



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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(PB2), DPV, OBPV, CBER, FDA

To: Carolina Panico, MD, PhD
Chair of the Review Committee
Office of Therapeutic Products

Through: Christopher Jason, MD
Branch Chief, PB2

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Acting Director DPV
OBPV, CBER, FDA

Sponsor: Neurotech Pharmaceuticals, Inc.

Product¹: revakinagene taroretcel (Encelto)

Application Type / Number BLA / STN 125798/0

Proposed Indication For the treatment of idiopathic macular telangiectasia type 2 (MacTel)

Submission Date: April 18, 2024

Action Due Date: March 4, 2025

¹ The product was referred to as NT-501 in the clinical development program.

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA /STN125798/0 based on the safety profile of NT-501. Our review will determine whether any safety-related studies will be needed as Post-Marketing Requirements (PMRs) and/or if there will be agreed-upon Post-Marketing Commitments (PMCs) for safety studies, or if Risk Evaluation and Mitigation Strategies (REMS) are required for NT-501, should the indication for this product be approved. Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Idiopathic Macular Telangiectasia Type 2 (Mac Tel) is a gradually progressive disease of the macula that typically affects both eyes and leads to central vision loss and functional impairment. It is thought to be a neurodegenerative disease with primary involvement of the Muller cells.¹ Muller cells are the primary glial cells of the retina and are hypothesized to mediate ciliary neurotrophic factor (CNTF) protection of retinal photoreceptors². Muller cell dysfunction and apoptosis impedes production and effectiveness of CNTF resulting in photoreceptor death³. Retinal pigment epithelium hyperplasia and subretinal neovascularization cause most of the advanced cases of vision loss.⁴ Mac Tel typically affects patients over the age of 40 years⁵ and is prevalent throughout the world with no racial predilection.⁵

Product Mechanism of action:

After intraocular implantation through the sclera, the NT-501 ECT implant provides continuous long-term delivery of recombinant human ciliary neurotrophic factor (rhCNTF) directly into the vitreous cavity of the eye and the retina. Studies have shown that exogenous CNTF initially targets Muller glial cells to trigger a cascade of signaling events that promote photoreceptor survival.

3 PRODUCT INFORMATION

3.1 Product Description

NT-501 (ENCELTO) is an ECT implant consisting of a sealed semipermeable hollow fiber membrane capsule that surrounds a scaffold of (b) (4) of polyethylene terephthalate yarn, which has been loaded with CNTF-secreting NTC-201-6A cells for surgical intravitreal placement. Each end of the semi-permeable capsule is sealed with medical grade methacrylate adhesive, and to one end a titanium fixation loop is attached. The implant is approximately 6.5 mm long with an external diameter of approximately 1.3 mm and an internal diameter of approximately 0.87 mm. It is packaged in an orange to pink clear liquid hold medium referred to as Endothelial Serum Free Media (Endo-SFM) that may contain visible particles.

NT-501 is implanted in the vitreous cavity of the study eye, anchored by a suture to the eye wall and placed outside the visual axis. The surgical procedure involves a small full-thickness scleral incision at the pars plana, which is generally closed after implantation with 2 sutures. The fixation anchor loop is sutured to the sclera within the vitreous cavity

with a single double armed 9-0 polypropylene suture. The NT-501 implantation procedure is performed using local anesthesia in accordance with the surgeon's usual protocol in the setting of monitored anesthesia care. NT-501 may be removed as required in the case of significant safety or tolerability concerns. Proposed Indication The sponsor's proposed indication statement in the package insert as submitted to the original BLA 125798/0 is "ENCELTO is indicated for the treatment of idiopathic macular telangiectasia type 2 (Mac Tel)".

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

Neurotech was granted Orphan Drug Designation on July 24, 2012 (see 1.12.17 Orphan Designation Approval Letter July 24, 2012) for allogenic retinal epithelial cells transfected with plasmid vector expressing ciliary neurotrophic growth factor for the treatment of macular telangiectasia (Mac Tel) type 2. Neurotech was also granted Fast Track Designation on December 17, 2018 (see 1.7.4 Correspondence Regarding Fast Track Designation December 17, 2018). This product has never been marketed, therefore there are no foreign approvals. In addition, there are no other drugs in this class which are approved.

5 DESCRIPTION OF NT-501 CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data submitted to BLA 125798/0 for individual NT-501 studies and the Integrated Summary of Safety (including appendices and datasets for the ISS) are provided in Module 2.7.4-Summary of Clinical Safety, and Module 5.3.5.3. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125798/0 be approved. Please refer to the package insert for the final clinical safety data.

In the sponsor's clinical development program, six clinical studies were done to evaluate the safety of NT-501 in subjects with Mac Tel (see Table 1 below). The product label includes the combined safety data from the two identical phase 3 clinical trials (studies NTMT-03-A and NTMT-03-B). All the studies were conducted in the United States (US), and except for study NTMT-01, the other 5 studies also included study centers in Australia. In addition, study NTMT-03A included study centers in United Kingdom and France, while study NTMT-03B included study centers in Germany. See Table 1 below.

Table 1. Summary of 6 Clinical Studies Contributing to Safety Evaluation of NT-501 in Type 2 Macular Telangiectasia (Mac Tel)

Study	Study Description	Number Subjects/Eyes Evaluated for Safety	Study Duration; Start and End Dates of study
NTMT-01	Phase 1, multicenter, open-label, non-randomized pilot study to evaluate safety and tolerability of NT-501 implant. The study eye from each eligible participant received the Ciliary Neurotrophic Factor (CNTF) secreting implant and the fellow eye served as control.	<u>Total Enrolled:</u> 7 subjects (7 eyes) exposed to NT-501 <u>Completed:</u> 6 subjects	60 months <u>Start Date:</u> 8/26/2011 <u>End Date:</u> 12/10/2016
NTMT-02	Phase 2, prospective, multi-center, randomized, single masked, sham control study. <u>Control:</u> Sham surgery control or Fellow eye sham surgery control. Participants with 1 eligible study eye randomized (1:1) to receive NT-501 implant or sham procedure in the study eligible eye. If both eyes eligible then right eye randomized (1:1) to receive NT-501 implant or sham procedure. Left (fellow) eye received the alternative surgery/sham.	<u>Total Enrolled:</u> 67 subjects (99 eyes; 48 exposed to NT-501; 51 exposed to sham <u>Completed:</u> 65 subjects (95 eyes)	24 months <u>Start Date:</u> 4/11/2014 <u>End Date:</u> 3/29/2017
NTMT-01/02E (and sub-study NTMT-01/02E-SS)	Phase 1/2 prospective multicenter single-masked, sham controlled extension study designed to provide long term safety & efficacy f/u data for subjects who received either NT-501 implant and/or had sham procedure in the respective parent study (NTMT-01 or NTMT-02). <u>Cohort 1:</u> NT-501 implantation occurred in parent study; visits continued until Month 108 from date study procedure with annual f/u at Months 72, 84, 96, and 108. <u>Cohort 2:</u> Additional treatment only given to participants from NTMT-02 study that received sham surgery in parent study as part of sub-study. Eligible patients received NT-501 after the 1st	Planned <u>Total Enrolled</u> = 73 subjects <u>Cohort 1:</u> 7 subjects (7 eyes) from NTMT-01 study <u>Cohort 2 :</u> 66 subjects (98 study eyes) from NTMT-02 study. Analyzed <u>Cohort 1:</u> 6 subjects (6 study eyes) 6 fellow eyes <u>Cohort 2:</u> 64 subjects (94 study eyes). 45 had NT-501	<u>Cohort 1:</u> 108 months <u>Cohort 2:</u> 72 months <u>Start Date:</u> 5/12/2017 <u>End Date:</u> 5/11/2021

	annual visit. Visits continued until Month 72 from date of study procedure, with annual f/u at Months 36, 48, 60, and 72.	implanted & 49 eyes had sham surgery. 34 fellow eyes.	
NTMT-01/02E-SS (sub-study)	Subjects enrolled in study NTMT-02, who had 1 eligible study eye that underwent sham procedure, were offered the option to receive the NT-501 implant in the same study eye during the sub-study. Approximate 48-month f/u period after NT-501 implantation during the extension study.	Enrolled: 16 subjects (16 eyes) exposed to NT-501	48 months <u>Start Date:</u> 6/14/2018 <u>End Date:</u> 5/11/2021
NTMT-03A	Phase 3, prospective, multicenter, randomized, masked, sham-controlled study. Study eye was randomized (1:1) to receive the NT-501 implant or undergo sham procedure. Only 1 eye per participant was randomized. If both eyes qualified for the study, the study eye was to be selected using the centralized randomization process.	<u>Total Enrolled:</u> 120 subjects. <u>Treated:</u> 115 subjects (115 eyes) received NT-501 (58 eyes) or sham surgery (57 eyes) <u>Completed:</u> 105 subjects	24 ^a to 48 months after implant or sham surgery. <u>Start Date:</u> 11/24/2017 <u>End Date:</u> 9/23/2022
NTMT-03B	Phase 3, prospective, multicenter, randomized, masked, sham-controlled study. Study eye was randomized (1:1) to receive NT-501 implant or undergo sham procedure. Only 1 eye per participant was randomized. If both eyes qualified for the study, the study eye was selected using the centralized randomization process.	<u>Total Enrolled:</u> 119 subjects. <u>Treated:</u> 113 subjects (113 eyes) received NT-501 (59 eyes) or sham surgery (54 eyes) <u>Completed:</u> 106 subjects	24 ^a to 48 months after implant or sham surgery <u>Start Date:</u> 2/6/2018 <u>End Date:</u> 9/23/2022
NTMT-02-B	Phase 2, multicenter, open label, bilateral implantation study in subjects with Mac Tel who received NT-501 in a single eye prior to or in the Phase 1/2 extension study (NTMT-01/02E) or in one of the Phase 3 studies (NTMT-03-A or NTMT-03-B) would receive a NT-501 implant in their fellow eye & followed for 6 months after implantation to assess safety and tolerability of bilateral NT-501.	<u>Total Enrolled:</u> 33 subjects <u>Completed:</u> 32 subjects (32 eyes) received a bilateral NT-501 implant.	6 months post 2 nd implantation <u>Start Date:</u> 8/13/2021 <u>End Date:</u> 12/23/2022

Adapted from Sponsor Table 1 (Section 5.2) and Sponsor Table 2 (Module 2.7.4 Summary Clinical Safety)

a A subset of subjects enrolled early into the Phase 3 studies were to have been followed through a Month 36 and/or a Month 48 visit, based on the date of the surgical procedure.

5.1.2 Study Populations

The clinical studies included adults ≥ 40 years of age and ≤ 79 years of age, multiple different countries across different races and ethnicities. Demographics and baseline characteristic were generally similar between treatment groups in the individual Mac Tel studies and across all 6 Mac Tel studies. Specific demographic data of the six clinical study populations are shown below in Table 2.

Table 2. Study Sites and Demographics of Participants in the 6 Clinical Studies (including demographics of 3 Pooled Studies) Supporting the Safety of NT-501

Study Number	Number Study Sites (Location)	Study Population
NTMT-01	2 study centers in US	<u>Total</u> (N=7) <u>Sex</u> : F (5; 71.4%) M (2; 28.6%) <u>Mean Age</u> : 55.6 years old <u>Age Range</u> : 46-67 yrs. <u>Ethnicity</u> : not Hispanic or Latino (7; 100.0%) <u>Race</u> : Caucasian (5; 71.4%); Asian (1; 14.3%); Other (1; 14.3%)
NTMT-01/02E	11 study centers (8 US, 3 AU)	Cohort 1 <u>Total</u> : (N= 6) <u>Sex</u> : F (4; 66.7%) M (2; 33.3%) <u>Mean Age</u> : 58.8 years old <u>Age Range</u> : 48-61 yrs. <u>Ethnicity</u> : not Hispanic or Latino (100.0%) <u>Race</u> : Caucasian (4; 66.7%) Cohort 2 <u>Total</u> (N= 64) <u>Sex</u> : F (40; 62.5%) M (24; 37.5%) <u>Mean Age</u> : 61.4 years old <u>Age Range</u> : 45-79 yrs. <u>Ethnicity</u> : not Hispanic or Latino (61; 95.3%) <u>Race</u> : Caucasian (55; 85.9%)
NTMT-02	11 study centers	<u>Total</u> : (N=67) <u>Sex</u> : F (41; 61.2%) M (26; 38.8%) <u>Mean Age</u> : 61.6 years old

	(8 US, 3 AU)	<u>Age Range:</u> 44.8-79.4 yrs. <u>Ethnicity:</u> not Hispanic or Latino (64; 95.5%) <u>Race:</u> Caucasian (58; 86.6%)
NTMT-02B	10 study centers (7 US, 3 AU)	<u>Total:</u> (N= 32) <u>Sex:</u> F (24; 75.0%) M (8; 25.0%) <u>Mean Age:</u> 63.0 years old. <u>Age Range:</u> 51-78 yrs. <u>Ethnicity :</u> not Hispanic or Latino (93.8%) <u>Race:</u> Caucasian (28; 87.5%)
NTMT-03A	20 study centers (US, AU, FR, UK)	<u>Total:</u> (N= 115) <u>Sex:</u> F (79; 68.7%) M (36; 31.3%) <u>Mean Age:</u> 61 years old <u>Age Range:</u> 40-79 yrs. (64% < 65 yrs) <u>Ethnicity:</u> Hispanic/Latino (6 (5.2%); Not Hispanic/Latino (109; 94.8%) <u>Race:</u> Caucasian (98; 85.2%); Other (8;7.0%); Asian (5; 4.3%); African American (3; 2.6%); American Indian/Alaska Native (1; 0.9%)
NTMT-03B	23 study centers (US, AU, GE)	<u>Total:</u> (N=113) <u>Sex:</u> F (82; 73.0%) M (31; 27.0%) <u>Mean Age:</u> 59 years old <u>Age Range:</u> 40-75 yrs. (69% < 65 yrs <u>Ethnicity:</u> Hispanic/Latino (8; 7.1%); Not Hispanic/Latino (104; 92%); Unknown (1; 0.9%) <u>Race:</u> Caucasian (102; 90.3%); Other (7; 6.2%); Asian (4; 3.5%)

AU= Australia; FR= France; GE= Germany; UK= United Kingdom; US= United States.

5.2 Adverse events

5.2.1 Pivotal Studies NTMT-03-A and NTMT-03-B (Pool 1)

Study Description

The safety data from the two identically designed Phase 3 pivotal studies (NTMT-03-A and NTMT-03-B) were combined for analysis and designated as Pool 1, with the safety results contributing to the label. The primary time point for the Phase 3 studies was Month 24; however, for some categories of safety data, such as deaths, SAEs, and significant events, the sponsor provided available data through the Month 48 visit. The sponsor states that the Phase 3 studies included assessments through 24 months post-surgery; however, a subset of subjects (36 NT-501, 35 sham) that enrolled early into the Phase 3 studies were to have been followed through a Month 36 and/or a Month 48 visit, based upon the date of the surgical procedure. The sponsor discontinued the Month 36 and 48 study visits due to the limited number of subjects completing these visits, which would not have provided sufficient statistical power to show a treatment effect. The sponsor states that the decision to terminate the Phase 3 studies early was not due to any related safety concerns. Therefore, the primary endpoint for the Phase 3 studies was Month 24.

One study-eligible eye for each subject was designated as the study eye. If both eyes were eligible, the study eye was selected by a centralized randomization process or by subject preference. The study eye for each eligible subject was randomized (1:1) to either have NT- 501 implanted or to undergo a sham procedure (surgery day designated Day 0). All subjects returned to the study center for post-surgical assessments on Day 1, Week 1, and at Months 6,12,16,20, and 24. Additional in-clinic visits were scheduled at Months 1 and 3 for subjects enrolled at study centers in France, whereas subjects in other countries had telephone check-ins at these time points. As stated previously, the sponsor included safety assessments primarily through 24 months after implant or sham surgery, but for some categories of safety data, such as deaths, SAEs, and significant events, the sponsor also summarized available data through month 48.

***Reviewer comment:** Pooling the two Phase 3 studies (NTMT-03A and NTMT-03B) for the integrated population is appropriate given these studies were identical in study design and study populations.*

Subject Disposition in Pool 1

Overall, 239 subjects were enrolled across the Phase 3 studies and were randomized to either have NT-501 implanted or undergo the sham procedure. There were no significant demographic differences between participants in the NT-501 and sham groups in Pool 1. Of the randomized subjects, 228 subjects (95.4%) underwent surgery (117; 96.7% NT-501, 111; 94.1% sham). All 228 subjects were evaluated for safety.

A total of 11 subjects (4 NT-501, 7 sham) were randomized but did not undergo surgery due to: withdrawal of consent (3 NT-501, 2 sham), COVID-19 (2 sham), being lost to follow-up (1 sham), physician decision (1 sham), and cardiac issues (1 NT-501, 1 sham).

