efficacy endpoint and demonstrated that NT-501 slowed the rate of change in the area of EZ loss and therefore the rate of disease progression over 24 months as shown in [Table 10](#). The observed differences exceeded the measurement uncertainties of the test grading used (SD-OCT) which are the following: 0.0132 mm² (SD =0.0114 mm²) of intra-grader variability and 0.018 mm² (SD =0.0343 mm²) of intergrader variability including an arbitrator making the observed changes attributable to the intervention in each arm.

Table 10. Primary Efficacy Endpoint, mITT population, Study NTMT-03-A

		NTMT-03A (N=115)
Mean rate of change (in mm ²) in EZ area loss from baseline to 24 months (95% CI)	NT-501	0.075 (0.05, 0.10)
Mean rate of change (in mm ²) in EZ area loss from baseline to 24 months (95% CI)	Sham	0.166 (0.14, 0.19)
Difference NT-501-sham (95% CI)	-	-0.091 (-0.13, -0.06)
P-value	-	<0.0001

Source: FDA statistical reviewer
N = number of patients

A series of sensitivity analyses were conducted to assess the robustness of the conclusions derived from the primary efficacy endpoint analysis (please see Section [6.1.9](#)). All results were consistent with the primary analysis results; a

significant mean difference between the NT-501 and sham groups in the rate of EZ area loss from baseline to 24 months was observed with p-value<0.0001.

The FDA statistical reviewer's additional analysis examining the missing data for the primary efficacy endpoint confirmed the Applicant's analysis.

Reviewer's comment

This study met the primary endpoint and demonstrated a 54.8% decrease in the area of EZ loss over 24 months when compared to the control group. Slowing of the rate of EZ loss reflects photoreceptor preservation and reflects clinical benefit through preserving retinal health and visual function in MacTel which is a progressive degenerative disease.

6.1.11.2 Analyses of Secondary Endpoints

The secondary efficacy endpoints, statistically tested in the order listed, were as follows:

- Mean change in aggregate retinal sensitivity loss within the EZ break area from baseline to Month 24 (please see Section [6.1.9](#))
- Mean change in monocular reading speed from baseline to Month 24
- Mean change in the NEI-VFQ-25 near activities subscale score (i.e., the average score for items 5, 6, and 7 in the questionnaire) from baseline to Month 24

Because the difference between NT-501 and sham in the analysis of the primary efficacy endpoint was statistically significant, the fixed-sequence testing continued with the analysis of the secondary efficacy endpoints in hierarchical order.

Table 11. Secondary Efficacy Endpoints Analysis, mITT Population, Study NTMT-03-A

Secondary Efficacy Endpoint	NT-501 Arm N=58	Sham Arm N=57
Aggregate retinal sensitivity loss (dB), N	51	53
Mean change from baseline to Month 24 (SD)	25.3 (34.2)	43.0 (41.8)
Two sample t-test p-value	0.02	-
Reading speed (words per minute), N	56	54
Mean change from baseline through 24 months (SD)	-6.2 (29.2)	-12.2 (42.2)
Two sample t-test p-value	0.39	-

Secondary Efficacy Endpoint	NT-501 Arm N=58	Sham Arm N=57
NEI-VFQ-25 near activities subscale score (units), N	55	54
Mean change from baseline through 24 months	-0.6 (19.2)	2.3 (18.6)
Two sample t-test p-value	0.42	-

Source: FDA statistical reviewer
N = number of patients

Mean Change in Aggregate Retinal Sensitivity Loss From Baseline to Month 24

A t-test was used to compare the change in aggregate retinal sensitivity loss from baseline to Month 24. This study met its first secondary efficacy endpoint and demonstrated that NT-501 slowed down the aggregate retinal sensitivity loss over 24 months. Although there was a mean increase in aggregate retinal sensitivity loss from baseline to Month 24 in both the NT-501 and sham groups, the magnitude of loss was significantly smaller in the NT-501 group relative to the sham group (25.3 versus 43 dB, respectively; $p=0.02$). Consistent results were confirmed from sensitivity analyses of both the mITT and PP populations.

Reviewer's comment

This study met the first secondary endpoint and demonstrated a 42% decrease in the aggregate retinal sensitivity loss in the treatment group over 24 months compared to the control group. Although it is unclear what degree of changes in aggregate retinal sensitivity loss are clinically meaningful, a correlation of the anatomic changes seen with the decrease of the rate of change of EZ break with measures of visual function, such as aggregate sensitivity loss in microperimetry, is important, as they reflect the changes seen in the ocular anatomy to changes in the way the patient feels and functions.

Mean Change in Reading Speed From Baseline To Month 24

Because the difference between NT-501 and sham in the analysis of the first secondary efficacy endpoint was significant, the fixed-sequence statistical testing continued with the analysis of the next secondary efficacy endpoint. There was a mean decrease in reading speed in both study groups from baseline to Month 24, with a smaller mean decrease in the NT-501 group relative to the sham group, but the difference between the two groups was not statistically significant (mean [SD] change from baseline: -6.2 [29.2] versus -12.2 [42.2] words per minute (wpm), respectively; $p=0.39$). Results of the sensitivity analysis were consistent with the primary analysis of this endpoint.

Mean Change in the National Eye Institute-Visual Function Questionnaire Near Activities Subscale Score From Baseline Through 24 Months

The difference between study groups was not significant for the second of three secondary efficacy endpoints above. Therefore, the results of the final secondary efficacy endpoint were only summarized descriptively herein. The mean (SD) change in the NEI-VFQ-25 near activities subscale score from baseline at Month 24 was -0.6 (19.2) and 2.3 (18.6) units in the NT-501 and sham groups, respectively, favoring the sham group.

6.1.11.3 Subpopulation Analyses

Post hoc exploratory subgroup analyses by age and sex were conducted. The majority of the patients were White and other racial groups were of very small sample size, so subgroup analyses by race are not informative.

In the age group <65 years, the difference in mean rate [SE] of change in EZ area loss from baseline over 24 months between the two groups was -0.141 [0.021] mm² (95% CI: -0.184, -0.099), favoring NT-501. In the age group ≥65 years, the difference between groups (0.011 [0.028] mm²; 95% CI: -0.044, 0.067), favoring the sham group.

Among females, the difference in mean rate [SE] of change in EZ area loss from baseline over 24 months between the two arms was -0.099 [0.022] mm² (95% CI: -0.141, -0.056), favoring NT-501. Among males, the difference between groups was -0.073 [0.030] mm² (95% CI: -0.133, -0.012), favoring NT-501.

Reviewer's comment

It seems that older patients did not benefit from NT-501. These differences may be due to chance or some unknown factor(s) impacting the NT-501 treatment effect on retinal preservation in those older than 65 years old. Overall, the interpretation of these findings is limited by small number of patients ≥65 years of age.

6.1.11.4 Dropouts and/or Discontinuations

Ten patients discontinued the study early. Please see [Table 9](#).

6.1.11.5 Exploratory and Post Hoc Analyses

Not performed.

6.1.12 Safety Analyses

6.1.12.1 Methods

All safety analyses were performed using the safety population. Safety analyses included all AEs recorded during the period from surgery through the Month 24 visit. A total of 38 patients (19 in each study group) provided consent to attend the Month 36 and Month 48 visits under protocol version 7.0. However, a

decision was subsequently made to discontinue the Month 36 and Month 48 study visits. As a result, the number of consented patients attending these visits was small (21 patients [10 NT-501 and 11 sham] at Month 36 and 3 patients [2 NT-501 and 1 sham] at Month 48). Although the primary time point of the study is considered to be Month 24, certain summaries of treatment-emergent adverse events (TEAEs) were produced through the Month 24 visit and, separately, through the end of the study/Month 48 visit.

The following definitions were used when assessing severity of an AE:

- Mild: Transient (<48 hours) or mild discomfort, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities
- Moderate: Mild to moderate limitation in activity, some assistance may be needed; possibly no but usually minimal intervention/therapy required; hospitalization possible
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely
- Life-Threatening: Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment, or hospice care probable
- Fatal: Death

Regarding AE causality, three possibilities were considered:

- Related to surgical procedure: Ocular events that occur immediately following the surgical procedure or later if they are directly related to the procedure.
- Related to the device: These would include malposition of the device with impingement of the patient's visual field, inflammation of the vitreous, or visible deterioration of the device on inspection via the ophthalmoscope.
- Related to CNTF: Dark adaptation and miosis (constriction of the pupils) is reported by the applicant in the reference safety information of the investigator's brochure, as a frequently encountered AR attributed to CNTF.

An SAE was an event that met any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received NT-501
- Other: Important medical events that may have not resulted in death, were life-threatening, or required hospitalization, may have been considered an

SAE when, based upon appropriate medical judgment, they had jeopardized the patient and had required medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs occurring during the study were recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0). A TEAE was defined as any AE that occurred after a patient underwent NT-501 implantation or sham surgery and while in study. A TEAE that was considered related to the surgical procedure, NT-501 or rhCNTF was categorized as an AR.

Ocular and systemic TEAEs and ARs were summarized by the number and percentage of patients with an event and numbers compared between the NT-501 and sham arms. Selected ocular TEAEs of special interest (cataract, delayed dark adaptation, and macular edema) were also reported by a combination of PTs and summarized by eye through the Month 24 visit and through the end of study/Month 48 visit.

The number and percentage of patients with ≥ 15 letters of vision loss from baseline in the study eye at Month 24 was tabulated by study group.

The study eye was assessed for the presence of the following: choroidal neovascularization (CNV), fluid leakage, subconjunctival hemorrhage, extrusion of NT-501, vitreous inflammation, retinal detachment, sectoral lens opacification, intraocular hemorrhage, change in IOP, dry eye, miosis, persistent chemosis, scleral leak, tractional retinal detachment, and fibrosis. In addition, patients were directly queried about their perceived changes in dark adaptation and the responses were recorded.

Pupil size, IOP, and changes from baseline in pupil size and IOP at each study visit were summarized by study group using mean, SD, median, minimum, and maximum. Based on clinical practice standards, the number and percentage of patients with an IOP of 21 mm Hg or greater and an increase of 5 mm Hg or more from baseline at postoperative visits were summarized.

All concomitant medications were coded using the World Health Organization Drug Dictionary (March 2022), and the frequency distributions and listings of concomitant medications used were presented with Anatomical Therapeutic Chemical drug classification, drug name, and study group for the mITT population. All concomitant medications were listed by patient.

6.1.12.2 Overview of Adverse Events

An overall summary of TEAEs is shown below in [Table 12](#), and ocular-related TEAEs are in [Table 13](#), and .

Table 12. TEAEs, Safety Population, Study NTMT-03-A

Characteristic	NT-501 Surgery N=58 n (%)	Sham Procedure N=57 n (%)
At least one TEAE	55 (94.8)	47 (82.5)
At least one ocular TEAE	52 (89.7)	33 (57.9)
At least one systemic TEAE	37 (63.8)	39 (68.4)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

Through the Month 24 visit, a higher percentage of patients in the NT-501 group than in the sham group experienced at least one ocular TEAE, while a similar percentage of patients in the NT-501 and sham groups experienced systemic TEAEs.

Most systemic (non-ocular) TEAEs were mild or moderate in intensity; severe systemic TEAEs were reported for 17 patients (14.8%), including 9 (15.5%) in the NT-501 group and 8 (14.0%) in the sham group. Of the 76 patients with systemic TEAEs, only 2 (1.7%; 1 in each study group) had events that were considered by the investigator to be related to the surgical procedure, to NT-501, or to CNTF. These events included a headache in the NT-501 group and constipation in the sham group, both of which were mild in severity, considered by the investigator to be related to the surgical procedure, and resolved the same day (headache) or 5 days after onset (constipation).

Most ocular TEAEs were mild or moderate in severity. Severe ocular TEAEs were reported in three patients (5.2%) in the NT-501 group, including one eye with severe ocular discomfort and two eyes with severe blurred vision. All three severe ocular events resolved within 15 days of onset. Only the severe TEAE of ocular discomfort were considered related to the surgical procedure.

The majority of ocular, related TEAEs in the NT-501 and sham groups were considered by the investigator to be related to the surgical procedure. Comparatively fewer patients in the NT-501 group had ocular ARs related to NT-501 or to CNTF, and none of the ocular ARs in the sham group were considered to be related to NT-501 or to CNTF.

Table 13. Ocular-Related TEAEs, Safety Population, Study NTMT-03-A

Variable	NT-501 Surgery N=58 n (%)	Sham Procedure N=57 n (%)
Surgery	36 (62.1)	26 (45.6)
NT-501	9 (15.5)	0 (0.0)
CNTF biologic	17 (29.3)	0 (0.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

The most common ocular, related TEAEs are shown in . The most frequently reported surgery-related ocular TEAEs in the NT-501 and sham groups

respectively were conjunctival hemorrhage (31.0% and 21.1%), eye pruritus (13.8% vs 5.3%) and eye pain (12.1% and 8.8%).

The only CNTF-related ocular events occurring in more than 2% of patients were delayed dark adaptation and miosis. Delayed dark adaptation was reported based on patient response to a direct query about their perceived changes in dark adaptation during the sham/implant site examination.

Table 14. Related TEAEs Occurring in ≥2% of Patients and With Higher Frequency in NT-501 Group Compared to Sham Group Through Month 24 Visit, Study NTMT-03-A

Adverse Reaction	NT-501 Surgery (N=58) n (%)	Sham Procedure (N=57) n (%)
Conjunctival hemorrhage	18 (31.0)	12 (21.1)
Delayed dark adaptation	12 (20.7)	0 (0.0)
Miosis	10 (17.2)	0 (0.0)
Eye pruritus	8 (13.8)	3 (5.3)
Eye pain	7 (12.1)	5 (8.8)
Ocular discomfort	7 (12.1)	1 (1.8)
Foreign body sensation	6 (10.3)	7 (12.3)
Conjunctival edema	4 (6.9)	2 (3.5)
Eye irritation	4 (6.9)	0 (0.0)
Suture related complication	4 (6.9)	1 (1.8)
Vision blurred	4 (6.9)	3 (5.3)
Vitreous hemorrhage	4 (6.9)	0 (0.0)
Iridocyclitis	3 (5.2)	0 (0.0)
Anterior chamber cell	2 (3.4)	0 (0.0)
Cataract	2 (3.4)	0 (0.0)
Eye discharge	2 (3.4)	0 (0.0)
Uveitis	2 (3.4)	0 (0.0)
Vitreous floaters	2 (3.4)	0 (0.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

No cases of infectious endophthalmitis occurred in either study group over the duration of the study.

6.1.12.3 Deaths

There was one death reported in the sham control arm through the Month 24 visit. Patient (b) (6) was a 73-year-old Caucasian female, with known history of coronary artery and valvular disease, hypertension and diabetes mellitus, who experienced an SAE of congestive cardiac failure on Day 430. The event was severe in intensity and not related to the surgery or product. The patient withdrew consent on Day 466 and died on Day 502 due to the SAE.

6.1.12.4 Serious Adverse Events

Through the Month 24 visit (730 days), a total of 19 patients, including 12 patients (20.7%) in the NT-501 group and 7 patients (12.3%) in the sham group

experienced an SAE ([Table 16](#)). Two additional patients in the NT-501 group experienced SAEs with onset after Month 24.

All non-ocular SAEs that occurred through the Month 24 visit or through the end of study/Month 48 visit were considered to be not related to the surgery, to NT-501, or to CNTF, and all had resolved by the end of the study.

A summary of SAEs through Month 24 is shown in [Table 15](#).

Table 15. Serious Adverse Events, Safety Population, Study NTMT-03-A

Category	NT-501 N=58 n (%)	NT-501 N=58 Events	Sham N=57 n (%)	Sham N=57 Events	Total N=115 n (%)	Total N=115 Events
Overall	12 (20.7)	17	7 (12.3)	8	19 (16.5)	25
Ocular	2 (3.4)	2	1 (1.8)	1	3 (2.6)	3
Eye	-	-	-	-	-	-
Study eye	2 (3.4)	2	0 (0.0)	0	2 (1.7)	2
Not in study eye	0 (0.0)	0 (0.0)	1 (1.8)	1	1 (0.9)	1
Preferred term	-	-	-	-	-	-
Suture-related complication	2 (3.4)	2	0 (0.0)	0	2 (1.7)	2
Choroidal Neovascularization	0 (0.0)	0 (0.0)	1 (1.8)	1	1 (0.9)	1
Severity	-	-	-	-	-	-
Moderate	2 (3.4)	2	1 (1.8)	1	3 (2.6)	3

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst

N = population size, n = number of patients

Table 16. Non-Ocular Serious Adverse Events by Preferred Term Through Month 24, Safety Population

MedDRA Preferred Term	NT-501 N=58 n (%)	Sham N=57 n (%)
Cardiac failure congestive	0 (0.0)	1 (1.8)
Coronary artery disease	1 (1.7)	1 (1.8)
Myocardial ischemia/infarction	1 (1.7)	1 (1.8)
Lower gastrointestinal hemorrhage	1 (1.7)	0 (0.0)
Chest pain	1 (1.7)	0 (0.0)
Appendicitis	0 (0.0)	1 (1.8)
COVID-19	1 (1.7)	0 (0.0)
Pneumonia	1 (1.7)	0 (0.0)
Sepsis	0 (0.0)	1 (1.8)
Limb injury	1 (1.7)	0 (0.0)
Soft tissue injury	0 (0.0)	1 (1.8)
Arthritis	1 (1.7)	1 (1.8)
Lumbar spinal stenosis	1 (1.7)	0 (0.0)
Basal cell carcinoma	1 (1.7)	0 (0.0)
Prostate cancer	1 (1.7)	0 (0.0)
Cystocele	1 (1.7)	0 (0.0)
Uterine prolapse	1 (1.7)	0 (0.0)
Asthma	1 (1.7)	0 (0.0)

Source: Provided by the Applicant, CSR for Study NTMT-03A, Table 14.3.1.4.3,
N = population size, n = number of patients

Ocular Serious Adverse Events

A total of three patients (3.5%), two in the NT-501 group and one in the sham group, experienced one ocular SAE each through the Month 24 visit ([Table 15](#)). In the NT-501 group, the ocular SAE occurred in the study eye of both patients and was a suture-related complication. Both events were moderate in intensity, were considered by the investigator related to the surgical procedure and resolved by the end of the study. In the sham group, the ocular SAE was CNV occurring in one fellow eye; the event was moderate in intensity, considered to be not related to the surgery or product, and ongoing at the end of the study. A third patient in the NT-501 group experienced an additional ocular SAE after Month 24, an inferior vitreous hemorrhage related to the implant that led to NT-501 explantation.

6.1.12.5 Adverse Events of Special Interest

Cataract, delayed dark adaptation, and macular edema were evaluated by the Applicant as AESI. In addition, clinical examinations were conducted to test visual acuity, intraocular pressure, and pupillary diameter.

Through the Month 24 visit, a larger percentage of study eyes in the NT-501 group than in the sham group experienced cataracts (13.8% [8 eyes] versus 3.5% [2 eyes]) and delayed dark adaptation (20.7% [12 eyes] versus 1.8% [1 eye]). Macular edema occurred in 3 (5.2%) NT-501 implanted eyes.

Only two of the cataract cases in the NT-501 group and none in the sham group were considered related. The TEAEs of delayed dark adaptation in NT-501-implanted eyes were all mild in severity. All events in the NT-501 group were considered by the investigator to be related: 10 related to CNTF alone and 1 each related to NT-501 alone and the surgery alone, while the one TEAE in the sham group was considered unrelated to surgery, NT-501, or CNTF. The onset of delayed dark adaptation in 8 of 12 implanted eyes occurred within approximately 3 months (range: 1 to 96 days) after implant surgery; the remaining four events had onset between 109 and 457 days after surgery. Seven events were ongoing at the end of the study.

Best-Corrected Visual Acuity

The number and percentage of patients with a clinically meaningful change of ≥ 15 letters of BCVA loss in the study eye at any time between baseline and Month 24 was a prespecified safety endpoint in this study. A total of 13 patients (11.3%), including 8 patients (13.8%) in the NT-501 group and 5 patients (8.8%) in the sham group, had a decrease in BCVA of ≥ 15 letters in the study eye at any time between baseline and Month 24.

Of the 8 patients with ≥ 15 letters of BCVA loss in the study eye in the NT-501 arm, the majority (7 of 8 patients) were phakic (still had their natural lens in their eye) at baseline. Four of the 8 patients had transient loss in BCVA of ≥ 15 letters that showed improvement toward baseline values by Month 24, whereas the remaining 4 patients displayed either a lack of improvement or worsening of BCVA at their last study visit. Of the latter four patients, two had at least one TEAE related to cataracts (age-related for one patient and NT-501- and surgery-related for the other patient), one patient had a newly diagnosed MacTel-related TEAE of macular hole, and one patient had an age-related vitreomacular traction; these events either preceded or were coincident with worsening vision for each patient and were unrelated to NT-501 or the surgical procedure.

Of the 5 patients in the sham group with ≥ 15 letters of BCVA loss in the study eye, the majority (3 of 5 patients) were pseudophakic at baseline. Three patients in this group had transient loss in BCVA of ≥ 15 letters that showed improvement toward baseline values or better by Month 24, whereas the remaining 2 patients displayed either a lack of improvement or worsening of BCVA at their last study visit. None of the patients in the sham group with ≥ 15 letters of BCVA loss in the study eye during the study experienced vitreous hemorrhage during the study or had ocular examination findings or TEAEs that would explain the loss in vision.

Intraocular Pressure

At all post-surgery visits through Month 24, there was a mean decrease in IOP from baseline in the NT-501 group compared with no appreciable change in the sham group: -1.2 to -1.6 mm Hg versus -0.5 to 0.4 mm Hg, respectively, across visits. No more than four patients in either study group had an IOP of 21 mm Hg

or greater and an increase in IOP of 5 mm Hg or more from baseline at any postoperative visit through Month 24. Through the Month 24 visit, a total of three patients (two in the NT-501 group and one in the sham group) had TEAEs of IOP increased in the study eye. All three events were mild or moderate in intensity and resolved by the end of the study; two events (one in each group) were considered related to the surgical procedure.

Pupillary Diameter

From Months 6 through 24, there was a greater mean decrease from baseline in pupil diameter in the NT-501 group compared with the sham group: -0.56 to -0.84 mm versus -0.01 to -0.17 mm across visits. Consistent with the observed decreases in pupil diameter, study eyes in the NT-501 group had TEAEs related to diminished pupil size, including miosis (10 study eyes) and anisocoria (1 study eye); all events were mild in severity and were considered by the investigator to be related to CNTF, while 2 of the 10 events of miosis were also considered related to NT-501. All but two events of miosis were ongoing at the end of the study.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluations were not performed.

6.1.12.7 Dropouts and/or Discontinuations

Please see [Table 9](#) (Section [6.1.10.1.3](#)).

6.1.13 Study Summary and Conclusions

The study met its primary efficacy endpoint and demonstrated that NT-501 was superior to sham in slowing the rate of EZ loss reflecting the rate of retinal photoreceptor degeneration (macular PR loss) progression over 24 months. Slowing of the rate of EZ loss reflects photoreceptor preservation and clinical benefit through preserving retinal health and visual function. In addition, NT-501 was superior to sham in reducing the magnitude of aggregate retinal sensitivity loss within the EZ break area, providing supportive evidence of slowing visual function loss. Although, none of the remaining secondary endpoints reached statistical significance, reading speed favored the NT-501 group, providing supportive evidence of the favorable treatment effect of NT-501 on photoreceptor preservation over 24 months of follow up. There were no deaths or non-ocular serious adverse events (SAEs) related to NT-501 or the implantation procedure. Suture related complications was the only ocular SAE. Delayed dark adaptation and miosis were the most common TEAEs related to NT-501. NT-501 was generally well-tolerated among adults with MacTel for a period of 24 months after intraocular implantation.

6.2 Trial #2: Study NTMT-03-B

Title: A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia Type 2.

NCT#03319849

6.2.1 Objectives

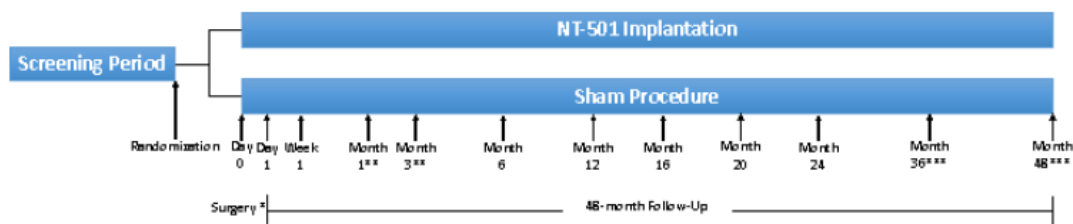
The primary objective was to assess the efficacy of NT-501 in patients with MacTel by determining the rate of change in the area of EZ loss (PR IS/OS loss) over 24 months, as measured by SD-OCT in the study eye of patients with MacTel. The secondary objective was to evaluate the safety of NT-501 in the same patient population.

