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Applicant	Neurotech Pharmaceuticals, Inc.
Established Name	revakinagene taroretcel (NT-501)
(Proposed) Trade Name	ENCELTO
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	An encapsulated cell-based gene therapy that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF) (NTC-201-6A cell line)
Dosage Form(s) and Route(s) of Administration	One implant containing 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF for surgical intravitreal placement

Dosing Regimen	One implant to deliver 20 ng/device/day of rhCNTF
Indication(s) and Intended Population(s)	For the treatment of idiopathic macular telangiectasia type 2 (MacTel)

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GLOSSARY

AESI	Adverse Events of Special Interest
Anti-VEGF	Anti-vascular endothelial growth factor
AREDS	Age-Related Eye Disease Study
AU	Australia
BCVA	best-corrected visual acuity
BLA	Biologics Licensing Application
CI	Confidence interval
CNV	choroidal neovascularization
dB	decibel
DE	Germany
ETDRS	the Early Treatment Diabetic Retinopathy Study
EZ (IS/OS)	ellipsoid zone (inner segment/outer segment)
F	female
FR	France
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
MacTel	macular telangiectasia Type 2
Max	Maximum
Min	Minimum
mITT	Modified intent to treat
mm	millimeters
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
PP	Per protocol
rhCNTF	Recombinant human ciliary neurotrophic factor
UK	United Kingdom
US	United States
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SD	Standard deviation
SD-OCT	Spectral-domain optical coherence tomography

1. EXECUTIVE SUMMARY

NT-501, under the trade name of ENCELTO, is an allogeneic encapsulated cell-based intraocular implant consisting of 200,000-440,000 recombinant human

ciliary neurotrophic factor (hCNTF)-secreting NTC-201-6A.02 cells encapsulated within supportive matrices and surrounded by a semipermeable polymer membrane. Neurotech Pharmaceuticals Inc. submitted results from two Phase 3 studies, NTMT-03-A and NTMT-03-B, in this original Biologics Licensing Application (BLA) to support the indication of NT-501 for the treatment of idiopathic macular telangiectasia Type 2 (MacTel). Both Phase 3 studies serve as the primary evidence of efficacy and safety.

NTMT-03-A and NTMT-03-B were identically designed. Both studies were a Phase 3, prospective, multicenter, masked, sham-controlled study to determine the safety and efficacy of NT-501 in subjects with MacTel. A total of 112 subjects were planned for each study. The primary efficacy endpoint was the rate of change in the ellipsoid zone (inner segment/outer segment) [EZ (IS/OS)] area loss over 24 months using spectral-domain optical coherence tomography (SD-OCT). The key secondary efficacy endpoints included the change from baseline to Month 24 in aggregate sensitivity of microperimetry within the EZ line break area, in reading speed, and in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) near activities subscale score.

In NTMT-03-A, 120 subjects were enrolled and randomized to either NT-501 implant or sham procedure, of whom 115 subjects underwent surgery (58 in the NT-501 group and 57 in the sham group). The mean rate of change in EZ area loss over 24 months was 0.075 millimeters [mm]² in the NT-501 group and 0.166 mm² in the sham group, with a statistically significant difference between the groups (−0.091 mm²; 95% confidence interval [CI]: −0.125, −0.056; $p < 0.0001$). For the first secondary efficacy endpoint, the magnitude of loss was statistically significantly smaller in the NT-501 group relative to the sham group (25.3 vs 43 decibel [dB], respectively; $p=0.02$). This study met its primary efficacy endpoint and its first secondary efficacy endpoint that NT-501 slowed down EZ area loss and aggregate retinal sensitivity loss over 24 months.

One subject in the sham group experienced a serious adverse event (SAE) of congestive cardiac failure and subsequently died. Two subjects in the NT-501 group and one subject in the sham group experienced at least 1 ocular SAE each through Month 24. Ten subjects (17.2%) in the NT-501 group and 7 subjects (12.3%) in the sham group experienced at least 1 nonocular SAE each through Month 24. Delayed dark adaptation was more common in the NT-501 group (20.7% [12 eyes]).

In NTMT-03-B, 119 subjects were enrolled and randomized to either NT-501 or sham, of whom 113 subjects underwent surgery (59 in the NT-501 group and 54 subjects in the sham group). The mean rate of change in EZ area loss over 24 months was 0.111 mm² in the NT-501 group and 0.160 mm² in the sham group, with a statistically significant difference between groups (−0.0486 mm²; 95% CI: −0.089, −0.0082; $p = 0.0186$). This study met its primary efficacy endpoint that

NT-501 slowed the rate of EZ area loss over 24 months, but none of the key secondary efficacy endpoints was statistically significant.

One NT-501 subject died due to a SAE of chronic obstructive pulmonary disease. Four study eyes (6.8%), all in the NT-501 group, experienced at least 1 ocular SAE each through Month 24. This included suture related complication occurring in 3 study eyes and device extrusion occurring in 1 study eye. A total of 18 subjects (15.9%), including 8 subjects (13.6%) in the NT-501 group and 10 subjects (18.5%) in the sham group, experienced at least 1 nonocular SAE each through Month 24.

We verified the primary efficacy and key secondary efficacy analyses results for NTMT-03-A and NTMT-03-B as prespecified in the Statistical Analysis Plan (SAP). The statistical evidence supports approval of NT-501 for the treatment of idiopathic MacTel.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Idiopathic macular telangiectasia type 2 (MacTel) is a bilateral degenerative condition of unknown etiology with characteristic neurosensory atrophy and perifoveal telangiectatic vessels which leak on fluorescein angiography. Other characteristic lesions include loss of retinal transparency, crystalline deposits, a decrease or absence of macular pigment and hyperplasia of the retinal pigment epithelium in the macular area. The spectral-domain optical coherence tomography (SD-OCT) assessments show disruption of IS/OS line or ellipsoid zone, and hypo-reflective cavities in both the inner and outer retina.

The natural course is a gradual progressive bilateral loss of vision with the progression of the EZ loss, occasionally accompanied by sub-retinal neovascularization, leading to severe vision loss.

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

There is currently no available treatment of MacTel. Anti-vascular endothelial growth factor (anti-VEGF) may be used to help prevent further vision loss in cases where new blood vessels have formed under the retina, i.e., sub-retinal neovascularization.

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

The following clinical studies were conducted during the development program to evaluate the efficacy of NT-501 in subjects with MacTel:

- NTMT-01: a Phase 1, open-label, nonrandomized pilot study to explore the safety and tolerability of NT-501 in subjects with MacTel. Seven

subjects were enrolled and received NT-501 in the study eye; the untreated fellow eye was used as the control eye.

- NTMT-02: a Phase 2, prospective, single-masked, sham controlled study. Subjects with 1 eligible study eye were randomized (1:1) to receive either NT-501 or a sham procedure in the study eye. Subjects with 2 eligible study eyes were randomized (1:1) to receive either NT-501 or a sham procedure, with the fellow eye receiving the alternative treatment. A total 67 subjects (99 eyes: 48 NT-501; 51 sham) were enrolled.
- NTMT-01/02E: subjects who completed NTMT-01 or NTMT-02 were evaluated for long-term efficacy and safety.
- NTMT-01/02E-SS: a sub-study of NTMT-01/02E to enable implantation of the NT-501 into the study eye of those subjects who had one eligible study eye and received sham procedure in NTMT-02. Sixteen subjects received NT-501 in an open-label manner.
- NTMT-02-B: a Phase 2, open-label study to evaluate the safety and tolerability of NT-501 when implanted in both eyes of subjects with MacTel. Thirty-three subjects who received NT-501 in a single eye prior to or in the NTMT-01/02E or in one of the two Phase 3 studies (NTMT-03-A or NTMT-03-B) were enrolled.
- NTMT-03-A and NTMT-03-B: 2 identically designed Phase 3 studies where subjects were randomized (1:1) to receive NT-501 or undergo a sham procedure in the eligible study eye. See Section 6 for more details.

