Summary Basis for Regulatory Action

Date:	March 5, 2025
From:	Carolina Panico, MD, PhD, CBER/OTP/OCTHT, Chair of the Review Committee
BLA STN:	125798/0
Applicant:	Neurotech Pharmaceuticals, Inc.
Submission Receipt Date:	April 18, 2024
PDUFA* Action Due Date:	March 18, 2025
Proper Name:	revakinagene taroretcel-lwey
Proprietary Name:	ENCELTO
Indication:	For the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel)

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Carolina Panico, MD, PhD, CBER/OTP/OCTHT Kyung Sung, PhD, CBER/OTP/OCTHT (Device) Shirin Marfatia, MSc, PhD, CQIA, CBER/OTP/OCTHT Edhriz Siraliev-Perez, PhD, CBER/OTP/OGT Miriam Ngundi, PhD, CBER/OCBQ/DMPQ Salil Ghosh, MS, PhD, CBER/OCBQ/DBSQC CAPT Simleen Kaur, MSc, CBER/OCBQ/DBSQC Jing Lin, PhD, RAC, CBER/OCBQ/DBSQC Marie Anderson, MS, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Ekaterini Tsilou, MD, CBER/OTP/OCE/DCEGM Victoria Moncada, MD, CBER/OBPV/DPV/PB2 Yakubu Wangabi, CBER/OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB)	Xiaoyu Zhang, PhD, CBER/OBPV/DB Tingting Zhou, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Ernesto Moreira, MD, CBER/OTP/OPT
Clinical Pharmacology	Xing Jing, PhD, CBER/OTP/OCE/DCEH
Labeling • Promotional (OCBQ/APLB) • Regulatory Review	Michael Brony, PharmD, CBER/OCBQ/DCM/APLB Afsah Amin, MD, MPH CBER/OTP/OCE
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Arlesa Hubbard, Human Factors Reviewer (CDRH/OPEQ/OHT3/DHT3C) Brychan (Brandy) Clark, Donor Eligibility Consult (DHT) Reviewer Harry Houghton, Clinical Analyst (Safety Data) Cinque Soto, PhD, CBER/OTP/OCTHT, Bioinformatics Reviewer

Discipline Reviews	Reviewer / Consultant - Office/Division
	Sandip De, PhD, CBER/OTP/OCTHT, Bioinformatics Reviewer Wojtek Tutak, PhD, CBER/OTP/OCTHT, CBER Device compatibility Reviewer Andrey Sarafanov, CMC OPPT/DH Reviewer Alexander Beylin, CDRH Device Consult Reviewer

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I. Introduction

Neurotech Pharmaceuticals Inc. (the Applicant) submitted Biologics License Application (BLA), STN 125798, for licensure of revakinagene taroretcel-lwey, with the proprietary name ENCELTO (also referred to as NT-501 implant) as a single-dose implant, containing 200,000 to 440,000 cells, per affected eye inserted by surgical intravitreal administration, seeking approval for the treatment of adults with idiopathic macular telangiectasia Type 2 (MacTel).

ENCELTO is a single use, allogeneic encapsulated cell-based gene therapy combination product that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF). The encapsulation device (referred to as the pre-assembled capsule (PAC)) is opaque, semi-permeable, and surrounds a scaffold of polyethylene terephthalate (PET). It contains a fixation hook that connects the capsule to a titanium gripper, which aids in the handling and surgical implantation of ENCELTO. ENCELTO is intended for surgical placement into the vitreous cavity of the eye via access through the sclera.

BLA 125798 is supported by six studies: (i) Phase 1 study (NTMT-01), (ii) Phase 2 study (NTMT-02), (iii) Phase 2 Study NTMT-01/02E, (iv) Phase 2 Study NTMT-02-B, and two Phase 3 studies, (v) NTMT-03-A and (vi) NTMT-03-B.