6.2.2 Design Overview

This was a randomized, multicenter, evaluator-masked, sham-controlled study in adults with MacTel. The study planned to enroll a total of 112 patients (56 per arm). To confirm eligibility, the study included a screening period of up to 30 days. All patients underwent the following ocular assessments to define eligibility: manifest refraction, BCVA testing, IOP and undilated pupil diameter measurements, slit-lamp biomicroscopy and dilated fundus examinations, microperimetry, SD-OCT imaging of the central macula, fundus autofluorescence imaging, color digital fundus photography, monocular reading speed, and NEI-VFQ-25. Images were evaluated by certified personnel at a central reading center using a standardized protocol. The EZ area, retinal sensitivity, and reading speed were measured with the same methods described in Section [6.1.2](#).

Eligible patients were randomized 1:1 to NT-501 or sham control, and all received the implant or sham procedure in a single eye designated as the study eye. If both eyes were eligible, then the study eye was selected by a centralized randomization process or by patient preference if they elected to exclude a study eye from consideration. Implant or sham surgery on Day 0 was to have occurred within 30 days after randomization and/or within 58 days after screening. A pre-surgery BCVA measurement was obtained (both eyes) within 1 week prior to the day of the surgery. On Day 0, prior to surgery, patients updated their medical and ophthalmic histories and concomitant medications, and their eligibility criteria were re-evaluated. All patients completed 24 months of follow-up, while a subset of patients enrolled early into the study were followed through Month 36 or 48.

Figure 2. Study Schematic, NTMT-03-B



Source: Applicant's submission, NTMT-03-B Appendix 5.3.5.1.16.1.1 Protocol and Amendments, Protocol version 7.0.

6.2.3 Population

Key eligibility criteria were the same as described in Section [6.1.3](#).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study treatments and agents mandated by the protocol were the same as described in Section [6.1.4](#).

6.2.5 Description of Procedure

Administration of the product and sham injection technique were the same as described in Section [6.1.5](#).

6.2.6 Sites and Centers

This was a multicenter study conducted at 23 study centers in the United States, Australia, and Germany.

6.2.7 Surveillance/Monitoring

Surveillance and monitoring were the same as described in Section [6.1.7](#).

Table 17. Schedule of Events, NTMT-03-B

Assessment/Procedure	Screening/ Baseline ^f	Surgery D 0	1 D Post- surgery	W 1 (= 2 D)	M 1 (= 7 D) Phone Call	M 3 (= 14 D) Phone Call	M 6 (= 30 D)	M 12 (=30 D)	M 16 (=30 D)	M 20 (=30 D)	M 24* (=30 D)	M 36* (=30 D)	M 48* (=30 D)
General Assessments													
Informed consent, demographics	X												
Informed consent addendum for visits at Months 36 and 48								X ^h	X ^h	X ^h	X ^h	X ^h	X ^h
Inclusion/exclusion criteria confirmed	X	X											
Medical evaluation	X ^a	X ^a											
Medical and ophthalmic history	X	X											
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X
Record current concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Implant/sham surgery/reconfirm inclusion/exclusion criteria		X											
Implant/sham site clinical examination			X	X	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Visual functioning questionnaire	X							X				X	X
Reading speed	X							X				X	X
Visual System Examination: Undilated													
Manifest refraction (each eye)	X			X ^c	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Best-corrected visual acuity (each eye)	X	X ^c		X	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Goldmann applanation tonometry (may be undilated)	X		X	X	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Measurement of pupil diameter	X			X ^d	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Visual System Examination: Dilated													
Microperimetry (macular integrity assessment)	X						X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X		X ^d	X ^d	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Dilated fundus examination	X		X ^d	X ^d	(X) ^g	(X) ^g	X	X	X	X	X	X	X
Spectral-domain optical coherence tomography (SD-OCT)	X						X	X	X	X	X	X	X
Fundus autofluorescence imaging (FAF)	X										X		
Color digital fundus photography (FP)	X										X		
Fluorescein angiography (FA)	X												
Laboratory Tests													
Urine pregnancy test	X ^e												

D = day; M = month (defined as 30 days); W = week

^a The medical evaluation may be performed during screening or on the day of surgery; the evaluation is standard for any surgical procedure or anesthesia (the tests performed will be site-specific)

^b Refraction is only required if there is a deterioration of 10 or more letters from baseline

^c Best-corrected visual acuity must be performed within 1 week prior to the day of surgery

^d There is no necessity to dilate the fellow eye for these examinations on Day 1 and Day 7

^e Urine pregnancy tests are required for premenopausal female participants only

^f In the event that a participant is rescreened and the rescreening occurs within 6 months of the initial screening, FA, FAF, and FP do not have to be repeated

^g In France, participants will attend in-clinic visits at Months 1 and 3 and undergo the assessments as indicated by (X) in the table.

^h The consent addendum for visits at M36 and M48 for applicable participants may be signed at any visit.

ⁱ Participants who have a M36 or M48 study visit scheduled to occur on or before 01DEC2021 will complete those visits as scheduled. Participants will exit from the study at that visit (complete Study Exit Form in Advantage eClinical). Participants who have not yet completed a Month-24 (M24) study visit, will complete the visit and exit from the study during the scheduled M24 visit (complete Study Exit Form in Advantage eClinical). All other participants who have already completed the M24 study visit and have a M36 or M48 visit scheduled after 01 December 2021, will complete a safety check-in call and exit the study on or before 01 December 2021 (complete Study Exit Form in Advantage eClinical).

Source: Applicant's submission, NTMT-03-B Appendix 5.3.5.1.16.1.1 Protocol and Amendments, Protocol version 7.0, page 7 of 48.

6.2.8 Endpoints and Criteria for Study Success

Efficacy

The primary efficacy endpoint was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline to Month 24, as assessed using SD-OCT in the study eye.

The secondary efficacy endpoints, statistically tested in the order listed, were as follows:

- Mean change in aggregate sensitivity of microperimetry within the EZ line break area from baseline to Month 24
- Mean change in monocular reading speed from baseline to Month 24

- Mean change in the NEI-VFQ-25 near activities subscale score from baseline at Month 24 (The near activities subscale score, was an average of the scores for items 5, 6, and 7 in the NEI-VFQ-25.)

Safety

- Number and proportion of patients with a loss in BCVA of ≥ 15 letters from baseline in the study eye using the ETDRS distance chart
- Number and proportion of patients with \geq one treatment-emergent SAE

6.2.9 Statistical Considerations & Statistical Analysis Plan

All statistical considerations and the Statistical Analysis Plan were the same as described in Section [6.1.9](#).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Overall, 119 patients were enrolled and randomized to either have NT-501 implanted or to undergo the sham procedure; of this, 113 patients (95.0%) underwent surgery (59 patients had NT-501 implanted and 54 patients underwent sham surgery). Of the six patients (one in the NT-501 group and five in the sham group) who were randomized but did not undergo surgery, one patient withdrew consent, one patient was lost to follow-up, one patient did not undergo surgery due to physician decision, one patient did not undergo the surgery due to COVID-19, and two patients withdrew for other reasons. All 113 patients who were randomized and underwent surgery were included in the mITT and safety populations, and 105 patients were included in the PP population.

Table 18. Analysis Populations, Study NTMT-03-B

Population	NT-501 Surgery N=59 n (%)	Sham Procedure N=54 n (%)	Total N=113 n (%)
Modified intent-to-treat population	59 (100.0)	54 (100.0)	113 (100.0)
Safety population	59 (100.0)	54 (100.0)	113 (100.0)
Per protocol population	55 (93.2)	50 (92.6)	105 (92.9)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

6.2.10.1.1 Demographics

The demographics of the mITT population are shown in [Table 19](#).

Table 19. Baseline Demographic Information, Modified Intention-to-Treat and Safety Populations, NTMT-03-B

Parameter	NT-501 Implant Arm N=59	Sham Control Arm N=54	All N=113
Age (years)	-	-	-
Mean (standard deviation)	58.46 (7.6)	58.72 (8.9)	58.58 (8.2)
Median (min, max)	58 (41, 71)	58 (40, 75)	58 (40, 75)
Age group at randomization n (%)	-	-	-
<65 years	42 (71.2)	36 (66.7)	78 (69.0)
≥65 years	17 (28.8)	18 (33.3)	35 (31.0)
Sex, n (%)	-	-	-
Female	46 (78)	36 (66.7)	82 (72.6)
Male	13 (22)	18 (33.3)	31 (27.4)
Race, n (%)	-	-	-
White	55 (93.2)	47 (87)	102 (90.3)
Asian	3 (5.1)	1 (1.9)	4 (3.5)
Other	1 (1.7)	5 (9.2)	6 (5.3)
Unable to specify	0 (0)	1 (1.9)	1 (0.9)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	55 (93.2)	4 (7.4)	8 (7.1)
Not Hispanic or Latino	4 (6.8)	49 (90.7)	104 (92.0)
Unknown	0 (0)	1 (1.9)	1 (0.9)

Source: FDA analysis of ADSL dataset, provided by statistical reviewer.

N = population size

6.2.10.1.2 Baseline Characteristics of the Population

Table 20. Baseline Characteristics, Modified Intention-to-Treat Population, Study NTMT-03-B

Parameter	NT-501 Arm N=59	Sham Arm N=54	All N=113
Best corrected visual acuity (letters)	-	-	-
Number (n)	59	54	113
Mean (standard deviation)	74.4 (7.76)	73.6 (9.22)	74.0 (8.5)
Median (min, max)	76 (52, 89)	73 (54, 96)	74 (52, 94)
EZ area loss (mm ²)	-	-	-
Number (n)	59	53	112
Mean (standard deviation)	0.52 (0.312)	0.46 (0.283)	0.49 (0.3)
Median (min, max)	0.48 (0.16, 1.63)	0.39 (0.16, 1.38)	0.46 (0.16, 1.63)
Aggregate sensitivity of microperimetry within the EZ break area	-	-	-
Number (n)	56	52	108
Mean (standard deviation)	55.54 (56.05)	49.27 (54.78)	52.52 (55.27)
Median (min, max)	40.07 (4.82, 291.52)	28.86 (0.33, 221.17)	34.7 (0.33, 291.52)

Parameter	NT-501 Arm N=59	Sham Arm N=54	All N=113
Reading speed (words per minute)	-	-	-
Number (n)	59	53	112
Mean (standard deviation)	96.493 (47.313)	94.09 (42.80)	95.357 (45.05)
Median (min, max)	97.689 (2.29, 197.11)	89.63 (5.6, 206.49)	92.98 (2.29, 206.5)

Source: FDA analysis of ADSL dataset, provided by statistical reviewer
N = population size

6.2.10.1.3 Patient Disposition

Most patients who underwent surgery (93.8%; 106 of 113) completed the study.

Table 21. Patient Disposition, Enrolled Patients, NTMT-03-B

Disposition	NT-501 Surgery N=60 n (%)	Sham Procedure N=59 n (%)	Total N=119 n (%)
Randomized	60 (100.0)	59 (100.0)	119 (100.0)
Received surgery	59 (98.3)	54 (91.5)	113 (95.0)
Retained implant throughout the study	59 (98.3)	0 (0.0)	59 (49.6)
Discontinued during the treatment period	2 (3.3)	5 (8.5)	7 (5.9)
Reason for discontinuation	-	-	-
Death	1 (1.7)	0 (0.0)	1 (0.9)
Eligible and did not enroll in amendment (M36 and M48)	1 (1.7)	3 (5.6)	4 (3.5)
Lost to follow-up	0 (0.0)	1 (1.9)	1 (0.9)
Other	0 (0.0)	1 (1.9)	1 (0.9)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

6.2.11 Efficacy Analyses

The mITT population was used for the analysis of the efficacy endpoints; the PP population was used to perform supportive analyses of the primary and secondary efficacy endpoints.

6.2.11.1 Analyses of Primary Endpoint(s)

The rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline to Month 24 was assessed using SD-OCT in the study eye of patients with MacTel as the primary efficacy endpoint.

The study met its primary efficacy endpoint and demonstrated that NT-501 was superior to sham in slowing the rate of change in the area of EZ loss and therefore the rate of disease progression over a period of 24 months, as measured by the rate of macular PR loss (i.e., rate of EZ area loss on SD-OCT).

The mean rate of change in EZ area loss (macular PR loss) from baseline to 24 months is shown in [Table 22](#) below.

The exhibited differences exceeded the measurement uncertainties, of 0.0132 mm² (SD =0.0114 mm²) of intragrader variability and 0.018 mm² (SD =0.0343 mm²) of intergrader variability including an arbitrator.

Table 22. Primary Efficacy Endpoint, mITT Population, Study NTMT-03-B

Endpoint	Arm	NTMT-03B (N=113)
Mean rate of change (in mm ²) in EZ area loss from baseline to 24 months (95% CI)	NT-501	0.111 (0.08, 0.14)
Mean rate of change (in mm ²) in EZ area loss from baseline to 24 months (95% CI)	Sham	0.160 (0.13, 0.19)
Difference NT-501-sham (95% CI)	-	-0.049 (-0.089, -0.008)
P-value	-	0.0186

Source: FDA statistical reviewer

Results of the primary efficacy endpoint for the PP population showed similar results to that observed for the mITT population, 0.119 versus 0.160 mm²; however, the difference between groups was not statistically significant (-0.0405 [0.0209] mm²; 95% CI: -0.0816, 0.00057; p=0.0532).

In a series of different sensitivity analyses performed for the primary efficacy endpoint, the overall trend in the results was consistent, showing a smaller mean rate of macular PR loss from baseline to 24 months in the NT-501 group relative to the sham group.

FDA Statistical Reviewer's Additional Analysis

Although the primary efficacy analysis was statistically significant, some of the sensitivity analyses were not statistically significant. However, it was reassuring that the overall trend in the results was consistent, showing a smaller mean rate of macular PR loss from baseline to 24 months in the NT-501 group relative to the sham group.

For more information, please see Statistical Review.

Reviewer's comment

This study met the primary endpoint and demonstrated a 30.6% decrease in the area of EZ loss over 24 months when compared to the control group.

A smaller overall decrease of the area of EZ loss in Study NTMT-03-B compared to Study NTMT-03-A could be due to more advanced disease at baseline in the NTMT-03-B treatment group (Median EZ area in mm² and median aggregate sensitivity of microperimetry within the EZ break area were higher than the corresponding values in the treatment arm of Study NTMT-03-A and sham control groups in both studies).

6.2.11.2 Analyses of Secondary Endpoints

The secondary efficacy endpoints, analyzed in the order listed, were as follows:

- Mean change in aggregate sensitivity of microperimetry within the EZ break area from baseline to Month 24 (Please see Section [6.1.9](#))
- Mean change in monocular reading speed from baseline to Month 24
- Mean change in the NEI-VFQ-25 near activities subscale score (i.e., the average score for items 5, 6, and 7 in the questionnaire) from baseline to Month 24

Mean Change in Aggregate Sensitivity of Microperimetry Within the Ellipsoid Zone Break Area From Baseline To Month 24

A t-test was used to compare the change in aggregate retinal sensitivity loss from baseline to Month 24. The change from baseline in aggregate retinal sensitivity loss at Month 24 was similar in the NT-501 and sham groups (40.02 versus 41.97 dB, respectively; $p=0.8351$).

Since the difference between the NT-501 and sham arm was not statistically significant, the fixed-sequence statistical testing ended and the results of the remaining two secondary endpoints were summarized only descriptively.

Mean Change in Reading Speed From Baseline To Month 24

There was a smaller mean decrease from baseline in monocular reading speed in the NT-501 group relative to the sham group (-5.46 versus -18.88 wpm, respectively).

Mean Change in the National Eye Institute Visual Function Questionnaire-25 Near Activities Subscale Score From the Baseline Visit Through the Month 24 Visit

The mean change in the NEI-VFQ-25 near activities subscale score from baseline at Month 24 was -2.31 units in the NT-501 group and -3.67 units in the sham group.

Table 23. Secondary Efficacy Endpoints Analysis, mITT, Study NTMT-03-B

Endpoint	Parameter	NT-501 N=59	Sham N=54
Aggregate retinal sensitivity loss (dB)	N	52	48
-	Mean change from baseline to 24 months (SD)	40.02 (51.28)	41.97 (41.11)
-	Two sample t-test p-value	0.83	-
Reading speed (words per minute)	N	54	50

Endpoint	Parameter	NT-501 N=59	Sham N=54
-	Mean change from baseline through 24 months (SD)	-5.46 (29.65)	-18.88 33.71
-	Two sample t-test p-value	0.034	-
NEI-VFQ-25 near activities subscale score (units)	N	54	50
-	Mean change from baseline through 24 months (SD)	-2.31 (17.24)	-3.67 (14.50)
-	Two sample t-test p-value	0.67	-

Source: FDA statistical reviewer

Across the three secondary efficacy endpoints, the results obtained using the supportive PP population were consistent with those obtained using the primary mITT analysis population. In addition, the results of the sensitivity analyses excluding visits occurring more than ± 30 days outside of the planned Month 24 visit were consistent with the respective primary analysis results for each endpoint.

In the protocol version 7.0, the secondary efficacy endpoints were proposed to be analyzed using a longitudinal mixed-effects model and the corresponding 95% CI, SE, test statistic, and p-value of the difference between treatment group means at the 24-month time point would be computed. The FDA statistical reviewer repeated analysis using a longitudinal mixed-effects model for these secondary efficacy endpoints and results were consistent with the results obtained using t-tests.

6.2.11.3 Subpopulation Analyses

Post hoc exploratory subgroup analyses by age and sex were conducted. The majority of the patients were White so subgroup analyses by race were not meaningful.

In the age group <65 years, the difference in mean rate [SE] of change in EZ area loss from baseline over 24 months between the two arms was -0.088 [0.026] mm² (95% CI: -0.14, -0.036), favoring NT-501. In the age group ≥ 65 years, the difference between groups (0.038 [0.028] mm²; 95% CI: -0.017, 0.093), favoring the sham group.

Among females, the difference in mean rate [SE] of change in EZ area loss from baseline over 24 months between the two arms was -0.059 [0.025] mm² (95% CI: -0.109, -0.059), favoring NT-501. Among males, the difference between groups was -0.028 [0.034] mm² (95% CI: -0.096, 0.039).

Reviewer's comment

It seems that older patients did not benefit from NT-501. These differences may be due to chance or some unknown factor(s) impacting the NT-501 treatment effect on retinal preservation in those older than 65 years old. Overall, the interpretation of these findings is limited by small number of patients ≥ 65 years of age.

6.2.11.4 Dropouts and/or Discontinuations

Seven patients discontinued the study early. Please see [Table 21](#).

6.2.11.5 Exploratory and Post Hoc Analyses

Not performed.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety analysis methods, definitions of AEs, ARs, SAEs, intensity and causality of AEs, and coding of concomitant medications were the same as described in Section [6.1.12.1](#). A total of 33 patients (17 in the NT-501 group and 16 in the sham group) provided consent to attend the Month 36 and Month 48 visits under protocol version 7.0. However, a decision was subsequently made to discontinue the Month 36 and Month 48 study visits. As a result, the number of consented patients attending these visits was small (24 patients [11 NT-501 and 13 sham] at Month 36 and 0 patients at Month 48). Although the primary time point of the study is considered to be Month 24, certain summaries of treatment-emergent adverse events (TEAEs) were produced through the Month 24 visit and, separately, through the end of the study/Month 48 visit.

6.2.12.2 Overview of Adverse Events

An overall summary of TEAEs and ocular related TEAEs are shown below in [Table 24](#) and through the Month 24 visit, a larger percentage of patients in the NT-501 group than in the sham group experienced one or more ocular TEAEs, while a smaller percentage of patients in the NT-501 group than in the sham group experienced systemic TEAEs.

Table 24. TEAEs, Safety Population, Study NTMT-03-B

Characteristic	NT-501 N=59 n (%)	Sham N=54 n (%)
At least one TEAE	57 (96.6)	48 (88.9)
At least one ocular TEAE	55 (93.2)	41 (75.9)
At least one systemic TEAE	39 (66.1)	42 (77.8)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

Through the Month 24 visit, a larger percentage of patients in the NT-501 group than in the sham group experienced one or more ocular TEAEs, while a smaller percentage of patients in the NT-501 group than in the sham group experienced systemic TEAEs.

Table 25. Ocular, related TEAEs, Safety Population, Study NTMT-03-B

TEAE Variable	NT-501 Surgery N=59 n (%)	Sham Procedure N=54 n (%)
Surgery	46 (78.0)	34 (63.0)
NT-501	8 (13.6)	1 (1.9)
CNTF biologic	19 (32.2)	1 (1.9)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

Most systemic (non-ocular) TEAEs were mild or moderate in intensity; severe systemic TEAEs were reported for nine patients, including four in the NT-501 group and five in the sham group. All severe systemic TEAEs with the exception of one were also considered SAEs.

None of the severe systemic TEAEs in either study group were considered by the investigator to be related to the surgery, NT-501, or CNTF. With the exception of two ongoing TEAEs of headache and intervertebral disc protrusion, reported for one patient each in the NT-501 group, all severe systemic TEAEs resolved by the end of the study. Of the 81 patients with systemic TEAEs, 8 (7 in the NT-501 group and 1 in the sham group) had events that were considered by the investigator to be related to the surgical procedure, for all 8 patients, the systemic TEAE experienced was headache.

Most ocular TEAEs were mild or moderate in intensity; severe ocular TEAEs were reported for two patients (3.4%) in the NT-501 group, including one study eye with severe eye pain and the other study eye with severe suture-related complication, which was also serious. Both severe ocular TEAEs were considered related to the surgical procedure. The SAE of suture-related complication resolved, while the event of eye pain was ongoing at the end of the study.

The most common ocular, related TEAEs are shown in [Table 26](#). The majority of ocular related TEAEs in the NT-501 and sham groups were considered by the investigator to be related to the surgical procedure. Comparatively fewer patients in the NT-501 group had ocular TEAEs related to NT-501 or to CNTF.

Table 26. Ocular-Related TEAEs Occurring in $\geq 2\%$ of Patients and With Higher Frequency in NT-501 Group Compared to Sham Group, Study NTMT-03-B

Ocular-Related TEAE	NT-501 Surgery (N=58) n (%)	Sham Procedure (N=57) n (%)
Conjunctival hemorrhage	18 (30.5)	17 (31.5)
Delayed dark adaptation	15 (25.4)	1 (1.9)
Suture related complication	14 (23.7)	2 (3.7)
Conjunctival hyperemia	12 (20.3)	7 (13.0)
Foreign body sensation in eyes	12 (20.3)	8 (14.8)
Eye pain	11 (18.6)	5 (9.3)
Miosis	8 (13.6)	0 (0.0)
Headache	7 (11.9)	1 (1.9)
Vitreous hemorrhage	6 (10.2)	0 (0.0)
Dry eye	5 (8.5)	0 (0.0)
Cataract	4 (6.8)	0 (0.0)
Vision blurred	4 (6.8)	1 (1.9)
Vitreous floaters	4 (6.8)	0 (0.0)
Ocular discomfort	3 (5.1)	0 (0.0)
Anterior chamber cell	2 (3.4)	0 (0.0)
Anterior chamber flare	2 (3.4)	0 (0.0)
Conjunctival edema	2 (3.4)	5 (9.3)
Diplopia	2 (3.4)	0 (0.0)
Eye discharge	2 (3.4)	1 (1.9)
Eye irritation	2 (3.4)	2 (3.7)
Eye pruritus	2 (3.4)	1 (1.9)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst

N = population size, n = number of patients

No events of infectious endophthalmitis occurred in either study group over the duration of the study.

6.2.12.3 Deaths

Through the Month 24 visit, one patient in the NT-501 group died. Patient (b) (6), with prior history of chronic obstructive pulmonary disease (COPD) and congestive heart failure experienced an SAE of COPD on Day 575 and died on Day 607 due to the SAE. The event was severe in intensity and not related to the surgery, NT-501, or CNTF. No other patient died through the end of study/Month 48 visit.

6.2.12.4 Nonfatal Serious Adverse Events

Through the Month 24 visit, a total of 21 patients, including 11 patients (18.6%) in the NT-501 group and 10 patients (18.5%) in the sham group, experienced at least 1 SAE, fatal and nonfatal, ocular (in either eye) and systemic combined. This was a prespecified secondary safety endpoint in this study. One patient in the NT-501 group experienced both a systemic SAE (endometriosis) and an ocular SAE (device extrusion) and is therefore counted in both categories. One additional patient in the NT-501 group had a nonfatal systemic SAE with onset after Month 24.