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

The studies supporting this BLA were conducted under IND 10931. Major regulatory history with statistical implications is summarized below:

Pre-submission:

1. On March 2, 2017, via preliminary response, FDA wrote, “It could potentially be acceptable for trials intended to support a marketing application if the change in the area demarcated by ellipsoid zone line break from baseline through month 24 were different enough between the NT-501 group and sham group to be considered not just statistically significant, but also clinically significant.” In addition, FDA agreed “with the use of visual acuity as a secondary endpoint to help the interpretation of the SD-OCT data,” but a clinically meaningful endpoint in visual acuity be defined as a loss of fewer than 15 letters or a gain of 15 letters in BCVA (best corrected distance visual acuity) from baseline.” Regarding reading speed as a secondary efficacy endpoint, the sponsor needed to establish the amount of change that would be considered clinically meaningful.

2. On July 21, 2017, the sponsor submitted protocols for two identical adequate and well-controlled clinical trials (NTMT-03-A and NTMT-03-B) in support of a marketing application for NT-501 for the treatment of MacTel.
3. On October 11, 2017, via email, FDA communicated to the sponsor that “the primary analysis be slope (best fit curve) from baseline through Month 24” and that “not all of the proposed secondary efficacy endpoints are necessarily clinically meaningful.”
4. On January 29, 2019, via email, FDA communicated to the sponsor regarding the following statistical issues regarding the two protocols (amendment 149): inclusion of all randomized subjects in the ITT analysis, sample size calculation, and missing data handling approach.
5. On March 10, 2023, the FDA recommended to Neurotech to conduct “a small (~10 patient) non-powered, no sham, 12-month clinical study (using the same endpoint as the completed Phase 3 trials), evaluating NT-501 implant manufactured with (b) (4) HFM membrane to demonstrate that NT-501 with (b) (4) HFM ‘works the same way’ as NT-501 manufactured with (b) (4) HFM, and that the clinical data show a ‘path similar’ to the data from the Phase 3 studies in subjects treated with NT-501 using (b) (4) HFM.”
6. On April 4, 2023, the FDA agreed with Neurotech’s proposal to “submit a Biologics License Application (BLA) for NT-501 manufactured with (b) (4) HFM on the basis of the existing Phase 3 data on NT-501 using (b) (4) HFM prior to completion of the new proposed study evaluating NT-501 manufactured with (b) (4) HFM.”
7. On August 1, 2023, the FDA held a pre-BLA meeting with the sponsor. The FDA did not agree with the primary analysis set to include only a subset of the mITT population (i.e., only the subjects with at least 3 visits recorded-baseline, Month 24, and at least one visit at Month 12, 16, or 20). The FDA asked the sponsor to provide analyses for the primary and key secondary efficacy endpoints on both mITT and the proposed subset of mITT and provide an explanation for any discrepancy. In addition, the FDA asked the sponsor to conduct sensitivity analyses to explore the impact of deviations from the missing at random assumption used in the mixed model.

Post-submission:

8. On August 28, 2024, the applicant provided response to FDA’s comment on test-retest variability and/or intergrader variability for the area of EZ loss.
9. On August 28, 2024, the applicant provided updated datasets, additional analyses as requested by FDA and reasons for missing data.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

There were no issues with data integrity identified when conducting data analyses.

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

5.1 Review Strategy

The primary source of evidence to support the efficacy and safety of NT-501 comes from the two studies, NTMT-03-A and NTMT-03-B, which are the focuses of this review memo. We verified the Applicant's efficacy results based on the Applicant's datasets.

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

The documents considered for statistical review include:

- Submission in BLA 125798/0 (original submission):
 - Module 1.2 Cover Letters
 - Module 1.6 Meetings
 - Module 1.14 Labeling
 - Module 2.5 Clinical Overview
 - Module 2.7 Clinical Summary
 - Module 5 Clinical Study Reports
- Submission in BLA 125798/4:
 - Module 5.3.5.1 Datasets
- Submission in BLA 125798/28:
 - Module 1.11.3 Clinical Information Amendment-Response to IR#20
- Submission in BLA 125798/29:
 - Module 1.11.3 Clinical Information Amendment-Response to IR#19
 - Module 5.3.5.1 Study Report Body Chapter and Datasets
- Submission in BLA 125798/30:
 - Module 1.11.3 Clinical Information Amendment-Response to IR#22

5.3 Table of Studies/Clinical Trials

Table 1 provides an overview of the clinical studies in the development of NT-501 for the treatment of MacTel.

Table 1: An overview of the clinical studies contributing to efficacy and safety evaluation of NT-501 in the treatment of MacTel.

Study Identifier	Number of subjects/Eyes per Treatment (M/F, Age Range)	Study Design and Population	Study Product, Route of Administration, Assessments Duration
NTMT-01 (Phase 1) US	7 subjects (7 eyes) (all NT-501) 5F/2M; 48.0-67.0 years	Open-label, nonrandomized, multicenter, pilot study using follow untreated eye as a control in subjects with MacTel	NT-501 intraocular implantation; assessments through 60 months
NTMT-02 (Phase 2) US, AU	67 subjects (99 eligible study eyes; 48 NT-501 and 51 sham) 41F/26M; 44.8-79.4 years	Prospective, multicenter, single-masked, sham-controlled study in subjects with MacTel	NT-501 intraocular implantation; assessments through 24 months
NTMT-01/02E (Phase 2) US, AU	Cohort 1: 6 subjects/study eyes (all NT-501 from NTMT-01) 4F/2M; 48-61 years Cohort 2: 64 subjects/94 study eyes (45 NT-501; 49 sham from NTMT-02); 40M/24F; 45-79 years	Prospective, multicenter, single-masked, sham-controlled extension study designed to provide long-term safety and efficacy follow-up data for subjects with MacTel who received either NT-501 and/or underwent a sham procedure in NTMT-01 or NTMT-02	NT-501 intraocular implantation occurred in parent study; assessments through 108 months (Cohort 1) or 72 months (Cohort 2) after surgery
NTMT-03-A (Phase 3) US, AU, UK, FR	115 subjects/eyes (58 NT-501; 57 sham) 79F/36M; (40-78 years)	Prospective, multicenter, evaluator-masked, sham-controlled study in subjects with MacTel	NT-501 intraocular implantation; assessments through Month 24
NTMT-03-B (Phase 3) US, AU, DE	113 subjects/eyes (59 NT-501; 54 sham) 82F/31M; (40-75 years)	Prospective, multicenter, evaluator-masked, sham-controlled study in subjects with MacTel	NT-501 intraocular implantation; assessments through Month 24
NTMT-02-B (Phase 2) US, AU	32 subjects/eyes (32 NT-501) 24F/8M; 51-78 years	Multicenter, open-label study in subjects with MacTel who received NT-501 in a single eye prior to or in the Phase ½ extension study (NTMT-01/02E) or in 1 of the Phase 3 studies (NTMT-03-A or NTMT-03-B)	NT-501 intraocular implantation; assessments through 6 months

AU=Australia, DE=Germany; FR=France; UK=United Kingdom; US=United States F=female; M=male

Source: Adapted from BLA 125798/0; Module 2.5, Clinical Overview, Table 1, p8.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study NTMT-03-A

The protocol for Study NTMT-03-A was entitled “A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia Type 2.” Here we reviewed protocol Version 7.0, dated August 31, 2021.

6.1.1 Objectives

Primary Objective:

- Determine the rate of change in the ellipsoid zone (EZ [IS/OS]) area loss over 24 months, as measured by study eye spectral-domain optical coherence tomography (SD-OCT) in subjects with MacTel

Secondary Objectives:

- Evaluate the safety of NT-501 in subjects with MacTel

6.1.2 Design Overview

NTMT-03-A was a Phase 3, prospective, multicenter, masked, sham-controlled study to determine the safety and efficacy of NT-501 in subjects with MacTel. A total of 112 subjects were planned. Only one study-eligible eye of each subject was designated as the study eye; if both eyes were eligible, then the study eye was selected by a centralized randomization process or by subject preference if they elected to exclude a study eye from consideration. The study eye of each subject was randomized (1:1) to either have NT-501 implanted or to undergo the sham procedure. Implant or sham surgery on Day 0 was to occur within 30 days after randomization and/or within 58 days after screening.