The primary efficacy evaluation is based on data from two adequate and well controlled, phase 3 studies of identical design, Studies NTMT-03-A and NTMT-03-B. The studies were multicenter, randomized, sham-controlled, and evaluator-masked and compared the rate of photoreceptor degeneration (loss) between ENCELTO treated and sham treated adults with MacTel. The primary efficacy endpoint in both studies was the mean rate of change in the area of Ellipsoid Zone (EZ) loss from baseline to 24 months. Loss of the EZ area reflects photoreceptor degeneration and mediates visual loss. Secondary efficacy endpoints included additional measures of photoreceptor degeneration and visual function including the mean change in aggregate retinal sensitivity loss of microperimetry within the EZ line break area, the change in monocular reading speed, and the change in the National Eye Institute-Visual Function Questionnaire (NEI-VFQ-25) near activities subscale score, from baseline at Month 24. The primary safety evaluation is based on data from the two phase 3 studies with additional, supportive safety analyses conducted on data from the early-phase studies in MacTel and on studies in patients with retinitis pigmentosa (RP), geographic atrophy (GA) associated with age-related macular degeneration (AMD), and achromatopsia.

1. Background

MacTel is a rare, retinal disease characterized by bilateral, asymmetric, slowly progressive macular photoreceptor (PR) degeneration.

MacTel is an adult-onset disease. Patients are typically diagnosed in their 40s and 50s. Reports suggest that MacTel has a genetic component, although no hereditary pattern

has been established. 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. The disease affects visual function with initial paracentral scotomas and later loss of Best Corrected Visual Acuity (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.

Fluorescein angiography is the gold standard for diagnosing MacTel; leakage on fluorescein angiography may precede 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. Using spectral domain ocular coherence tomography (SD-OCT), morphological changes highly characteristic of this disease include thinning of the central retina, low-reflective spaces ("cavities") in the inner and outer retina, and focal loss of the EZ area, also known as IS/OS break, that typically starts temporal to the foveal center and later spreads to involve the fovea.

There is no approved, disease modifying treatment for MacTel. 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. Anti-VEGF drugs have been reported to be associated with anatomical and functional improvement in most of studies of proliferative MacTel.

Table 1. Regulatory History

Regulatory Milestones	Date
1. IND submission	02-14-2003
2. Fast Track designation granted	12-17-2018
3. Orphan Drug designation granted	03-29-2012
4. Pre-BLA meeting	08-31-2023
5. BLA 125798/0 submission	04-18-2024
6. BLA filed	06-17-2024
7. Mid-Cycle communication	08-15-2024
8. Late-Cycle meeting	10-07-2024
9. Major Amendment	10-16-2024

2. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The review team concludes that the ENCELTO manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Product Description

ENCELTO is a single use, allogeneic encapsulated cell-based gene therapy combination product that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF. The capsule is opaque, semi-permeable and white to off-white, capped on both ends, and has a titanium loop on one end. The titanium anchor loop is used to facilitate placement and retrieval (if medically necessary). ENCELTO width is 1.2 ± 0.1 mm, length is 6.1 ± 0.4 mm, and its internal diameter is 0.88 ± 0.02 mm.

Manufacturing Summary

To manufacture ENCELTO, retinal pigment epithelial cells were obtained from a (b) (4) to obtain the NTC-201-6A stable cell line, (b) (4) Then, 200,000 to 440,000 cells are loaded into an opaque, semi-permeable white to off-white PAC that consists of a (b) (4) hollow fiber membrane (HFM) surrounding a polyethylene terephthalate (PET) scaffold yarn along with Endothelial-Serum Free Medium (Endo-SFM). Briefly, the (b) (4) is aseptically encapsulated within a sterile PAC. The cell-filled PAC is sealed with (b) (4) adhesive, and the cell-loaded PAC is secured in the inner container. The PAC is assembled with a fixation hook that connects the capsule to a titanium gripper that holds the PAC in the inner container. The gripper also aids in the handling, and surgical implantation of ENCELTO. The inner container is (b) (4) sealed and placed in the outer container, which is also (b) (4) sealed. The encapsulation operations are executed using semi-automated manufacturing equipment. The product is administered intravitreally, with the assistance of the gripper, and contains 200,000 to 440,000 cells expressing rhCNTF.

Manufacturing Controls

(b) (4)

The manufacturing of the device constituent of ENCELTO, including the PAC and gripper, is managed through the design control process, with device specifications determined by design inputs including essential performance requirements. PAC release testing includes assessment of (b) (4) Additionally, the gripper is released based on retention strength testing.

Lot release testing is performed on the final ENCELTO product, with the exception of (b) (4) which is performed on the (b) (4). Product release testing on the drug product includes: appearance (visual inspection), rhCNTF protein expression using (b) (4), pH, sterility, endotoxin, mycoplasma, viability, strength (b) (4) potency (b) (4)), and identity (rhCNTF expression using (b) (4)

Process Validation

The applicant validated the manufacturing process using (b) (4) process performance qualification (PPQ) batches. The process validation was assessed against established process parameters and predefined release criteria. Shipping and stability of the final product was established using PPQ and clinical batches.