Overall, 18 patients (15.9%), including 8 (13.6%) in the NT-501 group and 10 (18.5%) in the sham group experienced at least 1 systemic SAE each through the Month 24 visit ([Table 28](#)).

All non-ocular SAEs that occurred through the Month 24 visit were considered not related to the surgery, to NT-501, or to CNTF.

A summary of nonfatal SAEs is shown in [Table 27](#).

Table 27. Nonfatal Serious Adverse Events, Study NTMT-03-B

Category	NT-501 N=59 n (%)	NT-501 N=59 Events	Sham N=54 n (%)	Sham N=54 Events	Total N=113 n (%)	Total N=113 Events
Overall	11 (18.6)	13	10 (18.5)	13	21 (18.6)	26
Ocular	4 (6.8)	4	0 (0.0)	0	4 (3.5)	4
Eye	-	-	-	-	-	-
Study eye	4 (6.8)	4	0 (0.0)	0	4 (3.5)	4
Preferred term	-	-	-	-	-	-
Device extrusion	1 (1.7)	1	0 (0.0)	0	1 (0.9)	1
Suture-related complication	3 (5.1)	3	0 (0.0)	0	3 (2.7)	3
Severity	-	-	-	-	-	-
Mild	1 (1.7)	1	0 (0.0)	0	1 (0.9)	1
Moderate	2 (3.4)	2	0 (0.0)	0	2 (1.8)	2
Severe	1 (1.7)	1	0 (0.0)	0	1 (0.9)	1

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst

N = population size, n = number of patients

Table 28. Non-Ocular Serious Adverse Events, Study NTMT-03-B

MedDRA Preferred Term	NT-501 N=59 n (%)	Sham N=54 n (%)
Angina pectoris	1 (1.7)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (1.9)
Palpitations	0 (0.0)	1 (1.9)
Goiter	1 (1.7)	0 (0.0)
Small intestinal obstruction	0 (0.0)	1 (1.9)
Cellulitis	1 (1.7)	1 (1.9)
COVID-19	0 (0.0)	1 (1.9)
Osteomyelitis	1 (1.7)	0 (0.0)
Tendon rupture	0 (0.0)	1 (1.9)
Intervertebral disc protrusion	0 (0.0)	1 (1.9)
Osteoarthritis	0 (0.0)	1 (1.9)
Breast cancer	0 (0.0)	2 (3.8)
Colon cancer	0 (0.0)	1 (1.9)
Transient ischemic attack	2 (3.4)	0 (0.0)
Cerebrovascular accident	1 (1.7)	0 (0.0)
Depression	0 (0.0)	1 (1.9)
Endometriosis	1 (1.7)	0 (0.0)
Chronic obstructive pulmonary disease	1 (1.7)	1 (1.9)
Respiratory failure	1 (1.7)	0 (0.0)

Source: Provided by the Applicant, CSR for Study NTMT-03B, Table 14.3.1.4.3
N = population size, n = number of patients

Ocular Nonfatal Serious Adverse Events

In the NT-501 group, four patients (6.8%) experienced one ocular SAE each through the Month 24 visit ([Table 27](#)). All four ocular SAEs were encountered in the treatment eye and were considered by the investigator to be related to the surgical procedure. These ocular SAEs included three suture-related complications and one implant extrusion. All three SAEs of suture-related complications were considered by the investigator to be related to the surgical procedure, while the SAE of device extrusion was considered to be related to both the surgical procedure and to NT-501. In the case of implant extrusion, the implant was surgically repositioned and did not require explantation. All four SAEs had recovered by the end of the study.

6.2.12.5 Adverse Events of Special Interest

The Applicant evaluated cataract, delayed dark adaptation, and macular edema as adverse events of special interest (AESI). The Applicant also evaluated visual acuity, intraocular pressure, and pupillary diameter during the study.

Under combined MedDRA PTs, a larger percentage of study eyes in the NT-501 group than in the sham group experienced cataracts (6.8% versus 1.9%) and delayed dark adaptation (25.4% versus 3.7%) through the Month 24 visit. Macular edema was not reported in either group during the study.

None of the TEAEs of delayed dark adaptation in NT-501 implanted eyes were severe in intensity. All events were considered by the investigator to be related to the product or procedure. The onset of delayed dark adaptation in 10 of 15 implanted eyes occurred within approximately 3 months (range: 2 to 91 days) after implant surgery; the remaining five events had onset between 200 and 544 days after surgery. Almost all events (13 of 15) were ongoing at the end of the study.

Best-Corrected Visual Acuity

A total of 2 patients (3.4%) in the NT-501 group and 3 patients (5.6%) of patients in the sham group had a loss of ≥ 15 letters in BCVA in the study eye at any time between baseline and Month 24; this was a prespecified secondary safety endpoint in this study. Both patients in the NT-501 group with ≥ 15 letters of BCVA loss in the study eye had 1 or more TEAEs preceding or coincident with worsening vision. For 1 patient with a TEAE of vitreomacular traction, BCVA loss of ≥ 15 letters persisted through the Month 36 visit. For the other patient in the NT-501 group, vision decreased shortly after implant placement and appeared to improve at the Month 6 and Month 16 visits; however, the patient died after Month 16 due to a non-ocular SAE of chronic obstructive pulmonary disease. All 3 patients in the sham group with ≥ 15 letters of BCVA loss in the study eye were phakic without any evidence of cataract. Two of these patients had TEAEs (1 patient with epiretinal membrane and the other with punctate keratitis) coincident with vision loss while for the third patient no reason was identified for the visual acuity loss. For two of the patients BCVA was transient and showed improvement toward baseline values by Month 12 or Month 24, while the remaining patient had no further assessments after discontinuing from the study due to the non-ocular SAE of breast cancer.

Intraocular Pressure

In all postsurgery visits through the Month 24 visit, there was a mean decrease in IOP from baseline in the NT-501 group (range: -0.8 to -1.5 mm Hg) compared with a small mean increase from baseline in IOP in the sham group (range: 0.2 to 0.7 mm Hg). No more than two patients in either study group had an IOP of 21 mm Hg or greater and an increase in IOP of 5 mm Hg or more from baseline at any postoperative visit through Month 24. Through the Month 24 visit, a total of three study eyes (two in the NT-501 group and one in the sham group) had TEAEs of IOP increased that were mild or moderate in severity; two events (one in each group) were considered related to the surgical procedure, and all three events resolved by the end of the study.

Pupillary Diameter

In all post-surgery visits through Month 24, there was a greater mean decrease from baseline in pupil diameter in the NT-501 group (range: -0.14 to -0.84 mm) compared with the sham group (range: -0.04 to -0.20 mm). Eight patients in the

NT-501 group experienced TEAEs of miosis, the majority of which were mild in severity; the investigator considered all eight events to be related to CNTF.

6.2.12.6 Clinical Test Results

Clinical laboratory evaluations were not performed.

6.2.12.7 Dropouts and/or Discontinuations

Please see [Table 21](#) (Section [6.2.10.1.3](#)).

6.2.13 Study Summary and Conclusions

This second pivotal study also met its primary efficacy endpoint and demonstrated that NT-501 was superior to sham in slowing the rate of disease progression over a period of 24 months, as measured by the rate of macular PR loss in adult patients with MacTel. Slowing of the rate of EZ loss reflects photoreceptor preservation and clinical benefit through preserving retinal health and visual function. The difference between NT-501 and sham in the change in aggregate retinal sensitivity loss from baseline to Month 24 was smaller in the NT-501 group relative to the sham group but the difference did not reach statistical significance. For all remaining secondary endpoints assessing visual function and vision-related quality of life, differences favored the NT-501 group without reaching statistical significance. The directionally consistent results among all efficacy endpoints provide supportive evidence of the favorable treatment effect of NT-501 on photoreceptor preservation over 24 months of follow up. Safety results were similar to study NTMT-03A. There were no deaths or non-ocular serious adverse events (SAEs) related to NT-501 or the implantation procedure. Suture related complications was the most common ocular SAEs. Delayed dark adaptation and miosis were the most common TEAEs related to NT-501. NT-501 was generally well-tolerated among adults with MacTel for a period of 24 months after intraocular implantation.

6.3 Trial #3: NTMT-02-B

Title: Phase II, Multicenter, Open-label Safety Study of Bilateral NT-501 in Patients with Macular Telangiectasia Type 2

6.3.1 Objectives (Primary and Secondary)

The primary objective was to assess the incidence and severity of AEs following bilateral ocular implantation of NT-501. The secondary objective was to assess serum levels of CNTF and immunogenicity to NT-501 with quantification of antibodies (Ab) to CNTF, neutralizing antibodies (NAb) to CNTF, Ab to NTC-201-6A cells, and Ab to mouse dihydrofolate reductase (DHFR) based on samples collected at screening and Months 1, 3, and 6.

6.3.2 Design Overview

This was a multicenter, open-label, single-arm study in 30 adults with MacTel. All study patients who had received a NT-501 implant in one eye through participation in the Phase 1/2 extension study (NTMT-01/02E), or the Phase 3 (NTMT-03) study and met the eligibility criteria, received a NT-501 implant in their fellow eye and were followed for 6 months following the NT-501 implantation.

6.3.3 Population

Key General Inclusion Criteria

Patients should have:

1. Received the implant in one eye
2. Completed the Phase 1/2 extension study (NTMT-01/-2E) or the Month 24-visit of the Phase 3 study (NTMT-03)
3. Should have exited these studies prior to entering the Bilateral Implant safety study (NTMT-02-B)

Key Ocular Inclusion Criteria

1. Diagnosis of MacTel, with evidence of fluorescein leakage typical of MacTel, and at least one of the other features that include hyperpigmentation outside of a 500-micron radius from the center of the fovea, retinal opacification, crystalline deposits, right-angle vessels, or inner/outer lamellar cavities in their study eyes
2. Steady fixation in the foveal or parafoveal area in the study eye and sufficiently clear media for good quality photographs

Key General Exclusion Criteria

1. History or current evidence of severe hypersensitivity to the NT-501 implant
2. History or evidence of a medical condition (systemic or ophthalmic disease, metabolic dysfunction, physical examination finding or clinical laboratory finding) that might, in the opinion of the investigator, have precluded the safe administration of the NT-501 or adherence to the scheduled study visits, safe participation in the study or affect the results of the study (e.g., unstable or progressive cardiovascular, cerebral vascular, pulmonary, Parkinson's, liver or renal disease, depression, cancer, or dementia)

Key Ocular Exclusion Criteria

Patients had evidence of any of the following:

1. History or evidence of the following surgeries/procedures in the study eye, as assessed at Visit 1, including:
 - Submacular surgery
 - Vitrectomy
 - Retinal detachment
 - Incisional glaucoma surgery
 - Trabeculectomy or trabeculoplasty
 - Cataract surgery or laser-assisted in situ keratomileusis performed in the previous 6 months.
2. Uncontrolled glaucoma; or ocular hypertension, i.e., IOP ≥ 25 mm Hg in the study eye.
3. Evidence of intraretinal or subretinal neovascularization or central serous chorio-retinopathy in the study eye.
4. Evidence of ocular disorder(s) in the study eye of a severity that could confound the interpretation of study results, compromise visual acuity, or require medical or surgical intervention during the study period, including retinal vascular occlusion, severe non-proliferative or proliferative diabetic retinopathy, retinal detachment, macular hole, GA, intraretinal or subretinal neovascularization, central serous chorio-retinopathy, pathological myopia
5. Vitreous hemorrhage in the study eye at Visit 1 (Screening)
6. Spherical equivalent of refractive error in the study eye demonstrating more than 8 diopters of myopia
7. History or evidence of penetrating ocular trauma in the study eye
8. An anticipated need for cataract extraction in the study eye within 6 months of Visit 1 (Screening) such as cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the AREDS clinical lens grading system
9. Uveitis, history of uveitis in either eye or history of ocular herpes virus in either eye
10. Major surgery within the last 6 months (systemic or ocular in either eye) or patient who is likely to require major surgery within 6 months of Visit 1 (Screening)
11. Periocular or ocular/intraocular infection or inflammation in either eye (such as infectious conjunctivitis, keratitis, scleritis, endophthalmitis) within 3 months prior to Visit 1 (Screening)

12. Ocular hypotension in either eye (<6 mm Hg) that in the opinion of the Investigator would interfere with the NT-501 implantation
13. History of scleritis, scleral thinning, periocular, ocular, or intraocular infection or inflammation, cicatrizing conjunctival diseases any other ocular conditions in the study eye that could interfere with the administration of NT-501

6.3.4 Study Treatments

Patients received the high output encapsulated device NT501.6A.02, delivering a nominal CNTF dose of 20 ng/device/day as in studies NTMT-03-A and NTMT-03-B.

6.3.5 Description of Procedure

The product was inserted via sclerotomy into the vitreous cavity under a sterile technique by a qualified ophthalmologist.

6.3.6 Sites and Centers

A total of 10 study centers participated, including 7 in the United States and 3 in Australia. All study centers participating in the current study should have also participated in either Study NTMT-01/02E or Study NTMT-03-A/NTMT-03-B.

6.3.7 Surveillance/Monitoring

Table 29. Schedule of Visits and Procedures in the Assessment of Safety in Patients With Bilateral NT-501 Implants, NTMT-02-B

Procedures	Screening Day -28 to -1	Surgery Day 0	Post-Surgery Day 1	Post-Surgery Week 1	Post-Surgery Month 1	Post-Surgery Month 3	Post-Surgery Month 6
Visit Window				±2 days	±7days	±14 days	±14 days
Visit Number	1	2	3	4	5	6	7
STUDY DAY	-28 to -1	0	1	7	30	90	180
Informed Consent	X						
Demographics	X						
Medical & Ophthalmic History ^a	X	X					
Concomitant Medications and non-study procedures	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Vital Signs ^b	X						
Inclusion/exclusion criteria	X						
Eligibility Review	X	X					
Medical evaluation ^c	X	X					
Pregnancy Test ^d	X						
Serum Chemistry, Hematology & Urinalysis	X						
Visual Acuity (BCVA)	OU ^e	SE ^f		SE ^f	OU ^e	OU ^e	OU ^e
Measurement of pupil diameter	OU				OU	OU	OU
Complete Ophthalmic Exam ^g	OU		SE	SE	OU	OU	OU
Dilated Fundus Photography	OU						OU
SD-OCT ^h	OU			SE	OU	OU	OU
Fluorescein Angiography	OU						
Serum concentrations of CNTF, Ab or Nab to CNTF, Ab to NTC-201.6A cells; or Ab to DFHR (serum)	X				X	X	X
NT-501 implantation surgery		X					
Post NT-501 implant assessment			SE	SE	OU	OU	OU
External photograph of conjunctiva over implant					OU	OU	OU
Complete Exit Form							X

Abbreviations: BCVA= Best Corrected Visual Acuity; SD-OCT = spectral domain optical coherence tomography, OU = both eyes, SE = study eye

- a Demographic data includes height, weight, eye color and smoking history
- b Vital signs include body temperature, pulse rate, respiration rate and sitting blood pressure
- c The medical evaluation may be performed during screening or on the day of surgery; the evaluation is standard for any surgical procedure or anesthesia (the tests performed will be site-specific)
- d Females of childbearing potential only; additional pregnancy tests may be performed at any time/day during study
- e Manifest refraction will be performed prior to BCVA assessments except for the BCVA assessments performed prior to surgery and 1 week following surgery
- f Best-corrected visual acuity must be performed within 1 week prior to the day of surgery
- g Complete ophthalmic exam consists of an external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP assessment) Slit lamp biomicroscopy, indirect ophthalmoscopy and intraocular pressure (IOP). IOP measurements will be taken prior to pupil dilation. If possible, IOP measurements should take place at approximately the same time of the day at each visit and with the same equipment
- h The same SD-OCT instrument should be used for an individual participant throughout the entire study

Source: Applicant's submission, NTMT-02-A Appendix 16.1.1 Protocol and Amendments, Protocol version 4.0, page 10 of 51.

6.3.8 Endpoints and Criteria for Study Success

- Number and proportion of AEs, SAEs, ocular SAEs, and systemic SAEs from day of surgery through 6 months post-implantation
- Number and proportion of patients with a loss in BCVA of ≥ 15 letters from baseline in the study eye using the ETDRS distance chart
- Number and proportion of patients with at \geq one treatment-emergent SAE
- Serum levels of CNTF at Months 1, 3, and 6 post-implantation of NT-501
- Number and proportion of patients with serum Ab or NAb to CNTF, Ab to NTC-201.6A cells and Ab to DHFR at Baseline and Months 1, 3, and 6 post-implantation of NT-501

6.3.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were used to summarize the results. All analyses were performed using the safety population, defined as all patients who received NT-501 in the study eye and had at least one safety measurement in this study.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

A total of 33 patients enrolled and 32 (97.0%) of those patients received NT-501. All 32 patients who received NT-501 completed the study and were included in the safety population.

6.3.10.1.1 Demographics

The demographics of the safety population are shown in [Table 30](#).

Table 30. Demographics of Safety Population, NTMT-02-B

Parameter	All Patients N=32
Age (years)	-
Mean (standard deviation)	63 (6.5)
Median (min, max)	63 (51, 78)
Age group at randomization n (%)	-
<65 years	20 (60.6)
>65 years	13 (39.4)
Sex, n (%)	-
Female	24 (75)
Male	8 (25)
Race, n (%)	-
White	28 (87.5)
Asian	2 (6.3)
Black or African American	1 (3.1)
Other	1 (3.1)

Parameter	All Patients N=32
Ethnicity, n (%)	-
Hispanic or Latino	30 (93.8)
Not Hispanic or Latino	2 (6.2)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

6.3.10.1.2 Baseline Characteristics of the Enrolled Population

The patients had a mean BCVA in the study eye of 68.7 letters and a mean BCVA in the fellow eye of 70.1 letters.

6.3.10.1.3 Patient Disposition

A total of 33 patients were enrolled and 32 (97.0%) of those patients received NT-501; the exception was a patient whose surgery was canceled due to an event of arterial fibrillation that occurred prior to surgery and resulted in discontinuation from the study.

Table 31. Patient Disposition, Enrolled Patients, NTMT-02-B

Characteristic	NT-501 Surgery N=33 n (%)
Enrolled	33 (100.0)
Received NT-501 in the study eye	32 (97.0)
Completed study	32 (97.0)
Discontinued study	1 (3.0)
Reason for discontinuation	-
Adverse event	1 (3.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.

N = population size, n = number of patients

6.3.11 Efficacy Analyses

N/A

6.3.12 Safety Analyses

6.3.12.1 Methods

Definitions of AEs, ARs, SAEs, intensity and causality of AEs, and coding of concomitant medications were the same as described in Section [6.1.12.1](#).

The number and percentage of patients with positive serum CNTF concentrations, Ab to CNTF, Ab to NTC-201-6A cells (NTC), and Ab to mouse DHFR were tabulated at baseline and Months 1, 3, and 6. The actual CNTF concentrations, the presence of CNTF in serum, serum levels of Ab positive to CNTF, the presence of NAb to CNTF, serum levels for NAb to CNTF, the presence of Ab to NTC, the presence of Ab to mouse DHFR, and the serum levels for Ab to mouse DHFR were presented in a by-patient data listing at all applicable study visits.

6.3.12.2 Overview of Adverse Events

Overall, 26 of the 32 patients (81.3%) who received NT-501 in this study experienced at least 1 TEAE each, including 26 patients (81.3%) with at least 1 ocular event in the study eye, 6 patients (18.8%) with at least 1 ocular event in the fellow eye (that had also received the product in a previous study), and 13 patients (40.6%) with at least 1 systemic event. All patients who experienced ocular TEAEs had at least one event that was considered by the investigator to be related to the study drug or the surgery; no patient experienced a non-ocular event that was considered by the investigator to be related to the study drug or the surgery. Of the related events, two (delayed dark adaptation occurring in both eyes and iritis occurring in the study eye) were considered by the investigator to be related to NT-501; all other events were considered related to the surgical procedure. The two events related to NT-501 occurred in separate patients, were mild in intensity, and were nonserious. The event of iritis resolved, while the event of delayed dark adaptation was ongoing at the end of the study.

All reported events were mild or moderate in intensity; no patient discontinued the study due to a TEAE (serious or nonserious). Most individual ocular TEAEs occurring in the study eye were reported for one patient each.

ARs occurring in at least two study eyes in either group are shown in [Table 32](#).

Table 32. Ocular-Related Treatment-Emergent Adverse Events Occurring in $\geq 2\%$ of Patients, Study NTMT-02-B

TEAE Term	NT-501 Surgery (N=32) N (%)
Eye pain	9 (28.1)
Ocular discomfort	9 (28.1)
Conjunctival hemorrhage	8 (25.0)
Eye irritation	4 (12.5)
Allergy to surgical sutures	1 (3.1)
Anterior chamber cell	1 (3.1)
Anterior chamber flare	1 (3.1)
Conjunctival hyperemia	1 (3.1)
Delayed dark adaptation	1 (3.1)
Device extrusion	1 (3.1)
Dry eye	1 (3.1)
Eye pruritus	1 (3.1)
Foreign body sensation in eyes	1 (3.1)
Halo vision	1 (3.1)
Intraocular pressure decreased	1 (3.1)
Iritis	1 (3.1)
Pyogenic granuloma	1 (3.1)

TEAE Term	NT-501 Surgery (N=32) N (%)
Retinal hemorrhage	1 (3.1)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.
N = population size, n = number of patients

6.3.12.3 Deaths

There were no deaths reported in Study NTMT-02-B.

6.3.12.4 Nonfatal Serious Adverse Events

A total of two patients had one SAE each: one was non-ocular (feces discolored) and one was ocular (device extrusion). The event of feces discolored was unrelated, moderate in intensity, associated with an intercurrent illness, resulted in hospitalization, and resolved. The event of device extrusion – specifically, a slight extrusion of the loop of the implant in the study (left) eye noted at the Month 3 visit – was mild in intensity, considered related to the study procedure, and resolved following an unremarkable surgical revision.

Table 33. Nonfatal Serious Events, NTMT-02-B

Variable	NT-501 Surgery N=32 n (%)	NT-501 Surgery N=32 Cases
Overall	2 (6.2)	2
Ocular	1 (3.1)	1
Eye type	-	-
Study eye	1 (3.1)	1
Preferred term	-	-
Device extrusion	1 (3.1)	1
Severity	-	-
Mild	1 (3.1)	1

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

6.3.12.5 Adverse Events of Special Interest

N/A

6.3.12.6 Clinical Test Results

Of the 33 enrolled patients, 31 were tested for serum antibodies at baseline, 1, 2, 3 and 6 months. One out of 31 patients (3.2%) tested positive for serum antibodies against rhCNTF, and another patient tested positive for serum non-secreted, intracellular protein DHFR.

Reviewer's comment

Because of the low occurrence of anti-drug antibodies, the effect of serum anti-rhCNTF and anti-DHFR antibodies on the safety of NT-501 is unknown.

Clinical Tests

Best-Corrected Visual Acuity

Mean (SD) BCVA remained relatively stable. One patient at Week 1 and one patient at Month 6 had a loss of ≥ 15 letters in BCVA. Of these patients, the loss in the patient at Week 1 was transient, with the BCVA returning to near baseline levels by Month 1; the loss in the patient at Month 6 was associated with a TEAE of cataract subcapsular that was not considered related to study drug or the study procedure.

All changes observed in pupil responsiveness, slit-lamp biomicroscopy evaluations, anterior chamber cells and flare assessments, and IOP measurements were transient, associated with the surgical procedure, and resolved.

6.3.12.7 Dropouts and/or Discontinuations

Please see [Table 31](#) (Section [6.3.10.1.3](#)).

6.3.13 Study Summary and Conclusions

NT-501 was generally safe and well-tolerated in patients who received NT-501 in the second eye in this study and were followed for 6 months. There were no cases of severe inflammation encountered and no meaningful differences were observed between the safety profiles of the study and fellow eyes.

6.4 Trial #4 NTMT-02

Title: A Phase 2 Multicenter Randomized Clinical Trial of Ciliary Neurotrophic Factor (CNTF) for Macular Telangiectasia Type 2 (MacTel).

6.4.1 Objectives

The primary objective of this study was to investigate the effect of the NT-501-6A.02 ECT releasing CNTF (NT-501) on the change from baseline in the EZ (area of IS/OS loss) as measured by SD-OCT in eyes with evidence of MacTel at 24 months.