On Day 0, prior to surgery, subjects were re-evaluated against the inclusion/exclusion criteria. All subjects returned to the study center for postsurgical assessments on Day 1, Week 1, and at Months 6, 12, 16, 20, and 24. At Months 1 and 3, subjects had telephone check-ins.

Subjects were followed for 24 to 48 months after surgery. The duration of follow up was changed in protocol version 7.0:

- Subjects who were to have completed the Month 24 visit after 01 December 2021 exited the study when they completed the Month 24 visit and were not expected to complete their scheduled Month 36 and/or Month 48 visits.
- Subjects who completed the Month 24 visit and had a Month 36 and/or Month 48 study visit scheduled to occur on or before 01 December 2021 exited from the study after completing the scheduled visit(s).
- Subjects who completed the Month 24 visit and had a Month 36 and/or Month 48 visit scheduled after 01 December 2021 did not complete these

visits but completed a safety check-in telephone call and exited the study by 01 December 2021.

Reviewer's comment:

The rate of change in the EZ (IS/OS) area loss over the Month-36 and Month 48 time points were identified as secondary efficacy endpoints. The Sponsor decided to discontinue the Month-36 and Month 48 study visits because the limited number of subjects completing these visits does not provide sufficient statistical power for these secondary efficacy endpoints. These endpoints were removed.

6.1.3 Population

Inclusion criteria:

1. Participant must have at least 1 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. Participant must have an IS/OS PR break and EZ (area of IS/OS loss) as measured by SD-OCT between 0.16 and 2.00 mm²
3. Participant's BCVA is 54-letter score or better (20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at screening
4. Participant must have steady fixation in the foveal or parafoveal area and sufficiently clear media for good quality photographs
5. Participant must be over 21 years of age or under 80 years of age at screening
6. Participant must be able to provide written informed consent to participate in the study, in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and local regulations, before initiating any study-related procedures
7. Women of childbearing potential must agree to use highly effective contraception (Germany and France only)

Exclusion criteria:

1. Participant is medically unable to comply with study procedures or follow-up visits
2. Participant received intravitreal steroid therapy for non-neovascular MacTel within the last 3 months
3. Participant has ever received intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye OR has, within the past 3 months, received intravitreal anti-VEGF therapy in the fellow eye at randomization
4. Participant 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 (eg, glaucoma, severe non-proliferative or proliferative diabetic retinopathy, uveitis)

5. Participant has a chronic requirement (eg, ≥ 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)
6. Participant has evidence of intraretinal neovascularization or subretinal neovascularization (SRNV), as evidenced by hemorrhage, hard exudate, subretinal fluid or intraretinal fluid in either eye
7. Participant has evidence of central serous chorio-retinopathy in either eye
8. Participant has evidence of pathologic myopia in either eye
9. Participant has significant corneal or media opacities in either eye
10. Participant has had a vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
11. Participant 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 Age-Related Eye Disease Study (AREDS) clinical lens grading system
12. Participant has undergone lens removal in the previous 3 months or YAG laser within 4 weeks
13. Participant was a participant in any other clinical trial of an intervention (drug or device) within the last 6 months
14. Participant is on chemotherapy
15. Participant is pregnant or breastfeeding
16. Participant has a history of malignancy that would compromise the 24-month study survival
17. Participant with a history of ocular herpes virus in either eye
18. Participant 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
19. Participant has evidence of intraretinal hyperreflectivity by OCT

6.1.4 Study Treatments or Agents Mandated by the Protocol

Treatment arm:

Investigational product: NT-501

Dose:

Each implant consisting of 200,000-440,000 hCNTF-secreting NTC-201-6A.02 cells encapsulated within supportive matrices and surrounded by a semipermeable polymer membrane.

Route of administration: Intraocular implantation

Lot Numbers:

FP501-17-059; FP501-17-064; FP501-17-067; FP501-18-005A;
FP501-18-005B; FP501-18-008A; FP501-18-017A;
FP501-18-019A; FP501-18-028A; FP501-18-033;
FP501-18-043; FP501-18-046; FP501-19-003A;
FP501-19-006A; FP-501-19-011A; FP501-19-015A;
FP501-19-018A; FP501-19-027; FP501-19-030A;

FP501-19-033A; FP-501-19-036A; FP501-20-011A;
FP501-20-016A

Control arm:

Product: sham surgery performed to mimic implant procedure

6.1.6 Sites and Centers

Subjects were enrolled from 20 study centers in Australia, France, the United Kingdom, and the United States.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- The rate of change in the EZ (IS/OS) area loss from Baseline through Month 24, as assessed in the study eye of participants with MacTel using SD-OCT.

Key secondary efficacy endpoints:

1. Mean change in aggregate sensitivity of microperimetry within the EZ line break area from Baseline through Month 24
2. Mean change in reading speed from Baseline through Month 24
3. Mean change in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) near activities subscale score from Baseline through Month 24

Secondary safety endpoints:

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

Criteria for study success:

The study would be considered as success if the primary efficacy endpoint were statistically significant at a 2-sided Type I error rate of 0.05.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size estimation:

A total of 112 subjects were planned and randomized 1:1 to NT-501 implant or sham procedure. The sample size calculation was based on the comparison of the 2 groups over 24 months assuming a longitudinal mixed effects model. The response of change in EZ area was modeled as follows:

$$Y_{ij} = \beta_{0 NT-501} + \beta_{1 NT-501}x_{ij} + \epsilon_{ij}, j = 1, \dots, n; i = 1, \dots, m$$

$$Y_{ij} = \beta_{0 sham} + \beta_{1 sham}x_{ij} + \epsilon_{ij}, j = 1, \dots, n; i = 1, \dots, m$$

$x_{ij} = x_j$, $\beta_{1 \text{ sham}}$, $\beta_{1 \text{ NT-501}}$ represents the duration between the first and the j^{th} visit, the rate of change in Y for sham and NT-501, respectively.

The sample size in each group, m was calculated as follows.

$$m = \frac{2(z_{\alpha} + z_{\beta})^2 \sigma^2 (1 - \rho)}{n s_x^2 d^2}$$

where $d = \beta_{1 \text{ sham}} - \beta_{1 \text{ NT-501}}$, s_x^2 is within – subject variance of x_j

Using the above equation with a Type 1 error rate of 0.05 (2-sided); $\sigma^2 = 0.0256$; $\rho = 0.6$; $s_x^2 = 0.47$ and $n = 5$ (baseline and 12, 16, 20 and 24 months), a sample size of 50 subjects per group had 80% power 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 per group (112 total) to provide adequate power in the analysis of the population evaluable for efficacy.

Blinding/masking:

Subjects were masked to treatment assignment throughout the study. The refractionist, visual acuity examiner, photographers/imagers, and all personnel at the image reading center were masked to treatment assignment (implant or sham procedure) for all follow-up visits. The ophthalmologist, surgeon, and clinic coordinator were unmasked to treatment assignment.