Manufacturing Risks, Potential Safety Concerns, and Management

Virus and (b) (4) testing for human and animal-derived reagents are verified with a full Certificate of Analysis (CoA) from the supplier. Certificate of Origin/Certificate of Suitability is required for each lot of animal-derived material coming from manufacturers in acceptable Geographic BSE Risk (GBR) countries or regions. For human-derived materials, the documentation requirements cover donor or reagent testing which verifies no human adventitious agents are present. (b) (4) requires a traceable history and testing results for adventitious agents. Transmission of infectious diseases is controlled by testing of reagents and control of the manufacturing process. The risk of exposure to (b) (4) -derived proteins used during product manufacturing is managed by reagents that are verified to be free of potential adventitious agents.

Drug Product Stability and Shelf Life

ENCELTO is supplied as a single implant consisting of 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF and encapsulated in an opaque semi-permeable capsule. The stability of ENCELTO has been determined to be 12 weeks from the date of manufacture when stored at (b) (4) and shipped, (b) (4), at 16°C - 37°C.

CMC Post Marketing Commitments (PMCs)

The CMC team recommends two PMCs. The rationale for the PMCs is described below, and the PMC agreements are detailed in Section 11c of this document.

1. The Applicant performed (b) (4) validation studies that did not include a (b) (4) to assure the (b) (4) viability during

(b) (4). The Applicant agreed to a PMC to perform a (b) (4) validation study that includes a (b) (4) in accordance with Technical Report No. (b) (4) Revised (b) (4).

2. Based on the information provided, it is unclear if the (b) (4) rendered (b) (4) by the process (b) (4) processing conditions (b) (4) and/or the properties of the (b) (4). Therefore, the Applicant agreed to a PMC to perform (b) (4)

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ENCELTO drug product were found to be adequate for their intended use.

The final product commercial release specifications are shown in Table 2.

Table 2. Final Product Commercial Release Specifications

Attribute	Test	Analytical Method	Acceptance Criteria
Quality	Visual	Physical state, color, clarity	Physical state: ENCELTO is solid capsule with metallic loop on one end and cap on the other; Hold Medium (Endo-SFM) is liquid and may contain visible particles Color: ENCELTO is white/off-white; Hold Medium is orange to pink Clarity: ENCELTO is opaque; Hold Medium is clear
	rhCNTF protein expression	(b) (4)	(b) (4)
	pH	(b) (4)	(b) (4)
	Viability	(b) (4)	(b) (4) Viability (b) (4) (b) (4) /ENCELTO
Safety	Sterility	(b) (4)	ENCELTO: No Growth ENCELTO Hold Medium: No Growth
	Bacterial Endotoxins	(b) (4)	(b) (4) /ENCELTO Hold Medium: (b) (4)
	Mycoplasma	(b) (4)	Negative
Potency	(b) (4)	(b) (4)	(b) (4)

Attribute	Test	Analytical Method	Acceptance Criteria
		(b) (4)	
Strength	(b) (4)	(b) (4)	200,000 – 440,000 cells/ENCELTO
Identity	rhCNTF protein expression	(b) (4)	Consistent with reference material

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA STN 125798/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ENCELTO are listed in Table3 below. The activities performed and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities for ENCELTO

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
Neurotech Pharmaceuticals, Inc. 900 Highland Corporate Dr. Building 1 Suite 101 Cumberland, RI 02864 *DS manufacturing; Device design control activities; Final product manufacturing; Final product packaging and labeling; Final product release testing*	3012545799	127708787	PLI	DMPQ/OCBQ July 2024 VAI
(b) (4)	(b) (4)	(b) (4)	RRA – 704(a)(4) Assessment	DMPQ/OCBQ (b) (4) rVAI

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
(b) (4)	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Final product release testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) NAI

Acronym key: DMPQ – Division of Manufacturing and Product Quality; DS – drug substance; NAI – No Action Indicated; OCBQ – Office of Compliance and Biologics Quality; ORA – the former Office of Regulatory Affairs; PAC – Pre-assembled capsule; RRA – Remote Regulatory Assessment; rVAI – Remote Voluntary Action Indicated; VAI – Voluntary Action Indicated

CBER/DMPQ conducted a pre-license inspection (PLI) at Neurotech Pharmaceuticals, Inc in July 22 – 26, 2024. A Form FDA 483 list of observations was issued at the end of the inspection, and the corrective actions were reviewed. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

CBER/DMPQ conducted a remote regulatory assessment (RRA) – 704(a)(4) Assessment of (b) (4) An observations letter was issued at the end of the records review, and the RRA was classified as remote voluntary action indicated (rVAI).