6.4.2 Design Overview

This was a multicenter, randomized, masked, sham-controlled study in adults with MacTel. All patients had a screening period of up to 14 days, with surgery/sham occurring within 7 weeks after screening was completed. One or both eyes of each patient could have been included in the study. Patients with

one study eye meeting the inclusion criteria were randomized (1:1) to receive either the NT-501 implant or sham procedure in the study-eligible eye. If both eyes were eligible, then the right eye was randomized (1:1) to receive either the NT-501 implant or sham procedure and the left eye received the alternative surgery/sham. Patients were followed for 24 months.

6.4.3 Population

Key Inclusion Criteria

Patients had the following:

1. One study eye with a positive diagnosis of MacTel with evidence of fluorescein leakage typical of MacTel or at least one of the other features including retinal opacification, crystalline deposits, right angle vessels, inner/outer lamellar cavities or hyperpigmentation not involving the center of the fovea, but no evidence of intraretinal/subretinal neovascularization
2. An IS/OS PR break in the study eye(s) and en-face EZ (area of IS/OS loss) as measured by SD-OCT between 0.16 mm² and 4.00 mm²
3. BCVA is 64 letter score or better (20/50 or better) in the study eye(s) as measured by the ETDRS chart
4. Steady fixation in the foveal or parafoveal area of each eye and sufficiently clear media for good quality photographs
5. Manifest consistent responses on microperimetry, including reproducible consistent absolute scotomas on two consecutive tests conducted within 7 days during screening (may be done within same day)

Key Exclusion Criteria

1. Patient is <21 years of age or >80 years of age
2. Patient received intravitreal therapy for non-neovascular MacTel within the last 3 months (steroids) and within the last month (anti-VEGF)
3. Patient has evidence of ocular disease other than MacTel that, in the judgment of the examining physician, may confound the diagnosis, procedures or outcome of the study (e.g., glaucoma, severe nonproliferative or proliferative diabetic retinopathy, uveitis, etc.)
4. Patient has a chronic requirement (e.g., 4 weeks at a time) for ocular medications and/or has a diagnosed disease that, in the judgment of the examining physician, may be vision-threatening or may affect the primary outcome (artificial tears are permitted)
5. Patient has evidence of intraretinal/subretinal neovascularization in either eye
6. Patient has evidence of central serous chorioretinopathy in either eye
7. Patient has evidence of pathologic myopia in either eye

8. Patient has significant corneal or media opacities in either eye
9. Patient has had a vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
10. Patient has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the AREDS clinical lens grading system
11. Patient has undergone lens removal in the study eye(s) in the previous 3 months or YAG laser within 4 weeks
12. Patient was a study patient in any other clinical trial of an intervention (drug or device) within the last 6 months
13. Patient on antiherpetic nucleoside analogs for treatment of prophylaxis (such as Acyclovir, Valaciclovir, Penciclovir, Famciclovir) or anti-cytomegaloviral nucleoside analogs (such as Ganciclovir, Foscarnet) or has required these agents in the last year or is anticipated to require any antiherpetic or anti-cytomegaloviral nucleoside analog treatment during the trial
14. Patient is on chemotherapy
15. Patient is pregnant or breastfeeding
16. Patient has a history of malignancy that would compromise the 24-month study survival
17. Patient is on immunosuppressive therapy
18. Patient is considered immunodeficient or has a known history of HIV
19. Patient with a history of ocular Herpes virus
20. Patient has, in the opinion of the investigator, any physical or mental condition that would increase the risk of participation in the study or may interfere with the study procedures, evaluations and outcome assessments

6.4.4 Study Treatments

Both eyes were to be included in the study if eligible. Patients with one study eye meeting inclusion criteria were randomized (1:1) to receive either the NT-501 implant or sham procedure in the study-eligible eye. If both eyes were eligible, the right eye was randomized (1:1) to receive the NT-501 implant or sham procedure. The left eye received the alternative surgery/sham. The NT-501-6A.02 high output device was used in the study. Each device produced approximately 20 ng/device/day of rhCNTF.

6.4.5 Description of Procedure

The device was placed in the posterior chamber of the eye as described in Section [6.1.5](#).

6.4.6 Sites and Centers

This was a multicenter study conducted across 11 centers (8 in the United States and 3 in Australia).

6.4.7 Surveillance/Monitoring

Study eyes received the NT-501 implant or underwent the sham procedure on Day 0 and were assessed for efficacy and safety on Day 1, Week 1 (± 2 days), and Months 1 (± 1 week), 3 (± 1 week), 6 (± 2 weeks), 12 (± 2 weeks), 18 (± 2 weeks), and 24 (± 2 weeks).

Table 34. Assessment and Examination Schedule, NTMT-02

Assessment/Examination Schedule:

	Screening/Baseline (completed w/in 14 days)	Surgery (w/in 7 weeks of screening)	1 Day Post-Surgery	1 Week (± 2 days)	1 Month (± 1 week)	3 Months (± 1 week)	6 Months (± 2 weeks)	12 Months (± 2 weeks)	18 Months (± 2 weeks)	24 Months (± 2 weeks)
GENERAL ASSESSMENTS										
Inclusion/Exclusion criteria confirmed / ICF	X									
Medical & Ophthalmic History / ConMeds	X	X								
AE Assessment / Record ConMeds	X	X	X	X	X	X	X	X	X	X
Visual Functioning Questionnaire	X							X		X
Reading Speed	X							X		X
VISUAL SYSTEM EXAMS: UN-DILATED										
Manifest Refraction	X		X ¹	X ¹	X ¹	X ¹	X	X	X	X
Best Corrected Visual Acuity (each eye)	X	X ⁰	X	X	X	X	X	X	X	X
Applanation Tonometry	X		X	X	X	X	X	X	X	X
Microperimetry	X ² / X ²				X	X	X	X	X	X
Humphrey Visual Field (HVF) 30-2	X						X	X	X	X
VISUAL SYSTEM EXAMS: DILATED										
Slit lamp Biomicroscopy	X		X	X	X	X	X	X	X	X
Dilated Fundus Examination	X		X	X	X	X	X	X	X	X
SD-OCT	X				X	X	X	X	X	X
Autofluorescence Imaging	X							X		X
Color Digital Fundus Photographs	X							X		X
Fluorescein Angiography* (✓ for dye allergy)	X ³							X		X
ERG (at selected sites)**	X**						X**	X**		X**
AOSLO (for selected participants)** - requires separate consent at screening	X**							X**		X**
STUDY THERAPY										
Medical Examination ⁶	X									
Implant Surgery/Reconfirm Inc/Exc criteria		X								
Implant Site Clinical Examination			X	X	X	X	X	X	X	X
LABORATORY										
Urine Pregnancy ^{4,5}	X									
HIV Testing ⁵	X									

⁰ BCVA must be performed within 1 week of surgery

¹ Perform if deterioration of 10 or more letters from baseline

² Microperimetry at Screening/Baseline must be done twice (the 2nd measure should be done within 7 days after the initial measure, and may be done within the same visit).

³ Fluorescein angiography done within 1 month of the initial screening/baseline visit will be accepted.

*Patients with known allergies to any iodine or iodine containing dyes will be exempted from the fluorescein angiography procedure.

⁴ Urine pregnancy test should only be performed on premenopausal women.

⁵ These tests should be conducted during follow-up if there is clinical suspicion.

⁶ Medical examination as per requirements of the surgical facility.

Source: Applicant's submission, NTMT-02, Appendix 5.3.5.1.16.1.1 Protocol and Amendments, Protocol version 4.0.

6.4.8 Endpoints and Criteria for Study Success

Efficacy Endpoints

The primary efficacy endpoint was the change in the EZ area loss from baseline to Month 24 as measured by en-face imaging by SD-OCT in study eye(s).

The secondary efficacy endpoints were as follows:

- Change in the EZ (area of IS/OS) loss from baseline to Month 12
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 12 and 24
- Proportion of study eyes with an increase of 35% or more from baseline in the EZ (area of IS/OS loss) at Months 12 and 24
- Change in BCVA from baseline to Months 12 and 24
- Proportion of study eyes with a loss of ≥ 15 letters from baseline in BCVA at Months 12 and 24
- Proportion of study eyes with a loss of ≥ 10 letters from baseline in BCVA at Months 12 and 24
- Change in reading speed from baseline to Months 12 and 24

Exploratory Efficacy Endpoints

Change in the NEI-VFQ-25 (overall and subscale) from baseline to Months 12 and 24.

Safety Endpoints

- TEAEs: Ocular and systemic
- The following ocular events (regardless of attribution) were considered safety outcomes if they occurred:
 - Rejection or extrusion of the NT-501 device
 - Development of peri-implant fibrosis, which either blocked the visual axis of the implanted eye or affected the lens or retina (minor/moderate fibrosis around the implant and/or the attachment point was an expected possibility and was considered safe on ocular function); attention was focused on fibrosis that may have detached the retina
 - Development of choroidal or retinal neovascularization in the study eye
 - The number and proportion of eyes experiencing events affecting ocular function, which were different from those expected in the normal course of MacTel, and which were potentially related to the surgical procedure, implant, or CNTF including: endophthalmitis; vitreal inflammation; tractional retinal detachment; sectorial lens opacification; intraocular

- hemorrhage; high or low IOP; dry eye; change in dark adaptation; miosis; persistent chemosis; scleral leak
- Change in visual field from baseline measured by the Humphrey Visual Field 30-2

6.4.9 Statistical Considerations & Statistical Analysis Plan

Results were summarized using descriptive statistics.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

6.4.10.1.1 Demographics

The demographics of the ITT and safety population (identical) are shown in [Table 35](#).

Table 35. Baseline Demographic Information, Intention-to-Treat and Safety Population, NTMT-02

Parameter	NT-501 N=16	Sham Arm N=19	NT-501 + Sham N=32	Total N=67
Age (years)	-	-	-	-
Mean (standard deviation)	60.1 (10.7)	59.42 (7.6)	63.4 (8.4)	61.5 (8.9)
Median (min, max)	60 (45, 79)	61 (47, 73)	64 (45, 76)	63 (45, 79)
Sex, n (%)	-	-	-	-
Female	9 (56.3)	11 (57.9)	21 (65.6)	41 (61.2)
Male	7 (33.7)	8 (42.1)	11 (34.4)	26 (38.8)
Race, n (%)	-	-	-	-
White	12 (75.0)	16 (84.2)	30 (93.8)	58 (86.6)
Asian	0	1 (5.3)	0	1 (1.5)
Black or African American	0	0	1 (3.1)	1 (1.5)
Other	4 (25.0)	2 (10.5)	1 (3.1)	7 (10.4)
Not collected	-	-	-	-
Ethnicity, n (%)	-	-	-	-
Hispanic or Latino	15 (93.8)	18 (94.7)	31 (96.9)	64 (95.5)
Not Hispanic or Latino	1 (6.3)	-	1 (3.1)	2 (3.0)
Unknown	0	1 (5.3)	0	1 (1.5)

Source: FDA analysis of ADSL dataset.
N = population size

6.4.10.1.2 Baseline Characteristics of the Enrolled Population

There were no clinically meaningful differences between treatment groups in any of the ocular parameters (BCVA, EZ area, reading speed, pupil diameter, IOP, and slit-lamp and dilated fundus parameters) at baseline.

Table 36. Baseline Population Characteristics, Study NTMT-02

Parameter	NT-501 N=48	Sham N=51	Total N=99
Best corrected visual acuity (letters)	-	-	-
Number (n)	48	51	99
Mean (standard deviation)	76.94	76.12	76.52
Median (min, max)	76.50 (63, 92)	76 (65, 90)	76 (63, 92)
Reading speed (words per minute)	-	-	-
Number (n)	47	49	96
Mean (standard deviation)	119.5	101.4	110.28
Median (min, max)	94 (45.6, 324)	90.3 (49.8, 300)	91.20 (45.60, 324)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

N = population size

6.4.10.1.3 Patient Disposition

Table 37. Patient Disposition, Enrolled Patients, NTMT-02

Patient Disposition	NT-501 Surgery N=16 n (%)	Sham Surgery N=19 n (%)	NT-501 + Sham Surgery N=32 n (%)	Total N=67 n (%)
Screened	-	-	-	112 (-)
Randomized	16 (100.0)	19 (100.0)	32 (100.0)	67 (100.0)
Completed	15 (93.8)	19 (100.0)	31 (96.9)	65 (97.0)
Withdrew	1 (6.2)	0	1 (3.1)	2 (3.0)
Reason for withdrawal	-	-	-	-
Death	1 (6.2)	0	1 (3.1)	2 (3.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst

N = population size, n = number of patients

6.4.11 Efficacy Analyses

The primary efficacy endpoint of Study NTMT-02 was different than the primary efficacy endpoint of the two pivotal studies. This study therefore did not contribute to the efficacy assessment of this product and data were used to conduct additional safety analyses.

6.4.12 Safety Analyses

6.4.12.1 Methods

Safety analysis methods, definitions of AEs, ARs, SAEs, intensity and causality of AEs, and coding of concomitant medications were the same as described in Section [6.1.12.1](#)

6.4.12.2 Overview of Adverse Events

The safety results did not significantly differ from Studies NTMT-03-A and NTMT-03-B. No unusual TEAEs were encountered. Safety data of this study are included in the integrated summary of safety (ISS), Pool 2.

6.5 Trial #5: NTMT-01

Title: A Phase 1 Multicenter Open Label Safety and Tolerability Clinical Trial of Ciliary Neurotrophic Factor (CNTF) in Patients with Macular Telangiectasia Type 2 (MacTel).

6.5.1 Objectives

The primary objectives were to explore the safety and tolerability of the NT-501 device in adults with MacTel.

6.5.2 Design Overview

This study was a Phase 1, open-label, nonrandomized, single-arm, multicenter pilot study that evaluated the safety and tolerability of NT-501 implants in 7 adults with MacTel. Each patient received the NT-501 device in the study eye; the fellow eye served as the control eye. Patients were followed for 60 months.

6.5.3 Population

Key Inclusion Criteria

To participate in this study, patients met the following criteria:

1. Diagnosis of bilateral MacTel
2. Medically able to undergo ophthalmic surgery for ECT implant
3. BCVA of 64 letters or better (20/50 or better) in the study eye
4. IS/OS EZ line break
5. Steady fixation in the foveal or parafoveal area of both eyes and sufficiently clear media for good quality photographs
6. Consistent responses on microperimetry

6.5.4 Study Treatments

The NT-501-6A.02 high output device producing approximately 20 ng/device/day of rhCNTF was implanted in the study eyes.

6.5.5 Description of Procedure

The product was administered via intravitreal placement under sterile technique by a qualified ophthalmologist as described in Section [6.1.5](#).

6.5.6 Sites and Centers

Multicenter study

6.5.7 Surveillance/Monitoring

Table 38. Schedule of Assessments, NTMT-01

	SCHEDULED VISITS												
	Screening / Baseline	Surgery (w/in 7 weeks of screening)	1 Day Post Implant	1 Week ± 2 days	1 Month ± 7 days	3 Months ± 7 days	6 Months ± 14 days	9 Months ± 7 days	12 Months ± 14 days	18 Months ± 14 days	24 Months ± 14 days	30, 42 & 54 Months ± 14 days	36, 48 & 60 Months ± 14 days
GENERAL ASSESSMENTS													
Inclusion/Exclusion Criteria	X												
Medical/ Ophthalmic/Medication History	X												
AE assessment /Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X
Implant site clinical examination			X	X	X	X	X	X	X	X	X	X	X
Visual Function Questionnaire	X								X		X		X
VISUAL SYSTEM EXAMS													
Full Field ERG	X					X		X	X	X	X	X	X
Manifest Refraction	X						X	X	X	X	X	X	X
Visual Acuity (both eyes)	X		X	X	X	X	X	X	X	X	X	X	X
IOP	X		X	X	X				X	X	X	X	X
Slit lamp exam	X		X	X	X	X	X	X	X	X	X	X	X
Ophthalmoscopic exam	X		X	X	X	X	X	X	X	X	X	X	X
Microperimetry ²	X (x2) ¹			X	X	X	X		X	X	X	X	X
Adaptive Optics ³	X						X		X	X	X		X
Spectralis OCT	X				X	X	X	X	X	X	X	X	X
Autofluorescence Imaging	X				X	X	X		X	X	X	X	X
Digital Fundus photographs	X				X	X	X		X	X	X	X	X
Fluorescein angiography	X					X			X		X		X
STUDY THERAPY													
Implant Surgery		X											
LABORATORY													
Serum chemistry	X								X		X		X
Serum CNTF	X								X		X		X
Antibodies to CNTF and NTC-201	X								X		X		X
Hematology	X								X		X		X
Urine Pregnancy	X ²								X ²		X ²		X ²
Urinalysis and urine chemistry	X								X				X ⁴
HIV testing	X												

¹ Microperimetry at Screening/Baseline must be done twice (the 2nd measure should be done within 5 days after the initial measure).

² Urine pregnancy test should only be performed on premenopausal women.

³ Adaptive Optics will be done in the 2 safety participants who had this imaging done during the first 12 months of the Safety Study.

⁴ Procedure at 60 months (last study visit).

Source: Section 5.3.5.2, NTMT-01 Clinical Study Report, Appendices, Protocol NTMT-01, v5.0

6.5.8 Endpoints and Criteria for Study Success

The following safety parameters were evaluated:

- A $\geq 30\%$ reduction in electro-retinogram (ERG) potentials
- A decrease in BCVA of 15 or more letters
- Rejection or extrusion of the NT-501 device
- Protocol-related abnormal findings from serum chemistry, hematology, and urinalysis/urine chemistry (abnormal implying clinically significant out of range findings as determined by the Principal Investigator, or if clinical chemistry toxicity is \geq Grade 2)
- Serum CNTF levels and the circulating antibodies to CNTF and NTC-201
 - Peri-implant fibrosis, which either blocked the visual axis of the implanted eye or affects the lens or retina (minor/moderate fibrosis around the implant and/or the attachment point was an expected possibility and was considered safe on ocular function). Attention focused on fibrosis that could have detached the retina
- Development of CNV in the study eye, in which case it could have been considered a safety event and explant was considered
- AEs affecting ocular function, which were different from those expected in the normal course of MacTel, which were potentially related to the implant
- Local or systemic toxicities considered SAEs that were potentially related to the implant

6.5.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were used to summarize the results.

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

Seven patients enrolled in the study. All patients who received an implant were included in the safety population.

6.5.10.1.1 Demographics

Demographics of the seven patients enrolled are shown in [Table 39](#)

Table 39. Demographics of Population, Study NTMT-01

Parameter	All Patients N=7
Age (years)	-
Mean (standard deviation)	55.71 (6.82)
Median (min, max)	55 (48, 67)
Sex, n (%)	
Female	5 (71.0)
Male	2 (29.0)
Race, n (%)	-
White	5 (71.4)
Asian	1 (14.3)
Other	1 (14.3)
Ethnicity, n (%)	-
Hispanic or Latino	-
Not Hispanic or Latino	7 (100.00)

Source: FDA analysis of ADSL dataset
N = population size

6.5.10.1.2 Baseline Characteristics of the Enrolled Population

The mean BCVA for study eyes was 73.7 (SD =8.0) letters and was 78.6 (SD =8.4) letters for fellow eyes. The mean EZ for the study eyes was 0.8 (SD =0.8) mm² and was 0.9 (SD =0.9) mm² for fellow eyes.

Table 40. Baseline Population Characteristics, Study NTMT-01

Parameter	NT-501 N=7
Best corrected visual acuity (letters)	-
Number (n)	4
Mean (standard deviation)	77.6 (10.7)
Median (min, max)	82 (61, 87)
EZ area (mm ²)	-
Number (n)	4
Mean (standard deviation)	0.6 (0.75)
Median (min, max)	0.41 (0.043, 1.86)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.
N = population size

6.5.10.1.3 Patient Disposition

Table 41. Patient Disposition, Enrolled Patients, NTMT-01

Patient Disposition	NT-501 Surgery N=7 n	NT-501 Surgery N=7 (%)
Enrolled patients	7	(100.0)
Received surgery	7	(100.0)
Completed protocol	6	(85.7)
Did not complete protocol	1	(14.3)

Patient Disposition	NT-501 Surgery N=7 n	NT-501 Surgery N=7 (%)
Reason not completed per protocol	-	-
Patient missed four visits due to SAEs	1	(14.3)
Retaining the implant	7	(100.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.
N = population size, n = number of patients

6.5.11 Efficacy Analyses

N/A

6.5.12 Safety Analyses

6.5.12.1 Methods

Safety analysis methods, definitions of AEs, ARs, SAEs, intensity and causality of AEs, and coding of concomitant medications were the same as described in Section [6.1.12.1](#)

6.5.12.2 Overview of Adverse Events

Safety analysis of this study was reviewed and did not significantly differ from Studies NTMT-03-A and NTMT-03-B. No unusual signals were identified. Safety data of this study are included in the ISS, Pool 2.

6.6 Trial #6: NTMT-01/02E (Includes Substudy NTMT-01/02E-SS)

Title: Extension Study of NT-501 Ciliary Neurotrophic Factor (CNTF) Implant for Macular Telangiectasia (MacTel) (NTMT-01/02E) and Sub-study to the Extension Study to Provide the NT-501 Implant to Participants Who Contributed a Single Eligible Eye Randomized to the Sham Procedure in the Phase 2 NTMT-02 Study (NTMT-01/02E-SS).

6.6.1 Objectives (Primary, Secondary, etc.)

Main Extension Study (NTMT-01/02E)

The primary objective was to investigate the long-term safety and efficacy of NT-501 in patients previously enrolled in the NTMT-01 and NTMT-02 studies.

The secondary objective was to investigate the change in the EZ area (IS/OS loss) in patients previously enrolled in the NTMT-01 and NTMT-02 studies, as measured SD-OCT in study eye(s).

Substudy NTMT-01/02E-SS

The main objective was to enable implantation of NT-501 into the study eye of those patients who contributed a single eligible eye randomized to the sham procedure in the NTMT-02 study.

6.6.2 Design Overview

Main Extension Study (NTMT-01/02E)

This was a noninterventional study designed to provide long-term safety and efficacy follow-up for patients who had NT-501 implanted intraocularly and/or underwent sham surgery in the respective precursor study (NTMT-01 or NTMT-02).

The extension study was planned to include 7 patients (7 study eyes), previously enrolled in the open-label NTMT-01 study, who had already completed 60 months of follow-up (Cohort 1) and 66 patients (98 study eyes) previously enrolled in the NTMT-02 study, who had completed 24 months of follow-up (Cohort 2).

In Cohort 1, patients had received the product in only one eye during the precursor study, NTMT-01.

In Cohort 2, patients with one eye meeting the inclusion criteria had been randomized (1:1) and had already received the implant or undergone the sham procedure in the study-eligible eye in parent study NTMT-02. In patients with both eyes eligible, the right eye had been randomized (1:1) and had received the product or underwent the sham procedure, and the left eye had received the other intervention. As a result of that, Cohort 2 included the following study groups based on the intervention received in the precursor study:

- NT-501 group: Included patients who each had one study-eligible eye that had NT-501 implanted and a fellow eye that did not undergo any study intervention
- Sham group: Included patients who each had one study-eligible eye that underwent sham surgery and a fellow eye that did not undergo any study intervention
- Sham+NT-501 group: Included patients who had both eyes that were study-eligible and had NT-501 implanted in one eye and underwent sham surgery in the contralateral eye

Although patients in Cohort 2 were unmasked to study group assignments after completing Month 24 of the precursor study, assessors remained masked for the duration of the main extension study.

Patients were to be followed annually for 48 months in this extension protocol, for a total of 108 months postproduct administration in Cohort 1 and 72 months in Cohort 2.

Substudy of the Extension Study (NTMT-01/02E-SS)

This was an open-label, single-dose study which offered the option to patients enrolled in study (NTMT-02), who had one study-eligible eye that underwent sham surgery, to have NT-501 implanted in the same study eye.

After the first (annual) visit in the NTMT-01/02E study, eligible patients in Cohort 2 provided written informed consent specifically for the substudy and underwent a presurgical medical and ophthalmic evaluation. On the day of implant surgery, patients had their medical and ophthalmic histories and concomitant medication uses updated (if necessary) and had NT-501 implanted in the study eye (the same eye designated as the study eye in the precursor study). Patients in the substudy received NT-501 in an open-label manner. Assessors remained masked during the substudy.

6.6.3 Population

Main Extension Study (NTMT-01/02E)

To participate in this study, patients previously enrolled in the NTMT-01 or NTMT-02 protocol and received the NT-501 implant and/or underwent a sham procedure.

Substudy of the Extension Study (NTMT-01/02E-SS)

To participate in the substudy patients participated in Study NTMT-02, had one eligible eye, and received sham injection in that eye.

6.6.4 Study Treatments or Agents Mandated by the Protocol

Main Extension Study (NTMT-01/02E)

This was an observational study.