Most subjects who underwent surgery (92.5%; 211/228) completed the study through at least the Month 24 follow-up visit. A total of 17 subjects (7 NT-501, 10 sham)

discontinued during the treatment period of the Phase 3 studies. Of these, 12 subjects (5 NT-501, 7 sham) who were eligible did not enroll under the protocol amendment (version 7.0) and discontinued. Of the remaining 5 subjects (2 NT-501, 3 sham), 1 subject in the NT-501 group died and 1 subject in the same group discontinued due to an AE related to the study (vitreous hemorrhage considered related to the surgical procedure that resulted in explantation). In the sham group, 1 subject withdrew consent, 1 subject was lost to follow-up, and 1 subject discontinued for other reasons. 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 the study.

Adverse Events (AEs)

For Pool 1, ocular events were listed by "eye" (i.e., as having occurred in the study eye [NT-501 or sham] or the fellow [untreated] eye). Overall, no subject in Pool 1 had a treatment emergent AE prior to Month 24 that led to treatment discontinuation, NT-501 explantation, or study discontinuation.

A secondary end point in the Phase 3 studies was the number and proportion of participants with at least 1 treatment emergent SAE. Through the Month 24 visit in Pool 1, a total of 41 (18%) of participants (including 23 [19.7%] in NT-501 group, and 18 [16.2%] in the sham group) each had at least 1 SAE (ocular, in either eye, and non-ocular combined) regardless of outcome (fatal/nonfatal/led to explantation). After Month 24, one subject (b) (6) in the NT-501 group of study NTMT-03-A, had a SAE of vitreous hemorrhage in the study eye that resulted in the NT-501 device being explanted, and the subject being discontinued from the study (see discussion under "SAE").

Three additional subjects in the NT-501 group had nonfatal non-ocular SAEs with onset after the Month 24 visit. One subject (b) (6) in the NT-501 group of Study NTMT-03-B had both a non-ocular SAE (endometriosis) and an ocular SAE (device extrusion).

1. Ocular AEs

Overall, across the Phase 3 studies through the Month 24 visit, a larger number of study eyes in the NT-501 group than in the Sham group experienced 1 or more ocular treatment emergent AEs (88.9%; 104 eyes versus 66.7%; 74 eyes respectively). There were no treatment emergent AEs of infectious endophthalmitis in either study group in Pool 1.

i) Most Common Ocular AEs

Ocular treatment adverse events occurring in the study eyes at the 3 highest frequencies in each study group in Pool 1 were:

- NT-501: conjunctival hemorrhage (31.6%; 37 eyes), delayed dark adaptation (23.1%; 27 eyes), and eye pain and foreign body sensation in eyes (17.1%; 20 eyes each).

- Sham: conjunctival hemorrhage (27.0%; 30 eyes), foreign body sensation (13.5%; 15 eyes), and eye pain (9.9%; 11 eyes).

Of the AEs listed above, conjunctival hemorrhage and foreign body sensation in eyes occurred at similar frequencies in both the NT-501 and Sham groups, while eye pain occurred more frequently in the NT-501 group versus the Sham group. The sponsor noted that these events are commonly associated with ocular surgery and most occurrences were considered by the investigator to be related to the surgical procedure. These events primarily occurred within 90 days after surgery, were transient, and were mostly mild in intensity; no more than 2 study eyes in either group had onset of these events after 365 days post-surgery.

Ocular treatment emergent AEs occurring at a frequency $\geq 5\%$ higher in the NT-501 group compared with the sham group were as follows:

- delayed dark adaptation (NT-501: 23.1%; 27 eyes; vs Sham: 2.7%; 3 eyes)
- eye pain (NT-501: 17.1% ; 20 eyes, vs Sham: 9.9%; 11 eyes),
- vision blurred (NT-501: 11.1% ; 13 eyes, vs Sham: 5.4% ; 6 eyes)
- eye pruritus (NT-501: 9.4% ; 11 eyes, vs Sham: 3.6% ; 4 eyes),
- ocular discomfort (NT-501: 10.3% ; 12 eyes, vs Sham: 1.8%; 2 eyes)
- suture related complication (NT-501: 15.4%; 18 eyes, vs Sham: 2.7%; 3 eyes).

Adverse events that occurred *only* in implanted eyes (NT-501 group) at a frequency of $\geq 5\%$ were miosis (15.4% ; 18 eyes), vitreous floaters (11.1% ; 13 eyes), and vitreous hemorrhage (8.5%; 10 eyes). Most occurrences of miosis had an onset within 365 days post-implantation, were mild in intensity and none led to the removal of the NT-501 implant. Likewise, most occurrences of vitreous hemorrhage had an onset within 365 days after surgery, but in 3 implanted eyes (2.6%) the onset occurred 365 days after surgery and one of these events was serious and resulted in NT-501 removal on Day 912 post-surgery (see discussion under “SAE”).

Cataract formation (including preferred terms of cataract, cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities) occurred more frequently in the NT-501 group versus the Sham group (10.3%; 12/117 eyes vs 2.7%; 3/111 eyes, respectively). The sponsor stated that the higher rate of cataract formation in the implanted eyes may possibly be due to CNTF but may also be related to surgical trauma or the malposition of the NT-501 device during the placement procedure.

In the fellow eyes in Pool 1, the overall incidence of ocular treatment emergent AEs was similar in the NT-501 and Sham groups (29.9% ; 35 eyes vs 25.2%; 28 eyes, respectively). The ocular treatment emergent AEs occurring in fellow eyes at the 3 highest frequencies were dry eye (NT-501: 5.1 %; 6 eyes, vs Sham: 5.4% ; 6 eyes), visual impairment (NT-501: 2.6% ; 3 eyes, vs Sham: 3.6% ; 4 eyes), and choroidal neovascularization (NT-501: 2.6% ; 3 eyes, vs Sham: 2.7% ; 3 eyes).

ii) Ocular SAEs

A total of 6 study eyes (5.1%) in the NT-501 group and 1 (0.9%) fellow eye in the sham group, had 1 ocular SAE each through the Month 24 visit. In the NT-501 group, the ocular SAEs occurring in study eyes through the Month 24 visit were suture related complication (5 eyes) and device extrusion (1 study eye); 3 events of suture related complication had onset within 365 days of surgery, while the remaining SAEs had late onset, after 365 days post-surgery. The SAE of device extrusion (subject (b) (6)) had onset on Day 701 post-surgery and was considered to be related to both NT-501 and the surgical procedure; NT-501 was surgically repositioned and did not require explantation (See details of this case below under “Reviewer Comment”). All 5 SAEs of suture related complication were considered by the investigator to be related to the surgical procedure and none resulted in NT-501 removal. None of the ocular SAEs occurring in implanted eyes, with onset prior to the Month 24 visit, resulted in NT-501 explantation, and all these events had recovered by the end of the study.

After Month 24, 1 additional study eye (subject (b) (6)) in the NT-501 group had an ocular SAE of vitreous hemorrhage. The SAE was considered by the investigator to be related to the surgical procedure, was moderate in intensity, and resulted in NT-501 being explanted (study day 912) and subsequent discontinuation of the subject from the study (on study day 1101). See details of this case below under “Reviewer Comment”.

In the sham group, the ocular SAE of choroidal neovascularization (subject (b) (6)) occurred in 1 fellow (non-study) eye with onset after 365 days post-surgery; the event was considered to be not related to the surgery, to NT-501, or to CNTF, and was ongoing at the end of the study. See details of this case under Reviewer Comment below. See Table 3 below.

Table 3. SAEs in Pool 1 (Phase 3 Studies NTMT-03-A and NTMT-03-B)

NTMT-03-A		
Subject Number	Study Group	MedDRA Preferred Term or Description of Abnormality
(b) (6)	NT-501	Asthma
	NT-501	Arthritis
	NT-501	Basal cell carcinoma; Acute myocardial infarction; Arrhythmia; Supraventricular Tachycardia
	NT-501	Vitreous hemorrhage (NT-501 explantation)
	NT-501	Lower gastrointestinal hemorrhage; Myocardial ischemia
	NT-501	Chest pain; limb injury
	NT-501	Arthritis
	NT-501	Suture related complication
	NT-501	Pneumonia
	NT-501	Uterine prolapse; cystocele; COVID-19 pneumonia
	NT-501	Lumbar spinal stenosis
	NT-501	Suture related complication
	NT-501	Prostate cancer
	NT-501	Covid-19; Coronary arterial stent insertion

(b) (6)	Sham	Appendicitis
	Sham	Coronary artery disease
	Sham	Osteoarthritis
	Sham	Soft tissue injury
	Sham	Choroidal neovascularization
	Sham	Cardiac failure congestive (fatal)
	Sham	Sepsis
	Sham	Myocardial infarction
	NTMT-03-B	
	NT-501	Endometriosis; Device extrusion
	NT-501	Breast cancer stage II
	NT-501	Transient ischemic attack
	NT-501	Goiter
	NT-501	Transient ischemic attack
	NT-501	Angina pectoris
	NT-501	Suture related complication
	NT-501	Respiratory failure; Chronic obstructive pulmonary disease (fatal)
	NT-501	Osteomyelitis; Cellulitis
	NT-501	Cerebrovascular accident
	NT-501	Suture related complication
	NT-501	Suture related complication
	NTMT-03-B	
Subject Number	Study Group	MedDRA Preferred Term or Description of Abnormality
(b) (6)	Sham	Intervertebral disc protrusion
	Sham	Atrial fibrillation
	Sham	Tendon rupture
	Sham	Cellulitis
	Sham	COVID-19; Osteoarthritis; Chronic obstructive pulmonary disease
	Sham	Palpitations
	Sham	Invasive ductal breast carcinoma
	Sham	Depression; Breast cancer
	Sham	Small intestinal obstruction
	Sham	Colon cancer
	Sham	Colon cancer

Modified from Sponsor Table 18 (5.3.5.1 NTMT-03-A) and Table 17 (5.3.5.1 NTMT-03-B)

Highlighted Subject Numbers = Participants with ocular SAEs.

Bolded Subject Numbers = Participant deaths.

Reviewer Comment: Narrative details for subjects who experienced SAEs of suture related complications, device extrusion, vitreous hemorrhage and choroidal neovascularization are presented below. Overall, this reviewer agrees with the study investigator as to the determined causality for each SAE.

Suture Related Complications:

Subject (b) (6) is a 42-year-old Asian male who developed anterior uveitis on 1 day after the implant procedure. The subject was being followed in clinic for this event, when it was noted, during a follow-up clinic visit, that he had an exposed scleral suture. Eye examination showed the implant was in good position without wound leak or exposure over the suture. Ultrasound of the vitreous cavity was clear without signs

of infection or inflammation around the conjunctiva, wound, sclera, or vitreous. Ultimately, the participant was taken to surgery to repair the scleral wound. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have causal relationship to the surgical procedure but no causal relationship to the study product (CNTF) or study device (NT-501 implant).

Subject (b) (6) is a 72- year-old Caucasian female who, at the 12-month study visit, was noted to have erosion of a suture through the conjunctiva. This suture was noted to be holding the implant device. The participant only complained of mild irritation symptoms. The conjunctiva around the suture was injected but without signs of infection. The participant underwent surgical wound revision and at the post-operative examination showed “excellent” conjunctival apposition with no bare area. At a subsequent post operative follow-up visit the sutures were trimmed x 2 and she was advised to follow up again in 4 weeks for removal of the sutures. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have causal relationship to the surgical procedure but no causal relationship to the study product (CNTF) or device (NT-501).

Subject (b) (6) is a 58-year-old-Caucasian female who received NT-501 in the left eye with no surgical complications. At Day 1 post-op visit the investigator reported non-clinically significant subconjunctival hemorrhage and low intraocular pressure. At the Day 1 visit, the participant reported adverse events of dry eye and slow adaptation in the dark. At the one-month follow-up visit the scleral wound opening was first noted and was monitored at each visit since then. At 6 months it was stable, however the participant continued to have dry eye and slow adaptation in the dark. The participant had surgical intervention to repair the scleral opening to reduce the risk of chronic discomfort or development of endophthalmitis. At Day 1 post-op examination, the investigator reported the procedure site was normal except for a mild subconjunctival hemorrhage. Participant was seen one week later, and it was noted that there was conjunctival injection temporally, the two sutures were intact, and the incision was not easily visible; the event was considered resolved. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have a causal relationship with the study surgical procedure but no causal relationship to the study product (CNTF) or device.

Subject (b) (6) is a 69-year-old Caucasian male who received NT-501 in the left eye with no surgical complications. At Day 1 post-op visit the investigator reported non-clinically significant subconjunctival hemorrhage and an adverse event (AE) of injection. At Day 1 visit, the participant reported AEs of headache, upset stomach, and left eye pain, blurriness, and diplopia. At the one-week post-op visit the participant reported that his diplopia and upset stomach had resolved, but he complained of “ghosting of images” in his left eye. At an unscheduled follow-up visit one month after surgery, the investigator reported an AE of posterior vitreous detachment. At the 6-month visit the investigator reported non-clinically significant extrusion, dry eye, change in dark adaptation, and an AE of “metallic loop exposed through scleral wound”. At an unscheduled follow-up visit approximately 7 months following the

surgical procedure the investigator reported non-clinically significant extrusion of the device. Surgery was successfully done to reposition and re-anchor the implant. One day following this procedure the investigator reported the procedure site was normal except for a mild inferotemporal subconjunctival hemorrhage; the event was considered resolved. The study investigator determined this event to be serious (required surgical intervention to adjust positioning of implant), severe in intensity, and to have causal relationship with the study surgical procedure but no causal relationship to the study product (CNTF) or device.

Subject (b) (6) is a 61-year-old Caucasian female who received NT-501 in the left eye without surgical complications. At the Day 1 post-op visit the investigator reported non-clinically significant subconjunctival hemorrhage. The participant presented with foreign body sensation after 6 months following surgery, she reported chronic surface irritation due to exposed scleral suture. Slit lamp exam showed protruding suture causing irritation. The participant underwent scleral wound repair surgery, and the post-operative period was uneventful. Follow-up exam showed well closed conjunctiva, no scleral suture visible. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have causal relationship with study surgical procedure but no causal relationship to the study product (CNTF) or device.

Device Extrusion:

Subject (b) (6) is a 43-year-old Asian female who received NT-501 in the right eye, and at the Month 24 study visit (Day 701 post-surgery) examination showed extrusion of the metal loop into the scleral wound. The NT-501 was noted to be attached but needed to be repositioned and re-sutured. The participant had reported no adverse side effects from the device. Following repositioning surgery, Day 1 post-op visit was uneventful, and the device was noted to be in a good position. On post-op Day 2, the participant reported blurrier vision, increasing eye pain; she was seen by a local ophthalmologist and endophthalmitis was ruled out. On post-op Day 8, the participant was seen for a follow-up study visit and examination showed clear cornea, quiet anterior chamber, clear lens, and vitreous hemorrhage. NT-501 was noted to be in good position. On post op Day 21 follow-up visit, the participant reported “gritty” feeling at suture site and stinging eye pain. She reported seeing a horizontal line in her vision when looking down. Examination findings were unchanged from previous exam on post-op Day 8. On post-op Day 57 follow-up visit the participant reported less gritty feeling at the suture site and reported feeling a pull in her right eye when looking left. On examination, cornea and lens were clear, anterior chamber was quiet, wound was intact, sutures well buried and NT-501 was in good position. The event was reported as resolved at this study visit. The study investigator determined this event to be serious (medically important), mild in severity, and to have a causal relationship with the study procedure and the device; but not to study product (CNTF). Per the investigator, there was a causal relationship to the device because it was the loop on the device that had extruded into the wound and exposed under the conjunctiva. The Medical Monitor’s Assessment was that this event was serious, expected based on NT-501 Investigator brochure, and related to surgery but not to the

device or the study product (CNTF).

Vitreous Hemorrhage

Subject (b) (6) is a 66-year-old Caucasian female who received NT-501 in the left eye. She completed the 24-month study follow-up on Dec. 7, 2020. The subject reported on March 29, 2021 (study day 846) symptoms of blurred vision (x 2 weeks) and burning sensation in the study eye (x 1 day). She was brought to the study clinic on the same day and examination showed a small vitreous hemorrhage at the site of the implant. The subject was monitored for the next five weeks and there was no improvement in her symptoms. On study day 912, a peritomy was performed to expose inferotemporal synchysis. Poor red reflex was noted. Posterior lens capsule was intact. Soft lens material was very adherent. No posterior vitreous detachment noted. Vitreous was very formed-thick. Blood was stuck to the capsule. Capsulotomy was done during the procedure as blood was encapsulated around the NT-501 and the implant was removed. A new implant was inserted and secured with sutures. Day 1 post-operative visit was unremarkable. The participant was discontinued from the study on day 1101. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have causal relationship to the surgical procedure but no causal relationship to the NT-501 implant or the study product (CNTF).