Statistical hypothesis:

Assuming a random intercept model,

$$Y_{ij} = (\beta_0 + b_0) + \beta_1 * TRT + \beta_2 * TIME + \beta_3 * TRT * TIME + \epsilon_{ij}$$

where Y_{ij} is the efficacy endpoint (EZ area) measurement for subject $i = 1, \dots, n$, $j=1, \dots, K$. TRT is the treatment indicator (ie, TRT = 1 for NT-501; TRT = 0 for sham) and TIME is the annualized time. To compare the rate of change from baseline in EZ area between the 2 treatment groups, the primary hypothesis was as follows:

$$H_0: \beta_3 = 0 \text{ versus } H_1: \beta_3 \neq 0$$

Analysis population:

- Modified Intent-to-Treat (mITT) Population included all randomized subjects who received surgery (NT-501 implant or sham surgery) irrespective of participant's adherence to study protocol. Primary efficacy analyses were performed using the mITT.
- Per Protocol (PP) Population was a subset of the mITT Population and included all available data from participants who followed the protocol without major protocol violations(s). Major protocol violations were defined as deviations that may have a substantial impact on efficacy assessments. Supportive efficacy analyses were performed using the PP.
- Safety Population was defined as all subjects who were randomized and received surgery (NT-501 implant or sham surgery) and had at least 1

safety measurement. Safety analyses were conducted using the Safety Population.

Reviewer's comment:

The efficacy analyses were based on the mITT population. Ideally, to reduce selection bias, all randomized subjects should be included in the primary efficacy analysis set. Because implant or sham surgery occurred within 30 days after randomization, there were a number of subjects who dropped out before receiving treatment. Supplemental analyses were conducted to assess the robustness of the study conclusion. The reasons for dropout in these subjects were examined. That subjects were masked to treatment assignment might reduce chance of selection bias.

Statistical method:

Primary efficacy endpoint-the rate of EZ area loss

The area of EZ loss was defined as the mean of 2 independent readings of the single eligible SD-OCT enface image taken at baseline and at Months 12, 16, 20, and 24. The difference between groups in the rate of EZ area loss (macular photoreceptor 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-subject variability, study group, time as a continuous variable, and the interaction between treatment and time. The baseline and Months 12, 16, 20, and 24 visits were included. The rate of EZ area loss and the corresponding 95% confidence interval (CI), standard error (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.

Due to COVID-19, subjects might not be able to attend their scheduled study visits within the protocol-specified visit window (+/- 30 days). To accommodate COVID-19 related delays, visits conducted within +119 days of the planned visit timepoints for Month 12, 16, 20 and 24 would be included.

Additional analyses were performed to assess the robustness of the primary analysis.

- The primary efficacy endpoint was analyzed using the ITT and PP populations restricted to only those subjects with at least 3 visits recorded: baseline, Month 24, and at least 1 visit at Month 12, 16, or 20.
- The longitudinal mixed model repeated with a categorical measure of time, adjusted for continuous baseline EZ area loss and continuous age at surgery, excluding out of window visits occurring more than ± 30 days outside of the planned time points, and including all observed efficacy data, regardless of timing.
- The longitudinal mixed model for the mITT population using a control-based imputation method for missing results at Month 24

Reviewer's comment: Based on the finalized SAP (Version 4, dated May 24, 2024), the primary efficacy analysis set was restricted to only those participants in the mITT set with at least 3 visits recorded: Baseline, Month 24, and at least one of Month 12, 16, or 20 visits. The applicant agreed in the NTME-03A SAP Addendum (version 1, dated September 19, 2023) to change the primary efficacy analysis set to the full mITT set. Supplemental analysis was performed on the restricted mITT set to only participants with at least 3 visits recorded: Baseline, Month 24, and at least one of Month 12, 16, or 20 visits. Additional supportive analyses were performed on the PP set, including the full PP set and the restricted PP set to participants with at least 3 visits recorded: Baseline, Month 24, and at least one of Month 12, 16, or 20 visits.

The primary efficacy endpoint is an anatomic endpoint. As stated in the FDA guidance document on Human Gene Therapy for Retinal Disorders, "Rate of photoreceptor loss, determined by measures such as optical coherence tomography or autofluorescence photography. A 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 FDA agreed with the primary efficacy endpoint.

Secondary efficacy endpoints

For the secondary efficacy endpoints, the observed changes from baseline at Month 24 between groups were compared using two-sample t-test. The estimated mean treatment effect, a 95% CI, and a 2-sided p-value were provided. The analyses were based on the actual values observed at the Baseline and the Month-24 visit efficacy assessment, regardless of timing of the visit as long as it occurs within +/- 30 days for pre-COVID period or within +119 days post-visit timepoint for COVID-related delays. No imputation of missing data was done. The secondary endpoints were analyzed using the mITT set and the PP set.

Sensitivity analyses were conducted excluding any out of window visits occurring more than +/- 30 days outside of the planned timepoints, and by conducting time-adjusted analysis by adjusting the actual efficacy assessment results to the nominal timepoint.

Reviewer's comment: In the protocol Version 7.0, the secondary efficacy endpoints were 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. For the mixed effects model, fixed effects will include the treatment group (between-participant factor) and the visit (within-participant factor). The best covariance structure would be chosen based on Akaike's Information Criteria. However, in the SAP (version 4, dated May 20, 2021), the secondary efficacy endpoints were

compared using t-test and the analyses were based on actual values observed at Baseline and Month 24 and the results are presented in this BLA.

Safety analyses:

All safety analyses were performed using the safety population. The number and percentage of subjects with 15 or more letters of vision loss from baseline in the study eye at Month 24 was tabulated by study group and compared using a 2-sample test of proportions.

Handling of multiple testing

A hierarchical testing procedure was applied to the secondary efficacy analyses to control the overall Type I error rate. If 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 as listed in Section 6.1.8.

If any of the secondary endpoints were found to be not statistically significant at the 2-sided 0.05 level, the hypothesis testing would stop. Later endpoint(s) would be summarized descriptively, and p-values may be produced for descriptive purposes only. P-values produced for safety analyses and treatment group comparisons of demographic and baseline characteristics would be considered descriptive statistics that support the results of the primary efficacy analysis and not as formal tests of hypotheses.

Handling of missing data:

Missing post-baseline values were not imputed for the primary efficacy analysis conducted using longitudinal mixed effects methods, which make use of all available data even if a participant has missing data at some post-baseline visits. For safety analysis, no imputation was used. Missing data (e.g., dates) remained as missing, and conservative conventions established, as required.

Reviewer's comment: In the NTME-03A SAP Addendum (version 1, dated September 19, 2023), the sponsor added additional sensitivity analysis on the full mITT Population for the primary efficacy endpoint. For subjects who were missing the primary endpoint at the Month 24 visit, a control-based imputation was proposed. If the Month 24 visit was out of window as defined in SAP Section 7.5, the out of window value was used.

Multiple imputations would be considered for primary and secondary analyses should the dropout rate and proportion of missing values be higher than expected.

Handling of intercurrent event

No strategies were proposed.

Subgroup analysis

No subgroup analyses were proposed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Overall, 120 subjects were enrolled and randomized to either have NT-501 implanted or undergo a sham procedure, of whom 115 subjects (95.8%) underwent surgery (58 subjects had NT-501 implanted and 57 subjects underwent sham surgery). All 115 subjects were included in the mITT and safety population, and 111 subjects (55 in the NT-501 group and 56 in the sham group) were included in the PP population.

Table 2 summarizes the analysis populations. Four subjects were excluded from the PP population. Of the 3 subjects in the NT-501 group who were excluded from the PP population, 1 did not meet eligibility due to visual acuity OD of 44 letters and did not have a Month 24 OCT assessment, 1 did not have a baseline OCT assessment, and 1 did not have a Month 24 OCT assessment. One subject in the sham group was excluded from the PP population for not having a baseline OCT assessment.

Table 2. Analysis populations

Number of subjects	NT-501	Sham	Total
Randomized	61	59	120
Modified intent to treat (mITT) population	58	57	115
Safety population	58	57	115
Per protocol (PP) population	55	56	111

Source: Adapted from BLA 125798/0; Module 5.3.5.1, NTMT-03-A Clinical Study Report, Table 3, p.55.