Substudy of the Extension Study (NTMT-01/02E-SS)

Patients who participated in the Substudy NTMT-02 received NT-501, each implant consisting of 200,000-440,000 rhCNTF-secreting NTC-201-6A.02 cells encapsulated within supportive matrices and surrounded by a semipermeable polymer membrane.

6.6.5 Description of Procedure

Substudy of the Extension Study (NTMT-01/02E-SS)

The product was administered via intravitreal placement under sterile technique by a qualified ophthalmologist.

6.6.6 Sites and Centers

There were eight sites in the United States and three sites in Australia.

6.6.7 Surveillance/Monitoring

Main Extension Study (NTMT-01/02E)

Patients in both cohorts were followed annually for 48 months.

Table 42. Scheduled Visits, NTMT-01/02E

VISITS ARE SCHEDULED FROM THE DATE OF THE NTMT-01 OR NTMT-02 SURGERY				
	VISIT 1 (+/- 1 month)	VISIT 2 (+/- 1 month)	VISIT 3 (+/- 1 month)	VISIT 4 (+/- 1 month)
GENERAL ASSESSMENTS				
NTMT-01/02 Extension Study Consent	X			
Review Eligibility Criteria	X			
Review Demographics and Participant Contact Information	X			
Update Medical & Ophthalmic History from NTMT-01 and NTMT-02 - This will include AEs collected during NTMT-01 and NTMT-02 and up to Visit 1 of the Extension Study as applicable. Any events between the last NTMT-01 or NTMT-02 visit will be recorded here.	X			
AE Assessment – starting from date of NTMT-01/02E Consent		X	X	X
Concomitant Medications – continue from NTMT-01 and NTMT-02	X	X	X	X
Reading Speed* *Completed for NTMT-02 (Cohort 2) participants only	X*	X*	X*	X*
VISUAL SYSTEM EXAMS: UN-DILATED				
Manifest Refraction	X	X	X	X
Best Corrected Visual Acuity	X	X	X	X
Applanation Tonometry (Goldmann applanation tonometer)	X	X	X	X
Microperimetry	X	X	X	X
VISUAL SYSTEM EXAMS: DILATED				
Slit lamp Biomicroscopy	X	X	X	X
Dilated Fundus Examination	X	X	X	X
Implant Site Clinical Examination	X	X	X	X
SD-OCT	X	X	X	X
Fundus Autofluorescence Imaging	X	X	X	X
Digital Color Fundus Photographs	X	X	X	X
AOSLO (for participants enrolled at NTMT-02 baseline) **Requires separate consent at AOSLO Center	X	X**	X**	X**

Source: Applicant's submission, NTMT-01/02E Appendix 5.3.5.1.16.1.1 Protocol and Amendments, Protocol version 2.0, page viii.

Substudy of the Extension Study (NTMT-01/02E-SS)

Table 43. Schedule of Procedures, NTMT-01/02E-SS

	Surgery	1 Day Post-Surgery	1 Week (\pm 2 days)	1 Month (\pm 1 week) Phone Call
GENERAL ASSESSMENTS				
Informed Consent	X			
Pre-operative Ophthalmic Evaluation	X ¹			
Medical Evaluation	X ¹			
AE Assessment	X	X	X	X
Record Current ConMeds	X	X	X	X
Implant Surgery	X			
Implant Site Clinical Examination		X	X	
Applanation Tonometry		X	X	
VISUAL SYSTEM EXAMS: DILATED				
Slit lamp Biomicroscopy		X	X	
Dilated Fundus Examination		X	X	

¹ The Medical and Ophthalmic Evaluation may be performed after consent is obtained up to the day of surgery

Source: Applicant's submission

6.6.8 Endpoints and Criteria for Study Success

Main Extension Study (NTMT-01/02E)

Efficacy Endpoints

Cohort 1

- Change in the EZ (area of IS/OS loss) from baseline to Months 72, 84, 96 and 108
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 72, 84, 96, and 108
- Proportion of study eyes with $\geq 35\%$ increase from baseline in the EZ (area of IS/OS loss) at Months 72, 84, 96, and 108
- Change in BCVA from baseline to Months 72, 84, 96, and 108

- Proportion of study eyes with ≥ 15 letter loss from baseline in BCVA at Months 72, 84, 96, and 108
- Proportion of study eyes with ≥ 10 letter loss from baseline in BCVA at Months 72, 84, 96, and 108.

Cohort 2

- Change in EZ (area of IS/OS loss) from baseline to Months 36, 48, 60, and 72
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 36, 48, 60, and 72
- Proportion of study eyes with a $\geq 35\%$ increase from baseline in the EZ (area of IS/OS loss) at Months 36, 48, 60, and 72
- Change in BCVA from baseline to Months 36, 48, 60, and 72
- Proportion of study eyes with ≥ 15 letter loss from baseline in BCVA at Months 36, 48, 60, and 72
- Proportion of study eyes with ≥ 10 letter loss from baseline in BCVA at Months 36, 48, 60, and 72
- Change in reading speed from baseline to Months 36, 48, 60, and 72

Safety Endpoints

Safety in the main extension study was evaluated by monitoring AEs, SAEs, AESI, and the results of ophthalmic examinations.

Substudy of the Extension Study (NTMT-01/02E-SS)

Safety was evaluated by monitoring AEs, SAEs, and the results of ophthalmic examinations.

6.6.9 Statistical Considerations & Statistical Analysis Plan

6.6.10 Study Population and Disposition

Main Extension Study (NTMT-01/02E)

Expected enrollment was as follows:

- Cohort 1 – Seven patients (seven study eyes) – previously enrolled in NTMT-01 protocol
- Cohort 2 – 66 patients (98 study eyes) – previously enrolled in NTMT-02 protocol

Substudy of the Extension Study (NTMT-01/02E-SS)

A total of 19 patients had 1 study-eligible eye and underwent sham surgery in the Cohort 2 precursor study (NTMT-02) were eligible to participate in the substudy.

6.6.10.1 Populations Enrolled/Analyzed

Main Extension Study (NTMT-01/02E)

The study populations in Study NTMT-01/02E are shown in [Table 44](#) below.

Table 44. Analysis Sets by Patient, Study NTMT-01/02E

Number of Patients (%)	Cohort 1 NT-501	Cohort 2 NT-501	Cohort 2 Sham	Cohort 2 Sham+NT-501	Total
ITT Population	6 (100.0)	15 (100.0)	19 (100.0)	30 (100.0)	64 (100.0)
PP Population	6 (100.0)	14 (93.3)	2 (10.5)	28 (93.3)	44 (68.8)

Source: Provided by the Applicant, CSR for Study NTMT-01/02E, Table 14.1.1

After Month 36, 16 out of 19 patients who had 1 study-eligible eye and underwent sham surgery were selected to have NT-501 implanted in the same study eye during the substudy (NTMT-01/02E-SS). Therefore, they were excluded for the PP population.

Substudy of the Extension Study (NTMT-01/02E-SS)

A total of 16 patients elected to have NT-501 implanted in the same study eye during the substudy.

6.6.10.1.1 Demographics

Main Extension Study (NTMT-01/02E)

Table 45. Demographics, NTMT-01/02E

Variable	Cohort 1 NT-501 N=6	Cohort 2 NT-501 N=15	Cohort 2 Sham N=19	Cohort 2 NT501+Sham N=30	Total N=70
Age (years)	-	-	-	-	-
Mean (standard deviation)	53.8 (5.1)	59.5 (10.8)	59.4 (7.6)	63.6 (8.6)	60.7 (9.0)
Median (min, max)	53.5 (48, 61)	60 (45, 79)	61 (47, 73)	64 (45, 76)	61 (45, 79)
Age group at randomization N (%)	-	-	-	-	-
<65 years	6 (100)	10 (66.7)	16 (84.2)	16 (53.3)	48 (68.6)
≥65 years	0	5 (33.3)	3 (15.8)	14 (46.7)	22 (31.4)
Sex, N (%)	-	-	-	-	-
Female	4 (66.7)	9 (60)	11 (57.9)	20 (66.7)	44 (62.9)
Male	2 (33.3)	6 (40)	8 (42.1)	10 (33.3)	26 (37.1)

Variable	Cohort 1 NT-501 N=6	Cohort 2 NT-501 N=15	Cohort 2 Sham N=19	Cohort 2 NT501+Sham N=30	Total N=70
Race, N (%)	-	-	-	-	-
White	4 (66.7)	11 (73.3)	16 (84.2)	28 (93.3)	59 (84.3)
Asian	1 (16.7)	0	1 (5.3)	0	2 (2.9)
Black or African American	0	0	0	1 (3.3)	1 (1.4)
Other	1 (16.7)	4 (26.7)	2 (10.5)	1 (3.3)	8 (11.4)
Not collected	-	-	-	-	-
Ethnicity, N (%)	-	-	-	-	-
Hispanic or Latino	0	1 (6.7)	0	1 (3.3)	2 (2.9)
Not Hispanic or Latino	6 (100)	14 (93.3)	18 (94.7)	29 (96.7)	67 (95.7)
Unknown	-	-	1 (5.3)	-	1 (1.4)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.
N = population size

Substudy of the Extension Study (NTMT-01/02E-SS)

The demographics of the population enrolled are shown in [Table 46](#).

Table 46. Demographics, NTMT-01/02E-SS

Variable	NTMT-0102-SS N=16
Age (years)	-
Mean (standard deviation)	60.1 (6.6)
Median (min, max)	62 (51, 73)
Age group at randomization N (%)	-
<65 years	14 (87.5)
≥65 years	2 (12.5)
Sex, N (%)	-
Female	10 (62.5)
Male	6 (37.5)
Race, N (%)	-
White	14 (87.5)
Asian	1 (6.3)
Other	1 (6.3)
Ethnicity, N (%)	-
Hispanic or Latino	0 (0.0)
Not Hispanic or Latino	15 (93.8)
Unknown	1 (6.3)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.
N = population size

6.6.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Main Extension Study (NTMT-01/02E)

Table 47. Medical/Behavioral Characterization of the Enrolled Population, NTMT-01/02E

Variable	Cohort 1 NT-501 N=6	Cohort 2 NT-501 N=15	Cohort 2 Sham N=19	Cohort 2 NT501+Sham N=60	Total N=100
Best corrected visual acuity (letters)	-	-	-	-	-
Number of eyes (N)	6	15	19	60	100
Mean (standard deviation)	75 (7.9)	75.9 (5.1)	75.3 (7.2)	78.3 (6.5)	77.1 (6.6)
Median (min, max)	76.5 (61, 85)	78 (63, 83)	76 (64, 86)	78 (67, 93)	77 (61, 93)
EZ area (mm ²)					
Number of eyes (n)	6	15	19	60	100
Mean (standard deviation)	0.63 (0.81)	0.65 (0.49)	0.70 (0.65)	0.78 (0.44)	0.73 (0.51)
Median (min, max)	0.24 (0, 1.86)	0.57 (0.19, 1.98)	0.51 (0.15, 2.79)	0.695 (0.18, 2.41)	0.61 (0, 2.79)
Aggregate sensitivity of microperimetry within the EZ break area	-	-	-	-	-
Retinal sensitivity (dB)					
Number of eyes (n)	N/A	15	19	60	94
Mean (standard deviation)	N/A	24.9 (2.6)	26.2 (2.4)	25.7 (2.5)	25.7 (2.5)
Median (min, max)	N/A	25.5 (18.8, 28.7)	26.6 (19.4, 29.7)	26.2 (19.5, 30.9)	26 (18.8, 30.9)
Reading speed (words per minute)	-	-	-	-	-
Number of eyes (n)	N/A	15	19	57	91
Mean (standard deviation)	N/A	97.8 (47.2)	100.0 (31.6)	102.5 (46.2)	101.2 (43.3)
Median (min, max)	N/A	96.0 (25.6, 185.7)	102.6 (47.3, 160.7)	100.5 (0, 202.6)	99.2 (0, 202.6)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

N = population size

Substudy of the Extension Study (NTMT-01/02E-SS)

Table 48. Medical/Behavioral Characterization of the Enrolled Population, NTMT-01/02E-SS

Variable	NTMT-0102-SS
Best corrected visual acuity (letters)	-
Number of eyes (n)	16
Mean (standard deviation)	77.2 (12.4)
Median (min, max)	81 (50, 93)
EZ area (mm ²)	-
Number of eyes (n)	16
Mean (standard deviation)	0.54 (1.1)
Median (min, max)	0.04 (0, 3.52)
Aggregate sensitivity of microperimetry within the EZ break area	-
Number of eyes (n)	16
Mean (standard deviation)	26.1 (3.4)
Median (min, max)	27.4 (17.9, 30.1)
Reading speed (words per minute)-	-
Number of eyes (n)	16
Mean (standard deviation)	125.6 (73.3)
Median (min, max)	145.3 (2.8, 230.5)

Source: FDA analysis of ADSL dataset, generated by FDA statistical reviewer.

6.6.10.1.3 Patient Disposition

Table 49. Patient Disposition, Enrolled Patients, NTMT-01-02-E

Patient Disposition	Cohort 1 NT-501 Surgery N=7 n (%)	Cohort 2 Sham Surgery N=19 n (%)	Cohort 2 NT-501 Surgery N=16 n (%)	Cohort 2 NT501 + Sham Surgery N=32 n (%)	Cohort 2 Total N=67 n (%)
Enrolled	7 (100.0)	19 (100.0)	16 (100.0)	32 (100.0)	67 (100.0)
Randomized	0 (0.0)	19 (100.0)	16 (100.0)	32 (100.0)	67 (100.0)
Received surgery	7 (100.0)	19 (100.0)	16 (100.0)	32 (100.0)	67 (100.0)
Participated in extension study	6 (85.7)	19 (100.0)	15 (93.8)	30 (93.8)	64 (95.5)
Switched to NT-501	-	16 (84.2)	--	-	16 (23.9)
Retained NT-501 throughout the study	6 (85.7)	16 (84.2)	14 (87.5)	30 (93.8)	60 (89.6)
Completed extension study	6 (85.7)	18 (94.7)	13 (81.2)	27 (84.4)	58 (86.6)
Discontinued extension study	0 (0.0)	1 (5.3)	2 (12.5)	3 (9.4)	6 (9.0)
Reason for discontinuation	-	-	-	-	-
COVID-19/Coronavirus	0 (0.0)	1 (100.0)	0 (0.0)	1 (33.3)	2 (33.3)
Death	0 (0.0)	(0.0)	1 (50.0)	1 (33.3)	2 (33.3)
Other	0 (0.0)	(0.0)	0 (0.0)	1 (33.3)	1 (16.7)
Adverse event related to study	0 (0.0)	(0.0)	1 (50.0)	(0.0)	1 (16.7)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.

N = population size, n = number of patients

6.6.11 Efficacy Analyses

Although this study was not designed to provide conclusive efficacy outcomes and was not included in the ISE, it has provided data to support durability of benefit beyond Month 24. These data are discussed in Section [7.1.8](#).

6.6.12 Safety Analyses

6.6.12.1 Methods

Safety analysis methods, definitions of AEs, TEAEs, ARs, SAEs, intensity and causality of AEs, and coding of concomitant medications were the same as described in Section [6.1.12.1](#). All AEs and SAEs described within this section had onset after the patient signed the extension study ICF. Safety results from this study contributed to long term safety of NT-501 and are discussed by cohort.

6.6.12.2 Overview of Adverse Events

None of the non-ocular TEAEs (serious and nonserious) were considered by the investigator to be related to the surgical procedure, NT-501 or CNTF in either Cohort 1 or 2.

Ocular ARs in Cohorts 1 and 2 are shown in [Table 50](#).

Table 50. Ocular Adverse Reactions Occurring in $\geq 2\%$ of Patients and With Higher Frequency in NT-501 Group Compared to Sham Group, NTMT-0102-E

Preferred Term	Cohort 1 NT-501 Eye (N=6) n (%)	Cohort 1 Fellow Eye (N=6) n (%)	Cohort 2 NT-501 eye (N=45) n (%)	Cohort 2 Sham Eye (N=49) n (%)	Cohort 2 Fellow Eye (N=34) n (%)
Miosis	0 (0.0)	0 (0.0)	3 (6.7)	1 (2.0)	0 (0.0)
Vitreous hemorrhage	0 (0.0)	0 (0.0)	2 (4.4)	2 (4.1)	0 (0.0)
Vitreous floaters	0 (0.0)	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)
Device expulsion	1 (16.7)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Conjunctival cyst	0 (0.0)	0 (0.0)	1 (2.2)	1 (2.0)	0 (0.0)
Eye irritation	0 (0.0)	0 (0.0)	1 (2.2)	1 (2.0)	0 (0.0)
Implant site hemorrhage	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Macular oedema	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Non-infectious endophthalmitis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Suture related complication	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Uveitis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

6.6.12.3 Deaths

There were no deaths encountered in Cohort 1. In Cohort 2, two patients (one each in the NT-501 and NT-501+sham groups) experienced fatal SAEs during

the study; Patient (b) (6) had a metastatic neoplasm and Patient (b) (6) a malignant peritoneal neoplasm, both deaths were unrelated to NT-501.

6.6.12.4 Nonfatal Serious Adverse Events

Cohort 1

There were 3 systemic SAEs encountered in cohort 1. One patient had SAEs of duodenal ulcer perforation and incarcerated hernia, while another patient experienced an SAE of vascular pseudoaneurysm. All 3 SAEs were severe and were not related to the surgical procedure or to NT-501/CNTF. There were no ocular SAEs in Cohort 1.

Cohort 2

A total of 14 SAEs were encountered in cohort 2. Twelve were non-ocular and not related. From these systemic SAEs, three were encountered in the NT-501 group, pain and metastatic neoplasm in one patient and diverticulitis in another and two in the sham group, prostate cancer and hyponatremia. In the NT-501+sham group, the systemic SAEs were malignant peritoneal neoplasm, Prinzmetal angina, ventricular tachycardia, sinusitis, constipation, femur fracture, and asthma, reported for 1 patient each.

There were two ocular SAEs in Cohort 2, noninfectious endophthalmitis in one patient and device expulsion (extrusion) in another. Noninfectious endophthalmitis was due to exposed suture, had onset on Day 2015 post product administration and gram stain and cultures were negative. Intravitreal ceftazidime and dexamethasone were injected. The SAE was moderate in severity, was considered related to NT-501 and resolved by Day 2229 (Month 72 visit). The SAE of device expulsion (extrusion) had onset on Day 2367 post product administration, was moderate in severity, was considered related to the surgical procedure, and resulted in NT-501 explantation (Day 2461) and patient discontinuation from the study.

6.6.12.5 Adverse Events of Special Interest

N/A

6.6.12.6 Clinical Test Results

N/A

6.6.12.7 Dropouts and/or Discontinuations

N/A

6.6.13 Study Summary and Conclusions

There were no new safety concerns identified during the long-term follow-up of patients that would suggest any new risk of treatment with NT-501.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication: Macular Telangiectasia Type 2

7.1.1 Methods of Integration

The two Phase 3 studies, NTMT-03-A and NTMT-03-B, contributed to the ISE.

Both Phase 3 studies were conducted under identical protocols. Patients were pooled across the two studies. Any patient who received NT-501 implant or sham procedure in Study NTMT-03-A or NTMT-03-B were included in this ISE.

Descriptive analyses based on pooled data from both studies were performed. The pooled evaluations did not include hypothesis testing or inferential statistics.

Although efficacy results were also generated by the Applicant for Studies NTMT-01, NTMT-02 and NTMT-0102SS, these studies had different designs with different entry requirements, different procedures (open-label treatment in Phase 1; masked, randomized, sham-controlled treatment in Phase 2; and observational assessments in Phase 1/2 extension), different endpoints, and different statistical analysis methods. As such, the data from these studies could not be pooled for the ISE.

7.1.2 Demographics and Baseline Characteristics

In the Phase 3 studies, 228 patients who were randomized and underwent surgery were included in the pooled mITT population. A total of 216 patients were included in the pooled PP population. Please see [Table 1](#) for demographics of mITT population.

Table 51. Baseline Characteristics, Pooled mITT Population, Studies NTMT-03-A and NTMT-03-B

Parameter	NT-501 N=117	Sham N=111	Total N=228
Best corrected visual acuity (letters)	-	-	-
Number (n)	117	111	228
Mean (standard deviation)	72.6 (8.6)	73.44 (8.9)	73.01 (8.7)
Median (min, max)	74.0 (41.0, 89.0)	73 (51, 94)	73 (41, 94)
EZ area loss (mm ²)	-	-	-
Number (n)	117	110	227
Mean (standard deviation)	0.52 (0.4)	0.48 (0.3)	0.5 (0.4)
Median (min, max)	0.42 (0.15, 1.99)	0.37 (0.16, 1.70)	0.38 (0.15, 1.99)
Aggregate sensitivity of microperimetry within the EZ break area	-	-	-
Number (n)	112	107	219
Mean (standard deviation)	59.7 (69.3)	53.91 (58.7)	56.87 (64.2)
Median (min, max)	37.88 (0.75, 398.78)	32.94 (0.33, 281.33)	35.54 (0.33, 398.79)

Parameter	NT-501 N=117	Sham N=111	Total N=228
Reading speed (words per minute)	-	-	-
Number (n)	116	109	225
Mean (standard deviation)	94.33	95.08	94.69
Median (min, max)	90.21 (1.00, 200.42)	94.93 (0, 238.19)	94.27 (0, 238.19)

Source: Reviewer table

N = population size

7.1.3 Patient Disposition

Table 52. Patient Disposition, pooled mITT Population, Studies NTMT-03-A and NTMT-03-B

Patient Disposition	NT-501	Sham	Total
Randomized, n ^a	121	118	239
Received surgery	117 (96.7)	111 (94.1)	228 (95.4)
Retained implant throughout the study	116 (99.1)	0 (0.0)	116 (50.9)
Discontinued during the treatment period	7 (6.0)	10 (9.0)	17 (7.5)
Reason for discontinuation	-	-	-
Eligible and did not enroll in amendment	5 (4.3)	7 (6.3)	12 (5.3)
Withdrawal by the patient ^b	0	1 (0.9)	1 (0.4)
Lost to follow-up ^c	0	1 (0.9)	1 (0.4)
Death ^d	1 (0.9)	0	1 (0.4)
Adverse event related to study ^e	1 (0.9)	0	1 (0.4)
Other ^f	0	1 (0.9)	1 (0.4)

Source: Modified from applicant's table, Module 2.7.3—Summary Of Clinical Efficacy, table 2

^a Percentages for the number of patients who underwent surgery are based on number of randomized patents; all other percentages are based on the number of patients who were randomized and underwent surgery.

^b Cardiac failure congestive

^c Colon cancer

^d Chronic Obstructive Pulmonary Disease, Respiratory failure

^e Vitreous hemorrhage

^f Invasive Ductal Breast Carcinoma

7.1.4 Analysis of Primary Endpoint(s)

For both Phase 3 studies the primary efficacy endpoint was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline to Month 24, as assessed using SD-OCT. Both Phase 3 studies met their primary efficacy endpoint and demonstrated that NT-501 was superior to sham in slowing the rate of retinal disease progression over a period of 24 months, as measured by the rate of EZ area loss on SD-OCT.

In the pooled phase 3 mITT population, the mean rate of change in EZ area loss from baseline to 24 months was 0.093 mm² in the pooled NT-501 group and 0.163 mm² in the pooled sham group; the mean (SE) difference between groups was -0.070 (0.0135) mm² (95% CI=-0.0096, -0.043).

Analysis based on the PP population and sensitivity analyses performed supported the conclusions of the primary analysis.

Reviewer's comment

Several prospective natural history studies in patients with MacTel have estimated the annual EZ area loss to be 0.057 to 0.140 mm²/ year (15, 18, 19). The product therefore demonstrated an annual decrease of EZ loss and macular PR loss by 18 to 66% compared to the natural history data.