Choroidal Neovascularization

Subject (b) (6) is a 58-year-old Caucasian male who received NT-501 in the right eye. One month after the implantation surgery, the participant noted a subjective decrease in the vision of his left (non-study) eye and new retinal neovascularization was diagnosed. The study investigator determined this event to be serious (Important Medical Event), moderate in severity, and to have no causal relationship with the study surgical procedure, study product (CNTF) or study device (NT-501).

iii) Deaths:

There were no deaths associated with ocular adverse events.

iv) Ocular AESIs

Most ocular adverse events that occurred in the Phase 3 studies through the Month 24 study visit were mild or moderate in intensity. Severe ocular treatment emergent AEs were reported for 5 study eyes (4.3%) in the NT-501 group, including 2 study eyes with severe blurred vision and 1 study eye each with severe eye pain, ocular discomfort, and suture related complication (which was also serious). All severe ocular events reported through the Month 24 visit had onset within 90 days post-surgery, except for suture related complication, which occurred after 90 days but within 365 days post-surgery. The severe AEs of ocular discomfort, eye pain and suture related complication were considered to be related to the study surgical procedure. The severe events of ocular discomfort, suture related complication, and blurred vision resolved but the event of eye pain was ongoing at the end of the study. No severe ocular inflammatory events occurred in the pivotal studies.

None of the treatment emergent AEs of delayed dark adaptation in NT-501 implanted eyes were severe in intensity, and most were considered by the investigator to be related to CNTF. The onset of delayed dark adaptation in 18/27 implanted eyes occurred within approximately 3 months (range: 1 to 96 days) after implant surgery; the remaining 9 events had onset between 109 and 544 days after surgery. Most events (20/27) were ongoing at the end of the study.

In Pool 1 all clinically significant abnormal findings from the study eye implant/sham site examinations which occurred through the Month 24 visit were reported as adverse events. A larger proportion of the study eyes in the NT-501 group (39.3%; 46 eyes) versus the Sham group (21.6%; 24 eyes) had 1 or more clinically significant abnormal findings during the implant/sham site examination that were reported as ocular treatment emergent AEs; with the 3 highest frequencies of AEs reported in each group being:

- NT-501: delayed dark adaptation (12.0%; 14 eyes), conjunctival hemorrhage (9.4%; 11 eyes), and vitreous hemorrhage (6.0%; 7 eyes)
- Sham: conjunctival hemorrhage (10.8%; 12 eyes), conjunctival edema (3.6%; 4 eyes), choroidal neovascularization and conjunctival hyperemia (2.7%; 3 eyes each)

Of the most common events listed above, conjunctival hemorrhage occurred at a similar frequency in both the NT-501 and Sham groups (9.4% and 10.8%, respectively).

2.Non-Ocular AEs

i) Most Common Non-ocular AEs

In Pool 1 through the Month 24 visit, there were less frequent non-ocular treatment emergent AEs in the NT-501 group versus the sham group (65%; 76 subjects, and 73.0%; 81 subjects, respectively). Most non-ocular treatment emergent AEs occurred in 1 subject each in one or both groups.

The system organ classes in which non-ocular events occurred at the 3 highest frequencies in the NT-501 and sham groups were infections and infestations (22.2%; 26 subjects, and 36.9%; 41 subjects, respectively), nervous system disorders (22.2% ; 26 subjects, and 15.3%; 17 subjects, respectively), and musculoskeletal and connective tissue disorders (17.1%; 20 subjects, and 18.0%; 20 subjects, respectively). Most of the individual non-ocular events occurred in 1 subject each.

The non-ocular treatment emergent AEs occurring at the 3 highest frequencies in the NT-501 and Sham groups in Pool 1 included:

NT-501: headache (9.4%; 11 subjects), arthralgia (8.5%; 10 subjects), and nasopharyngitis (6.0%; 7 subjects).

Sham: headache (8.1%; 9 subjects), influenza, COVID-19, and osteoarthritis (6.3%; 7 subjects), and hypertension (5.4%; 6 subjects).

Only headache was common to both the NT-501 and sham groups and occurred at similar frequencies in both groups (9.4% vs 8.1%, respectively).

The only non-ocular treatment emergent AEs considered by the investigator to be related to the surgery were headache, reported for 8 subjects (6.8%) in the NT-501 group and 1 subject (0.9%) in the sham group, and constipation, reported for 1 subject (0.9%) in the sham group. No subject in either group had a non-ocular event that was considered by the investigator to be related to NT-501 device, or to CNTF.

ii) Non-ocular SAEs

A total of 35 subjects (15.4%) in Pool 1, including 18 subjects (15.4%) in the NT-501 group and 17 subjects (15.3%) in the sham group, had at least 1 non-ocular SAE each through the Month 24 visit. The non-ocular SAEs occurring in more than 1 subject overall were COVID-19 (1 NT-501, 1 sham), cellulitis (1 NT-501, 1 sham), chronic obstructive pulmonary disease (1 NT-501, 1 sham), osteoarthritis (2 sham), and transient ischemic attack (2 NT-501).

Two additional subjects in the NT-501 group had nonfatal SAEs with onset after Month 24 (arthritis and breast cancer stage II reported for 1 subject each). Further, 2 subjects in the NT-501 group who had SAEs prior to Month 24 experienced additional non-ocular SAEs with onset after Month 24 (acute myocardial infarction, arrhythmia, and supraventricular tachycardia all in the same subject and COVID-19 pneumonia in the other subject).

All non-ocular SAEs that occurred in the Phase 3 studies through the Month 24 visit or through the Month 48 visit were considered to be not related to the surgery, to NT-501, or to CNTF, and all had resolved by the end of the study.

iii) Deaths

Overall, in Pool 1, there were two reported deaths, one subject (b) (6) in the sham group from Study NTMT-03-A, died of chronic congestive heart failure; and one subject (b) (6) from the NT-501 group in study NTMT-03-B died from chronic obstructive pulmonary disease (see Reviewer Comment below). For both cases, the respective study investigators did not consider the deaths related to NT-501, to CNTF, or to the surgery.

Reviewer Comment: The following deaths occurred in the two pivotal Phase 3 studies and this reviewer agrees with the study investigators that the deaths are not related to the study surgery, study device (NT-5010 or the study product (CNTF).

In Study NTMT-03-A:

Subject (b) (6) was a 73-year-old Caucasian female who received the sham surgery in the left eye. She had a past medical history of Type 2 diabetes, hypertension, coronary artery disease s/p coronary bypass surgery, valvular disease with mitral regurgitation and tricuspid regurgitation, mechanical aortic valve, atrial fibrillation, stage IV chronic kidney disease (baseline creatinine of 1.9), chronic congestive heart failure, motion sickness and depression. She was on appropriate medications for these conditions. The subject presented with shortness of breath and leg swelling and was hospitalized (study day 430) for management of congestive heart failure exacerbation. She was also evaluated by palliative care. Her clinical status improved, she was advised to follow-up with heart failure clinic as an outpatient, and she was discharged home. The study site became aware of this event one month later at the next scheduled study visit (study day 466), at which time the subject's family requested that the participant be withdrawn from the study. The subject died on (b) (6) (study day 502). The site investigator early terminated the subject from the study on Oct. 27, 2020, and the site was notified of the participant's death on Nov. 4, 2020. The study investigator determined the event to be severe, serious (Death), with no causal relationship with study procedure, study product (CNTF) or device (NT-501).

In Study NTMT-03-B:

Subject (b) (6) was a 68- year- old Caucasian male who received NT-501 in the right eye. He had a past medical history of severe chronic obstructive pulmonary disease (requiring ICU admission and intubation in the past), gout, fibromyalgia, edema, skin infection, constipation, osteoporosis, asthma, back pain, poor muscle control/spasms, congestive heart failure, arthritis, spine fracture, neuropathy, neuromyopathy and restless leg syndrome. He was on appropriate medications for these conditions. The subject was hospitalized for respiratory distress on study day 575. Details of the subject's hospitalization were not provided. He was discharged home after 11 days and later died at home on study day 607. Official cause of death was unknown and medical records were not available to the study site staff. The study investigator determined the event to be severe, serious (death and inpatient hospitalization) and to have no causal relationship with study procedure, study product (CNTF), or device (NT-501).

iv) Non-ocular AESIs

Most non-ocular treatment emergent AEs that occurred in Pool 1 studies through the Month 24 visit, were mild or moderate in intensity. Severe non-ocular treatment emergent AEs occurred at similar frequencies for subjects in both the NT-501 and sham groups (11.1% and 11.7%, respectively). Most severe non-ocular treatment emergent AEs that occurred in Pool 1 were reported for 1(0.9%) subject each in either treatment group. The severe events that occurred in more than 1 subject overall included COVID-19 (1 subject in each group), arthritis (1.7%; 2 NT-501), osteoarthritis (1.8%; 2 sham), migraine (1.7%; 2 NT-501), and chronic obstructive pulmonary disease (1 NT-501; 1 sham). All severe non-ocular treatment emergent AEs in the NT-501 and sham groups were considered by the study investigator to be unrelated to the surgical procedure, NT-501 device, or CNTF.

120- Day Safety Update: Neurotech Safety Report (BLA 125798/0.23, Sequence Number: 0025) Received August 16, 2024.

The sponsor submitted 6 new serious adverse events (SAEs) since the submission of BLA 125798. There were 3 SAEs in subjects enrolled in the Phase 3 pivotal studies, (NTMT-03-A and NTMT-03-B), and 3 SAEs in subjects enrolled in the Phase 2 studies (2 in study NTMT-02 and 1 in NTMT-02). Two of these SAEs were fatal (refer to studies NTMT-02 and NTMT-02B in this memo for further discussion). See Table 4 below.

Table 4. Summary of New Serious Adverse Events Reported for Subjects in Studies Submitted as Part of the BLA for NT-501 in the Treatment of Mac Tel Type2

Study	Subject	Sex	Event	Onset Date	Stop Date	Sponsor Causal ^a	Hosp	Outcome	Action Taken
NTMT-03-A	(b) (6)	M	Suture exposure	2/2/2024	2/22/2024	R	Yes	Resolved	No change
NTMT-02	(b) (6)	F	Death	(b) (6)	(b) (6)	NR	UNK	Fatal	NA
NTMT-02/ NTMT-02B	(b) (6)	F	Abdominal perforation	1/9/2023	1/9/2023	NR	Yes	Fatal	NA
NTMT-02	(b) (6)	F	Recurrent vitreous hemorrhage	UNK	5/18/2023	R	No	Explant	Withdrawn
NTMT-03-A	(b) (6)	F	Recurrent vitreous hemorrhage	UNK	11/9/2020	R	No	Explant	Withdrawn
NTMT-03-B	(b) (6)	M	Vitreous hemorrhage	UNK	7/13/2023	R	No	Explant	Withdrawn

Adapted from Sponsor Table 1 (NT-501 BLA 125798 120-Day Safety Update)

Causal = causality; F = female; Hosp = hospitalization; M = male; NA = not applicable; NR = not related; R = related; Sponsor = (Neurotech); UNK = unknown

The table presents a summary of newly reported, serious adverse events occurring in subjects who participated in one of the studies conducted with NT-501 in the treatment of macular telangiectasia type 2. Regardless of the onset date, Neurotech only became aware of the events within the 120-day period after submission of the BLA.

^a A clinician's assessment of causality was not reported, because there was no ongoing clinical study. Each subject was a former study participant who, at the time of exiting the applicable study, chose to retain the NT-501 implant.

Subject narratives for the 3 SAES that occurred in the Phase 3 studies are as follows:

Subject (b) (6) was a male study participant who received NT-501 in the left eye on (b) (6), during Study NTMT-03-A. He had a suture related complication after exiting the study and opting to retain the NT-501 implant. Specifically, a suture exposure was reported on February 2, 2024. The subject was followed, and a surgical procedure (on (b) (6)) was done to trim the suture; no surgical complications or sequelae reported. Although the clinician did not assess causality, Neurotech considers the event to be related to NT-501 and the surgical procedure.

Subject (b) (6) was a female subject who received NT-501 in the left eye on (b) (6), during Study NTMT-03-A and experienced a vitreous hemorrhage after exiting the study and opting to retain the NT-501 implant. The event resulted in an explant on

(b) (6) (approximately 32 months after implantation). No additional details regarding this case were available. Although the investigator did not assess causality, Neurotech considers the event to be related to NT-501 and the surgical procedure.

Subject (b) (6) was a male subject who received NT-501 in the left eye on (b) (6), during Study NTMT-03-B, and experienced a vitreous hemorrhage after exiting the study and opting to retain the NT-501 implant. The event resulted in an explant on (b) (6) (approximately 48 months after implantation). No additional details regarding this case were available. Although the clinician did not assess causality, Neurotech considers the event to be related to NT-501 and the surgical procedure.

Reviewer comment: This reviewer agrees with Neurotech's assessment regarding the causality of the 3 SAEs described above in the 120-day Safety Update. Suture related complications and (recurrent) vitreous hemorrhage are identified risks in the sponsor's pharmacovigilance plan (see Section 6 Sponsor's Pharmacovigilance Plan in this memo) and are also listed in the label (see discussion in Section 7.1.1. Suture Related Complications, and Section 7.1.3 Delayed Vitreous Hemorrhage, of this memo). Thus, these SAEs do not represent new safety signals or new adverse event safety trends.

The overall safety results in the Phase 3 pivotal studies showed that the most common ocular treatment emergent AEs were those associated with the implant surgery, which requires conjunctival incisions and conjunctival wound closure. These included conjunctival hemorrhage (NT-501 31.6%; Sham 27.0%), foreign body sensation in eyes (NT-501 17.1% vs Sham 13.5%) and eye pain (NT-501 17.1%, vs Sham 9.9%). Except for eye pain (reported more frequently in implanted eyes vs sham group), the common ocular AEs occurred in a similar percentage of study eyes in the NT-501 and Sham groups. These ocular AEs primarily occurred within 90 days after surgery, were transient, and considered mild in intensity.

Cataract formation occurred more frequently in eyes receiving the NT-501 implant compared to eyes that underwent the Sham surgery (10.3% vs 2.7% respectively).

Overall, suture related complication occurred more frequently in the NT-501 group vs the Sham group (15.4% vs 2.7%) and in all cases was related to the study surgery. This AE was the most frequent ocular SAE in the implanted eyes (4.5%; 5/117 eyes) and did not result in NT-501 removal. The sponsor's 120-day Safety Update reported an additional SAE of suture related complication, which increases the incidence of this event to 6/117 (5.1%) implanted eyes.

Vitreous hemorrhage occurred only in the NT-501 group, with 10 eyes (8.5%) experiencing this adverse event. In 3 (2.6%) of these implanted eyes, vitreous hemorrhage occurred 365 days after surgery, and one of these events was considered serious, related to the surgery and resulted in NT-501 removal (30.2 months after implantation). In addition, the sponsor's 120-day Safety Update reported two additional serious adverse events of vitreous hemorrhage that occurred in subjects after exiting the Phase 3 studies, with both events leading to NT-501 removal at 32 and 48 months

after implantation. Thus, vitreous hemorrhage occurred in 12 implanted eyes (10.5%) with 3 (2.6%) of these eyes undergoing removal of the NT-501 device. Overall, in the Phase 3 studies, the rate of NT-501 explantation was low.

The most frequently reported AEs in implanted eyes, considered to be related to CNTF were miosis and delayed dark adaptation (15.4% and 23.1% respectively). Most of these events occurred within 365 days after surgery, were mostly mild in intensity and none led to NT-501 explantation.

All non-ocular SAEs and deaths that occurred in the Phase 3 studies were not considered to be related to the study surgery, study drug (CNTF), or study device (NT-501) and this reviewer agrees with those assessments.

Overall, review of the safety data from the Phase 3 pivotal studies, including the 3 serious adverse events reported in the 120-day Safety Update, did not reveal any new safety signals or adverse event safety trends.

5.2.2 Clinical study NTMT-01

Study Description

The primary objective of this Phase 1 open-label non-randomized multicenter pilot study was to assess safety and tolerability of NT-501 implantation in subjects with Mac Tel. Subjects received a single NT-501 implant (configured to release a nominal dose of CNTF at 20 ng/day) in the eligible study eye; the untreated fellow eye was used as a control. All subjects retained the implant for the duration of the study. A secondary objective was visual assessments at 24,36,48 and 60 months. Seven subjects were enrolled, and 6 participants completed the study.

Subject Disposition

One participant (subject (b) (6)) did not complete the study protocol because four study visits (months 24, 42, 48, and 60) were missed due to multiple serious adverse events (SAEs) during the 60-month study observation period. None of the SAEs were considered related to NT-501.