6.1.10.1.1 Demographics

Table 3 summarizes demographic and other baseline characteristics of the mITT population. The mean age of the subjects in the mITT population was 60.7 years (range: 40-78 years), with 64.3% of the subjects aged < 65 years. Females comprised 68.7% of the subjects in the mITT population; the majority of subjects were White (85.2%) and not Hispanic or Latino (94.8%). There were no meaningful differences in these baseline characteristics between the NT-501 and sham groups.

Table 3. Subject baseline characteristics (mITT population)

Arms	NT-501 (N = 58)	Sham (N = 57)	Total (N = 115)
Age, years			
Mean (SD)	61.1 (8.0)	60.2 (8.4)	60.7 (8.2)
Median (Min, Max)	61 (40, 77)	59 (47, 78)	60 (40, 78)
Age category, 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 (68.7)
Male	19 (32.8)	17 (29.8)	36 (31.3)
Race, n (%)			
White	50 (86.2)	48 (84.2)	98 (85.2)
Asian	2 (3.5)	3 (5.3)	5 (4.3)
Black or African American	1 (1.7)	2 (3.5)	3 (2.6)
American Indian or Alaska native	0	1 (1.8)	1 (0.9)
Other	5 (8.6)	3 (5.3)	8 (7.0)
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)

Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation
Age was calculated from date of informed consent except in countries that do not permit collection of date of birth.

Source: Adapted from BLA 125798/0; Module 5.3.5.1, NTMT-03-A Clinical Study Report, Table 4, p.55.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4 shows the baseline ocular characteristics of the mITT population. The mean (standard deviation [SD]) of BCVA was 72.0 (8.9), the mean (SD) area of EZ loss was 0.50 (0.42) mm², the mean (SD) of aggregate sensitivity loss was 61.1 (71.9) dB, and the mean (SD) reading speed at baseline was 94.0 (48.9) words per minute. There were no meaningful differences between the NT-501 and sham groups regarding BCVA, EZ area loss, aggregate sensitivity loss, and reading speed.

Table 4. Baseline ocular characteristics (mITT population)

Arms	NT-501 (N = 58)	Sham (N = 57)	Total (N = 115)
Best Corrected Visual Acuity (letters)			
n	58	57	115
Mean (SD)	70.8 (9.1)	73.3 (8.6)	72.0 (8.9)
Median (min, max)	71.5 (41, 89)	74 (51, 89)	73 (41, 89)
EZ area loss (mm ²)			
n	58	57	115
Mean (SD)	0.51 (0.48)	0.49 (0.36)	0.50 (0.42)
Median (min, max)	0.35 (0.15, 1.99)	0.36 (0.16, 1.7)	0.35 (0.15, 1.99)
Aggregate sensitivity loss (dB)			
n	56	55	111
Mean (SD)	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)			
n	57	56	113
Mean (SD)	92.1 (43.7)	96.0 (54.0)	94.0 (48.9)
Median (min, max)	87.6 (1.0, 200.4)	100.0 (0, 238.2)	94.3 (0, 238.2)

Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation; EZ = ellipsoid zone; BCVA = best-corrected visual acuity; n = number of subjects

Source: FDA reviewer

6.1.10.1.3 Subject Disposition

The subject disposition is listed in Table 5. Overall, 120 subjects were enrolled and randomized to either have NT-501 implanted or undergo the sham procedure, of whom 115 subjects (95.8%) underwent surgery (58 subjects had NT-501 implanted and 57 subjects underwent sham surgery). A total of 5 subjects (3 in the NT-501 group and 2 in the sham group) were randomized but did not undergo surgery. Of these subjects, 4 withdrew consent prior to surgery and 1 did not undergo surgery due to COVID-19.

Most subjects who underwent surgery (91.3%; 105 of 115) completed the study through at least Month 24. A total of 10 subjects (5 in each group) discontinued during the study treatment period. Of these, 8 subjects (4 in each study group) who were eligible did not enroll under the protocol amendment (version 7.0) and discontinued; 1 subject in the sham group withdrew consent; and 1 subject in the NT-501 group discontinued after Month 24 due to an AE related to the study (vitreous hemorrhage considered related to the surgical procedure that resulted in explantation). Note that the subject in the sham group who withdrew consent did so due to an SAE of cardiac failure congestive that led to the subject's death after the subject discontinued from the study.

Table 5. Subject disposition (enrolled subjects)

Number of Subjects	NT-501	Sham	Total
Randomized	61	59	120
Received surgery	58	57	115
Retained implant throughout the study	57	0	57
Discontinued during the treatment period	5	5	10
Reason for discontinuation			
Eligible and did not enroll in amendment	4	4	8
Withdrawal by the subject	0	1 ^a	1
Adverse event related to study	1 ^b	0	1

a: Subject (b) (6) in the sham group experienced an SAE of congestive cardiac failure congestive on Day 430 and withdrew consent on Day 466; the subject subsequently died on Day 502 due to the SAE.

b: Subject (b) (6) had NT-501 explanted on Day 912 due to an SAE of vitreous hemorrhage in the study eye and discontinued from the study on Day 1101.

Source: Original BLA 125798/0; Module 5.3.5.1, NTMT-03-A Clinical Study Report, Table 2, p.54.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

As shown in Table 6, the mean (SE) rate of change in EZ area loss from baseline over 24 months was 0.075 (0.012) mm² in the NT-501 group and 0.166 (0.013) mm² in the sham group, with a statistically significant difference between groups (-0.091 [0.0176] mm²; 95% CI: -0.13, -0.056; p < 0.0001). This study met its primary efficacy endpoint that NT-501 slowed the rate of EZ area loss over 24 months.

Results for the PP population were consistent with those obtained for the mITT population, with a statistically significant mean (SE) difference between NT-501 and sham in the rate of EZ area loss from baseline over 24 months. The analyses including all randomized subjects as described in Section 6.1.9 were consistent as well.

Table 6: Results of the primary efficacy endpoint-rate of change in EZ loss area over 24 Months.

	NT-501 Mean (SE) (mm ²)	Sham Mean (SE) (mm ²)	Difference Mean (SE) (mm ²)	Difference 95% CI and P value
mITT	0.075 (0.012)	0.166 (0.013)	-0.091 (0.0176)	(-0.13, -0.056) P<0.0001
PP	0.075 (0.013)	0.167 (0.013)	-0.091 (0.0181)	(-0.13, -0.06) P<0.0001

CI=confidence interval; mITT=modified intent-to-treat; mm²=millimeter squared; PP=per-protocol; SE=standard error

Source: FDA reviewer

6.1.11.2 Analyses of Secondary Endpoints

Since the primary efficacy analysis was statistically significant, a hierarchical testing procedure was performed to secondary efficacy endpoints. The results are shown in Table 7.

Table 7: Results of secondary efficacy endpoints from baseline to Month 24

		NT-501 Mean (SE)	Sham Mean (SE)	NT-501-Sham Difference (SE)
Aggregate retinal sensitivity loss (dB)	n	51	53	
	Mean change from baseline through Month 24	25.27 (4.79)	43.02 (5.74)	-17.75 (7.48) p=0.02*
Reading speed (words per minute)	n	56	54	
	Mean change from baseline through Month 24	-6.18 (3.90)	-12.20 (5.74)	6.02 (6.94) p=0.39**
NEI-VFQ-25 near activities subscale score (units)	n	55	54	
	Mean change from baseline through Month 24	-0.61 (2.58)	2.31 (2.53)	-2.92 (3.61) p=0.42**

n = number of subjects; SE = standard error; NEI-VFQ-25 = national eye institute visual function questionnaire-25

*: p value obtained from two sample t-test, statistically significant.

**: nominal p value obtained from two-sample t test

Source: FDA reviewer

According to the SAP, a two-sample t-test was used to compare the change from baseline at Month 24 for each of the secondary efficacy endpoints. This study

met its first secondary efficacy endpoint 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 at 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 vs 43 dB, respectively; $p=0.02$).