ORA performed a surveillance inspection at (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection at (b) (4) . A Form FDA 483 list of observations was not issued, and the inspection was classified no action indicated (NAI).

e. Container/Closure System

ENCELTO is suspended using a luer lock cap made up of a polycarbonate locking ring and polypropylene baffle cap (b) (4) that is placed into an inner container consisting of a polycarbonate blue tinted base (b) (4) and covered with a viny foil lid (b) (4) The inner container is placed within an outer container (i.e., sterile barrier) consisting of a polyethylene terephthalate glycol blue tinted base (b) (4) that is covered

with a viny foil lid (b) (4)). Each ENCELTO package contains one product implant. Neurotech Pharmaceuticals, Inc. performed the container closure integrity testing at the Cumberland, RI facility, employing a (b) (4) method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

3. Nonclinical Pharmacology/Toxicology

The nonclinical development program evaluated a product representative of ENCELTO, NT-501. An early pharmacology study showed that the outer nuclear layer (ONL) in dogs with retinitis pigmentosa caused by rod-cone dysplasia type 1 (rcd1) was protected from photoreceptor loss following implantation of NT-501. A pharmacology study in healthy (b) (4) rabbits showed that secretion of 5 ng/day of rhCNTF following NT-501 implantation had no deleterious effects on photoreceptors, but that high doses of 22 ng/day of rhCNTF could have negative effects on cones.

The nonclinical pharmacokinetic (PK) studies measured systemic exposure of rhCNTF in two distribution studies in rabbits and two toxicology studies in minipigs and pigs. There was no evidence of systemic exposure to rhCNTF after implantation of NT-501 in minipigs for up to 6 months or in rabbits for up to 9 months. In rabbits, NT-501 implants established rhCNTF levels averaging about 7-9 ng/day for up to 9 months.

The effect of long-term intraocular implantation of NT-501 was evaluated in a 3-part study toxicology study in 4–8-month-old (b) (4) minipigs, 4–10-year-old (b) (4) pigs, and catastrophic device failure of NT-501 was evaluated by intraocular injection of unencapsulated NTC-201-6A cells into the vitreous of 8-9 month old (b) (4) minipigs. Overall, data from this study suggests that the effects of NT-501 implantation were minimal: lens changes, focal refractive changes in the vitreous, and minimal to mild amounts of inflammatory cells and/or inflammation associated with the vitreous, the aqueous chamber, iris/ciliary body, and the corneoscleral junction. Although many of these appear to be triggered by the implantation of the NT-501 capsule itself or the implantation procedure, a dose-response to rhCNTF was present, with eyes implanted with empty capsules and capsules with a low rhCNTF output cell line exhibiting less intense changes than eyes implanted with NT-501. Microscopic analysis of ocular tissues corroborated these in-life findings. Intraocular pressures (IOP), pupillary response, cornea, and other clinical ophthalmic parameters were normal. Intraocular implantation of NT-501 did not cause any effects on systemic clinical signs, gross pathology, or histopathology of non-ocular organs.

Four Developmental and Reproductive Toxicity (DART) studies were conducted in rats and rabbits to establish the risks to fertility and teratogenicity associated with the subcutaneous (SC) administration of high doses of rhCNTF. In male rats administered rhCNTF at dose levels of 0, 10, 100, or 300 µg/kg/day subcutaneously (SC) for 62 days,

there were no adverse effects on mating performance, fertility, or the postnatal development of the offspring. In female rats administered rhCNTF at dose levels of 0, 10, 100, or 300 µg/kg/day SC for 2 weeks prior to mating to postpartum Day 21, mating performance, fertility and gestational parameters were normal. No adverse effects on fetuses or pup postnatal development were reported. In pregnant rats administered rhCNTF at 10, 100, 300, or1000 µg/kg/day SC on gestational Days 7-21, clinical changes were present in pregnant rats administered the highest dose level and decreased body weight gain was present at dose levels ≥100 µg/kg/day of rhCNTF. There were no rhCNTF-related teratologic changes reported in the fetuses. In pregnant rabbits administered SC rhCNTF at 2, 5, or 10 µg/kg/day SC on gestational Days 7-29, anorexia, abortion, and body weight loss occurred at 10 µg/kg/day. There were no rhCNTF-related teratologic changes reported in the fetuses.