Adverse Events (AEs)

Overall, 114 AEs were reported in this study and classified by severity as mild (n= 73), moderate (n= 32) and severe (n= 9). 7 (100%) subjects experienced 1 or more AEs during the study. 4 (57.1%) subjects had at least 1 severe AE (total events = 9). No SAE was considered related to the study product (CNTF) or study device (NT-501 implant). There were no AEs that led to study withdrawal, explantation of the NT-501 device, and there were no reported deaths during this 5-year study.

1. Ocular Adverse Events (AEs)

Overall, no participants reported any of the events that were prespecified in the protocol (rejection/extrusion of NT-501 implant; peri-implant fibrosis; or development of CNV in

the study eye.) 4 (57.1%) subjects experienced at least 1 AE that was considered by the investigator to be definitely related to the implant surgical procedure and, separately, 4 (57.1%) subjects experienced at least 1 AE that was considered by the investigator to be definitely related to the investigational treatment (NT-501 implant).

i) Most Common Ocular Adverse Events (AEs)

The most frequently occurring ocular treatment emergent AEs reported in the study are as follows:

Miosis occurred in 5 (71.4%) participants, was mild in severity, and was not resolved at the final study encounter. For 3 (42.9%) of the participants the study investigator considered the AE to be definitely related to the NT-501 CNTF secreting implant. For the other 2 participants the AE was considered by the study investigator to be possibly and probably related to the implant. The sponsor states that miosis was previously reported in other studies of NT-501 CNTF secreting implant for retinitis pigmentosa and dry age-related macular degeneration. It is thought that the miosis is likely related to the release of CNTF from the implant device. In this study, all 5 of the participants were able to tolerate the miosis and had retained the NT-501 implant by the 5th year of follow-up.

Eye pain occurred in 4 (57.1%) participants and was mild in severity in 3 participants (42.9%) and moderate in severity in 1 participant (14.3%).

Conjunctival hemorrhage and conjunctival edema occurred in 3 (42.9%) participants each, the two AEs were mild in severity and considered by the study investigator to be definitely related to the implant surgical procedure. For both participants the two AEs resolved without sequelae.

Photopsia occurred in 3 (42.9%) participants, was moderate in severity in 2/3 participants, considered by the study investigator to be possibly related to both the implant surgical procedure and NT-501 implant, and resolved without sequela for both participants. Photopsia was mild in severity in 1/3 participants, considered by the study investigator to be possibly related to the implant surgical procedure (but unrelated to the NT-501 implant) and was not resolved at the final study encounter.

Conjunctival hyperemia occurred in 2 (28.6%) participants, was mild in severity and resolved without sequela in both subjects. For one of the participants the study investigator considered the AE to be possibly related to the implant surgical procedure. For the second participant the study investigator considered the AE to be remotely related to both the implant surgical procedure and the NT-501 implant.

Delayed dark adaptation occurred in 2 (28.6%) participants. For one participant the AE was mild in severity and considered by the study investigator to be possibly related to the NT-501 implant. For the second participant the AE was moderate in severity and considered by the study investigator to be definitely related to the NT-501 implant. For both participants the AE was not resolved at the final study encounter.

Vitreous floaters occurred in 2 (28.6%) participants. For one participant the AE was mild in severity and considered by the study investigator to be possibly related to both the implant surgical procedure and the NT-501 implant. For the second participant the AE was moderate in severity and considered to be possibly related to the implant surgical procedure but unrelated to the implant. For both participants the AE resolved without sequela.

ii) Ocular Serious AEs (SAEs)

There were no reported ocular SAEs in NTMT-01 study.

iii) Deaths

No deaths were reported during the 5-year study period.

iv) Ocular AEs of Special Interest (AESIs)

One participant (subject (b) (6)) had a severe ocular event of suture related complication (conjunctival exposed suture) without implant extrusion, considered related to the implant surgical procedure, that was not resolved at the final study visit.

2. Non-Ocular AEs

i) Most Common Non-ocular AEs

Most non-ocular AEs were reported for 1 or 2 subjects each. The non-ocular AEs reported for more than 2 subjects during the study were upper respiratory tract infection and hypertension, occurring in 3 subjects (42.9%) each. No participants reported any of the prespecified adverse events in the protocol.

ii) Non-ocular SAEs

During the study, seven non-ocular SAEs occurred between two subjects: chronic lymphocytic leukemia (subject (b) (6)) and multiple orthopedic and cardiac events (subject (b) (6)) including hip fracture, spinal fracture, ankle fracture, coronary artery disease, myocardial infarction, and cardiac valve disease (see narratives below). The study investigator determined that none of these events had any causal relationship to the NT-50 implant.

Reviewer Comment: This reviewer agrees with the investigator's assessment that there is no causal relationship of the SAEs to the study product.

iii) Deaths

No deaths were reported during the 5-year study duration.

iv) AESIs

There were 3 subjects with severe non-ocular AEs. For two of these subjects (b) (6) the events were also considered serious and were previously discussed above. The third subject (b) (6) had worsening of Type 2 diabetes mellitus (condition did not exist prior to enrollment) 1434 days after implantation and was not

resolved at the final study encounter. The study investigator determined the event had no causal relationship to the study product.

***Reviewer Comment:** Overall, the small sample size and open label design of this study is not powered to evaluate treatment efficacy and limits the conclusions that can be made with respect to the overall safety of the NT-501/CNTF secreting implant. However, the reviewer notes that the following study data supports the contention that the NT-501 implant did not result in significant injurious effects after implantation in the eyes of Mac Tel patients enrolled in the study: (1) overall, the majority of AEs in this study were mild or moderate (92%) with a small proportion (8%) classified as severe; (2) the ocular AEs were mostly related to the surgical implant procedure, were classified as mild and mostly resolved without sequela; (3) the AE of miosis, thought to be due to the CNTF released by the implant (a known side effect seen in previous implant studies) was considered mild in severity and although did not resolve by the end of the study, was tolerated by the 5/7 participants as they all retained the implant through the 60 month observation period; (4) all 7 participants with NT-501 implants appeared to tolerate the device as no implants required criteria driven explantation; likewise, no implants were extruded; (5) none of the reported SAEs were considered to be directly related to the NT-501 implant; (6) non-ocular AEs experienced by the study participants were generally consistent with those expected for their age and gender and were not related to the NT-501 implant; and (7) no deaths were reported for any of the study participants during the 5 year study.*

5.2.3 Clinical study NTMT-02

Study Description

This Phase 2 prospective, multicenter, randomized, single-masked, sham-controlled study included safety assessments through 24 months post-surgery. Subjects with 1 eligible study eye were randomized (1:1) to receive either NT-501 or undergo a sham procedure in the study eye; subjects with 2 eligible study eyes were randomized (1:1) to receive either NT-501 or undergo a sham procedure in the study eye, with the fellow eye receiving the alternate treatment. Overall, 67 subjects (99 study eyes: 48 eyes received NT-501 implant and 51 eyes had sham procedure) were evaluated for safety. Thus, study NTMT-02 included the following study groups:

- **NT-501 group:** included 16 subjects who each had 1 study-eligible eye that had NT-501 implanted and a fellow eye that did not undergo any study intervention.
- **Sham group:** included 19 subjects who each had 1 study-eligible eye that underwent sham surgery and a fellow eye that did not undergo any study intervention.
- **NT-501+sham group:** included 32 subjects who had both eyes that were study eligible and had NT-501 implanted in 1 eye and underwent sham surgery in the contralateral eye.

***Reviewer Comment:** The sponsor stated in the protocol that the risk of sham surgery has been minimized; the superficial conjunctival incision was performed under local anesthetic and closed with a single suture. There was no penetration of the globe, which minimized the risk of infection. Reportedly, this approach was used for all controlled studies of NT-501 to date, and there have been no reports of significant AEs in this cohort of more than 250 subjects.*

Subject Disposition

The 67 enrolled subjects (99 study-eligible eyes) were randomized to receive either the NT-501 implant or undergo the sham procedure. Most subjects (65/67) completed the study through the 24-month follow-up. 2 subjects (3 eyes) who underwent randomization were found to be ineligible at baseline due to subretinal neovascularization. The Mac Tel lesion in these eyes were severely disrupted by fluid leak. Two subjects (3 eyes) experienced fatal non-ocular SAEs during the study (see discussion of deaths below under “Non-Ocular AEs”). No other subject discontinued from the study.

Adverse Events

1. Ocular AEs

Overall, in study NTMT-02, there were no ocular adverse events that led to subject discontinuation or explantation of the NT-501 device.

i) Most Common Ocular AEs

In this study, 98/99 study eyes (99.0%) included in the safety population experienced at least 1 ocular treatment emergent AE, including all 48 implanted eyes and 50/51 eyes that underwent the sham surgery. Most ocular AEs (95 eyes; 96.9%) were mild or moderate in severity but ocular events reported for 3 eyes implanted with NT-501 were severe in intensity. These events included eye pain, vitreous floaters, and foreign body sensation in eyes, reported for 1 eye each.

Most ocular AEs were considered to be related to the study surgical procedure (97 eyes; 99.0%); in contrast, most ocular AEs were considered not related to NT-501 (92 eyes; 93.9%) or to CNTF (86 eyes; 87.8%). Of the ocular treatment emergent AEs considered related to the surgical procedure, the events occurring at the 3 highest frequencies in the NT-501 and sham groups were as follows:

- **NT-501:** eye irritation (87.5%; 42 subjects), vision blurred (77.1%; 37 subjects), eye pain (27.1%; 13 subjects)
- **Sham:** eye irritation (84.3%; 43 subjects), vision blurred (64.7%; 33 subjects), eye pain (23.5%; 12 subjects).

Of the ocular treatment emergent AEs that occurred at a frequency $\geq 5\%$ higher in the NT-501 implanted eyes vs the sham eyes, the events occurring at the 3 highest frequencies overall were as follows:

- **NT-501:** vision blurred (81.3% ; 39 eyes), eye pain (31.3% ;15 eyes) and eye swelling (29.2%; 14 eyes).
- **Sham:** vision blurred (66.7% ; 34 eyes), eye pain (25.5% ;13 eyes), and eye swelling (13.7%; 7 eyes).

Only eyes that received the NT-501 implant reported the events of delayed dark adaptation (18.8%; 9 eyes) and miosis (18.8%; 9 eyes).

ii) Ocular SAEs

3 subjects experienced ocular serious adverse events. For two of the subjects (b) (6) the events occurred during the study, for the third subject (b) (6) the event occurred after completion of the study, as reported by the sponsor in their 120-Day Safety Update report (BLA 125798/0.23) submitted to FDA on August 16, 2024.

Blurred vision in both eyes of subjects (b) (6) occurred in the NT-501+sham group. For both subjects, the blurred vision was moderate in intensity, resolved 2 days after onset, and did not result in discontinuation from the study due to the SAE. The investigator considered the event, in both subjects, to be related to the surgical procedure, but unrelated to the study product (CNTF) and study device (NT-501).

Subject (b) (6) was a female participant who received NT-501 in the left eye on May 16, 2014, during Study NTMT-02. She experienced a recurrent vitreous hemorrhage after exiting the study and opting to retain the NT-501 implant. The event occurred on May 18, 2023, and resulted in surgical explant of NT-501. No additional details regarding this case were available. Although the investigator did not assess causality, Neurotech considers the event to be related to NT-501 and the surgical procedure.

iii) Deaths:

No ocular death events reported.

iv) Ocular AESIs

The most commonly reported clinically significant ocular AEs of interest included a change in dark adaptation per the subject's perception, and miosis, both of which were reported only in the NT-501 group (10 eyes; 20.8% and 4 eyes; 8.3%, respectively).

"Other" events which occurred in the NT-501 group and sham group (6 eyes; 12.5%; and 3 eyes; 5.9% respectively) included:

NT-501 group: low luminance vision, chemosis and injection, exposed suture, mild fibrinous reaction, focal hyperemia, itch/allergic conjunctivitis, and small conjunctival cyst.

Sham group: subretinal fluid on OCT, focal hyperemia, itch/allergic conjunctivitis

2. Non-Ocular AEs

Overall, 58 of 67 subjects (86.6%) in the safety population (13 NT-501, 17 sham, and 28 NT-501+sham) had at least 1 non-ocular AE. Most subjects (48; 82.8%) had non-ocular AEs that were mild or moderate in severity and unrelated to the surgical procedure (50 subjects; 86.2%). All the non-ocular AEs were considered unrelated to both NT-501 and CNTF.

7 (12.1%) subjects (1 NT-501, 3 sham, and 3 NT-501+sham) had 10 severe AEs consisting of diverticulitis (NT-501 group); cellulitis, cystitis, meniscus surgery, and suicide attempt (sham group); atrial fibrillation, congestive cardiomyopathy, pneumonia, post laminectomy syndrome, and inguinal hernia (NT-501+sham group). Some of these AEs were also considered serious adverse events (see discussion below under “SAEs”).

i) Most Common Non-Ocular AEs

Across groups, the non-ocular AEs by preferred term (PT) reported at the 3 highest frequencies were as follows: viral upper respiratory tract infection and headache (reported by 8 subjects; 11.9% each), sinusitis and back pain (reported by 6 subjects; 9.0% each), and dizziness, anxiety, and cough (reported by 5 subjects; 7.5% each).

ii) Non-Ocular SAEs

Overall, 11/67 (16.4%) subjects (2 each in the NT-501 and sham groups and 7 in the NT-501+sham group) had a total of 14 non-ocular SAEs. The SAEs of aortic aneurysm (in NT-501 group) and cardiac arrest (in NT-501+sham group) were fatal (see discussion below under “Deaths”). No other subject discontinued the study due to the SAEs. The non-ocular SAE of anxiety (NT-501+sham group) was considered by the investigator to be related to the surgical procedure; none of the other non-ocular SAEs were considered related to the study surgery, study drug (CNTF), or study device (NT-501).

iii) Deaths

Two subjects had fatal non-ocular SAEs during the study. One subject (b) (6) in the NT-501 group and the second subject (b) (6) in the NT-501+sham group. The third subject (b) (6) in NT-501 group, had a fatal SAE of unknown cause that was reported by the sponsor in their 120-Day Safety Update report (BLA 125798/0.23) submitted to FDA on August 16, 2024. See narratives for these death events below.

Subject (b) (6) was a 67-year-old Caucasian male found unresponsive (on study day 460) at home by his wife. He was pronounced dead by emergency medical services. Subsequently, an autopsy determined the cause of death to be a dissected aortic aneurysm. The study investigator determined the event to be serious (Death), severe in severity, and to have no causal relationship to the study surgical procedure, study product (CNTF), or study device (NT-501).

Subject (b) (6) was a 66-year-old Caucasian female who had a fatal cardiac arrest on study day 740. The study site was unable to obtain any additional information regarding the event. The study investigator determined the event to be serious (Death), severe in intensity, and to have no causal relationship with study surgical procedure, study product (CNTF) or study device (NT-501).

Subject (b) (6) was a female participant who died due to unknown causes on (b) (6), which was after the subject exited the study and opted to retain the NT-501 implant. The study center reported the event based on an obituary notice and was unable to obtain any further information. Although the clinician did not assess causality, Neurotech considers the event to be not related to NT-501, CNTF, or the surgical procedure

Reviewer Comment: This reviewer agrees with the study investigator assessments that the deaths for subjects (b) (6) which occurred during the study, are not attributable to the study surgical procedure, study product (CNTF) or study device (NT-501 implant). For the subject (b) (6) death that occurred due to unknown cause(s) after the participant's exit from NTMT-02, although it is possible there is no causality to the study surgery, study product (CNTF), or study device (NT-501 implant), it cannot be stated with certitude without additional information pertaining to the subject's cause of death.

iv) Non-Ocular AESIs

None of the non-ocular AEs were considered related to NT-501 or to CNTF. Eight participants (13.8%) overall (2 NT-501, 1 sham, and 5 NT-501+sham) had 1 or more non-ocular events considered by the investigator to be possibly caused by the surgical procedure. These treatment emergent AEs were headache (2 NT-501), rhinorrhea (1 sham, 1 NT-501+sham), abdominal pain (1 NT-501), vomiting (1 NT-501), dizziness (2 NT-501+sham), anxiety (1 NT-501+sham), and orthostatic hypotension (1 NT-501+sham).

5.2.4 Clinical study NTMT-01/02E (and NTMT-01/02E-SS)

Study Description

NTMT-01/02E was a Phase 1/2 prospective, multicenter, single-masked, sham controlled extension study designed to provide long-term efficacy and safety follow-up data for subjects with Mac Tel who received either the NT-501 intraocular implant in Study NTMT-01 (Cohort 1) and/or underwent the sham procedure in Study NTMT-02 (Cohort 2).