Table 53. Primary Efficacy Endpoint – Rate of Change in the Area of Ellipsoid Zone (Macular Photoreceptor) Loss From Baseline Through Month 24, Modified Intention-to-Treat Population, NTMT-03-A, NTMT-03-B, and Pooled Data

Variable	NTMT-03-A NT-501 N=58	NTMT-03-A Sham N=57	NTMT- 03-B NT-501 N=59	NTMT-03-B Sham N=54	Pooled NT-501 N=117	Pooled Sham N=111
Rate of change over 24 months	0.075	0.166	0.111	0.160	0.093	0.163
95% CI	0.05, 0.10	0.14, 0.19	0.08, 0.14	0.13, 0.19	0.07, 0.11	0.14, 0.18
SE of the rate of change over 24 months (NT-501 – Sham)	-0.091 (0.0176)	–	-0.049 (0.0206)	–	-0.070 (0.0135)	–
95% CI	-0.13, -0.06	–	-0.0890, -0.0082	–	-0.096, -0.043	–
p-value	<0.0001	–	0.0186	–	–	–

Source: Provided by the Applicant, Summary of efficacy document, Integrated Summary of Efficacy Table 3.1.
N = population size

7.1.5 Analysis of Secondary Endpoint(s)

The secondary efficacy endpoints, which were analyzed in the order listed, were as follows:

- Mean change in aggregate sensitivity of microperimetry within the EZ break area from baseline to Month 24
- Mean change in monocular reading speed from baseline to Month 24
- Mean change in the NEI-VFQ-25 near activities subscale score from baseline to Month 24 (The near activities subscale score, was an average of the scores for items 5, 6, and 7 in the NEI-VFQ-25)

Study NTMT-03-A met the first secondary efficacy endpoint and demonstrated that NT-501 was superior to sham in preventing aggregate retinal sensitivity loss from baseline to Month 24. Although there was a mean increase in aggregate retinal sensitivity loss from baseline to Month 24 in both groups, the magnitude of loss was significantly smaller in the NT-501 group relative to the sham group

(25.27 versus 43.02 dB, respectively; $p=0.0199$). A mean increase in aggregate retinal sensitivity loss from baseline to Month 24 was also observed in both groups in Study NTMT-03-B. In this study, however, the mean increase was only slightly smaller in the NT-501 group compared with the sham group and the difference between groups was not significant (40.02 versus 41.97 dB, respectively; $p=0.8351$). Pooled analysis for both pivotal studies demonstrated that the magnitude of mean aggregate retinal sensitivity loss from baseline to Month 24 was smaller in the NT-501 group relative to the sham group (32.72 [44.093] versus 42.52 [41.251] dB, respectively). Supportive analyses yielded results that were generally consistent with results from the relevant secondary efficacy endpoint analyses.

Because the difference between NT-501 and sham for the first secondary efficacy endpoint (change in aggregate retinal sensitivity loss from baseline to Month 24) was only significant for Study NTMT-03-A, analysis for the next secondary endpoint, change in monocular reading speed from baseline to Month 24, was only performed for this study.

In Study NTMT-03-A, there was a mean decrease in monocular reading speed from baseline to Month 24 in both study groups, with a smaller mean decrease in the NT-501 group relative to the sham group (SD changes from baseline = -6.18 [29.188] and -12.20 [42.188] wpm), respectively); the difference between groups, however, was not significant ($p=0.3849$). In Study NTMT-03-B, a smaller mean decrease from baseline at Month 24 was also observed in the NT-501 group relative to the sham group (SD changes from baseline = -5.46 [29.648] and -18.88 [33.705] wpm, respectively).

In the pooled analysis, the SD changes in reading speed from baseline to Month 24 were -5.46 (29.648) wpm in the NT-501 group and -18.88 (33.705) wpm in the sham group. It was also observed at Month 24, that while a majority of patients in the sham group (76.0%) had either no change or a decrease from baseline in reading speed, a majority of patients in the NT-501 group (61.2%) had either no change or an increase from baseline in reading speed (where an increase/decrease in reading speed was defined as being a change of at least 10 wpm).

There was no formal analysis performed for the last secondary endpoint, mean change in the NEI-VFQ-25 near activities subscale score, from baseline to Month 24.

In the pooled analysis of the Phase 3 studies, the SD changes in the NEI-VFQ-25 near activities subscale score from baseline to Month 24 in the NT-501 and sham groups were -1.29 (18.173) and -0.56 (16.918) units, respectively (difference between groups= -0.727 ; 95% CI= $-5.46, 4.00$).

7.1.6 Other Endpoints

Exploratory Endpoint: Changes From Baseline in the Number of Scotomas at Month 24

This endpoint was not evaluated in the individual Phase 3 studies and was only included in the ISE. Overall, the SD change from baseline in the pooled NT-501 group was 5.86 (9.403), while the SD change from baseline in the pooled sham group was 5.41 (8.693). Across studies, a greater percentage of patients in the NT-501 group had no scotoma at Month 24 compared with patients in the sham group (35.9% versus 24.3%, respectively). The estimated rate of scotoma occurrence over a 24-month period was similar in each group (0.006 in the NT-501 group and 0.007 in the sham group); the estimated rate ratio was 0.894 (95% CI =0.637, 1.256).

Exploratory Endpoint: Response Rates

A responder analysis was included in the ISE but was not evaluated in the individual Phase 3 studies. Patients with a decline in the EZ area at Month 24 <80% of the decline at the same time point estimated from the pooled sham patients were categorized as responders. Patients were categorized as high responders if they had a decline in the EZ area at Month 24 that was <50% of the decline at the same time point estimated from the pooled sham patients.

Overall, the percentages of patients in the NT-501 group who were responders and high responders were 65.18% and 50.00%, respectively. By comparison, the respective percentages in the sham group were 51.89% and 35.85%. Overall, the odds ratio (95% CI) between groups for responders was 1.74 (1.01, 2.99), while the odds ratio (95% CI) between groups for high responders was 1.79 (1.04, 3.08).

7.1.7 Subpopulations

For subpopulation analysis please see Sections [6.1.11.3](#) and [6.2.11.3](#).

7.1.8 Persistence of Efficacy

The persistence of efficacy was evaluated through 108 months post product administration in Study NTMT-01/02E. Limited data generated from the two pivotal studies, NTME-03A and NTMT-03-B, up to Month 36 also contributed evidence of durability of benefit.

Study NTMT-01/02E

In this study, 6 patients previously enrolled in the open-label NTMT-01 study, who had already completed 60 months of follow-up (Cohort 1) and 64 patients previously enrolled in the NTMT-02 study, who had completed 24 months of follow-up (Cohort 2) were followed for an additional 48 months for a total of 108 months in Cohort 1 and 70 months in Cohort 2. In Cohort 2, after Month 36, 16

out of 19 patients who had 1 study-eligible eye and underwent sham surgery in the Phase 2 NTMT-02 study were selected to have NT-501 implanted in the same study eye during the substudy (NTMT-01/02E-SS). These patients were excluded from the PP population. For details on study design and populations enrolled, please see Section [6.6](#).

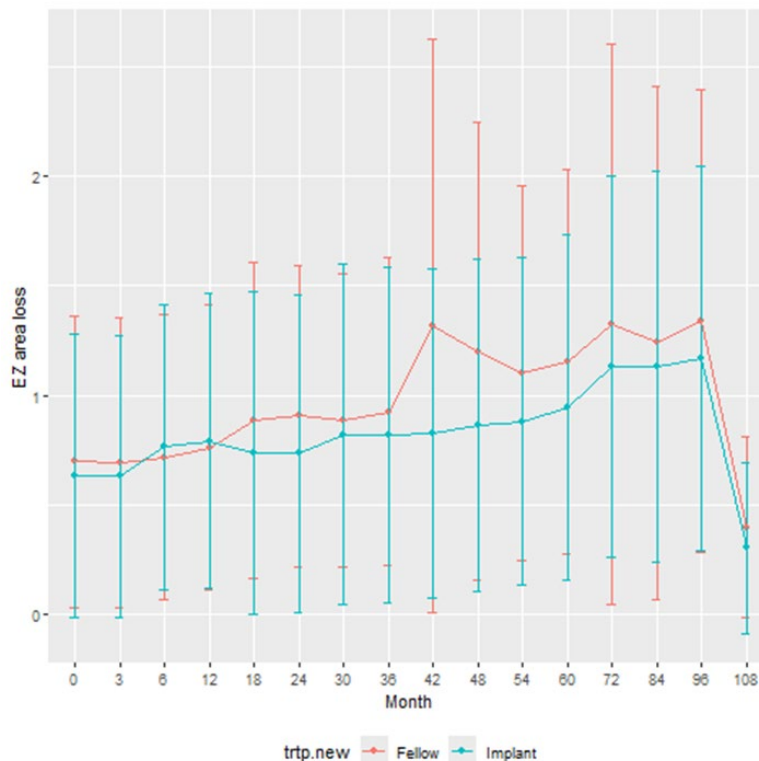
Efficacy analysis is presented by cohort.

Cohort 1

Change From Baseline in the Area of Ellipsoid Zone Loss

The rate of change in the area of EZ loss from baseline in the precursor study up to Month 108 is shown in [Figure 3](#) below.

Figure 3. Ellipsoid Zone Area Loss Over Time by Group, Cohort 1 (n=6)



Source: Figure generated by FDA statistical reviewer.
Data presented are means and 95% confidence intervals based on the observed data.

The rate of EZ loss was consistently lower in the NT-501 implanted eyes compared to the fellow eyes at each postsurgery time point up to Month 96.

Reviewer's comment

The number of eyes included in Cohort 6 was too small to generate reliable conclusions and only three eyes contributed to the data at Week 108.

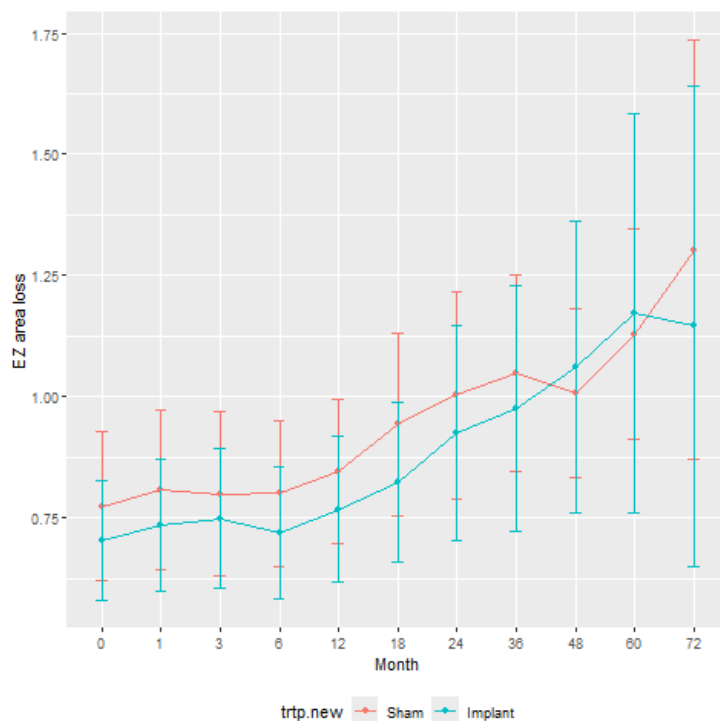
Cohort 2

For Cohort 2, analysis was performed separately for the ITT and PP populations. According to the Applicant, the PP analyses provide a better understanding of the long-term efficacy of NT-501 by eliminating the impact of the treatment switch.

Change From Baseline in the Area of Ellipsoid Zone Loss

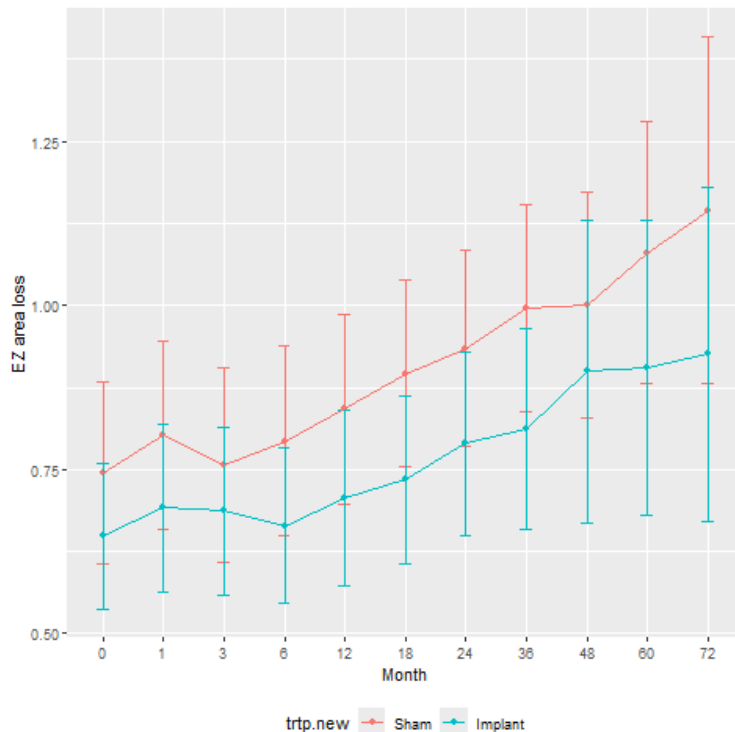
[Figure 4](#) and [Figure 5](#) provide the change from baseline in the area of ellipsoid zone loss in the ITT and PP populations over time.

Figure 4. Ellipsoid Zone Area Loss Over Time by Group, Cohort 2, Intention-to-Treat Population (n=64)



Source: Figure generated by FDA statistical reviewer.
Data presented are means and 95% confidence intervals based on the observed data.

Figure 5. Ellipsoid Zone Area Loss Over Time by Group, Cohort 2, Per Protocol Population (n=44)



Source: Figure generated by FDA statistical reviewer.
Data presented are means and 95% confidence intervals based on the observed data.

In the ITT population, eyes implanted with NT-501 and eyes that underwent sham surgery exhibited a similar mean increase from precursor study baseline in the area of EZ loss at each postsurgery time point. In the PP population, the area of EZ loss appeared to progress slower in the NT-501 implanted eyes compared to eyes that underwent sham surgery up to Month 72.

Monocular Reading Speed

A decrease was observed in monocular reading speed from precursor study baseline in both NT-501 implanted eyes and eyes that underwent sham surgery, but a smaller mean decrease was observed in implanted eyes compared with sham eyes in both the ITT and PP populations as shown in [Table 54](#) and [Table 55](#) below.

Table 54. Baseline and Change From Baseline in Monocular Reading Speed, Cohort 2, Intention-to-Treat Population (by Eye), NTMT-01/02E

Visit	Treatment Group	N (n) ^a	Mean (SE) Monocular Reading Speed (wpm)	Mean Difference (SE)
Baseline	NT-501	44 (44)	94.740 (6.4973)	-12.483 (8.9774)
Baseline	Sham	47 (47)	107.222 (6.2866)	-
Change at Month 36	NT-501	42 (42)	-8.838 (5.4428)	8.960 (6.1874)
Change at Month 36	Sham	46 (46)	-17.798 (5.2686)	-
Change at Month 48	NT-501	39 (39)	-18.931 (5.5846)	6.557 (6.3266)
Change at Month 48	Sham	45 (45)	-25.488 (5.3072)	-
Change at Month 60	NT-501	38 (38)	-28.627 (5.6369)	-10.304 (6.5187)
Change at Month 60	Sham	41 (41)	-18.324 (5.4825)	-
Change at Month 72	NT-501	33 (33)	-24.713 (5.9294)	9.765 (6.8643)
Change at Month 72	Sham	38 (38)	-34.478 (5.6311)	-

Source: Provided by the Applicant, CSR for Study NTMT-0102E, Table 23

^a N and n represent the number of patients and eyes observed, respectively.

Table 55. Baseline and Change From Baseline in Monocular Reading Speed, Cohort 2, Per Protocol Population (by Eye), NTMT-01/02E

Visit	Treatment Group	N (n) ^a	Mean (SE) Monocular Reading Speed (wpm)	Mean Difference (SE)
Baseline	NT-501	41 (41)	98.022 (6.8408)	-14.057 (10.7387)
Baseline	Sham	28 (28)	112.078 (8.2779)	-
Change at Month 36	NT-501	40 (40)	-8.142 (5.9518)	10.481 (7.5184)
Change at Month 36	Sham	27 (27)	-18.623 (6.8925)	-
Change at Month 48	NT-501	37 (37)	-18.073 (6.1188)	5.618 (7.6343)
Change at Month 48	Sham	27 (27)	-23.692 (6.8925)	-
Change at Month 60	NT-501	37 (37)	-27.996 (6.1163)	-15.284 (7.9180)
Change at Month 60	Sham	24 (24)	-12.712 (7.2064)	-
Change at Month 72	NT-501	32 (32)	-23.574 (6.4471)	12.121 (8.3501)
Change at Month 72	Sham	22 (22)	-35.695 (7.4529)	-

Source: Provided by the Applicant, CSR for Study NTMT-0102E, Table 23

^a N and n represent the number of patients and eyes observed, respectively.

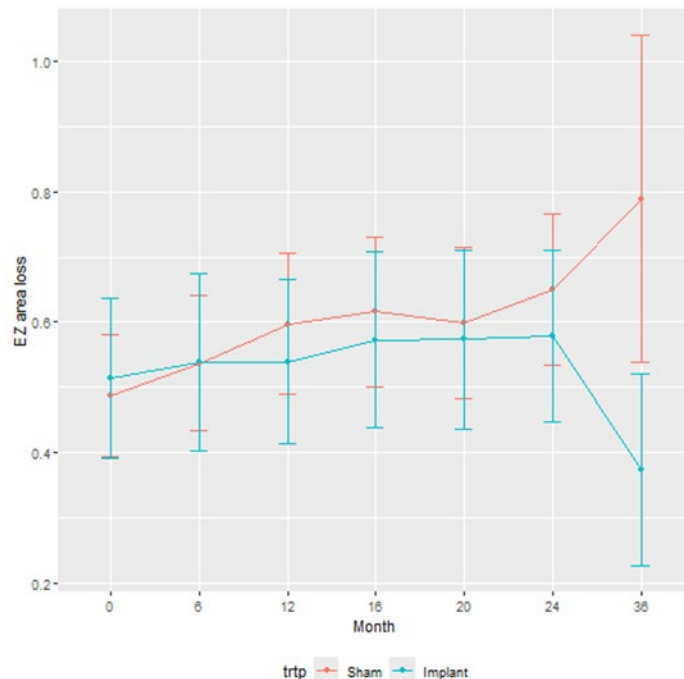
Long-Term Data Generated From Ellipsoid Zone Loss From Pivotal Studies NTMT-03-A and NTMT-03-B

Study NTMT-03-A

A total of 38 patients (19 in each study group) provided consent to attend the Month 36 and Month 48 visits under protocol version 7.0. However, a decision was subsequently made to discontinue the Month 36 and Month 48 study visits. As a result, the number of consenting patients attending these visits was small (21 patients [10 NT 501 and 11 sham] at Month 36 and only 3 patients [2 NT-501 and 1 sham] at Month 48). Data provided by the Applicant for the Month 36 visit for EZ loss were used by the FDA statistical reviewer to generate the following

graph of EZ loss over a 36-month period, which provides evidence of durability of treatment effect up to Month 36.

Figure 6. Ellipsoid Zone Area Loss Over Time by Group, Modified Intention-to-Treat Population (n=115), NTMT-03-A

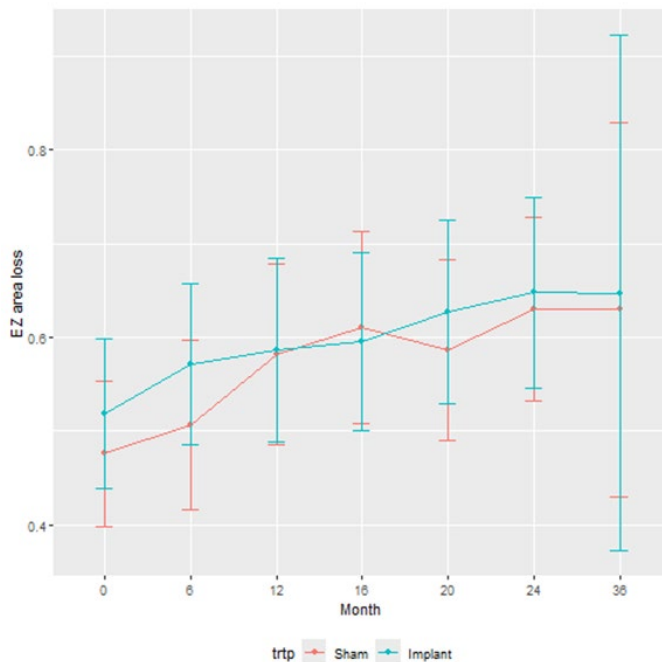


Source: Figure generated by FDA statistical reviewer.
Data presented are means and 95% confidence intervals based on the observed data.
Only 21 patients [10 NT 501 and 11 sham] contributed data for Month 36.

Study NTMT-03-B

A total of 33 patients (17 in the NT-501 group and 16 in the sham group) provided consent to attend the Month 36 and Month 48 visits under protocol version 7.0. However, a decision was subsequently made to discontinue the Month 36 and Month 48 study visits. As a result, the number of consenting patients attending these visits was small (24 patients [11 NT-501 and 13 sham] at Month 36 and 0 patients at Month 48). Data provided by the Applicant for the Month 36 visit for EZ loss were used by the FDA statistical reviewer to generate the following graph of EZ loss over a 36-month period, which provide evidence of durability of treatment effect up to Month 36.

Figure 7. Ellipsoid Zone Area Loss Over Time by Group, Modified Intention-to-Treat Population (n=115), NTMT-03-B



Source: Figure generated by FDA statistical reviewer.
Data presented are means and 95% confidence intervals based on the observed data.
Only 24 patients [11 NT-501 and 13 sham] contributed data for Month 36.

Reviewer's comment

In conclusion, long-term data on rate of EZ area loss and trends in reading speed from noninterventional study NTMT-01/02E and limited data from the rate of EZ loss from pivotal study NTMT-03-A capture the meaningful benefit of NT-501 on long-term disease progression in MacTel.

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

In summary, both studies met their primary endpoint and demonstrated that NT-501 slowed the rate of retinal disease progression over 24 months. In addition, Study NTMT-03-A also met its first secondary efficacy endpoint and demonstrated that NT-501 slowed down the aggregate retinal sensitivity loss from baseline through Month 24. For the rest of the secondary endpoints that were either not statistically significant or were not analyzed, changes were in favor of the NT-501 group except SD changes in the NEI-VFQ-25 near activities

subscale score for Study NTMT-03-A, which were more favorable for the sham control group.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The integrated review of safety discusses collectively the safety findings from three different population pools defined as:

- Pool 1: All patients with MacTel enrolled in the two Phase 3 studies (This pool contributed to the label)
- Pool 2: All patients with MacTel who have received NT-501 implant in all Phase 1, 2, and 3 studies
- Pool 3: All patients who have received the NT-501 implant (all diseases including MacTel)

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The two pivotal studies NTMT-03-A and NTMT-03-B were used to evaluate safety in Pool 1, and all six studies in patients with MacTel described in Section [6](#) were used to evaluate safety in Pool 2.

NT-501 has been evaluated in seven studies in other retinal degenerative conditions, including RP, GA associated with AMD, and achromatopsia.

- One Phase 1 study in RP: CNTF1
- Three Phase 2 studies in RP: CNTF3, CNTF4, and AOSLO-CNTF-FFB-01
- One Phase 2 study in GA: CNTF2
- One Phase 1 study in achromatopsia: CNTF5 (12-EI-0167)
- One Compassionate use study in RP, GA, and AMD: 201-CU01-RDD-2011 (CU-01)

These seven studies have been included along with the six MacTel studies in Pool 3.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 117 patients with MacTel received the NT-501-6A.02 (high output implant, producing a nominal dose of 20 ng/24 hours) in the two pivotal studies (Pool 1) while an overall 188 patients (220 eyes) with MacTel received the high output implant in all Phase 1, 2, and 3 studies (Pool 2). A total of 250 patients (438 eyes) have received the high output NT-501 implant and 17 additional patients received the NT-501-10.02 (low output device, producing a nominal dose of 10ng/24 hours) across all indications (RP), achromatopsia, AMD, and MacTel), (Pool 3).

In all cases, the discussions and presentations of the safety results are based on the safety population, which included all patients who had NT-501 implanted and/or underwent the sham surgery.

The Pool 1 demographics are shown in [Table 1](#) and Pool 2 in [Table 56](#).