The second secondary efficacy endpoint was not statistically significant. There was a mean decrease in reading speed in both study groups from baseline at Month 24, with a smaller mean decrease in the NT-501 group relative to the sham group, but the difference between two groups was not statistically significant (mean [SE] change from baseline: -6.2 [3.9] vs -12.2 [5.74] words per minute, respectively; nominal $p = 0.39$).

Since the difference between study groups was not statistically significant for the second secondary efficacy endpoint, the results of the last secondary efficacy endpoint here were only summarized descriptively. The mean (SE) change in the NEI-VFQ-25 near activities subscale score from baseline at Month 24 was -0.61 (2.58) and 2.31 (2.53) units in the NT-501 and sham groups, respectively (nominal $p = 0.42$).

According to the protocol Version 7.0, the secondary efficacy endpoints were proposed to be analyzed using a longitudinal mixed effects model. Per statistical IR, the applicant provided additional analysis results for secondary efficacy endpoints using longitudinal mixed effect models in Amendment 29 on August 28, 2024. The results obtained using longitudinal mixed effects model for these secondary efficacy endpoints were consistent with the results obtained using two-sample t-test.

6.1.11.3 Subpopulation Analyses

Post-hoc exploratory subgroup analyses by age and sex were conducted. The majority of the subjects were White and other racial groups were of very small sample size, 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 groups was -0.141 [0.021] mm^2 (95% CI: -0.184 , -0.099), favoring NT-501. In the age group ≥ 65 years, the difference between groups 0.011 [0.028] mm^2 ; 95% CI: -0.044 , 0.067), favoring the sham group. It seems NT-501 had no benefits for older subjects.

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] mm^2 (95% CI: -0.141 , -0.056), favoring NT-501. Among males, the difference between groups -0.073 [0.030] mm^2 ; 95% CI: -0.133 , -0.012), favoring NT-501.

6.1.11.4 Dropouts and/or Discontinuations

The mixed effects model used in the applicant's analysis assumes missing at random. In total, there were 26 missing visits for subjects in the mITT population for the measurement of EZ area loss among baseline, Month 12, 16, 20, 24 visits. Most missed visits were due to COVID-19 and there was no meaningful difference in number of missed visits between the two groups; thus, missing at random assumption was likely reasonable.

One subject in the sham group withdrew consent due to an SAE of cardiac failure congestive that lead to the subject's death after study discontinuation on Day 466. For this subject, missing data imputation using the worst decline observed in the data was used and the primary efficacy endpoint remained statistically significant, as expected.

6.1.12 Safety Analyses

6.1.12.3 Deaths

One subject in the sham group experienced an SAE of cardiac failure congestive on Day 430 and withdrew consent on Day 466. The subject subsequently died on Day 502 due to the SAE.

6.1.12.4 Nonfatal Serious Adverse Events

Ocular SAEs:

A total of 3 subjects (2.6%), including 2 in the NT-501 group and 1 in the sham group, experienced at least 1 ocular SAE each through Month 24. In the NT-501 group, the ocular SAE occurring in the study eye of both subjects was suture related complication and moderate in intensity. In the sham group, the ocular SAE was choroidal neovascularization (CNV) occurring in 1 fellow eye; the event was moderate in intensity and ongoing at the end of the study. After Month 24, 1 additional subject in the NT-501 group had an ocular SAE of vitreous hemorrhage in the study eye that led to NT-501 explantation.

Nonocular SAEs

A total of 17 subjects (14.8%), including 10 subjects (17.2%) in the NT-501 group and 7 subjects (12.3%) in the sham group, experienced at least 1 nonocular SAE each through Month 24. This included 10 subjects in the NT-501 group with a total of 14 nonocular SAEs and 6 subjects in the sham group with 7 nonocular SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

The NT-501 group had a high frequency of delayed dark adaptation (20.7% [12 eyes]), and miosis (17.2% [10 eyes]).

Reviewer's comment: Due to protocol change, only 21 subjects (10 NT-501 and 11 sham) were followed to Month 36 and 3 subjects (2 NT-501 and 1 sham) to Month 48. After Month 24, one subject in the NT-501 group had an ocular SAE of

vitreous hemorrhage in the study eye that led to NT-501 explantation. Long term safety data after Month 24 was limited.

6.2 NTMT-03-B

The protocol for Study NTMT-03-B was titled “A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasis Type 2.” Here I reviewed protocol Version 7.0, dated August 31, 2021.

6.2.1 Objectives (Primary, Secondary, etc)

NTMT-03-B had the same objectives as NTMT-03-A. Please refer to Section 6.1.1.

6.2.2 Design Overview

NTMT-03-B used the same study design as NTMT-03-A. Please refer to Section 6.1.2.

6.2.3 Population

The same inclusion and exclusion criteria as NTMT-03-A were used. Please refer to Section 6.1.3.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The same treatments as NTMT-03-A were used in NTMT-03-B, but lot numbers were different.

Lot Numbers:

FP501-17-067; FP501-18-005A; FP501-18-008A;
FP501-18-017A; FP501-18-019A; FP501-18-028A;
FP501-18-033; FP501-18-043; FP501-18-046; FP501-19-003A;
FP501-19-006A; FP-501-19-011A; FP501-19-015A;
FP501-19-018A; FP501-19-027; FP501-19-030A;
FP501-19-033A; FP-501-19-036A; FP501-20-004A;
FP501-20-006A; FP501-20-011A; FP501-20-016A

6.2.6 Sites and Centers

There were 24 sites in United States, Australia and Germany.

6.2.8 Endpoints and Criteria for Study Success

The same endpoints and study success criteria as NTMT-03-A. Please refer to Section 6.1.8.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The same statistical analysis plan as NTMT-03-A was used. Please refer to Section 6.1.9.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Overall, 119 subjects were enrolled and randomized to either have NT-501 implanted or to undergo the sham procedure, of whom 113 subjects (95.0%) underwent surgery (59 subjects had NT-501 implanted and 54 subjects underwent sham surgery). All 113 subjects who were randomized and underwent surgery were included in the mITT and safety populations, and 105 subjects were included in the PP population.

Eight subjects were excluded from the PP population. In the NT-501 group, of the 4 subjects who were excluded from the PP population, 2 did not have a Month 24 OCT assessment, 1 did not have a baseline OCT assessment, and 1 had a Month 24 visit that was outside the acceptable visit window. In the sham group, 3 subjects were excluded from the PP population for not having Month 24 OCT readings and 1 subject was excluded for having undergone the surgery in the wrong (ineligible) eye.

Table 8: Analysis populations

Number of subjects	NT-501	Sham	Total
Randomized	60	59	119
Modified intent to treat (mITT) population	59	54	113
Safety population	59	54	113
Per protocol (PP) population	55	50	105

Source: Adapted from BLA 125798/0; Module 5.3.5.1, NTMT-03-B Clinical Study Clinical Study Report, Table 3, Page 52

6.2.10.1.1 Demographics

Table 9 summarizes the demographic characteristics of the mITT population. The mean age of the subjects in the mITT population was 58.6 years (range: 40-75 years), with the majority (69.0%) aged < 65 years. The majority of subjects in the mITT population were female (72.6%) and most subjects were White (90.3%) and not Hispanic or Latino (92.0%). The proportion of female subjects was higher in the NT-501 group than the sham group (78.0% vs 66.7%, respectively). There were no other meaningful differences in subject demographic characteristics between the NT-501 and sham groups.

Table 9. Demographic characteristics (mITT)

Arms	NT-501 (N=59)	Sham (N=54)	Total (N=113)
Age (years)			
Mean (standard deviation)	58.46 (7.61)	58.72 (8.87)	58.58 (8.20)
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 %)
≥65 years	17 (28.8 %)	18 (33.3 %)	35 (31 %)
Sex			
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%)
Black- African American	0	0	0
Other	1 (1.7%)	5 (9.3%)	6 (5.3%)
Not collected	0	1 (1.9%)	1 (0.9%)
American Indian or Alaska Native	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	4 (6.8%)	4 (7.4%)	8 (7.1%)
Not Hispanic or Latino	55 (93.2%)	49 (90.7%)	104 (92%)
Unknown	0	1 (1.9%)	1 (0.9%)

Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation

Age was calculated from date of informed consent except in countries that do not permit collection of date of birth.