The extension study consisted of 4 visits that were scheduled from the date of surgery performed during the parent study as follows:

Cohort 1: study visits conducted at Months 72, 84, 96, and 108 after the date of the NT-501 implant surgery in the parent study (NTMT-01)

Cohort 2: study visits conducted at Months 36, 48, 60, and 72 after the date of the NT-501 implant and/or sham surgery in the parent study (NTMT-02).

NTMT-01/02E-SS was a safety sub-study of the extension study for subjects enrolled in parent study NTMT-02, who had 1 study eligible eye that underwent the sham procedure and were offered the option to have NT-501 implanted in the same study eye. Of the 19 subjects who underwent the sham procedure in the Cohort 2 parent study (NTMT-02), 16 subjects elected to undergo surgery for NT-501 implantation in the same study eye during the sub-study. The implant surgery was performed after the first (annual) visit in the NTMT-01/02E study (i.e., Month 36 after the date of the sham surgery in the parent study). Subsequent follow-up visits and assessments post-surgery in the sub-study were conducted at 12-month intervals after NT-501 implantation through Month 72 of the main extension study in conformity with the NTMT-01/02E study schedule. Therefore, sub-study participants had an approximate 48-month follow-up period after NT-501 implantation.

Subject Disposition

Cohort 1

All 7 subjects enrolled in the Cohort 1 parent study (NTMT-01) had NT-501 implanted in 1 study eye, with no intervention in the fellow eye. Of these 7 subjects, 6 (85.7%) consented to participate in the extension study (Cohort 1), for a total of 6 study eyes and 6 fellow eyes evaluated for safety. All subjects in Cohort 1 completed the extension study. A non-serious ocular treatment emergent AE (suture related complication) that occurred in 1 eye implanted with NT-501 (subject (b) (6)) led to explantation of the device *after* the subject completed the final study visit. Therefore, because explantation coincided with study completion, this subject was considered as having retained NT-501 throughout the study (see subject narrative under Cohort 1 Ocular AESI).

Cohort 2

In the Cohort 2 parent study (NTMT-02), 67 subjects were enrolled and randomized to have NT-501 implanted and/or undergo the sham procedure. Of these 67 subjects, 64 (95.5%) consented to participate in the extension study (Cohort 2), which included the following study groups:

- **NT-501 group:** 15 subjects who each had NT-501 implanted in 1 study-eligible eye (15 study eyes) and no study intervention in the contralateral eye (15 fellow eyes)
- **Sham group:** 19 subjects who each underwent sham surgery in 1 study-eligible eye (19 study eyes) and no study intervention in the contralateral eye (19 fellow eyes)
- **NT-501+sham group:** 30 subjects with both eyes that were study-eligible, who had NT-501 implanted in 1 eye and underwent sham surgery in the contralateral eye

Thus, Cohort 2 included 128 eyes overall: 94 study eyes (45 eyes implanted with NT-501 and 49 eyes that underwent sham surgery) and 34 fellow eyes (no study intervention).

Most subjects (58/64 subjects; 90.6%) in Cohort 2 completed the extension study. A total of 6 subjects in Cohort 2 (1 in the sham group, 2 in the NT-501 group, and 3 in the NT-501+sham group) discontinued: 2 subjects (1 each in the NT-501 and NT-501+sham groups) died; 2 subjects (1 each in the sham and NT-501+sham groups) discontinued due to COVID-19; 1 subject in the sham group discontinued for other reasons; and 1 subject in the NT-501 group had an AE related to the study (event of device expulsion/extrusion was considered related to the surgical procedure) and resulted in NT-501 explantation.

As noted previously, 16 (84.2%) of 19 subjects in the sham group in Cohort 2 elected to undergo surgery for NT-501 implantation in the same study eye during the extension study.

Safety Data

Analysis Sets

The sponsor defined the following data analysis sets:

- 1) Intent to Treat (ITT) Population: included all subjects enrolled in the extension study and had at least 1 study eye that either had NT-501 implanted or underwent sham surgery. Subjects/study eyes were analyzed according to the procedure that they underwent (i.e., NT-501 or sham) in the respective parent study.
- 2) Per Protocol (PP) Population: Included all subjects in the ITT population who did not have any major protocol deviations (in either the parent or extension study) that may have had an impact on efficacy assessments. In the final analysis, the PP population also excluded subjects who received any additional active treatment (i.e., NT-501) during the extension sub-study in order to provide a better understanding of the long-term efficacy of NT-501 by eliminating the impact of the treatment switch.

Adverse Events

Cohort 1

1.Ocular AEs

i) Most Common Ocular AEs

Ocular treatment emergent AEs were reported for 4 (66.7%) eyes implanted with NT-501 and 3 (50.0%) fellow eyes. All ocular treatment emergent AEs for NT-501 and fellow eye groups were mild (33.3% ; 2/6 subjects, vs 16.7% ; 1/6 subjects, respectively), or moderate (33.3%; 2/6 subjects; vs 33.3% ; 2/6 subjects, respectively) in intensity. No ocular treatment emergent AEs were severe in intensity. There were no serious AEs reported, and no ocular AEs led to subject discontinuation from the study.

The individual ocular treatment emergent AEs that occurred in both 1 study eye and 1 fellow eye included dry eye, irritation, conjunctivitis allergic, and periorbital dermatitis. The remaining events occurred only in the eyes implanted with NT-501, and included

cataract cortical, dacryostenosis acquired, eye allergy, injection site hemorrhage, suture related complication, and device extrusion.

Only 1 ocular treatment emergent AE (suture related complication) that occurred in 1 eye implanted with NT-501 (subject (b) (6)), was considered by the investigator to be related to the surgical procedure. The event led to explantation of the NT-501 device after the subject completed the study (see subject narrative below under AESIs).

ii) Ocular SAEs

No subject in Cohort 1 experienced an ocular SAE during the extension study.

iii) Deaths

No deaths reported in Cohort 1 during the extension study.

2. Cohort 1

Non-Ocular AEs

i) Most Common Non-Ocular AEs

Five of the six subjects (83.3%) in Cohort 1 had at least 1 non-ocular treatment emergent AE during the study. None of the reported non-ocular treatment emergent AEs led to NT-501 explantation. Two subjects had a total of 3 non-ocular SAEs (see discussion below in “SAEs” section). Two subjects had non-ocular treatment emergent AEs that were severe; the remaining subjects had non-ocular events that were mild or moderate in severity. None of the non-ocular treatment emergent AEs (serious or nonserious) were considered by the investigator to be related to the study surgical procedure, study drug product (CNTF) or study device (NT-501 implant).

5 subjects in Cohort 1 had 1 or more non-ocular treatment emergent AEs. Two subjects experienced multiple non-ocular events. The non-ocular treatment emergent AEs of duodenal ulcer, duodenal ulcer perforation, incarcerated hernia, procedural nausea, procedural pain, seroma, wound dehiscence, gout, pain in extremity, malignant melanoma, pulmonary mass, pruritus, and hypotension all occurred in the same subject (b) (6). Likewise, the events of influenza, sinusitis, contusion, computerized tomogram abnormal, and neuropathy peripheral all occurred in another subject. The remaining events of vascular pseudoaneurysm, nerve compression, and hyperkalemia occurred in 1 subject each.

ii) Non-Ocular SAEs

Two subjects (33.3%) in Cohort 1 experienced a total of 3 non-ocular SAEs during the study. The events, which were considered severe in intensity, included duodenal ulcer perforation and incarcerated hernia, both occurring in one subject (b) (6) and vascular pseudoaneurysm, reported for the second subject (b) (6). None of these non-ocular SAEs were considered by the investigator to be related to the surgical procedure, the study product (CNTF) or study device (NT-501).

Reviewer comment: This reviewer agrees with the investigator assessments regarding causality of the SAEs described above not being attributed to the study surgery, study product (CNTF), or study device (NT-501).

iii) Deaths

No deaths reported in Cohort 1.

Cohort 2

1. Ocular AEs

i) Most Common Ocular AEs

Excluding subjects who received an implant in the sub-study, ocular treatment emergent AEs in the Cohort 2 ITT population were reported more frequently in eyes implanted with the NT-501 device (66.7%; 30/45 eyes) than in eyes that had sham surgery (48.5%; 6/33 eyes) or in the fellow eyes (33.3%; 6/18 eyes). Of the individual ocular treatment emergent AEs occurring in 2 or more study eyes, the events that were common to the NT-501 and sham groups and reported at similar frequencies in both groups, included cataract (13.3% and 15.2%, respectively) and retinal hemorrhage (8.9% and 6.1%, respectively).

Most ocular treatment emergent AEs were mild or moderate in intensity for the NT-501 and sham study eyes. Severe ocular treatment emergent AEs were reported for 3 eyes (6.7%) implanted with NT-501. The AEs consisted of vitreoretinal traction syndrome (associated with epiretinal membrane), hyalosis asteroid (considered likely related to the natural history of Mac Tel), and scar excision (related to chemosis and exposed suture), which occurred in 1 eye each. None of the severe ocular events were serious, none were considered by the investigator to be related to the study surgery, study product (CNTF) or study device (NT-50), and all 3 events resolved by the end of the study.

Only eyes implanted with NT-501 had ocular events related to surgery (3/45 ; 6.7%) and NT-501 (5/45 ; 11.1%). There were no surgery related ocular AEs that occurred in more than 1 eye implanted with NT-501 with the exception of vitreous hemorrhage, which was reported for 2 eyes with the NT-501 implant. Both events of vitreous hemorrhage occurred in subjects in the sham+NT-501 group (participants (b) (6) with onset > 1200 days after surgery in the parent study. The event occurring in 1 eye was moderate in intensity and resolved approximately 1 year after onset, while the other event was mild in intensity and had not resolved at the end of the study. The vitreous hemorrhage reported for both subjects was a clinically significant finding at the implant site examination. Subject narratives are provided for both events in the AESI section of this review below.

Treatment emergent AEs considered related to CNTF were reported for 5 eyes (4/45; 8.9% in NT-501 group and 1/33; 3.0% in sham group). Miosis was the only CNTF related ocular AE that occurred in more than 1 eye (3 eyes implanted with NT-501). The events of miosis all had an onset > 1100 days after surgery in the parent study and were mild (2 eyes) or moderate (1 eye) in intensity; 1 event resolved by the end of the study, while the remaining 2 events were ongoing at the end of the study. The remaining ocular treatment emergent AEs for 43 eyes (27 NT-501 and 16 sham) were

not considered to be related to the study surgery, study drug (CNTF), or study device (Nt-501).

Two nonfatal ocular SAEs, noninfectious endophthalmitis (subject (b) (6) and device expulsion (subject (b) (6) were reported for two participants implanted with NT-501. See subject narratives under “Ocular SAEs” section below.

All fellow eyes with ocular treatment emergent AEs had events that were nonserious, mild or moderate in severity, and considered by the study investigator to be unrelated to the study surgery, study drug (CNTF), or study device (NT-501). The only ocular treatment emergent AE that occurred in more than 1 fellow eye was cataract (3 eyes ; 8.8%).

ii) Ocular SAEs

In Cohort 2, a total of 2 eyes implanted with NT-501 experienced 1 ocular SAE each during the extension study; the events were noninfectious endophthalmitis (subject (b) (6) and device extrusion (subject (b) (6)

iii) Deaths

No deaths reported due to ocular adverse events.

iv) Ocular AESIs

The most commonly reported clinically significant AEs of special interest were miosis (occurred in 4 eyes implanted with NT-501), change in dark adaptation per the subject's perception (occurred in 3 eyes implanted with NT-501 and 1 eye in sham surgery group), and intraocular hemorrhage (occurred in 3 eyes implanted with NT-501, and choroidal neovascularization (CNV) (occurred in 2 eyes implanted with NT-501 and 1 eye in sham surgery group) and dry eye (occurred in 2 eyes implanted with NT 501).

The 3 events of intraocular hemorrhage were vitreous hemorrhages observed > 1200 days after surgery in the parent study and occurred adjacent to NT-501 in 2 eyes

In eyes that underwent sham surgery in the parent study, no clinically significant AEs of interest occurred in more than 1 eye during the extension study. In addition, none of the prespecified ocular AEs of interest were observed in the fellow eyes during the extension study.

2. Intraocular Hemorrhage in Sub-Study Subjects

Although the sponsor excluded subjects in the sub-study (n= 16 subjects/eyes) from their analysis, 3 participants experienced adverse events of special interest related to intraocular hemorrhage. Two of these events were considered mild and resolved, but for the third event, the AESI narrative did not include causality or outcome for the intraocular hemorrhage because the site study team did not enter an adverse event form for the event.

Cohort 2

2. Non-Ocular AEs

None of the reported non-ocular treatment emergent AEs led to NT-501 explantation, and none of the AEs (serious or nonserious) were considered by the investigator to be related to the study surgery, study product (CNTF), or study device (NT-501).

i) Most Common Non-Ocular AEs

Overall, 45/64 (70.3%) subjects in the ITT population of Cohort 2 had at least 1 non-ocular treatment emergent AE during the study, including 10 (66.7%) subjects in the NT-501 group, 15 subjects (78.9%) in the sham group, and 20 (66.7%) subjects in the sham+NT-501 group. Most non-ocular treatment emergent AEs occurred in 1 subject each in any group (NT-501, sham, or sham+NT-501) in Cohort 2 and were mild or moderate in severity. The 3 most frequently reported individual non-ocular events were:

- Hypertension
 - Overall: 6/64 subjects; 9.4%
 - Sham+ NT-501: 3/30 subjects; 10.0%
 - NT-501: 2/15 subjects; 13.3%
 - Sham: 1/19 subjects; 5.3%
- Urinary tract infection
 - Overall: 5/64 subjects; 7.8%
 - Sham+NT-501: 2/30 subjects; 6.7%
 - NT-501: 1/15 subjects; 6.7%
 - Sham: 2/19 subjects; 10.5%
- Diabetes mellitus
 - Overall: 4/64 subjects; 6.3%
 - Sham+NT-501: 1/30 subjects; 3.3%
 - NT-501: 1/15 subjects; 6.7%
 - Sham: 2/19 subjects; 10.5%

Overall, 10 (15.6%) subjects, including 2 (13.3%) in NT-501 group and 4 each in sham (21.1%) and sham+NT-501 groups (13.3%), had non-ocular treatment emergent AEs that were severe. In the NT-501 group, the severe non-ocular AEs were tendon rupture (1 subject) and pain and cerebral infarction (1 subject). In the sham group, the severe non-ocular AEs were arthralgia (2 subjects), and syncope, prostate cancer, and vertigo (1 subject each). In the sham+NT-501 group, the severe non-ocular AEs were constipation, Prinzmetal angina, asthma, and femur fracture (1 subject each). None of the severe non-ocular events that occurred in Cohort 2 were considered related to the study surgical procedure, study drug (CNTF) or study device (NT-501).

ii) Non-Ocular SAEs

Overall, 12 subjects (18.8%), including 2 (13.3%) in NT-501 group, 3 (15.8%) in sham group, and 7 (23.3%) in the sham+NT-501 group, had at least 1 nonfatal, non-ocular,

SAE each. During the study, 2 fatal non-ocular SAEs occurred in 2 subjects (1 each in NT-501 and sham+NT-501 groups). See subject narratives below under “Deaths”. All non-ocular SAEs were considered by the investigator to be unrelated to the study surgery, study product (CNTF) or study device (NT-501). See **Table 5** below.

Table 5. Study NTMT-01/02 E: Non-ocular Serious Adverse Events in Cohort 2 (ITT Population -by Subject)

Subject # (age/sex)	MedDRA PT n (%)	Severity of AE (date onset)	Outcome (date resolution)	Sham (N=19)	NT- 501 (N=15)	Sham+NT- 501 (N= 30)	Overall ^a (N=64)
(b) (6) (67/F)	Malignant peritoneal neoplasm	Severe (9/12/2018)	Fatal (study day 2133)	0	0	1 (3.3)	1 (1.6)
(b) (6) (84/M)	Metastatic neoplasm	Severe (11/25/2019)	Fatal (b) (6)	0	1 (6.7)	0	1 (1.6)
	Epigastric pain	Severe (3/19/2019)	Resolved (3/21/2019)	0	1 (6.7)	0	1 (1.6)
(b) (6) (74/M)	Prostate cancer	Severe (2/15/2018)	Ongoing	1 (5.3)	0	0	1 (1.6)
(b) (6) (61/F)	Prinzmetal Angina	Severe (11/25/2020)	Stress test & cardiac catheterization (Nov 2020)	0	0	1 (3.3)	1 (1.6)
(b) (6) (77/M)	Supraventricular tachycardia	Moderate (5/18/2018)	Resolved (5/25/2018)	0	0	1 (3.3)	1 (1.6)
(b) (6) (63/F)	Diverticulitis	Moderate (6/10/2019)	Resolved (6/12/2019)	0	1 (6.7)	0	1 (1.6)
(b) (6) (64/F)	Sinusitis	Moderate (5/24/2018)	Resolved (6/1/2018)	0	0	1 (3.3)	1 (1.6)
(b) (6) (80/M)	Constipation	Severe (5/20/2020)	Resolved (6/1/2020)	0	0	1 (3.3)	1 (1.6)
(b) (6) (57/M)	Fractures of right radius, tibia, femur. R pneumothorax (s/p fall)	Severe (6/4/2019)	Hospital d/c (b) (6) Resolved (as of Month 72 study visit on (b) (6)	0	0	1 (3.3)	1 (1.6)
(b) (6) (67/F)	Hyponatremia	Moderate (7/31/2018)	No information	1 (5.3)	0		1 (1.6)
(b) (6) (66/M)	Syncope (d/t medication)	Severe (1/15/2018)	Resolved (1/17/2018)	1 (5.3)	0		1 (1.6)
(b) (6) (63/F)	Asthma/Bronchitis	Severe (4/3/2020)	Resolved (4/10/2020)	0	0	1 (3.3)	1 (1.6)

Adapted from sponsor Table 32 (Clinical Study Report for NTMT-01/02E and NTMT-01/02E-SS)

ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; PT= preferred term

All events were coded using MedDRA, version 25.0.

a The overall group includes all of the study groups in Cohort 2.