Table 56. Demographics, All Pool 2 Patients

Characteristic	NT-501 N=172	Sham N=130	NT-501+Sham N=32	Total N=334
Age at screening, years	-	-	-	-
Mean (SD)	60.2 (8.00)	59.5 (8.45)	63.4 (8.43)	60.2 (8.26)
Min, max	40, 79	40, 78	45, 76	40, 79
Age category, n (%)	-	-	-	-
<65 years	115 (66.9)	89 (68.5)	17 (53.1)	221 (66.2)
≥65 years	57 (33.1)	41 (31.5)	15 (46.9)	113 (33.8)
Sex, n (%)	-	-	-	-
Female	123 (71.5)	87 (66.9)	21 (65.6)	231 (69.2)
Male	49 (28.5)	43 (33.1)	11 (34.4)	103 (30.8)
Race, n (%)	-	-	-	-
White	150 (87.2)	111 (85.4)	30 (93.8)	291 (87.1)
Asian	8 (4.7)	5 (3.8)	0	13 (3.9)
Black or African American	2 (1.2)	2 (1.5)	1 (3.1)	5 (1.5)
American Indian or Alaska Native	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Other	12 (7.0)	11 (8.5)	1 (3.1)	24 (7.2)
Ethnicity, n (%)	-	-	-	-
Hispanic or Latino	8 (4.7)	9 (6.9)	1 (3.1)	18 (5.4)
Not Hispanic or Latino	164 (95.3)	119 (91.5)	31 (96.9)	314 (94.0)
Unknown	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)

Source: Provided by Applicant, Module 2.7.4 - Summary of Clinical Safety, page 47
N = population size

8.2.3 Categorization of Adverse Events

All AEs and SAEs described within this section were TEAEs. A TEAE was defined as any AE that occurred after a patient underwent NT-501 implantation or sham surgery and while on study. All AEs were recorded and coded using MedDRA. A study eye/patient with a TEAE considered by the investigator to be related to more than one category (i.e., surgery, NT-501, or CNTF) was counted separately in each category.

For Pool 3, patients in non-MacTel studies had received both the low and high output implant. There were only 17 total patients who received the low output implant across studies.

The primary time point for Pool 1 was Month 24, however, for some categories of events, such as deaths, SAEs, and significant events a summary through Month 48 visit was provided.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Study design and duration, objectives, patient populations, and safety assessments differed between the Phase 1 and 2 MacTel studies and pivotal studies. For more details, please see individual studies description in Section 6.

8.4 Safety Results

8.4.1 Deaths

Across the six clinical studies evaluating NT-501 in patents with MacTel, a total of six patients died due to systemic SAEs. None of the fatal SAEs were considered related to NT-501, CNTF or surgery.

Table 57. Deaths, Pool 2

Study	Patient ID	Adverse Event Leading to Death	Treatment
NTMT-02	NTMT (b) (6)	Aortic aneurysm	Implant
NTMT-02	NTMT (b) (6)	Cardiac arrest	Implant + Sham
NTMT-02	NTMT (b) (6)	Malignant peritoneal neoplasm	Implant + Sham
NTMT-02	NTMT (b) (6)	Metastatic neoplasm	Implant
NTMT-03-A	NTMT- (b) (6)	Cardiac failure congestive	Sham
NTMT-03-B	NTMT- (b) (6)	Chronic obstructive pulmonary disease	Implant

Source: Provided by the FDA Clinical Analyst

In the pivotal studies, two patients (one each in the NT-501 and sham groups) died. Patient (b) (6) in the NT-501 group experienced a severe SAE of chronic obstructive pulmonary disease on Day 575 and died on Day 607 due to the SAE. Patient (b) (6) in the sham group experienced a severe SAE of cardiac failure congestive on Day 430. The patient withdrew consent on Day 466 and died on Day 502 due to the SAE.

In NTMT-02, two patients experienced fatal systemic SAEs during the study. Patient (b) (6), in the NT-501 group, had an aortic aneurysm and Patient (b) (6), in the NT-501+sham group, died from cardiac arrest.

In Cohort 2 of NTMT-01/02E, two patients (one each in the NT-501 and NT-501+sham groups) experienced fatal SAEs during the study; Patient (b) (6) had a metastatic neoplasm and Patient (b) (6) had a malignant peritoneal neoplasm.

No patient died across any of the seven studies in the other retinal degeneration indications.

8.4.2 Nonfatal Serious Adverse Events

Pool 1 (Phase 3 Studies)

The number and proportion of patients with at least one treatment-emergent SAE was a secondary safety endpoint in the Phase 3 studies. Through the Month 24 visit, a total of 40 patients (17.1%) in Pool 1, including 23 patients (19.7%) in the NT-501 group and 17 patients (115.3%) in the sham group, each experienced at least 1 nonfatal SAE (ocular [in either eye] and non-ocular combined) regardless of outcome. Three additional patients in the NT-501 group experienced nonfatal, systemic SAEs with onset after Month 24. One patient in the NT-501 group experienced both a systemic SAE (endometriosis) and an ocular SAE (device extrusion) and is therefore counted in both categories. A summary of nonfatal SAEs through Month 24 is shown in [Table 58](#).

Table 58. Nonfatal Serious Adverse Events Through Month 24, Pool 1

Category	NT-501 Surgery N=117 n (%)	NT-501 Surgery N=117 Events	Sham Procedure N=111 n(%)	Sham Procedure N=111 Events	Total N=228 n (%)	Total N=228 Events
Overall	23 (19.7)	30	17 (15.3)	21	40 (17.5)	51
Ocular	6 (5.1)	6	1 (0.9)	1	7 (3.1)	7
Eye type	-	-	-	-	-	-
Study eye	6 (5.1)	6	0 (0.0)	0	6 (2.6)	6
Not in study eye	0 (0.0)	0	1 (0.9)	1	1 (0.4)	1
Type of ocular SAE	-	-	-	-	-	-
Device extrusion	1 (0.9)	1	0 (0.0)	0	1 (0.4)	1
Suture-related complication	5 (4.3)	5	0 (0.0)	0	5 (2.2)	5
Choroidal neovascularization	0 (0.0)	0	1 (0.9)	1	1 (0.4)	1
Severity	-	-	-	-	-	-
Mild	1 (0.9)	1	0 (0.0)	0	1 (0.4)	1
Moderate	4 (3.4)	4	1 (0.9)	1	5 (2.2)	5
Severe	1 (0.9)	1	0 (0.0)	0	1 (0.4)	1

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst
N = population size, n = number of patients

Ocular Nonfatal Serious Adverse Events

Seven of the nonfatal SAEs that were encountered until Month 24 were ocular, six (5.1%) were encountered in the study eye in the NT-501 group and one (0.9%) in the fellow eye in the sham group ([Table 58](#)). In the NT-501 group, all nonfatal ocular SAEs were related, resolved by the end of the study, and included five suture-related complications and one device extrusion. One SAE of suture-related complication occurred within 90 days of surgery, 2 additional SAEs of suture-related complication had onset within 365 days of surgery, and the remaining ocular SAEs had onset after 365 days postsurgery. All five events of suture-related complication were considered by the investigator to be related to the surgical procedure and none resulted in NT-501 removal. The SAE of device extrusion was considered to be related to both NT-501 and the surgical procedure; NT-501 was surgically repositioned and did not require explantation. In the sham group, the ocular SAE was choroidal neovascularization (CNV), with onset after 365 days postsurgery and was considered not related to the surgery, to NT-501, or to CNTF, and was ongoing at the end of the study.

After Month 24, one additional study eye in the NT-501 group had an ocular SAE of vitreous hemorrhage in the study eye that led to NT-501 explantation.

Overall, the most frequent ocular SAE in the implanted eyes was suture-related complication (five eyes), which was considered related to surgery in all instances.

Systemic Nonfatal Serious Adverse Events

A total of 34 patients in Pool 1, including 18 patients in the NT-501 group and 16 patients (15.3%) in the sham group, experienced at least 1 systemic SAE each through the Month 24 visit. Two additional patients in the NT-501 group had nonfatal SAEs with onset after Month 24. Most systemic SAEs occurred in one patient each. Systemic SAEs occurring in more than one patient were COVID-19 (one NT-501, one sham), cellulitis (one NT-501, one sham), chronic obstructive pulmonary disease (one NT-501, one sham), osteoarthritis (two sham), and transient ischemic attack (two NT-501).

All systemic SAEs that occurred in the Phase 3 studies were considered to be not related to the surgery, to NT-501, or to CNTF, and all had resolved by the end of the study. For more details about systemic not related nonfatal SAEs in Pool 1 please see [Table 16](#) and [Table 28](#).

Pool 2

SAEs reported in Pool 2 include all events occurring in the Phase 3 studies through the Month 48 visit.

Table 59. Nonfatal Serious Adverse Events, Pool 2

Category	Sham N=172 n (%)	Sham N=172 Events	Implant N=130 n (%)	Implant N=130 Events	Implant + Sham N=32 N (%)	Implant + Sham N=32 Events	Total N=334 N (%)	Total N=334 Events
Overall	20 (15.4)	29	37 (21.5)	57	11 (34.4)	16	68 (20.4)	102
Ocular	1 (0.8)	1	11 (6.4)	12	2 (6.2)	4	14 (4.2)	17
Eye type	-	-	-	-	-	-	-	-
Fellow eye	1 (0.8)	1	1 (0.6)	1	0 (0.0)	0	2 (0.6)	2
Study eye	0 (0.0)	0	11 (6.4)	11	2 (6.2)	4	13 (3.9)	15
Ocular SAE by procedure	-	-	-	-	-	-	-	-
Implant	0 (0.0)	0	11 (6.4)	12	2 (6.2)	2	13 (3.9)	14
Device expulsion	0 (0.0)	0	1 (0.6)	1	0 (0.0)	0	1 (0.3)	1
Device extrusion	0 (0.0)	0	2 (1.2)	2	0 (0.0)	0	2 (0.6)	2
Noninfectious endophthalmitis	0 (0.0)	0	1 (0.6)	1	0 (0.0)	0	1 (0.3)	1
Suture-related complication	0 (0.0)	0	5 (2.9)	5	0 (0.0)	0	5 (1.5)	5
Vision blurred	0 (0.0)	0	0 (0.0)	0	2 (6.2)	2	2 (0.6)	2
Visual impairment	0 (0.0)	0	1 (0.6)	2	0 (0.0)	0	1 (0.3)	2
Vitreous hemorrhage	0 (0.0)	0	1 (0.6)	1	0 (0.0)	0	1 (0.3)	1
Sham	1 (0.8)	1	0 (0.0)	0	2 (6.2)	2	3 (0.9)	3
Choroidal neovascularization	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	1 (0.3)	1
Vision blurred	0 (0.0)	0	0 (0.0)	0	2 (6.2)	2	2 (0.6)	2
Severity, by procedure	-	-	-	-	-	-	-	-
Implant	0 (0.0)	0 (0.0)	11 (6.4)	12	2 (6.2)	2	13 (3.9)	14
Mild	0 (0.0)	0 (0.0)	2 (1.2)	2	0 (0.0)	0	2 (0.6)	2
Moderate	0 (0.0)	0 (0.0)	8 (4.7)	9	2 (6.2)	2	10 (3.0)	11
Severe	0 (0.0)	0 (0.0)	1 (0.6)	1	0 (0.0)	0	1 (0.3)	1
Sham	1 (0.8)	1	0 (0.0)	0	2 (6.2)	2	3 (0.9)	3
Moderate	1 (0.8)	1	0 (0.0)	0	2 (6.2)	2	3 (0.9)	3

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.
N = population size, n = number of patients

Ocular Nonfatal SAEs

Across the MacTel studies, 13 study eyes (5.9%) in the NT-501 group and 2 study eyes (1.2%) in the sham group experienced 1 ocular SAE each. The ocular SAEs occurring in more than one study eye were suture-related complication (five NT-501 [2.3%]), device extrusion, (two NT-501 [0.9%]), and vision blurred (two NT-501 [0.9%] and two sham [1.2%]). Vision blurred occurred in both eyes of two patients in the NT-501+sham group who received NT-501 in one eye and underwent sham surgery in the contralateral eye. The remaining events, all occurring in one study eye (0.5%) each in the NT-501 group, included visual impairment, noninfectious endophthalmitis, vitreous hemorrhage, and device expulsion.

Device expulsion was considered to be related to both NT-501 and surgery, noninfectious endophthalmitis was considered to be related to NT-501, and all other ocular SAEs were considered by the investigator to be related to the surgical procedure.

Noninfectious endophthalmitis was attributed to exposed suture, and vitreous cultures were negative. Intravitreal ceftazidime and dexamethasone were administered to the patient. The SAEs of device expulsion and vitreous hemorrhage both resulted in NT-501 explantation and the SAE of device extrusion required NT-501 to be surgically repositioned.

The four SAEs of vision blurred, one instance of suture-related complication, and one event of device extrusion had onset within 90 days of surgery. Two additional SAEs of suture-related complication had onset within 365 days of surgery, and the remaining ocular SAEs had onset after 365 days postsurgery.

With the exception of visual impairment, which was ongoing at the end of the study, all ocular SAEs occurring in implanted eyes had recovered by the end of the study.

Ocular SAEs were also reported in two fellow eyes and included visual impairment and CNV (one eye each), both events started more than after 365 days after surgery and were ongoing at the end of the study.

Consistent with Pool 1, the most frequent ocular SAE in the implanted eyes in Pool 2 was suture-related complication (five eyes); in all instances, this was considered related to surgery and did not result in NT-501 explantation.

Systemic Nonfatal Serious Adverse Events

In Pool 2, systemic nonfatal SAEs occurred in a similar percentage of patients in the NT-501 and sham groups (13.2% [26 of 188 patients] and 14.6% [19 of 130 patients] respectively), and at a higher percentage (37.5%, 10 of 32 patients) in the NT-501+sham group. Most systemic SAEs reported for Pool 2 occurred in one patient each with the exception of pneumonia that was reported for three patients overall (one NT-501, one sham, one NT-501+sham), and the following SAEs that occurred in two patients each: atrial fibrillation (one sham, one NT-501+sham); coronary artery disease (one NT-501, one sham); myocardial infarction (one NT-501, one sham); COVID-19 (one NT-501, one sham); cellulitis (one NT-501, one sham); arthritis (two NT-501);

osteoarthritis (two sham); prostate cancer (one NT-501, one sham); transient ischemic attack (two NT-501), and asthma (one NT-501, one NT-501+sham).

Other than an SAE of anxiety reported for one patient in the NT-501+sham group that was considered related to the surgery, all other systemic SAEs were considered unrelated to the surgery, to NT-501, or to CNTF, and most had resolved by the end of the study.

8.4.3 Study Dropouts/Discontinuations

Pool 1 (Phase 3 Studies)

Table 60. Patient Disposition Discontinuations With Associated Treatment-Emergent Serious Adverse Events, Pool 1

Number of Patients	NT-501	Sham	Total
Randomized	121	118	239
Received surgery, n (%) ^a	117 (96.7)	111 (94.1)	228 (95.4)
Retained implant throughout the study, n (%) ^a	116 (99.1)	0 (0.0)	116 (50.9)
Discontinued during the treatment period, n (%) ^a	7 (6.0)	10 (9.0)	17 (7.5)
Reason for discontinuation, n (%) ^a	-	-	-
Eligible and did not enroll in amendment	5 (4.3)	7 (6.3)	12 (5.3)
Withdrawal by the patient ^b	0 (0.0)	1 (0.9)	1 (0.4)
Lost to follow-up ^c	0 (0.0)	1 (0.9)	1 (0.4)
Death ^d	1 (0.9)	0 (0.0)	1 (0.4)
Adverse event related to study ^e	1 (0.9)	0 (0.0)	1 (0.4)
Other ^f	0 (0.0)	1 (0.9)	1 (0.4)

Source: Reviewer table

^a Percentages for the number of patents who underwent surgery are based on number of randomized patients; all other percentages are based on the number of patients who were randomized and underwent surgery.

^b Cardiac failure congestive

^c Colon cancer

^d Chronic Obstructive Pulmonary Disease, Respiratory failure

^e Vitreous hemorrhage

^f Invasive Ductal Breast Carcinoma

Pool 2

Table 61. Patient Disposition, Pool 2

Number of Patients	NT-501	Sham	NT-501 + Sham	Total ^b
Received surgery (safety population), n	188	130	32	334
Completed study, n (%) ^a	176 (93.6)	119 (91.5)	27 (84.4)	307 (91.9)
Retained implant throughout the study, n (%)	185 (98.4)	-	32 (100.0)	-
Study, n (%)	-	-	-	-
NTMT-01	7 (3.7)	0 (0.0)	0 (0.0)	7 (2.1)
Extension	6 (3.2)	0	0 (0.0)	6 (1.8)

Number of Patients	NT-501	Sham	NT-501 + Sham	Total ^b
NTMT02	16 (8.5)	19 (14.6)	32 (100.0)	67 (20.1)
Extension	15 (8.0)	19 (14.6)	30 (93.8)	64 (19.2)
Substudy ^b	16 (8.5)	0 (0.0)	0 (0.0)	16 (4.8)
NTMT-03-A	58 (30.9)	57 (43.8)	0 (0.0)	115 (34.4)
NTMT-03-B	59 (31.4)	54 (41.5)	0 (0.0)	113 (33.8)
NTMT-02-B	32 (17.0)	0	0 (0.0)	32 (9.6)
Discontinued study, n (%) ^{ab}	12 (6.4)	11 (8.5)	5 (15.6)	27 (8.1)
Primary reason for discontinuation, n (%)	-	-	-	-
Eligible and did not enroll in amendment ^c	5 (2.7)	7 (5.4)	0 (0.0)	12 (3.6)
Death ^d	3 (1.6)	0 (0.0)	2 (6.3)	5 (1.5)
Other	1 (0.5)	1 (0.8)	2 (6.3)	4 (1.2)
Adverse event ^e	2 (1.1)	0 (0.0)	0	2 (0.6)
COVID-19	1 (0.5) ^b	1 (0.8) ^b	1 (3.1)	2 (0.6) ^b
Lost to follow-up	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Consent withdrawn	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)

Source: Provided by the Applicant.

^a Refers to completion of the parent study or the parent and extension studies if the patient continued in the NTMT-01/02E study. If a patient discontinued prematurely from either the parent or the extension study, they are included in the summary for discontinuation and primary reason for early discontinuation

^b A total of 16 patients in NTMT-02 with one study-eligible eye received sham in the original protocol and received NT-501 implant in the same eye during the extension study. These patients, identified as 'substudy' are included in both the 'Sham' and 'NT-501' columns, and only once in the 'Total' column.

^c Applicable for Phase 3 studies only

^d Aortic Aneurysm, Metastatic Neoplasm, Chronic Obstructive Pulmonary Disease and Respiratory failure, Cardiac Arrest, Malignant Peritoneal Neoplasm

^e Device expulsion and vitreous hemorrhage

8.4.4 Common Adverse Events

Pool 1

Common Ocular Adverse Reactions

Common ocular ARs occurring in $\geq 2\%$ of Patients in Pool 1 are presented in [Table 62](#). The only events related to NT-501 or CNTF occurring in more than two implanted eyes were delayed dark adaptation and miosis. Delayed dark adaptation was reported based on patient response to a direct query about their perceived changes in dark adaptation during the sham/implant site examination; no further work-up was performed.

Miosis (15.4%), vitreous floaters (5.1%), and vitreous hemorrhage (8.5%) were events that occurred exclusively in implanted eyes at a frequency of $\geq 5\%$. No events of infectious endophthalmitis occurred in either study group.

Most ocular ARs occurring in the Phase 3 studies through Month 24 were mild or moderate in intensity; severe ocular reactions were reported for five study eyes in the NT-501 group. This included two study eyes with severe blurred vision and one study eye each with severe reactions of eye pain, ocular discomfort, and suture-related complication (which was also serious).

In both the NT-501 and sham groups in Pool 1, the majority of ocular ARs occurring in study eyes through the Month 24 visit were considered by the investigator to be related to the surgical procedure (70.9% and 55.0%, respectively). The only events related to NT-501 or CNTF occurring in more than two implanted eyes were delayed dark adaptation and miosis. Delayed dark adaptation was reported based on patient response to a direct query about their perceived changes in dark adaptation during the sham/implant site examination; no further work-up was performed.

Table 62. Ocular TEAEs Occurring in ≥2% of Patients and With Higher Frequency in NT-501 Group Compared to Sham in Pool 1

Adverse Reactions	NT-501 (N=117) n (%)	Sham (N=111) n (%)
Conjunctival hemorrhage	36 (30.8)	29 (26.1)
Delayed dark adaptation	27 (23.1)	1 (0.9)
Foreign body sensation in eyes	18 (15.4)	15 (13.5)
Eye pain	18 (15.4)	10 (9.0)
Suture related complication	18 (15.4)	3 (2.7)
Miosis	18 (15.4)	0
Conjunctival hyperemia	13 (11.1)	9 (8.1)
Eye pruritus	10 (8.5)	4 (3.6)
Ocular discomfort	10 (8.5)	1 (0.9)
Vitreous hemorrhage	10 (8.5)	0
Vision blurred	8 (6.8)	4 (3.6)
Headache	8 (6.8)	1 (0.9)
Dry eye	7 (6.0)	2 (1.8)
Conjunctival edema	6 (5.1)	7 (6.3)
Eye irritation	6 (5.1)	2 (1.8)
Cumulative cataract incidence	6 (5.1)	0
Vitreous floaters	6 (5.1)	0
Temporary or permanent severe visual loss >15 letters	4 (3.4)	0
Eye discharge	4 (3.4)	1 (0.9)
Anterior chamber cell	4 (3.4)	0
Iridocyclitis	3 (2.6)	0

Source: FDA analysis of ADAE dataset, generated by FDA Clinical Data Analyst.

Common Non-Ocular Adverse Events

Across the Phase 3 studies through the Month 24 visit, a smaller percentage of patients in the NT-501 group than the sham group experienced systemic TEAEs (65.0% and 73.0% respectively).

The systemic TEAEs occurring at the three highest frequencies in each group in Pool 1 were headache (9.4%), arthralgia (8.5%), and nasopharyngitis (6.0%) for the NT-501 group and headache (8.1%), COVID-19, influenza, and osteoarthritis (6.3% each), and hypertension (5.4%) for the sham group.

Most systemic TEAEs occurring in the Phase 3 studies through the Month 24 visit were mild or moderate in intensity; severe systemic TEAEs were reported for a similar

percentage of patients in the NT-501 and sham groups (11.1% and 11.7% respectively). The severe events occurring in more than one patient overall included COVID-19 (one patient in each group), arthritis (two NT-501), osteoarthritis (two sham), migraine (two NT-501), and chronic obstructive pulmonary disease (one NT-501; one sham). All severe systemic TEAEs in either study group in Pool 1 were considered by the investigator to be not related to the surgery, NT-501, or CNTF.

The only systemic TEAEs considered by the investigator to be related to the surgery were headache, reported for eight patients (6.8%) in the NT-501 group and one patient (0.9%) in the sham group, and constipation, reported for one patient (0.9%) in the sham group. No patient in either group had a systemic event that was considered by the investigator to be related to NT-501 or to CNTF.

Pool 2

Common Ocular Adverse Reactions

The most common ocular ARs seen in Pool 2 are shown in [Table 63](#). Across the six MacTel studies, no events of infectious endophthalmitis occurred in either study group. The types and frequencies of ocular ARs reported in Pool 2 were consistent with those observed for Pool 1.

Table 63. Ocular-Related TEAEs Occurring in ≥2% of Patients in NT-501 Group, Pool 2

Adverse Reaction, n (%)	NT-501 (N=220 Eyes)	Sham (N=162 Eyes)
Conjunctival hemorrhage	59 (26.8)	46 (28.4)
Eye irritation	53 (24.1)	45 (27.8)
Eye pain	49 (22.3)	19 (11.7)
Vision blurred	48 (21.8)	37 (22.8)
Delayed dark adaptation	46 (20.9)	2 (0.9)
Miosis	40 (18.2)	0 (0.0)
Foreign body sensation in eyes	27 (12.3)	20 (12.3)
Suture related complication	26 (11.8)	4 (2.5)
Eye pruritus	22 (10.0)	11 (6.8)
Ocular discomfort	21 (9.5)	4 (2.5)
Conjunctival hyperemia	18 (8.2)	9 (5.6)
Vitreous hemorrhage	17 (7.7)	0 (0.0)
Dry eye	14 (6.4)	6 (3.7)
Vitreous floaters	14 (6.4)	1 (0.6)
Eye swelling	14 (6.4)	7 (4.3)
Conjunctival edema	11 (5.0)	8 (4.9)
Cataract	9 (4.1)	0 (0.0)
Photopsia	8 (3.6)	1 (0.6)
Eye discharge	7 (3.2)	4 (2.5)
Visual acuity reduced	6 (2.7)	1 (0.6)
Anterior chamber cell	5 (2.3)	0 (0.0)
Iridocyclitis	6 (2.7)	0 (0.0)

Source: Generated by Clinical Reviewer based on information provided by Applicant, Summary of Safety Report

Common Non-Ocular Adverse Events

In Pool 2, a smaller percentage of patients in the NT-501 group experienced non-ocular TEAEs than patients in the sham and NT-501+sham groups (63.8%, 77.7% and 93.8% respectively).