A battery of genotoxicity studies was conducted to support licensure of NT-501 in keeping with ISO-10993, guidance for biological evaluation of medical devices. These studies included a (b) (4) study, (b) (4) study in mammalian cells, mouse bone marrow micronucleus study, and a Kligman maximization test. No genotoxicity was observed in these studies.

Studies to evaluate the carcinogenicity/tumorigenicity of NT-501 were not conducted. These studies are not warranted based on the safety profile described in the provided toxicological risk assessments (TRAs).

4. Clinical Pharmacology

Given the intraocular route of administration and the local action of ENCELTO, significant serum exposure to rhCNTF is not expected, and systemic exposure to rhCNTF 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 rhCNTF at 12, 24, and 36 months after ENCELTO implantation. Therefore, no pharmacokinetic or pharmacodynamic analyses were performed.

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

5. Clinical/Statistical

a. Efficacy

The efficacy assessment is based on two adequate and well-controlled phase 3 studies, Studies NTMT-03-A and NTMT-03-B.

Studies NTMT-03A and NTMT-03B were randomized, multicenter, evaluator-masked, sham-controlled 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 line break 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).

The EZ as measured by 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. The integrity and intensity of the EZ are important indicators of photoreceptor health and significant loss (thinning or break) in the EZ is associated with photoreceptor degeneration and visual loss. Published studies (1-5) have shown that the EZ is an important retinal structural component and that loss of the EZ area reflects photoreceptor degeneration and mediates visual loss. 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 represents clinical benefit on vision preservation.

Retinal sensitivity (reported in dB) was measured in both studies using macular integrity assessment microperimetry. Microperimetry results were transferred electronically to a central reading center and evaluated by masked readers. 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.

In Study NTMT-03-A, 115 patients were randomized of whom 58 received ENCELTO implant and 57 underwent sham surgery. The demographic characteristics of the efficacy analysis population were as follows: the mean age was 61 years (range 40 to 78 years), 79 patients (69%) were female, 98 patients (85%) were White, 5 patients (4%) were Asian, 3 patients (3%) were Black or African American, 1 patient (1%) was American Indian, and 8 patients (7%) were of “other” race. Six patients (5%) were Hispanic. The mean (standard deviation) baseline EZ area was 0.51 (0.477) mm^2 for the ENCELTO group and 0.49 (0.358) mm^2 for the sham group. The mean (standard deviation) baseline aggregate sensitivity of microperimetry within the EZ line break area was 63.9 (80.6)) dB for the ENCELTO group and 58.3 (62.3) dB for the sham group.

The efficacy results for the primary endpoint in Study NTMT-03A are shown in Table 4 below.

Table 4. Primary Efficacy Results in Study NTMT-03A

		NTMT-03A (N=115)
Mean rate of change (in mm^2) in EZ area loss from baseline to 24 months (95% CI)	ENCELTO	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 ENCELTO-Sham (95% CI)		-0.091 (-0.13, -0.06)
P- value		<0.0001

CI=Confidence Intervals

Study NTMT-03-A met its first secondary efficacy endpoint and demonstrated that ENCELTO slowed the 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 the ENCELTO and sham groups, the magnitude of loss was significantly smaller in the ENCELTO group relative to the sham group (25.3 versus 43 decibels (dB), respectively; p=0.02). This finding provides supportive evidence of slowing of photoreceptor degeneration. Although, none of the remaining secondary endpoints reached statistical significance, results on mean change in monocular reading speed favored the ENCELTO group, providing supportive evidence of the favorable treatment effect of ENCELTO on photoreceptor preservation over 24 months of follow up.