The table includes all non-ocular SAEs reported for subjects in Cohort 2. Subjects with more than 1 event within a given system organ class or preferred term were counted once within that system organ class or preferred term

iii) Deaths

Two subjects had fatal non-ocular SAEs during the study. See subject narratives below.

Subject (b) (6) was an 84 -year-old male who was previously enrolled in the NTMT-02 parent study and received the study implant in the left eye. After enrollment in NTMT-01/02E he presented to the hospital with back pain in Nov. 2019 (study day 1869). CT scan showed a mass in the lumbar spine area, mass in right kidney and nodules in both lungs. Subject was sent home on hospice care with oncology follow-up. On 2/20/2020, the subject's spouse informed the site that the participant died on (b) (6) (study day 1906). No further details available at the time of the report. The study investigator determined the event to be serious (Death), severe in severity, and to have no causal relationship with study surgical procedure, study product (CNTF) or study device (NT-501).

Subject (b) (6) was a 67-year-old Caucasian female who was previously enrolled in the NTMT-02 parent study and received the study implant in the left eye and sham procedure in the right eye. After enrollment in NTMT 01/02E, she informed the site staff of her diagnosis of peritoneal cancer in Sept. 2018 (study day 1450). She reported that a genetic blood test done several years ago to assess the likelihood of developing cancer indicated she was at high risk (this information was not disclosed at study screening). She was scheduled to begin chemotherapy with plans for possible surgery in the future. Subject died on study day 2133. The study investigator determined the event to be serious (Important Medical Event), severe in severity, and to have no causal relationship to the study surgical procedure, study product (CNTF), or study device (NT-501).

The sponsor states that after database lock some clinically significant abnormal findings in the study eye on implant/sham examination, that were prespecified AEs of interest, did not have associated AE forms completed during the study. The sponsor summarized these events in **Table 6** below.

In Cohort 1: A participant in the NT-501 group had a finding of CNV that occurred in the study eye and was not reported as an adverse event.

In Cohort 2 (excluding sub-study subjects): 10 participants (4 in NT-501 group; 6 in sham+NT-501 group) had 14 clinically abnormal findings in the study eye that were not reported as AEs.

Table 6. Study NTMT-01/02E: Summary of Subjects with Clinically Significant Findings in the Study Eye Not Reported as Adverse Events (ITT Population Excluding Sub-study Subjects)

Subject ID	Treatment Group	CS Significant Finding on Implant/Sham Exam	Assessment Time Point
<i>Cohort 1</i>			
(b) (6)	NT-501	CNV	Month 108 (Day 3331)

Cohort 2			
(b) (6)	NT-501	Change in dark adaptation	Month 36 (Day 1088)
		Miosis	
	NT-501	Change in dark adaptation	Unscheduled visit (Day 895)
		Vitreous inflammation	Unscheduled visit (Day 2016)
		Intraocular hemorrhage	Unscheduled visit (Day 2019)
	NT-501	Change in dark adaptation	Month 60 (Day 1823)
	NT-501	Persistent chemosis	Month 36 (Day 1179)
	Sham (OD) + NT-501 (OS)	Sectoral lens opacification (OD)	Month 48 (Day 1469)
	Sham (OS) + NT-501 (OD)	Change in dark adaptation (OD)	Month 48 (Day 1462)
	Sham (OS) + NT-501 (OD)	Miosis (OD)	Month 48 (Day 1456)
	Sham (OS) + NT-501 (OD)	Miosis (OD)	Month 36 (Day 1113)
	Sham (OD) + NT-501 (OS)	Sectoral lens opacification (OS)	Month 48 (Day 1501)
	Sham (OS) + NT-501 (OD)	Change in dark adaptation (OD)	Months 36 through 72 (Day 1117 onwards)
		Miosis (OD)	

CNV = choroidal neovascularization; CS = clinically significant; ID = identification; ITT = intent-to-treat; OD = right eye; OS = left eye

Verbatim terms from the eCRFs for the implant/sham site examination are presented.

Source: Data on file; Listing 16.2.9.1; Listing 16.2.7.1

***Reviewer Comment:** Most of the clinically significant findings listed in the table above have not been typically regarded as serious adverse events throughout the Mac Tel studies (and the sponsor states the events did not meet SAE criteria); therefore these 15 events are not likely to affect the overall safety profile of the study device (NT-501).*

5.2.5 Clinical study NTMT-02B

Study Description

The primary objective of this Phase 2 multicenter open-label, bilateral implantation study was to assess the incidence and severity of AEs following bilateral ocular implantation of NT-501 in subjects with Mac Tel who received NT-501 in a single eye prior to or in the Phase 1/2 extension study (NTMT-01/02E) or in one of the Phase 3 studies (NTMT-03A or NTMT-03B). Subjects in NTMT-02B received a second NT-501 in the eye not previously implanted. Safety assessments were done through 6 months after the second implantation surgery.

Subject Disposition

A total of 35 subjects were screened and 33 subjects were enrolled in the study. Of the 33 enrolled subjects, 32 (97.0%) received NT-501; the exception was a subject whose surgery was canceled due to an event of arterial fibrillation that occurred prior to surgery and resulted in subject discontinuation. All 32 subjects who received NT-501 completed the study and were included in the safety population.

Adverse Events

Overall, 26/32 subjects (81.3%) who received NT-501 in this study had at least 1 treatment emergent AE each, including 26 subjects (81.3%) with at least 1 ocular event in the study eye, 6 subjects (18.8%) with at least 1 ocular event in the fellow eye, and 13 subjects (40.6%) with at least 1 non-ocular event. All reported events were considered mild or moderate in intensity. The 6 moderate AEs consisted of: ocular discomfort (2 subjects), and cataract subcapsular, hyalosis asteroid, punctate keratitis, feces discolored, and intervertebral disc disorder (1 subject each).

No subject discontinued the study due to a treatment emergent AE (serious or nonserious). Two subjects had 1 SAE each: an ocular event (device extrusion) and a non-ocular event (feces discolored). No subject required removal of the NT-501 implant from either eye.

1. Ocular AEs

i) Most Common Ocular AEs

- In the study eye (eye that received NT-501 implant in NTMT-02-B)

Most individual ocular treatment emergent AEs in the study eye were reported for 1 subject each. The following ocular AEs were reported in the study eye for multiple subjects: eye pain and ocular discomfort (9 subjects; 28.1% each), conjunctival hemorrhage (8 subjects; 25.0%), eye irritation (4 subjects, 12.5%) and dry eye (2 subjects; 6.3%).

- In the fellow eye (eye that received NT-501 in an earlier study (i.e., prior to or in Study NTMT-01/02E, Study NTMT-03-A, or Study NTMT-03-B).

7 subjects had a least 1 ocular treatment emergent adverse event each in the fellow eye. None of the individual ocular events in the fellow eye occurred in more than 1 subject each, and included allergic conjunctivitis (1 eye; 3.1%); corneal pigmentation (1 eye; 3.1%); delayed dark adaptation (1 eye; 3.1%); hyalosis asteroid (1 eye; 3.1%); iris transillumination defect (1 eye; 3.1%); photophobia (1 eye; 3.1%); punctate keratitis (1 eye; 3.1%); infections and infestations (1 eye; 3.1%); and periorbital cellulitis (1 eye; 3.1%).

ii) Ocular SAEs

One subject (b) (6) had a SAE of device extrusion. There was a slight extrusion of the loop of the implant in the study (right) eye noted at the Month 3, specifically, sutures used to close the sclera were intact but loose. Approximately 15 days after the extrusion was observed, the subject underwent a surgical revision procedure for the study eye implant, during which a Tutoplast graft was placed. There were no surgical complications, and the event of device extrusion was resolved. The study investigator

considered the event to be mild in intensity and related to the study surgical procedure, but not the study drug (CNTF) nor study device (NT-501).

iii) Deaths

No deaths reported in this study.

iv) Ocular AESIs

All subjects who had ocular treatment emergent AEs had at least 1 event considered by the study investigator to be related to the study surgery or study drug and most individual events occurred in 1 subject each. Most AEs were considered to be related to the surgical procedure except for the events of delayed dark adaptation (occurred in both eyes) and iritis (occurring in the study eye) which were considered related to NT-501. These 2 events occurred in separate subjects, were mild in intensity and nonserious. The AE of iritis resolved while the AE of delayed dark adaptation was ongoing at the end of the study.

2. Non-Ocular AEs

i) Most common Non-Ocular AEs

With the exception of nasopharyngitis (6.3%; 2/32 subjects) and urinary tract infection (6.3%; 2/32 subjects each), the individual non-ocular treatment emergent AEs occurred in 1 subject each. None of the non-ocular treatment emergent AEs were severe in intensity nor were they considered related to the study surgery, study drug (CNTF) or study device (NT-501).

ii) Non-Ocular SAEs

One subject (b) (6) experienced a non-life-threatening SAE of “feces discolored” (black stool) which was associated with an intercurrent illness that resulted in hospitalization and resolved. The study investigator considered the event to be moderate in intensity and not associated with the study surgical procedure, study drug (CNTF), or study device (NT-501).

iii) Deaths

No participant deaths occurred during the study, but in the sponsor’s 120-Day Safety Update (BLA 125798/0.23) submitted to the FDA on August 16, 2024, a participant death was reported that occurred after completion of the study. See subject narrative below.

Subject (b) (6) was a female participant who received NT-501 in the left eye on (b) (6), during Study NTMT-02, and in the right eye on (b) (6), during Study NTMT-02B. She died due to a perforation (coded term) that occurred after the subject exited the study and opted to retain the NT-501 implant. This subject had a history of gastric ulcers and a previous bariatric surgery. On (b) (6), the subject underwent emergency surgery to repair an abdominal perforation (verbatim term) and subsequently died. Although the clinician did not assess causality, Neurotech considers the event to be not related to NT-501, CNTF, or the surgical procedure.

Reviewer comment: This reviewer agrees with the Sponsor's assessment that the cause of death was unrelated to the study surgical procedure, study product (CNTF) or study device (NT-501).

iv) Non-Ocular AESIs

No subject had a non-ocular event that was considered by the investigator to be related to the study surgery or study drug (CNTF).

Reviewer comment: During the 6-month observation period of this bilateral ocular implant study, all reported adverse events were mild or moderate in intensity with only 2 serious adverse events occurring; one ocular event of device extrusion (considered related to the study surgical procedure) and one non-ocular event of discolored stool (unrelated to the study treatment). No subject was discontinued from the study due to any of the adverse events. There were no deaths in this study. Based upon adverse event data reported here, NT-501 appeared to be well tolerated when implanted in both eyes of the study subjects.

5.2.6 Integrated Population

Description of pooled studies

For the integrated safety analysis the sponsor created three integrated populations: Pool 1 (safety results of the two combined Phase 3 studies), Pool 2 (safety results from all 6 Mac Tel studies submitted to BLA 125798/0 in support of licensure for NT-501) and Pool 3 (safety results of 13 studies conducted across various retinal indications, including the 6 Mac Tel studies and 7 earlier studies that evaluated NT-501 in various other retinal degeneration indications other than Mac Tel).

1) POOL 1 (NTMT-03-A, NTMT-03-B)

Presented under Section 5.2.1 Pivotal Studies NTMT-03-A and NTMT-03-B (Pool1).

2) POOL 2 (included all Mac Tel studies: NTMT-01, NTMT-02, NTMT-01/02E, NTMT-02B, NTMT-03-A, NTMT-03-B)

Subject Disposition in Pool 2 (6 Mac Tel Studies)

Overall, the safety population (participants who received surgery) consisted of 334 subjects enrolled across the 6 Mac Tel studies (Pool 2), that had NT-501 implanted and/or underwent the sham procedure, including 188 (56.3%) subjects in the NT-501 group, 130 (38.9%) subjects in the Sham group, and 32 subjects (9.58%) in the NT-501+sham group. Overall, the Pool 2 studies included 684 eyes, including 382 study eyes (220 NT-501, 162 sham) and 302 fellow eyes (no study intervention). All 334 subjects and 684 eyes were evaluated for safety. Most subjects in the safety population completed the respective study through the final study visit (307/334; 91.9%) and 185/188 subjects (98.4%) who received NT-501 retained the implant for the duration of

the respective study (6 months in study NTMT-02B, to 108 months for Cohort 1 subjects in study NTMT-01/02E).

Overall, in Pool 2, 27 subjects (8.1%) discontinued study participation, including 12 subjects (6.4%) in NT-501, 11 subjects (8.5%) in sham, and 5 subjects (15.6%) in NT-501+sham). Of these, 12 subjects (3.6%) [5 NT-501, 7 sham] who were eligible did not enroll under the protocol amendment (version 7.0 of studies NTMT-03-A and NTMT-03-B). 5 subjects (1.5%) died* (3 NT-501, 2 NT-501+sham), 4 subjects (1.2%) [1 NT-501, 1 sham, 2 NT-501+sham] had other reasons for discontinuation, 2 subjects (0.6%) [both NT-501] had AEs that led to discontinuation, 2 subjects (0.6%), 1 sham [sub study subject], 1 NT-501+sham) discontinued due to COVID-19, 1 sham subject (0.3%) was lost to follow-up and 1 sham subject (0.3%) withdrew consent due to an SAE that led to the subject's death after discontinuation from the study (subject (b) (6) was previously discussed in this memo).

Reviewer comment: In the Pool 2 studies there were 8 deaths due to non-ocular SAEs (see **Table 7 under Non-Ocular Deaths below) . The 3 additional deaths include 1 participant (b) (6) in the Sham group of NTMT-03A who withdrew consent from the study prior to her death and two participants(subjects (b) (6) in NTMT-02 and NTMT-02B respectively, who died after completion of their respective studies.*

Adverse Events (AEs)

1. Ocular AEs

i) Most Common Ocular AEs

Across the Mac Tel studies, one or more ocular treatment emergent AEs occurred with greater frequency in the NT-501 group than in the Sham group (89.5%; 197/220 eyes vs 77.8%; 126/162 eyes, respectively). Notably, across all 6 Mac Tel studies, there were no treatment emergent AEs of infectious endophthalmitis in either study group.

The types and frequencies of ocular treatment emergent AEs reported in Pool 2 were consistent with those observed for Pool 1. The individual events occurring at the 3 highest frequencies in each group in Pool 2 were:

- **NT-501:** conjunctival hemorrhage (27.7% ; 61 eyes), vision blurred (24.5% ; 54 eyes), and eye irritation (24.1% ; 53 eyes)
- **Sham:** conjunctival hemorrhage (29.0% ; 47 eyes), eye irritation (28.4% ; 46 eyes), and vision blurred (25.3% ; 41 eyes)

Most occurrences of these events were considered by the investigator to be related to the surgical procedure.

Similar to Pool 1, ocular treatment emergent AEs that occurred at a frequency $\geq 5\%$ higher in the NT-501 group vs the Sham group in Pool 2 included: eye pain (22.3%;

49 eyes, vs 13.6%; 22 eyes, respectively), delayed dark adaptation (19.1%; 42 eyes, vs 3.1%; 5 eyes, respectively), ocular discomfort (10.5%; 23 eyes, vs 3.1%; 5 eyes, respectively), vitreous floaters (10.9%; 24 eyes, vs 1.2%; 2 eyes, respectively), and suture related complication (10.9%; 24 eyes, vs 2.5%; 4 eyes, respectively).