The non-ocular TEAEs occurring at the three highest frequencies in each group were headache and nasopharyngitis (8.0% each), hypertension (7.4%), and arthralgia (5.9%) for the NT-501 group, headache (8.5%), hypertension and osteoarthritis (7.7% each), and COVID-19 and influenza (6.9% each) for the sham group and basal cell carcinoma (15.6%), constipation, nasopharyngitis, back pain, headache, dizziness, and hypertension (12.5% each), and gastroesophageal reflux disease, hypersensitivity, sinusitis, urinary tract infection, meniscus injury, anxiety, and sleep apnea syndrome (9.4% each) for the NT-501+sham group.

Of the most frequently reported non-ocular TEAEs, headache and hypertension were common to all three study groups and occurred at similar frequencies across groups.

Overall, 52 patients (15.6%) in Pool 2 had severe non-ocular TEAEs, with a similar incidence in the NT-501 and sham groups (13.3% [and 13.8% respectively]), and at an incidence of 31.3% in the NT-501+sham group. Most severe systemic TEAEs were reported for one patient each in a treatment group, with no more than two patients in any group experiencing a given event. The only severe non-ocular event occurring in more than two patients across groups was arthralgia (two NT-501, one sham).

A total of 18 patients (5.4%), including 10 in the NT-501 group, 3 in the sham group, and 5 in the NT-501+sham group, had related non-ocular events. All non-ocular events were considered related to the surgery. The only surgery related events occurring in more than one patient in any treatment group were headache (10 NT-501, 1 sham, 2 NT-501+sham) and dizziness (2 NT-501+sham).

Pool 3

Common ocular and non-ocular AEs observed in Pool 3 were similar to Pool 1 and Pool 2 and no unusual safety concerns were encountered. Notably, there were no differences in the overall incidence of ocular TEAEs in eyes implanted with low output or high output NT-501 (92.3% and 89.8% respectively) and overall incidence of systemic TEAEs (64.7% and 63.7% respectively).

8.4.5 Clinical Test Results

Clinical laboratory evaluations were only performed in Study NTMT-01 and NTMT-02-B (baseline only) and were not included in safety database.

Clinical Test Findings

Best Corrected Visual Acuity

In Pool 1, 18 total patients (7.9%) experienced a temporary or permanent severe visual acuity loss of ≥ 15 letters, 10 (8.5%) patients in the NT-501 group and 8 (7.2%) patients

in the sham group. Four of these patients in the NT-501 group had severe visual loss related to NT-501 or procedure, in two of those patients the severe visual acuity loss was due to cataract related to NT-501 or surgery and in the other two related to surgery. For the remaining patients visual acuity loss was unrelated. Four patients from the 18 total in each group experienced a ≥ 15 letter decrease of BCVA that did not improve by the end of the study.

In Pool 2, 25 study eyes (16 in the NT-501 group and 9 in the sham group) experienced such a decrease and did not exhibit an improvement in vision by the end of the study; 9 of these eyes had one TEAE and 7 eyes had multiple TEAEs in the study eye that either preceded or were coincident with worsening vision for each patient. The most frequently occurring events that occurred in the NT-501 group included cataracts/lens opacification (nine eyes), vitreomacular/vitreoretinal traction (four eyes), epiretinal membrane (three eyes), vitreous hemorrhage (two eyes), and macular hole (two eyes). Of the nine eyes in the sham group, one eye had an epiretinal membrane, one eye worsening MacTel, one eye retinal and inferior vitreous hemorrhage, one eye macular fibrosis and CNV, and five eyes did not have ocular examination findings and/or TEAEs that would explain the loss in vision.

Intraocular Pressure

In Pool 1, the number of patients with IOP of 21 mm Hg or greater and an increase in IOP of 5 mm Hg or more from baseline was largest at Week 1 and similar between groups (six NT-501; five sham). The number decreased over time in both study groups, with no more than three patients in the NT-501 group and two patients in the sham group meeting these criteria at subsequent postoperative visits through Month 24.

In Pool 2, the percentage of patients in Pool 2 who had an IOP of 21 mm Hg or greater and an increase in IOP of 5 mm Hg or more from baseline at any time during the MacTel studies was similar in the NT-501 and sham groups (11.4% versus 9.9%, respectively).

8.4.6 Local Reactogenicity

N/A

8.4.7 Adverse Events of Special Interest

Dark Adaptation

Delayed dark adaptation was reported in 23% and 21% of patients receiving NT-501 in Pool 1 and Pool 2 respectively. These reports were consistently mild, did not progress, and did not lead to explantation.

Delayed dark adaptation was reported based on patient response to a direct query about their perceived changes in visual adaptation to low/no light in environment during the sham/implant site examination. No psychophysical or electrophysiologic investigations were performed to assess this finding during the trials. At each study visit, patients were specifically asked if they perceived a change in dark adaptation. If the

patient responded affirmatively, further AE questions were posed to evaluate the severity, onset, and duration of the dark adaptation difficulty. These queries were standardized across study sites and patient responses were documented. ERGs performed in the seven patients enrolled in the Phase 1 Study NTMT-01 demonstrated reduced amplitude in the ERG b-wave obtained from study eyes to a dark-adapted dim flash (DA 0.01) in a total of four patients at Months 3 and 6, which resolved by Month 12. None of these patients reported delayed dark adaptation while another patient with no evidence of ERG changes complained of abnormal dark adaptation associated with miosis (20). Based on existing preclinical and clinical data from the RP studies, and the nature of the delayed dark adaptation observed in the MacTel studies, the Applicant determined that further psychophysical or electrophysiologic testing was not warranted.

Reviewer's comment

During the BLA review, the review team determined that the complaint of delayed dark adaptation has not been efficiently assessed by the Applicant. In addition, the way the question was posed to the patients might have led to underestimation of the actual incidence of the AE. Because dark adaptation reports were consistently mild, did not progress, and did not lead to explantation and since delayed dark adaptation is also part of the natural history of MacTel, which would make further investigations difficult, the review team concluded that a postmarketing requirement for additional studies is not necessary. Delayed dark adaptation was added in the "Warnings and Precautions" section of the USPI to alert providers about this AE.

Cataract Formation

In Pool 1, a higher incidence of cataract formation following placement of NT-501 was observed in the NT-501 arms (10.3%; 12/117) compared to the sham arms (2.7%; 3/111) through Month 24. Of the 12 cases in the NT-501 arms, 6 (5.1%) cases were attributed to the product (related to NT-501 or implant procedure) compared to none in the sham group. A similar pattern was noted in Pool 3, with 9 related cases (4.1%) in the NT-501 group and 0 (0.0%) related cases in the sham group.

Endophthalmitis

There were no cases of infectious endophthalmitis. There was one case of noninfectious endophthalmitis considered to be related to NT-501 in Pool 2, that resolved by Month 72.

Retinal Tear and/or Detachment

No retinal tears or retinal detachment were observed.

Vitreous Hemorrhage

In the Phase 3 clinical trials (Pool 1), vitreous hemorrhage was reported in 8.5% (10/117) of patients who received the NT-501 through Month 24. The majority of these hemorrhages occurred within 90 days following surgical implantation and resolved spontaneously. In Pool 2, 8.3% of eyes experienced vitreous hemorrhage with late

onset (after 365 days post-surgery) vitreous hemorrhage occurring in nine implanted eyes (4.1%); of those, one of event was serious and resulted in NT-501 removal. An additional three vitreous hemorrhages were reported in the Applicant's 120-Day Safety Update Report submitted to the BLA; those occurred 31 months, 4 and 9 years after surgical implantation and resulted in NT-501 removal.

Device Extrusion

In the Phase 3 clinical trials (Pool 1), one patient (0.9%; 1/117) experienced device extrusion which occurred 701 days (23 months) after implantation and was corrected with surgical repositioning and wound revision.

Suture-Related Complications

In the Phase 3 clinical trials (Pool 1), 18 of 117 patients (15.4%) of patients in the NT-501 arms experienced suture-related complications compared to 3 of 111 patients (2.7%) in the sham arm.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

Pool 1

Most ocular TEAEs occurring in the study eyes in Pool 1 had onset within 90 days post-surgery, with either no change or a small increase in the number of eyes with the same events having onset after 90 days but within 365 days postsurgery, and a notable decline in the frequency of occurrence of the same events with onset after 365 days post-surgery. With the exception of miosis, reported for seven study eyes (6.0%) in the NT-501 group, no more than three study eyes in either group had ocular events with onset after 365 days postsurgery. Late onset vitreous hemorrhage and subcapsular cataract occurred in three study eyes each (2.6%) in the NT-501 group.

Pool 2

Similar to the pattern of incidence over time observed for Pool 1, most ocular TEAEs occurring in the study eyes in Pool 2 had onset within 90 days post-surgery, with either no change or an increase in the number of eyes with the same events having onset after 90 days but within 365 days postsurgery, and a notable decline in the incidence of the same events with onset after 365 days postsurgery with the following exceptions:

- The events in both study groups with the highest frequencies occurring after 365 days post-surgery were cataract (NT-501: 4.1% [nine eyes]; sham: 3.7% [six eyes]), retinal hemorrhage (NT-501: 2.3% [five eyes]; sham: 1.9% [three eyes]), epiretinal

membrane (NT-501: 2.3% [five eyes]; sham: 1.2% [two eyes]), and vitreoretinal traction syndrome (NT-501: 2.7% [six eyes]; sham: 0 eyes).

- A similar percentage of implanted eyes had vitreous hemorrhage with onset within 90 days postsurgery (4.5% [10 eyes]) and after 365 days postsurgery (4.1% [9 eyes]).
- There was a notable increase in the occurrence of miosis in implanted eyes between the early postsurgery period (5 eyes [2.3%]) and the period between 90 to 365 days postsurgery (15 additional implanted eyes), which continued to be high after 365 days postsurgery (16 eyes [7.3%]).

8.5.3 Product-Demographic Interactions

Patients in Pool 1 were predominantly White (n=200 [105 NT-501; 95 sham]), with a small number of non-White patients (n=28 [12 NT-501; 16 sham]). In the NT-501 group, ocular TEAEs occurred in a similar percentage of study eyes in White and non-White patients (88.6% versus 91.7%, respectively). In addition, the types and frequencies of ocular TEAEs reported in White and non-White patients were generally similar.

The patients in Pool 2 were predominantly not Hispanic or Latino (n=214 [112 NT-501; 102 sham]), with a small number of Hispanic or Latino patients (n=14 [5 NT-501; 9 sham]). In the NT-501 group, ocular TEAEs occurred in 88.4% of study eyes in patients who were not Hispanic or Latino and in 100.0% of study eyes in Hispanic or Latino patients. In addition, the types and frequencies of ocular TEAEs reported in the ethnicity subgroups were generally similar.

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

Clinical drug interaction studies were not conducted.

8.5.6 Human Carcinogenicity

There were no reports of cancer related to NT-501 during the studies. There is no mechanistic reason to expect a higher risk of cancer based on exposure to NT-501.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

NT-501 is intended for surgical intravitreal placement and is associated with no/negligible systemic exposure to CNTF. Therefore, overdose/drug abuse/withdrawal/rebound effects are not applicable to this product.

8.5.8 Immunogenicity (Safety)

In the six-month, Phase 2 study NTMT-02B, immunogenicity assessments were conducted. Study NTMT-02B enrolled 33 adults with MacTel who previously received the NT-501 implant in a single eye (in a phase 1, 2 or 3 study); in this study, patients

received NT-501 in the other, previously untreated eye. Of the 33 enrolled patients, 31 were tested for antibodies at baseline, 1, 2, 3 and 6 months. One out of 31 patients (3.2%) tested positive for serum antibodies against rhCNTF, and another patient tested positive for serum nonsecreted, intracellular protein DHFR.

Because of the low occurrence of anti-drug antibodies, the effect of serum anti-rhCNTF and anti-DHFR antibodies on the safety of NT-501 is unknown.

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 Safety Conclusions

The primary safety assessment for NT-501 is based on data from the phase 3 studies NTMT-03-A and NTMT-03-B and formed the basis for the USPI safety sections. Additional safety analyses conducted on data from Phase 1 and 2 studies of NT-501 in MacTel and in studies of the product in other retinal conditions did not reveal additional safety risks.

Overall, in the phase 3 studies, there were no deaths or systemic serious adverse events (SAEs) related to NT-501 or the implantation procedure. There were 7 ocular SAEs (7/117; 6%) of which 6 occurred in the NT-501 group and 1 in the sham group until month 24, an additional SAE, a device explantation occurred beyond Month 24 due to vitreous hemorrhage in the NT-501 group. Of the 6 ocular SAEs occurring in the NT-501 group, 5 were suture-related complications and one was device extrusion. The only SAE reported in the sham group, choroidal neovascularization, was considered unrelated to NT-501 or procedure. Most ocular treatment emergent adverse events (TEAEs) were mild or moderate in intensity. There were 5 severe ocular TEAEs (4.3%) reported in the NT-501 group: 2 events of severe blurred vision and one event each of eye pain, ocular discomfort, and suture-related complication (the latter also being serious). The most common TEAEs related to NT-501 are shown in [Table 62](#).

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

For subgroup analysis by age and sex please see Sections [6.1.11.3](#), [6.2.11.3](#), and [9.1.5](#).

9.1.1 Human Reproduction and Pregnancy Data

There are no human data on the use of NT-501 in pregnant women. Endogenous CNTF is naturally found in maternal plasma, placental cells, and umbilical cord blood. It is not known if the use of NT-501 increases CNTF above naturally occurring levels in these tissues.

In animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of teratogenic effects on the fetus. However, in

rabbits, high-dose levels of 10 µg/kg/day resulted in a decrease in implantation and live fetuses. In rats, dose levels ≥100 µg/kg/day resulted in fewer corpora lutea. These doses are much higher than the 20ng/day released by a single NT-501 implant.

9.1.2 Use During Lactation

There are no human data on the presence of NT-501 in human milk, the effects of NT-501 on breastfed infants, or the effects of NT-501 on milk production.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

MacTel typically affects adults over 40 years of age. The NT-501 clinical development program did not include pediatric patients. NT-501 has orphan drug designation for treatment of MacTel and is therefore exempt from Pediatric Research Equity Act (PREA) requirements.

9.1.4 Immunocompromised Patients

No clinical data are available.

9.1.5 Geriatric Use

In the Phase 3 studies, the majority of patients (152/228; 67%) were younger than 65 years old and, in those, the difference (NT-501-Sham) in rate [SE] of change in EZ area loss from baseline to Month 24 was -0.114 [0.017] mm² (95% CI: -0.148, -0.081) indicating a slower rate of EZ loss in NT-501-treated patients. By comparison, that difference was 0.023 [0.02] mm² (95% CI: -0.017, 0.062) in patients ≥65 years of age indicating no significant difference in the rate of change over 24 months. This could be because older patients are in more advanced stages of their disease. However, the interpretation of these findings is limited given the small number of patients who were ≥65 years of age.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

Substantial evidence of effectiveness for NT-501 in adults with MacTel is established based on evidence derived from the two adequate and well-controlled Phase 3 studies that demonstrated visual function preservation reflected in the slowing of macular photoreceptor degeneration in NT-501-treated patients compared to sham treated patients. NT-501 was generally well-tolerated over a follow up duration of up to 9 years after intraocular implantation.

Serious adverse events were associated with the implantation procedure and included suture-related complications and implant extrusion.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations are described in [Table 64](#).

Table 64. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Macular telangiectasia type 2 (MacTel) is a bilateral, asymmetric, slowly progressive neurodegenerative disease with localized retinal degeneration The natural course of MacTel is that of gradual bilateral macular photoreceptor loss and consequent loss of vision, occasionally accompanied by the development of neovascularization and severe vision loss. It primarily affects central vision with visual acuity decrease and central and paracentral scotomas 	<p>MacTel is a sight threatening disease that can limit patients reading and driving capabilities.</p> <p>It has the potential to alter the patients' quality of life and limit their independence</p>
Unmet Medical Need	<p>Although anti-VEGF drugs have been reported to be associated with anatomical and functional improvement of proliferative MacTel type 2, the use of existing treatment (focal and grid laser photocoagulation, photodynamic therapy, intravitreal steroids, and anti-VEGF drugs) for treatment of non-proliferative MacTel remains controversial.</p>	<p>There is an unmet need for products targeting underlying mechanism of the disease in patients with MacTel</p>
Clinical Benefit	<p>The pivotal studies NTMT-03A and NTMT-03B were randomized, multicenter, evaluator-masked, sham-controlled studies in adults with MacTel. In both studies, the primary efficacy endpoint was the mean rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline to Month 24. The area of EZ loss (EZ break) was measured in enface OCT at different time points from baseline to month 24 and the rate of change from baseline to month 24 was calculated. The secondary efficacy endpoints tested in hierarchical order were: (i) mean change in aggregate retinal sensitivity loss of microperimetry within the EZ lbreak area from baseline to Month 24, (ii) mean change in monocular reading speed from baseline to Month 24, and (iii) mean change in the National Eye Institute-Visual Function Questionnaire (NEI VFQ 25) near activities subscale score from baseline at Month 24 (The near activities subscale score, was an average of the scores for items 5, 6, and 7 in the NEI VFQ 25).</p> <p>Both pivotal studies met their primary endpoint and demonstrated a reduction in the rate of EZ area loss over 24 months. In Study NTMT-03A, the difference between NT-501 and sham in the rate of EZ are loss over 24 months was -0.091 (-0.13, -0.06) with p value <0.0001 and the difference in the mean change in aggregate retinal sensitivity loss from baseline to month 24 was -17.75 (-32.58, -2.91) with p value 0.02. In Study NTMT-03-B, the difference between NT-501 and sham in the rate of EZ are loss over 24 months was -0.049 (-0.089, -0.008) with p value <0.0186 and the difference in the mean change in aggregate retinal sensitivity loss from baseline to month 24 was -1.95 (-20.33, 16.43) with p value 0.83.</p>	<p>Studies NTMT-03-A and NTMT-03-B demonstrated a clinically and statistically significant beneficial effect of NT-501 in slowing the EZ area loss (photoreceptor loss) in NT-501-treated patients compared to sham surgery treated patients which represents clinical benefit based on preservation of vision. Results on secondary and other efficacy endpoints in both studies demonstrated clinical effects that were consistent with the primary efficacy results.</p>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	<p>There were no deaths or systemic serious adverse events (SAEs) related to NT-501 or the implantation procedure.</p> <p>In the phase 3 studies, there were 7 ocular SAEs (7/117; 6%) of which 6 occurred in the NT-501 group and 1 in the sham group until month 24. An additional SAE, a device explantation occurred beyond month 24 due to vitreous hemorrhage in the NT-501 group. Of the 6 ocular SAEs occurring in the NT-501 group, 5 were suture-related complications and one was device extrusion. The only SAE reported in the Sham group, choroidal neovascularization, was considered unrelated to NT-501 or procedure.</p> <p>Most ocular treatment emergent adverse events (TEAEs) were mild or moderate in intensity. There were 5 severe ocular TEAEs (4.3%) reported in the NT-501 group: 2 events of severe blurred vision and one event each of eye pain, ocular discomfort, and suture-related complication (the latter also being serious). The most common TEAEs reported in over 15% of patients in the NT-501 group (and with higher frequency in the treatment arm) included conjunctival hemorrhage, delayed dark adaptation, foreign body sensation in the eye, eye pain, suture related complications, miosis. Of those, delayed dark adaptation and miosis, both non-serious, were related to NT-501. Delayed dark adaptation was consistently reported as non-progressive. Cataract formation (related to NT-501 or the procedure) and vitreous hemorrhage were reported in NT-501 implanted eyes only.</p>	<p>NT-501 was generally well-tolerated over a follow up duration of up to 9 years after intraocular implantation.</p> <p>Serious adverse events were associated with the implantation procedure and included suture-related complications and implant extrusion.</p>
Risk Management	<ul style="list-style-type: none"> The Applicant plans to mitigate the risks with routine pharmacovigilance, a Phase 3 extension sham dosing study and through an ongoing National History Observation Study (NHOR) questionnaire. 	<p>The risks can be mitigated through routine pharmacovigilance and the postmarketing plan proposed by the Applicant without requiring other regulatory measures such as REMS, PMR, or clinical PMC. A voluntary study to further investigate delayed dark adaptation with psychophysical testing is planned by the Applicant.</p>

11.2 Risk-Benefit Summary and Assessment

The efficacy and safety data in the BLA support a favorable benefit-risk profile for patients with MacTel. NT-501 is effective in slowing down the progression of retinal disease in patients with MacTel and all identified risks can be adequately mitigated in the postmarketing setting.

11.3 Discussion of Regulatory Options

N/A

11.4 Recommendations on Regulatory Action

Substantial evidence of effectiveness for NT-501 in adults with MacTel is established based on evidence derived from two adequate and well-controlled Phase 3 studies that demonstrated visual function preservation, as measured by the slowing of photoreceptor degeneration in NT-501 treated patients compared to the control group. The demonstrated benefits on visual function outweigh the identified serious risks which are predominantly associated with the implantation procedure and can be mitigated through labeling and post-marketing pharmacovigilance activities. Based on the favorable benefit-risk assessment of NT-501 in adults with MacTel, the review team recommends approval of NT-501 for the indication of treatment of adults with idiopathic macular telangiectasia type 2.

11.5 Labeling Review and Recommendations

Several revisions were made to the Applicant's proposed USPI, patient information, and instructions for use. Please see [Table 65](#) below for a summary of significant changes.

Table 65. Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	ENCELTO is indicated for the treatment of idiopathic macular telangiectasia type 2 (MacTel).	ENCELTO is indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 2: Dosage and Administration	General dose and administration information Section 2.2: ENCELTO Surgical placement	Revised to include recommended dose section including dose delivered by ENCELTO (20 ng/device/day of recombinant human ciliary neurotrophic factor (rhCNTF). Section 2.2 was revised to include surgical steps as numerical bullets and figures as needed to improve readability and comprehension.
Section 3: Dosage forms and strengths	ENCELTO implant description	Revised to include dimensions of ENCELTO implant
Section 4: Contraindications	Included active or suspected ocular or periocular infections	Revised to include know hypersensitivity to Endothelial Serum Free Media (Endo-SFM)
Section 5: Warnings and Precautions	-	Warnings in this section were re-ordered based on clinical significance. The information for each warning was reorganized to firstly define the risk, cross-reference supportive data, and then specify recommendation for mitigation of the risk. Negative data were deleted as it is not informative. Delayed Dark Adaptation was added to the section because of the reported cases in the clinical trial.
Section 6: Adverse Reactions (safety)	Table 1 listed adverse events related to the surgery, ENCELTO, and rhCNTF related.	Table 1 was revised to list the most common adverse reactions reported in $\geq 2\%$ patients in ENCELTO and Sham group. Overall, the information in this section was revised based on the current labeling practice for concise presentation of data and to remove redundant information.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 12: Clinical Pharmacology	Immunogenicity placed as section 6.3	This section was moved to Section 12 based on FDA immunogenicity guidance which recommends the use of a dedicated subsection, 12.6 Immunogenicity, under the CLINICAL PHARMACOLOGY section when summarizing results from immunogenicity studies.
Section 14: Clinical Studies (efficacy)		This section was revised and reorganized to include the individual study descriptions, and population characteristics. Table 2 and Table 3 was added to summarize efficacy data from Study NTMT-03-A and Study NTMT-03-B.
Section 17: Patient Counseling Information		This section was revised for clarity, use of command language, and to include important risks listed in Section 5 (Warning and Precautions).

Source: Created by FDA Clinical Reviewer and the Associate Director of Labeling

Patient information and instructions for use were revised to ensure consistency with USPI.

11.6 Recommendations on Postmarketing Actions

The applicant's proposed PVP is adequate to monitor postmarketing safety for NT-501 with routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for delayed dark adaptation events.

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APPENDIX 1: HUMAN FACTOR STUDIES

The Applicant has followed the [Applying Human Factors and Usability Engineering to Medical Devices | FDA](#) guidance and IEC 62366-1:2015+A1:2020 to establish its HF validation process and has conducted the following evaluations to assess the usability of NT-501 including its packaging, labeling, and IFU:

- An iterative expert review of the IFU
- A formative usability study with 13 representative users including 7 ophthalmologists and 6 ophthalmic surgical staff team members in the United States. Results from the usability study were incorporated into the risk analysis and improvements were made to the IFU and training as a result of the study.

- A comprehensive URRRA, that was pre-reviewed and agreed upon by the Agency. The URRRA correctly identified all tasks that needed to be evaluated in the HF protocol.
- An adequate HF validation testing with sufficiently representative test patients (ophthalmologists [n =15] and ophthalmic surgical team members [n =15]) in a representative test environment. The results of the HF validation testing do not illustrate any patterns of use error or raise additional questions of use safety and/or effectiveness. Therefore, the results of the HF validation testing adequately support the conclusion that the patient device is able to be used safely and effectively for its intended uses by its intended users in its intended use environments.