In Study NTMT-03-B, 113 patients were randomized with 59 receiving ENCELTO implant and 54 undergoing sham surgery. The demographic characteristics of the efficacy analysis population were as follows: the mean age was 59 years (range: 40 to 75 years), 82 patients (73%) were female, 102 patients (90%) were White, 4 patients (4%) were Asian, and 7 patients (6%) were of “other” race or “unable to specify” race. Eight patients (7%) were Hispanic. The mean (standard deviation) baseline EZ area was 0.52 (0.312) mm^2 for the ENCELTO and 0.46 (0.283) mm^2 for the sham group. The mean (standard deviation) baseline aggregate sensitivity of microperimetry within the EZ line break area 55.54 (56.05) dB for the ENCELTO group and 49.27 (54.78).

The efficacy results for the primary endpoint for study NTMT-03B are shown in Table 5 below.

Table 5. Primary Efficacy Results in Pivotal Study NTMT-03B

		NTMT-03B (N=113)
Mean rate of change (in mm^2) in EZ area loss from baseline to 24 months (95% CI)	ENCELTO	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 ENCELTO-Sham (95% CI)		-0.049 (-0.089, -0.008)
P- value		0.0186

CI=Confidence Intervals

In Study NTMT-03-B, the difference between ENCELTO and sham in the mean change in aggregate retinal sensitivity loss from baseline to Month 24 was smaller in the ENCELTO group relative to the sham group (40.02 versus 41.97 dB) but the difference did not reach statistical significance (p=0.83). For all remaining secondary endpoints assessing visual function and vision-related quality of life, differences favored the ENCELTO group without reaching statistical significance. The directionally consistent results among all efficacy endpoints provide supportive evidence of the favorable treatment effect of ENCELTO on photoreceptor preservation over 24 months of follow up.

The reliability and reproducibility of the EZ area measurement (EZ area loss) by graders using SD-OCT are important analytical factors considered in the interpretation of this data. The intra-grader and inter-grader variability in measurement of the EZ area loss were provided by the Applicant and are as follows: a) intra-grader variability: mean absolute difference 0.0132 mm^2 (SD=0.0114 mm^2) in the EZ area loss, and b) intergrader variability: mean absolute difference 0.018 mm^2 (SD=0.0343 mm^2) when an arbitrator was included. The observed differences in EZ area loss between the ENCELTO and sham groups in both phase 3 studies exceed both the intra-grader and inter-grader measurement variability and, thus, support that the observed effects in the studies are attributable to the interventions (ENCELTO or sham).

In summary, the ENCELTO phase 3 studies similarly demonstrated that patients treated with ENCELTO implant experienced a slower rate of photoreceptor loss (retinal degeneration) compared to those in the sham group. Specifically, ENCELTO slowed the rate of EZ area loss by 54.8% in Study NTMT-03-A and by 30.6% in Study NTMT-03-B over 2 years of follow up. These findings are further supported by the similarly favorable and directionally consistent secondary efficacy results in both studies showing beneficial

effects on aggregate retinal sensitivity loss (another measure of photoreceptor degeneration), as well as visual function.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for one foreign and two domestic clinical investigators (CI) that participated in the conduct of Protocols NTMT-03-A and NTMT-03-B. The inspections did not reveal substantive issues that impact the data integrity or quality submitted in this Biologics License Applications (BLA).

c. Pediatrics

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

d. Other Special Populations

Geriatric Use
In the Phase 3 studies, the majority of patients (152 of 228; 67%) were younger than 65 years of age at baseline and, in these patients, the difference (ENCELTO-Sham) in rate [SE] of change in EZ area loss from baseline to Month 24 was -0.114 [0.017] mm^2 (95% CI: -0.148, -0.081) indicating a slower rate of EZ loss in ENCELTO treated patients compared to sham. By comparison, that difference was 0.023 [0.02] mm^2 (95% CI: -0.017, 0.062) in patients ≥ 65 years of age, indicating no significant difference in the rate of change over 24 months in this subgroup. These differences may be due to chance or some unknown factor(s) impacting the ENCELTO 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. Safety and Pharmacovigilance

The primary safety assessment is based on data from the phase 3 studies NTMT-03-A and NTMT-03-B and formed the basis for the ENCELTO USPI safety sections. Overall, there were no deaths or systemic serious adverse events (SAEs) related to ENCELTO or the implantation procedure. There were 7 ocular SAEs (7/117; 6%) of which 6 occurred in the ENCELTO 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 ENCELTO group. Of the 6 ocular SAEs occurring in the ENCELTO 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 ENCELTO 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

ENCELTO 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 are shown in Table 6. Of those, delayed dark adaptation and miosis, both non-serious, were related to ENCELTO. Delayed dark adaptation was consistently reported as non-progressive. Cataract formation (related to ENCELTO or the procedure) and vitreous hemorrhage were reported in ENCELTO implanted eyes only.