Miosis (16.4%; 36 eyes) and vitreous hemorrhage (8.6%; 19 eyes) occurred only in implanted eyes. For miosis, there was a notable increase in the occurrence of this AE for implanted eyes between the early post-surgery period (5 eyes; 2.3%) and between 90-365 days post-surgery (15 additional implanted eyes), which continued to be high after 365 days post-surgery (16 eyes; 7.3%). A similar percentage of implanted eyes had vitreous hemorrhage with onset within 90 days post-surgery (4.5% ;10 eyes) and after 365 days post-surgery (4.1%; 9 eyes). One of these events was considered serious and resulted in NT-501 removal. (See discussion below in SAEs section).

As in Pool 1, the occurrence of treatment emergent AEs in study eyes of participants in Pool 2 was highest for the period within 365 days post-surgery (NT-501: 79.1%;174 eyes and Sham: 72.8%; 118 eyes), with most events occurring within 90 days post-surgery (NT-501: 75.5%; 166 eyes, and Sham: 69.1%; 112 eyes). A lower percentage of study eyes in both groups had ocular AEs with onset after 365 days post-surgery (NT-501: 41.8%; 92 eyes, and Sham: 31.5%; 51 eyes). The AEs in both study groups with the highest frequencies occurring over 365 days post-surgery were cataract (NT-501: 4.1%; 9 eyes, Sham: 3.7%; 6 eyes), retinal hemorrhage (NT-501: 2.3%; 5 eyes, Sham:1.9%; 3 eyes), epiretinal membrane (NT-501: 2.3%; 5 eyes, Sham: 1.2%;2 eyes), and vitreoretinal traction syndrome (NT-501: 2.7%; 6 eyes, Sham: 0 eyes).

In Pool 2, most of the ocular treatment emergent AEs occurring in the study eyes of participants in both the NT-501 and sham groups were considered by the investigator to be related to the surgical procedure (77.7% ; 171/220 eyes, and 67.9%; 110/162 eyes, respectively). The surgery related ocular treatment emergent AEs in the study eye occurring at the 3 highest frequencies in each group were as follows:

- **NT-501:** conjunctival hemorrhage (26.8%; 59 eyes), eye irritation (23.6%; 52 eyes), and eye pain (20.9% ; 46 eyes)

- **Sham:** conjunctival hemorrhage (28.4% ; 46 eyes), eye irritation (27.8% ; 45 eyes), and vision blurred (22.8% ; 37 eyes)

In the NT-501 group in Pool 2, a comparatively smaller percentage of study eyes had events that were considered NT-501 related (17.7% ; 39 eyes) or CNTF related (25.5%; 56 eyes). The most frequently occurring events related to NT-501 or CNTF were delayed dark adaptation and miosis. The investigator attributed delayed dark adaptation to NT-501 in 10 implanted eyes (4.5%) and to CNTF in 33 implanted eyes (15.0%); similarly, the investigator attributed miosis to NT-501 in 7 implanted eyes (3.2%) and to CNTF in 28 implanted eyes (12.7%).

In the sham group in Pool 2, only 3 study eyes (1.9%) had treatment emergent AEs that were considered to be related to CNTF: choroidal neovascularization and visual field defect, occurring in 1 study eye each (0.6%); and delayed dark adaptation, in 1 study eye (0.6%), considered by the investigator to be related to both CNT and NT-501. This subject (b) (6) was a participant in the sham group of study NTMT-03-B (see reviewer comment below).

***Reviewer comment:** Subject (b) (6) was a 65-year-old Caucasian male enrolled in study NTMT-03-B who had the sham procedure performed in the right eye. He reportedly experienced delayed dark adaptation in the right eye and the investigator determined the event to be non-serious, mild in severity, and to have a causal relationship with the study device or CNTF, **although the participant did not receive the NT-501 implant.** The event was not resolved at the final study visit.*

Overall, in Pool 2, ocular treatment emergent AEs in the fellow eyes (regardless of whether the contralateral eye received NT-501 or underwent sham surgery) occurred at an incidence of 32.5% (98/302 eyes), which, compared to the study eyes, was lower. The ocular treatment emergent AEs occurring in the fellow eyes at the 3 highest frequencies were: dry eye (5.3%; 16 eyes), visual impairment (3.6%, 11 eyes), and choroidal neovascularization (3.3%; 10 eyes). The sponsor noted that although designated as fellow eyes in the source study, 32 eyes in Study NTMT-02B were eyes that received NT-501 in an earlier study. Of these 32 eyes, only 6 had at least 1 ocular treatment emergent adverse event each.

ii) Ocular SAEs

Across the Mac Tel studies, 13 study eyes (5.9%) in the NT-501 group and 2 study eyes (1.2%) in the sham group, had 1 ocular SAE each. Ocular SAEs that occurred in more than 1 study eye included:

- Suture related complication: NT-501: 5 eyes; 2.3%
- Device extrusion: NT-501: 2 eyes; 0.9%
- Vision blurred: NT-501: 2 eyes; 0.9%; Sham: 2 eyes; 1.2%

Consistent with Pool 1, suture related complication was the most frequent ocular SAE in the implanted eyes in Pool 2, which in all cases, were considered related to the study surgery.

The remaining AEs all occurred in 1 study eye (0.5%) each in the NT-501 group and included: visual impairment, noninfectious endophthalmitis, vitreous hemorrhage, and device expulsion. All 4 SAEs of vision blurred, 1 event of suture related complication, and 1 event of device extrusion had onset within 90 days of surgery; 2 additional SAEs of suture related complication had onset within 365 days of surgery; and the remaining ocular SAEs had onset after 365 days post-surgery. Device expulsion was considered to be related to both NT-501 and surgery, noninfectious endophthalmitis was

considered to be related to NT-501, and all other ocular SAEs were considered by the investigator to be related to the surgical procedure.

In Pool 2, a total of 3 subjects in the NT-501 group had ocular treatment emergent AEs in the study eye that led to NT-501 explantation. In two of the subjects, vitreous hemorrhage, which occurred after Month 24 (subject (b) (6), in NTMT-03A), and device expulsion (subject (b) (6), in NTMT-01/02E) were both serious and also led to both subjects' discontinuation from their respective studies. For the third subject (b) (6); Cohort 1 of NTMT-01/02E), NT-501 was explanted due to a non-serious ocular treatment emergent AE of suture related complication. Since explantation coincided with study completion, this subject was considered to have retained NT-501 for the duration of the study. The SAE of device extrusion (subject (b) (6) in NTMT-03B) required NT-501 to be surgically repositioned (no explantation). All ocular SAEs in implanted eyes recovered by the end of the study, except for visual impairment, which was ongoing at the end of the study.

Ocular SAEs were also reported in 2 fellow eyes and included visual impairment and choroidal neovascularization (1 eye each); both events had onset after 365 days post-surgery and both events were ongoing at the end of the study.

Reviewer comment: The subject narratives for the cases of explantation were discussed earlier in this memo under the subjects' respective studies.

iii) Deaths: There were no reported deaths due to ocular related adverse events.

iv) Ocular Adverse events of special interest (AESIs)

Most ocular treatment emergent AEs occurring in Pool 2 were mild or moderate in intensity; but severe ocular AEs were reported for 14 study eyes (6.4%) in the NT-501 group, of which the only events occurring in more than 1 implanted eye were eye pain (3 eyes), vision blurred (2 eyes), and suture related complication (2 eyes). No severe ocular inflammatory events occurred across the Mac Tel studies.

2. Non-Ocular AEs

No subject in any group had a non-ocular event that was considered by the investigator to be related to NT-501 or to CNTF.

i) Most Common Non-Ocular AEs

Overall, in Pool 2, a smaller proportion of subjects in the NT-501 group had non-ocular treatment emergent AE than subjects in the sham and NT-501+ sham groups (63.8%; 120/188 subjects, 77.7%; 101/130 subjects, and 93.8%; 30/32 subjects, respectively). Non-ocular treatment emergent AEs occurring in more than 2 subjects in any study group in Pool 2 are shown in sponsor Table 16 in the Appendix of this memo.

In Pool 2, the system organ classes in which non-ocular events occurred at the 3 highest frequencies in the NT-501 and sham groups were infections and infestations

(27.7%; 52 subjects, and 41.5%; 54 subjects, respectively), musculoskeletal and connective tissue disorders (19.1%; 36 subjects, and 21.5%; 28 subjects, respectively), and nervous system disorders (20.2%; 38 subjects, and 16.2%; 21 subjects, respectively). Most of the individual non-ocular events occurred in 1 subject each. See sponsor Table 16 in Appendix.

The non-ocular treatment emergent AEs occurring at the 3 highest frequencies in each group were:

- **NT-501:** headache and nasopharyngitis (8.0% ; 15 subjects each), hypertension (7.4% 14 subjects), and arthralgia (5.9% ; 11 subjects).
- **Sham:** headache (8.5% ; 11 subjects], hypertension and osteoarthritis (7.7% ;10 subjects each) and COVID-19 and influenza (6.9% ; 9 subjects each).
- **NT-501+sham:** basal cell carcinoma (15.6% ; 5 subjects), constipation, nasopharyngitis, back pain, headache, dizziness, and hypertension (12.5% ; 4 subjects each), and gastroesophageal reflux disease, hypersensitivity, sinusitis, urinary tract infection, meniscus injury, anxiety, and sleep apnea syndrome (9.4% ; 3 subjects each).

Of the most frequently reported non-ocular treatment emergent AEs, headache and hypertension were common to all 3 study groups and occurred at similar frequencies: NT-501 (8.0% and 7.4%, respectively), Sham (8.5% and 7.7%, respectively), and NT-501+sham groups (12.5% for both events).

A total of 18 subjects (5.4%), including 10 in the NT-501 group, 3 in the sham group, and 5 in the NT-501+sham group, had non-ocular events considered related to the surgery. The only surgery related events occurring in more than 1 subject in any treatment group were headache (10 NT-501, 1 sham, 2 NT-501+sham) and dizziness (2 NT-501+sham). No subject in any group had a non-ocular event considered by the study investigator to be related to NT-501 or to CNTF.

ii) Non-Ocular SAEs

In Pool 2, non-ocular SAEs occurred in a similar percentage of subjects in the NT-501 and sham groups (15.4%; 29/188 subjects, and 15.4%; 20/130 subjects, respectively), and at an incidence of 37.5% (12/32 subjects) in the NT-501+sham group. Most non-ocular SAEs occurred in 1 subject each. 3 subjects (1 NT-501, 1 sham, 1 NT-501+sham) had the non-ocular SAE of pneumonia. Non-ocular SAEs that occurred in 2 subjects included: arthritis (2 NT-501); atrial fibrillation (1 sham, 1 NT-501+sham); asthma (1 NT-501, 1 NT-501+sham), cellulitis (1 NT-501, 1 sham); coronary artery disease (1 NT-501; 1 sham); chronic obstructive pulmonary disease (1 NT-501, 1 sham), Covid-19 (1 NT-501, 1 sham); myocardial infarction (1 NT-501, 1 sham), osteoarthritis (2 sham), prostate cancer (1 NT-501, 1 sham), and transient ischemic attack (2 NT-501).

An SAE of anxiety reported for 1 subject in the NT-501+sham group was considered by the investigator to be related to the surgery; all other non-ocular SAEs that occurred across the Mac Tel studies were considered to be not related to the surgery, to NT-501, or to CNTF, and most nonfatal non-ocular SAEs had resolved by the end of the study.

iii) Non-Ocular Deaths

In Pool 2, a total of 8 subjects (5 NT-501, 1 sham, 2 NT-501+sham) died due to non-ocular SAEs. 2 of these deaths, reported by the sponsor in a 120-Day Safety Update (BLA 125798/0.23) occurred after the subjects completed their respective studies.

In the Pool 1 studies (NTMT-03-A and NTMT-03B) two deaths occurred, 1 each in the sham and NT-501 group due to cardiac failure congestive (subject (b) (6)) and chronic obstructive pulmonary disease (subject (b) (6)) respectively. In Cohort 2 of study NTMT-01/02E, two deaths occurred, 1 each in the NT-501 and NT-501+sham groups, due to metastatic neoplasm (subject (b) (6)) and malignant peritoneal neoplasm (subject (b) (6)) respectively. In study NTMT-02, three deaths occurred, 2 each in NT-501 and 1 in NT 501+sham, due to aortic aneurysm (subject (b) (6)), unknown death, which occurred after study completion (subject (b) (6)) and cardiac arrest (subject (b) (6)) respectively. In study NTMT-02B 1 death occurred due to abdominal perforation, which occurred after study completion (subject (b) (6)). None of these deaths were considered by the study investigator or sponsor to be related to the surgical procedure, study product (CNTF) or the study device (NT-501 implant). See **Table 7** below (subject narratives previously provided under “Non-Ocular Deaths”, within each subjects’ respective study).

Table 7. Listing of Deaths in the NT-501 Mac Tel Clinical Program

Study	Subject #	Study Group	MedDRA Preferred Term	SAE Onset Day ^a	Day of Fatal Outcome ^a	Related ^b ?
NTMT-03A	(b) (6)	Sham	Cardiac failure congestive	430	502	No
NTMT-03B		NT-501	Chronic obstructive pulmonary disease	575	607	No
NTMT-01/02E		NT-501	Metastatic neoplasm	1869	1906	No
		NT501+sham	Malignant peritoneal neoplasm	1450	2133	No
NTMT-02		NT-501	Aortic aneurysm	460	460	No
		NT501+sham	Cardiac arrest	740	740	No
		NT-501	Death (unknown cause)	Unknown (b) (6)	Unknown (b) (6)	No
NTMT-02B		NT-501	Abdominal perforation	Unknown (b) (6)	Unknown (b) (6)	No

MacTel = macular telangiectasia type 2; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

a Relative to the date of surgery; for the extension study, day is relative to the date of surgery in the respective parent study.

b Whether or not the event was considered by the investigator to be related to NT-501, CNTF, or surgical procedure

Source: NTMT-01/02E CSR, Table 14.3.2.3; NTMT-02 CSR, Listing 16.2.10; NTMT-03-B CSR, Listing 16.2.7.1; NTMT-03-A CSR, listing 16.2.7.1

iv) Non-Ocular AESIs

Severe non-ocular treatment emergent AEs were reported for a similar percentage of subjects in the NT-501 and sham groups (13.3%; 25/188 subjects, and 13.8%; 18/130 subjects, respectively), and at an incidence of 31.3% (10/32 subjects) in the NT-501+sham group. Most severe non-ocular treatment emergent AEs were reported for 1 subject each in a treatment group, with no more than 2 subjects in any group experiencing a given event. The only severe non-ocular event occurring in more than 2 subjects across groups was arthralgia (2 NT-501, 1 sham). No subject in any group had a non-ocular event that was considered by the investigator to be related to NT-501 or to CNTF. A total of 18 subjects (5.4%), including 10 in the NT-501 group, 3 in the sham group, and 5 in the NT-501+sham group, had non-ocular events considered related to the surgery. The only surgery related events occurring in more than 1 subject in any treatment group were headache (10 NT-501, 1 sham, 2 NT-501+sham) and dizziness (2 NT-501+sham).

Reviewer comment: The safety results for the Pool 2 studies were consistent with those observed for the Pool 1 studies. In the NT-501 group, suture related complication was the most frequently reported adverse event considered related to surgery, while miosis and delayed dark adaptation were the most frequently reported adverse events considered related to CNTF. As in Pool 1, the most frequent ocular SAE in the implanted eyes in Pool 2 was suture related complication (6 eyes), which was considered related to surgery and did not result in NT-501 explantation. Across the Mac Tel studies in Pool 2, explantation of NT-501 occurred in a total of 6 eyes (3 eyes during the studies and 3 eyes after completion of the studies). The rate of explantation was low (2.7%; 6/220 NT-501 eyes) with the earliest removal occurring 18.6 months after implantation. The incidence of death across the Pool 2 studies was low (8/334 subjects; 2.4%) with 2 of the deaths occurring in participants who completed their respective studies. 7 of the deaths were unrelated to the study surgery, study product (CNTF) or study device (NT-501). The remaining death was due to unknown cause(s) and therefore, although not likely related to the study surgery, NT-501 or CNTF, this cannot be stated with certitude. Overall, this reviewer did not observe any unexpected safety signals or adverse safety trends within the safety data presented in the Pool 2 studies.

3) Pool 3 (13 clinical studies in all indications)

Study Description

In response to regulatory agency request to provide AE data for all subjects who have been exposed to NT-501 during any clinical studies of NT-501 (August 31, 2023 Pre-BLA FDA Meeting Minutes) the sponsor provided safety data for 7 clinical studies (see **Table 8** in Appendix of this memo) where NT-501 was also evaluated in various other retinal degenerative conditions (including retinitis pigmentosa [RP], geographic atrophy (GA) associated with age-related macular degeneration (AMD) and achromatopsia) other than Mac Tel:

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

These earlier studies, conducted between 2003 to 2016, were discontinued due to lack of efficacy, however all treatment emergent AEs and serious AEs (SAEs) for the 7 clinical studies were combined with the 6 BLA studies in Mac Tel for a total of 13 studies that were designated Pool 3. Sponsor states that data presentations for this pool are limited to disposition, demographics, AE and VA data only. Collectively, across the 13 studies, NT-501 was implanted intraocularly in 438 eyes of subjects with various retinal degenerative conditions.