Source: Adapted from BLA 125798/0; Module 5.3.5.1, NTMT-03-B Clinical Study Clinical Study Report, Table 4, Page 53.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 10 summarizes the baseline medical characteristics of the mITT population. The mean (SD) of BCVA was 74.02 (8.47), the mean (SD) area of EZ loss was 0.49 (0.30) mm², the mean (SD) of aggregate sensitivity loss was 52.52 (55.27) dB, and the mean (SD) reading speed at baseline was 95.36 (45.05) words per minute. There were no meaningful differences between the NT-501 and sham groups regarding BCVA, EZ area loss, aggregate sensitivity loss, and reading speed.

Table 10: Baseline medical characteristics (mITT)

Parameter	NT-501 (N=59)	Sham (N=54)	Total (N=113)
Best Corrected Visual acuity (letters)			
Number (n)	59	54	113
Mean (standard deviation)	74.41 (7.76)	73.59 (9.23)	74.02 (8.47)
Median (min, max)	76 (52, 89)	73 (56, 94)	74 (52, 94)
EZ area (mm ²)			
Number (n)	59	54	113
Mean (standard deviation)	0.52 (0.31)	0.47 (0.29)	0.50 (0.30)
Median (min, max)	0.48 (0.16, 1.63)	0.40 (0.16, 1.38)	0.46 (0.16, 1.63)
Aggregate sensitivity of microperimetry within the EZ line 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)
Reading Speed (words per minute)			
Number (n)	59	53	112
Mean (standard deviation)	96.49 (47.31)	94.09 (42.81)	95.36 (45.05)
Median (min, max)	97.69 (2.29, 197.11)	89.64 (5.60, 206.49)	92.98 (2.29, 206.49)

Max = maximum; Min = minimum; mITT = modified intent-to-treat; SD = standard deviation; EZ = ellipsoid zone; BCVA = best-corrected visual acuity; n = number of subjects
Source: FDA reviewer

6.2.10.1.3 Subject Disposition

Overall, 119 subjects were enrolled and randomized to either have NT-501 implanted or to undergo the sham procedure, of whom 113 subjects (95.0%) underwent surgery (59 subjects had NT-501 implanted and 54 subjects underwent sham surgery). A total of 6 subjects (1 in the NT-501 group and 5 in the sham group) were randomized but did not undergo surgery. For these subjects, the reasons for not undergoing the surgery were withdrawal of consent, COVID-19, being lost to follow-up, physician decision (reported for 1 subject) and other reasons (cardiac related issues) reported for 2 subjects.

Most subjects who underwent surgery (93.8%; 106 of 113) completed the study through at least Month 24. Of the 7 subjects who discontinued early, 4 subjects (1 in the NT-501 group and 3 in the sham group) who were eligible did not enroll under the protocol amendment (version 7.0) and discontinued; 1 subject in the NT-501 group died due to a nonocular SAE of chronic obstructive pulmonary

disease; 1 subject in the sham group was lost to follow-up; and 1 subject in the sham group discontinued for other reasons.

Table 11: Subject disposition

Number of subjects	NT-501	Sham	Total
Randomized	60	59	119
Received surgery	59	54	113
Retained implant throughout the study	59	0	59
Discontinued during treatment period	2	5	7
Reasons for discontinuation			
Eligible and did not enroll in amendment	1	3	4
Lost to follow up	0	1	1
Death	1	0	1
Others ^a	0	1	1
Reasons that randomized subjects did not receive surgery			
Covid-19	0	1	1
Lost to follow up	0	1	1
Others ^b	1	1	2
Physician decision	0	1	1
Withdrawal of consent	0	1	1

a: the subject was unable to get clearance from cardiologist for surgery.

b: both reasons are related to cardiac issues

Source: Adapted BLA 125798/0; Module 5.3.5.1, NTMT-03-B Clinical Study Report, Table 2, page 51

Reviewer's comment:

Five randomized subjects in the placebo arm did not receive surgery. Only one randomized subject in the treated arm did not receive surgery. There were more subjects from the placebo arm that were randomized but did not receive surgery. This could be due to chance as the subjects were masked.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Table 12 summarizes the result on the primary efficacy endpoint, rate of change in EZ area loss from baseline through Month 24. The mean (SE) rate of change in EZ area loss from baseline over 24 months was 0.111 (0.0142) mm² in the NT-501 group and 0.160 (0.0149) mm² in the sham group, with a statistically

significant difference between groups (-0.0486 [0.0206] mm^2 ; 95% CI: -0.089 , -0.0082 ; $p = 0.0186$). The rate of EZ area loss over time was slower in the NT-501 group compared with a more rapid loss in the sham group. This study met its primary efficacy endpoint that NT-501 was superior to sham in slowing the rate of EZ area loss over a period of 24 months.

Results of the primary efficacy endpoint for the PP population showed a trend similar to that observed for the mITT population, with a smaller mean (SE) rate of EZ area loss from baseline over 24 months in the NT-501 group relative to the sham group (0.119 [0.0145] vs 0.160 [0.0151] mm^2 , respectively); however, the difference between groups was not statistically significant (-0.0405 [0.0209] mm^2 ; 95% CI: -0.0816 , 0.00057 ; $p = 0.0532$).

Table 12: Results of the primary efficacy endpoint-rate of change in EZ loss area over 24 Months.

	NT-501 Mean (SE) (mm^2)	Sham Mean (SE) (mm^2)	Difference Mean (SE) (mm^2)	Difference 95% CI and P value
mITT	0.111 (0.0142)	0.160 (0.0149)	-0.0486 (0.0206)	(-0.089 , -0.0082) $p=0.0186$
PP	0.119 (0.0145)	0.160 (0.0151)	-0.0405 (0.0209)	(-0.0816 , 0.00057) $p=0.0532$

CI=confidence interval; mITT=modified intent-to-treat; mm^2 =millimeter squared; PP=per-protocol; SE=standard error

Source: FDA reviewer

Additional analyses showed that the overall trend of the results was consistent, showing a smaller mean rate of EZ area loss from baseline over 24 months in the NT-501 group relative to the sham group.

6.2.11.2 Analyses of Secondary Endpoints

Table 13 summarizes the results on the three key secondary efficacy endpoints. A two-sample t-test was used to compare the change from baseline at Month 24.

Table 13. Results on secondary efficacy endpoints from baseline to Month 24.

		NT-501 Mean (SE)	Sham Mean (SE)	NT-501-Sham Difference (SE)
Aggregate retinal sensitivity loss (dB)	n	52	48	
	Mean change from baseline to Month 24	40.02 (7.11)	41.97 (5.93)	-1.95 (9.26) p=0.83*
Reading speed (words per minute)	N	54	50	
	Mean change from baseline to Month 24	-5.46 (4.03)	-18.88 (4.77)	13.42 (6.24) p=0.034*
NEI-VFQ-25 near activities subscale score (units)	n	54	50	
	Mean change from baseline to Month 24	-2.31 (2.35)	-3.67 (2.05)	1.35 (3.12) p=0.67*

n = number of subjects; SE = standard error; NEI-VFQ-25 = national eye institute visual function questionnaire-25

*: all p values are nominal p values; none of the secondary efficacy endpoints was statistically significant.

The change from baseline in aggregate retinal sensitivity loss at Month 24 was similar in the NT-501 and sham groups (40.02 vs 41.97 dB, respectively; nominal $p = 0.83$). The difference between NT-501 and sham in the change in aggregate retinal sensitivity loss from baseline at Month 24 was not statistically significant, so the fixed-sequence testing ended and the results of the remaining 2 secondary endpoints were summarized descriptively.