Table 6. Adverse Reactions in ≥2% of patients in Studies NTMT-03-A and NTMT-03-B over 24 months

Adverse Reactions	**ENCELTO (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 (0.0)
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 (0.0)
Vision blurred	8 (6.8)	4 (3.6)
Headache	8 (6.8)	1 (0.9)
Dry eye	7 (6.0)	2 (1.8)
Eye irritation	6 (5.1)	2 (1.8)
Cumulative cataract incidence	6 (5.1)	0 (0.0)
Vitreous floaters	6 (5.1)	0 (0.0)
Severe vision loss ≥ 15 letters temporary or permanent	4 (3.4)	0 (0.0)
Eye discharge	4 (3.4)	1 (0.9)
Anterior chamber cell	4 (3.4)	0 (0.0)

Adverse Reactions	ENCELTO (N=117) n (%)	Sham (N=111) n (%)
Iridocyclitis	3 (2.6)	0 (0.0)

Additional safety analyses were conducted on data from early-phase ENCELTO studies in adults with MacTel and from studies in patients with retinitis pigmentosa (RP), geographic atrophy (GA) associated with age-related macular degeneration (AMD), and achromatopsia. The additional safety analyses were generally consistent with the primary safety analysis and did not identify additional serious safety risks except a higher rate of explantation of 1.4% (3 eyes) across all MacTel studies. The reasons for explantation included vitreous hemorrhage, suture- related complication, and expulsion with the earliest removal occurring 130 weeks (18.6 months) post implantation.

7. Labeling

The proposed proprietary name, ENCELTO, was received by the Advertising and Promotional Labeling Branch (APLB) on April 25, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on July 12, 2024. Proposed name suffixes were submitted on April 18, 2024 and the proposed suffix *-lwey* was found acceptable on January 21, 2025.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

8. Advisory Committee Meeting

This BLA was not referred to an Advisory Committee because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefitted from an advisory committee discussion.

9. Other Relevant Regulatory Issues

ENCELTO received orphan drug designation and fast track designation for treatment of adults with MacTel, and the BLA received priority review designation.

10. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Substantial evidence of effectiveness for ENCELTO 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 ENCELTO 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 ENCELTO in adults with MacTel, the review team recommends approval of ENCELTO for the indication of treatment of adults with idiopathic macular telangiectasia type 2.

b. Benefit/Risk Assessment

Studies NTMT-03-A and NTMT-03-B demonstrated a clinically and statistically significant beneficial effect of ENCELTO in slowing the EZ area loss (photoreceptor loss) in ENCELTO-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 results of the primary efficacy findings. ENCELTO 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. Other, non-serious adverse reactions included conjunctival hemorrhage and delayed dark adaptation which were mild or moderate in intensity and non-progressive. The identified risks can be adequately mitigated through product labeling and post-marketing pharmacovigilance. Overall, the assessment of the efficacy and safety data in this BLA support a favorable benefit-risk determination of ENCELTO in adults with MacTel.

c. Recommendation for Post marketing Activities

The Applicant's pharmacovigilance plan (PVP) includes the identified risks of suture related complications, device extrusion, delayed vitreous hemorrhage, miosis, and delayed dark adaptation, the potential risks of cataract formation/cataract surgery related complications, risks associated with vitreoretinal surgery (such as infections/ endophthalmitis, retinal tear/detachment) and risks associated with intraocular devices.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for delayed dark adaptation (for 3 years following licensure, the Applicant will include aggregate safety assessment for delayed dark adaptation events in periodic safety reports). The Applicant voluntarily agreed that the follow up of clinical trial participants will continue with a Phase 4 extension clinical study (NTMT-04) and with focused patient surveys from the Natural History Observation Registry (NHOR) study.

The identified risks can be adequately mitigated through product labeling and the Applicant's proposed post-marketing pharmacovigilance activities. A Risk Evaluation and Mitigation Strategy (REMS) or post-marketing safety studies through PMR or PMC are not warranted.

The Applicant agreed to the following CMC PMCs:

1. Neurotech commits to perform a (b) (4) validation study that includes (b) (4) The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2025.

2. Neurotech commits to perform (b) (4) The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2025

11. References

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