The mean change in reading speed (words per minute) from baseline at Month 24 was -5.46 in the NT-501 group and -18.88 in the sham group. There was a smaller mean decrease from baseline in monocular reading speed in the NT-501 group relative to the sham group, but the difference between the groups was not statistically significant (nominal $p = 0.03$).

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. The difference between the groups was not statistically significant (nominal $p=0.67$).

Across the 3 secondary efficacy endpoints, the results using PP population were consistent. Overall, these secondary efficacy endpoints were not statistically significant.

In the protocol Version 7.0, the secondary efficacy endpoints were proposed to be analyzed using longitudinal mixed effects model. Per statistical IR, the applicant provided additional analysis results for secondary efficacy endpoints using longitudinal mixed effect models in Amendment 29 on August 28, 2024. The results obtained using longitudinal mixed effects model for these secondary

efficacy endpoints were consistent with the results obtained using two-sample t-test.

6.2.11.3 Subpopulation Analyses

Post-hoc exploratory subgroup analyses by age and sex were conducted. The majority of the subjects 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. It seems that older subjects did not benefit from NT-501.

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, -0.009), favoring NT-501. Among males, the difference between groups -0.028 [0.034] mm² (95% CI: -0.096, 0.039).

6.2.11.4 Dropouts and/or Discontinuations

The mixed model used in the applicant's analysis assumes missing at random. A total of 32 missing visits been noted: 12 in the treated group and 20 in the sham group. Most of the missed visits were due to COVID-19 pandemic, so missing at random assumption was likely reasonable for these missed visits. Seven subjects from the sham group and 2 subjects from NT-501 group had missed visits not due to COVID-19.

One treated subject NTMT-03-B-(b) (6) died with an end of study date of (b) (6), 607 days from treatment, but missed Month 12, Month 20, and Month 24. For this subject, we assumed missing not at random by imputing the missed visits using the worst decline observed in the data and the primary efficacy endpoint remained statistically significant.

6.2.12 Safety Analyses

6.2.12.3 Deaths

One subject in the NT-501 group died. The subject experienced an SAE of chronic obstructive pulmonary disease on Day 575 and died on Day 607 due to the SAE. The event was severe in intensity and was considered by the investigator to be not related to the surgery, to NT-501, or to CNTF.

6.2.12.4 Nonfatal Serious Adverse Events

Ocular SAE:

Four study eyes (6.8%), all in the NT-501 group, experienced at least 1 ocular SAE each through Month 24. This included suture related complication occurring

in 3 study eyes and device extrusion occurring in 1 study eye. In the latter subject, NT-501 was surgically repositioned and did not require explantation. All 4 SAEs had recovered by the end of the study.

Nonocular SAE:

A total of 18 subjects (15.9%), including 8 subjects (13.6%) in the NT-501 group and 10 subjects (18.5%) in the sham group, experienced at least 1 nonocular SAE each through Month 24. Four subjects overall (2 in each group) experienced multiple nonocular SAEs through Month 24. One subject in the NT-501 group died due to an SAE of chronic obstructive pulmonary disease; this subject had also experienced a nonfatal SAE of respiratory failure earlier in the study. Transient ischemic attack (occurring in 2 subjects in the NT-501 group) was the only nonfatal nonocular SAE reported for more than 1 subject in either study group.

6.2.12.5 Adverse Events of Special Interest (AESI)

The NT-501 group had a higher frequency of delayed dark adaptation (25.4% [15 eyes]).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

NT-501 is an allogeneic encapsulated cell-based intraocular implant consisting of 200,000-440,000 hCNTF-secreting NTC-201-6A.02 cells encapsulated within supportive matrices and surrounded by a semipermeable polymer membrane. Results from two Phase 3 studies, NTMT-03-A and NTMT-03-B, in this BLA were used to support the indication of NT-501 for the treatment of idiopathic MacTel. Both Phase 3 studies serve as the primary evidence of efficacy and safety.

NTMT-03-A and NTMT-03-B were identical. Both studies were a Phase 3, prospective, multicenter, masked, sham-controlled study to determine the safety and efficacy of NT-501 in subjects with MacTel. A total of 112 subjects were planned for each study. Only one study-eligible eye of each subject was designated as the study eye and randomized (1:1) to either have NT-501 implanted or to undergo the sham procedure. The primary efficacy endpoint was the rate of change in EZ (IS/OS) area loss over 24 Months using SD-OCT. The key secondary efficacy endpoints included mean change from baseline to Month 24 in aggregate sensitivity of microperimetry within the EZ line break area, in reading speed, and in the NEI-VFQ-25 near activities subscale score.

In NTMT-03-A, 120 subjects were enrolled and randomized to either NT-501 implant or sham procedure, of whom 115 subjects (95.8%) underwent surgery. Fifty-eight subjects had NT-501 implanted and 57 subjects underwent sham surgery. All 115 subjects were included the primary efficacy analysis set. This study met its primary efficacy endpoint that NT-501 slowed the rate of EZ area loss over 24 months. The mean (SE) rate of change in EZ area loss from

baseline over 24 months was 0.075 (0.012) mm² in the NT-501 group and 0.166 (0.013) mm² in the sham group, with a statistically significant difference between the groups (-0.091 [0.018] mm²; 95% CI: -0.125, -0.056; p < 0.0001). This study also met its first secondary efficacy endpoint that NT-501 slowed down the aggregate retinal sensitivity loss from baseline to Month 24. There was a mean increase in aggregate retinal sensitivity loss from baseline to Month 24 in both groups, but the magnitude (SE) of loss was statistically significantly smaller in the NT-501 group relative to the sham group (25.3 [4.79] vs 43 [5.74] decibel [dB], respectively; p=0.02). The other two secondary efficacy endpoints were not statistically significant.

One subject in the sham group experienced an SAE of congestive cardiac failure and subsequently died. Two subjects in the NT-501 group and 1 in the sham group, experienced at least 1 ocular SAE each through Month 24. Ten subjects (17.2%) in the NT-501 group and 7 subjects (12.3%) in the sham group, experienced at least 1 nonocular SAE each through Month 24. Delayed dark adaptation was more common in NT-501 group (20.7% [12 eyes]). Although only 10 NT-501 subjects were followed at Month 36 and 2 subjects at Month 48, one subject in the NT-501 group had an ocular SAE of vitreous hemorrhage in the study eye that led to NT-501 explantation.

In NTMT-03-B, 119 subjects were enrolled and randomized to either NT-501 or sham, of whom 113 subjects (95.0%) underwent surgery. Fifty-nine subjects had NT-501 implanted and 54 subjects underwent sham surgery. All 113 subjects were included in the primary efficacy analysis set. This study met its primary efficacy endpoint that NT-501 slowed the rate of EZ area loss over 24 months. The mean (SE) rate of change in EZ area loss from baseline over 24 months was 0.111 (0.0142) mm² in the NT-501 group and 0.160 (0.0149) mm² 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). None of the key secondary efficacy endpoints was statistically significant.

One subject in the NT-501 group died. The subject experienced an SAE of chronic obstructive pulmonary disease on Day 575 and died on Day 607 due to the SAE. Four study eyes (6.8%), all in the NT-501 group, experienced at least 1 ocular SAE each through Month 24. This included suture related complication occurring in 3 study eyes and device extrusion occurring in 1 study eye. A total of 18 subjects (15.9%), including 8 subjects (13.6%) in the NT-501 group and 10 subjects (18.5%) in the sham group, experienced at least 1 nonocular SAE each through Month 24.

10.2 Conclusions and Recommendations

The efficacy evaluation of NT-501 is primarily based on the data from two studies NTMT-03-A and NTMT-03-B. Both studies met the usual criteria for an adequate and well-controlled study. The primary efficacy endpoint in both studies and one

key secondary efficacy endpoint in NTMT-03-A were statistically met. Based on the available data from NTMT-03-A and NTMT-03-B, there is substantial evidence to support approval of NT-501 for the treatment of MacTel.