Safety Data

For Pool 3, ocular and non-ocular treatment emergent adverse events for the post-surgical follow-up period of each contributing study were presented by the sponsor. Ocular events were reported as having occurred in the study eye (NT-501 or sham) or the fellow eye. Non-ocular events were presented by treatment group (NT-501 Low Output, NT-501 High Output, Sham, NT-501 Low Output+Sham, and NT-501 High Output+Sham).

Demographic Characteristics of Pool 3

Across the 13 studies comprising Pool 3, the mean age of the subjects in the safety population was 55.8 years (range=17-88 years) with 70.0% of the subjects less than 65 years old. There was a larger proportion of females than males (60.3% vs 39.7% respectively) and the majority of subjects were Caucasian (87.8%) and not Hispanic or Latino (92.7%).

Reviewer comment: Pool 3 demographic characteristics appear similar to those for Pool 1 and Pool 2, except for the wider age range of participants in the Pool 3 studies (17-88 years) vs the Pool 1 and Pool 2 studies (40-78years and 40-79 years respectively) but the mean participant age for Pool 3 (55.8 years) was similar to that of Pool 1 and Pool 2 (59.6 years and 60.2 years, respectively).

Subject Disposition

Overall, in Pool 3, 564 subjects were enrolled across the 13 studies and had NT-501 implanted and/or underwent the sham procedure in the following groups: NT-501 Low Output (17 subjects), NT-501 High Output (234 subjects), Sham (142 subjects), NT-501 Low Output+Sham (48 subjects), and NT-501 High Output+Sham (139 subjects).

The 564 subjects in Pool 3 included 1,144 eyes with 767 study eyes (438 NT-501, 329 sham) and 377 fellow eyes (no study intervention). All 564 subjects and 1,144 eyes were evaluated for safety. Most subjects in Pool 3 who underwent surgery (93.1%; 525/564 subjects) completed the respective study through the final study visit. In Pool 3, a total of 39 subjects (6.9%) discontinued study participation.

1. Ocular AEs

i) Most common Ocular AEs

In Pool 3, the NT-501 and Sham group experienced a similar frequency of ocular treatment emergent AEs (90.2 %; 395/438 eyes and 86.3%; 284/329 eyes, respectively). In addition, there were no differences in the overall incidence of ocular treatment emergent AEs in eyes implanted with low output or high output NT-501 (92.3%; 60/65 eyes, and 89.8% ; 335/ 373 eyes, respectively). Therefore, the sponsor's summary of ocular AE data focused on the sham group and the NT-501 overall group (i.e., includes all events reported for implanted eyes, regardless of CNTF output level).

Ocular treatment emergent AEs occurring at the 3 highest frequencies in each group were:

- **NT-501:** conjunctival hemorrhage (45.0%; 197 eyes), conjunctival hyperemia and eye pain (19.2%; 84 eyes), and eye irritation (18.3%; 80 eyes)
- **Sham:** conjunctival hemorrhage (46.8%; 154 eyes), eye irritation (18.2%; 60 eyes), and conjunctival hyperemia (17.6%; 58 eyes)

At least 1 ocular treatment emergent AE considered by the study investigator to be related to the study surgery, CNTF or NT-501 occurred in 290/438 implanted eyes (66.2%) and 144/329 eyes (43.8%) in the sham group.

Across treatment groups, the 3 most commonly reported related ocular treatment emergent AEs, occurring in a similar percentage of study eyes in each group, were:

- **NT-501:**conjunctival hemorrhage (14.6%; 64 eyes), eye irritation (14.2%; 62 eyes), and vision blurred (12.3%; 54 eyes)
- **Sham:** conjunctival hemorrhage (14.3%; 47 eyes), eye irritation (15.5%; 51 eyes), and vision blurred (11.6%; 38 eyes)

In the NT-501 group, ocular treatment emergent AEs related to CNTF and occurring in \geq 10% of implanted eyes, and at a frequency at least 2 times higher than that in the sham group, were miosis (12.6%) and delayed dark adaptation (10.5%). Suture related

complication, ascribed to the study surgical procedure, occurred in 8.4% of implanted eyes.

Ocular treatment emergent AEs occurred less frequently (30.5%; 115/377 eyes) in the fellow eyes (regardless of whether the contralateral eye received NT-501 or had sham surgery) than in the study eyes. The 3 highest frequencies of ocular treatment emergent AEs occurring in Pool 3 fellow eyes were dry eye (4.8%; 18 eyes), visual impairment (3.4%; 13 eyes), and choroidal neovascularization (2.9%; 11 eyes). This was consistent with what was observed in Pool 2 fellow eyes.

ii) Ocular SAEs

In Pool 3, 5 more SAEs (3 NT-501, 2 sham) than what occurred in Pool 2 were reported, for a total of 18 study eyes (4.1%) in the NT-501 group (regardless of CNTF output level) and 5 study eyes (1.5%) in the sham group. The ocular SAEs occurring in more than 1 study eye were similar to those reported for Pool 2 and included suture related complication (5 NT-501), device extrusion (2 NT-501), and vision blurred (2 NT-501, 2 sham). Additionally, an SAE of cataract operation was reported for 2 eyes in Pool 3 (1 NT-501, 1 sham).

iii) Deaths

There were no deaths related to ocular treatment emergent adverse events.

iv) Ocular AESIs

In Pool 3, a total of 15/1144 eyes (1.3%) had at least 1 treatment emergent AE leading to explantation of NT-501. This included 3 implanted eyes from the Mac Tel studies and 12 study eyes from the clinical studies in other retinal degeneration indications. In the latter, the only treatment emergent AEs leading to explantation that occurred in more than 1 implanted eye were miosis (3 eyes) and eye disorder (2 eyes).

Reviewer comment: In the sponsor's 120-Day Safety Update (BLA 125798/0.23) 3 additional participants, who completed their Mac Tel studies (NTMT-03-A, NTMT-03-B, and NTMT -02) developed vitreous hemorrhage which resulted in explantation of NT-501. Therefore, a total of 18/1144 eyes (1.6%) experienced explantation of NT-501.

2. Non-Ocular AEs

i) Most common Non-Ocular AEs

In the NT-501 Low Output group (n = 17), the only non-ocular treatment emergent AE occurring in more than 1 subject was nasopharyngitis (3; 17.6% of subjects). Non-ocular events occurring at the 3 highest frequencies in each of the remaining groups are listed below:

- **NT-501 High Output** (n = 234): nasopharyngitis and headache (8.1%; 19 subjects each), hypertension (6.8%; 16 subjects), and arthralgia (4.7%; 11 subjects)

- **Sham** (n = 142): hypertension and headache (8.5%; 12 subjects each), osteoarthritis and influenza (7.0%; 10 subjects each), and COVID-19 and sinusitis (6.3%; 9 subjects each)

- **NT-501 Low Output+Sham** (n = 48): nasopharyngitis (20.8%; 10 subjects), headache (12.5%; 6 subjects), and bronchitis (6.3%; 3 subjects)

- **NT-501 High Output+Sham** (n = 139): nasopharyngitis (12.2%; 17 subjects), headache (10.1% ; 14 subjects), and sinusitis (5.8%; 8 subjects)

At least 1 non-ocular treatment emergent AE considered by the study investigator to be study related (to study surgery, CNTF, or NT-501) occurred in 5.9% (26/438) of participants in the NT-501 “overall group” (i.e., all groups combined), compared to 2.1% (3/142) of participants in the sham group. The only related non-ocular treatment emergent AEs reported for more than 1 subject occurred in the NT-501 group and included headache (16 subjects; 3.7%), and dizziness and depression (2 subjects; 0.5% each).

ii) Non-Ocular SAEs

Overall, 14.7% (83/564) of participants reported non-ocular SAEs in Pool 3, which occurred in 1 subject each. Non-ocular SAEs that occurred in more than 2 subjects included atrial fibrillation (1 NT-501 Low Output, 1 sham, 1 NT-501 High Output+Sham); pneumonia (2 NT-501 High Output, 1 sham, 1 NT-501 High Output+Sham); cellulitis (2 NT-501 High Output, 1 sham); and chronic obstructive pulmonary disease (2 NT-501 High Output, 1 sham).

iii) Deaths

In the 13 studies that comprise Pool 3, there were no deaths across the 7 studies in other retinal degeneration indications, but as previously discussed, there were 8 deaths due to non-ocular SAEs in NT-501 participants in the 6 Mac Tel studies (see Non-Ocular Death section under Pool 2 discussion in this memo). None of the deaths were considered by the study investigators to be related to the study surgical procedure, study product (CNTF) or study device (NT-501 implant).

Reviewer comment: In the sponsor’s 120-Day Safety Update (BLA 125798/0.23) 2 participants, who completed their studies (NTM -02 and NTMT-02B), died. Thus, there was a total of 8 deaths for the 6 Mac Tel clinical studies. These additional 2 deaths were discussed in this memo under “Non-Ocular Deaths” in the participants’ respective studies.

Overall, the types and frequencies of ocular treatment emergent AEs reported in Pool 3 were consistent with those observed in both Pool1 and Pool 2. Thus, there were no unexpected safety signals or adverse safety trends observed in the Pool 3 studies.

Safety Report

FDA received a 120-Day Safety Update from NHOR Study -Lowy Medical Research Institute (BLA 125798/0.22, Sequence Number: 0024) with a reporting period of January to March 2024. See a summary of this safety report below.

4. NT-501 Safety Report (Jan. – Mar. 2024) NHOR Study, from Lowy Medical Research Institute (BLA 125798/0.22, Sequence Number: 0024) Received August 16, 2024.

Participants in the sponsor’s Mac Tel clinical studies (Phase NTMT- 01, NTMT-02, NTMT-02B, NTMT-03A and NTMT-03B) all consented to being followed by the Natural History Observation and Registry Study (NHOR) upon their exit from the NT-501 trials. NHOR is an independent registry sponsored by Lowy Medical Research Institute (LMRI). Participant follow-up through NHOR is done mainly through annual telephone calls, as per the NHOR study procedures.

LMRI submitted a safety report compiled from interviews with these participants between January to March 2024, and covers the time from when the participants exited their last NT-501 study to present. The LMRI safety report was submitted directly to the FDA on August 16, 2024.

For the safety review LMRI requested that currently active NHOR sites contact their NHOR study participants (i.e., former NT-501 trial subjects) and provide them with a Data Collection Form which mirrored questions, mainly related to overall health, asked during a participant’s NHOR annual assessment. Participants were also asked NT-501 trial related questions.

The LMRI table below (adapted by this reviewer) shows the number of subjects consented for each phase of the NT-501 trials and the number of subjects who were successfully contacted for the safety data collection. Also included in the table are the number of subjects who were not contacted and the reasons why (see categories under “Unable to Survey” in table below). Of importance, it was noted by LMRI that even if successful contact was made, not all respondents answered all questions.

***Reviewer comment:** Given that the events in this safety review are reported voluntarily and LMRI states that of those respondents successfully contacted, not all provided answers to the questionnaire, the respondent pool is of an unknown size, therefore estimates of frequency regarding reported adverse events cannot be made with accuracy.*

Table 9. NT-501 Safety Review-Participant/Site Compliance Report

Protocol	Enrolled	Withdrew Prior to Randomization/Surgery	Completed Surgeries	Unable to Survey	# Respondents Analyzed
NTMT-03A	120	5	115	32	83
NTMT-03B	120	7	113	21	92
NTMT-02	67	0	67	27	40
NTMT-01	7	0	7	4	3

Total Consented	314		302		218
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Adapted LMRI Table 1 found in Appendix F (NT 501-Safety Report RE: BLA 125798/CRMTS 15031).

Overall, the LMRI Safety Review states there were no unexpected findings or safety issues related to participation in the NT-501 trials with the survey results summarized below.

Summary of Study Findings:

1. Explants: Occurred in 4 participants since exiting their respective NT-501 trial.

Table 10.

Study	Surgery Date	Study Exit Date	Date of Explant	Reason	Issues Resolved?
NTMT-03A (b) (6)	(b) (6)	March 12, 2020	(b) (6)	Vitreous hemorrhage; retinal detachment; pain	Yes
NTMT-03B (b) (6)	(b) (6)	June 16, 2021	(b) (6)	Vitreous hemorrhage	Yes
NTMT-02 (b) (6)	(b) (6)	June 2, 2020	(b) (6)	Recurring vitreous hemorrhage	Yes
NTMT-02 (b) (6)	(b) (6)	May 28, 2019	(b) (6)	Vitreous hemorrhage; chronic uveitis	Yes

***Reviewer Comment:** In the two pivotal Phase 3 studies, participants who received the NT-501 implant experienced vitreous hemorrhage (8.5%; 10/117 subjects) but no subjects experienced retinal detachment. Vitreous hemorrhage is an identified risk and retinal detachment is a possible risk in the sponsor's pharmacovigilance plan and these adverse events are listed in the product label, and therefore do not represent new safety signals. Three of the explant cases listed above (subjects (b) (6)) were included in Neurotech's 120-Day Safety Update and were discussed previously in this memo.*

2. Implant-Related Surgical Procedures

Two participants had procedures related to the NT-501 implant:

- On participant from the NTMT-03A study had multiple suture "clippings" due to persistent pain and irritation

- One participant from the NTMT-03B study had an extruded device repositioned and repair of a scleral wound due to vitreous hemorrhage. This participant received Lucentis (ranibizumab injection) ¹

Reviewer Comment: In the two pivotal Phase 3 studies, participants who received the NT-501 implant experienced suture related complications (15.4%; 18/117 subjects), device extrusion (0.9%; 1/117 subjects) and vitreous hemorrhage (8.5%; 10/117 subjects). These adverse events are identified risks in the sponsor's pharmacovigilance plan and are listed as known adverse events in the label. Therefore, the two cases described above do not represent new safety signals.

¹ Lucentis is indicated for the treatment of wet age-related macular degeneration; macular edema following retinal vein occlusion; diabetic macular edema; diabetic retinopathy, and myopic choroidal neovascularization.

3. Survey Results Ophthalmology Visits

Since completing the NT-501 trials, most of the participants reported seeing an ophthalmologist or optometrist for routine visits for Mac Tel or diabetes mellitus, glasses prescriptions, and cataract surgery evaluations. Other visit reasons included glaucoma, non-specific vision changes, and anterior eye issues (e.g., styes and inflammation).

Reviewer Comment: CNV and vitreous hemorrhage both occurred in the NT-501 group of the pivotal Phase 3 studies, with CNV occurring less frequently than vitreous hemorrhage (1.7%; 2/117 subjects vs 8.5%; 10/117 subjects, respectively). Vitreous hemorrhage is an identified risk in the sponsor's pharmacovigilance plan and is listed in the product label. Due to the infrequency of the CNV adverse event, it is not listed as an identified or potential risk in the sponsor's pharmacovigilance plan and therefore is not listed in the product label. This seems appropriate at this time. The LMRI safety review reports that only 2/6 CNV events occurred in implanted eyes. In Neurotech's pivotal Phase 3 trials, CNV occurred less frequently in the implant study eye (1.7%) compared to the study eye in the sham group (2.7%) or the fellow eyes in either sham or implant group (2.7% and 2.6% respectively):

****Sham Group:*** Study eye (3/111 subjects; 2.7%); Fellow eye (3/111 subjects; 2.7%)

****Implant Group:*** Study eye (2/117 subjects; 1.7%); Fellow eye (3/117 subjects; 2.6%)

* Source: Table 14.3.1.2.1B in Module 5.5.5.3 Integrated Summary of Safety.

3.1.2 Other Ocular Treatments

- Phase 3A NT-501 Group: 3 participants received other treatments:
 - one had a macular hole repair;
 - one had a retinal detachment repair,
 - one had combination macular hole and retinal detachment repair
- Phase 2 NT-501 Group: 1 participant received vitrectomy for floaters

- Phase 2 Fellow Eye: 1 participant had a peel and vitrectomy for an epiretinal membrane

Reviewer Comment: *The adverse events of macular hole and retinal detachment did not occur in the study eye of the implant group in Neurotech's pivotal Phase 3 trials (although macular hole was reported in 2 fellow eyes (1.7%) of the implant group). The LMRI safety review findings of 3 implanted respondents experiencing events of macular hole and retinal detachment may represent a progression of the respondents' Mac Tel disease process since these are known ocular conditions associated with the disease. Currently, routine pharmacovigilance, as planned by the sponsor, is adequate for following these events.*

In Neurotech's 2 pivotal Phase 3 trials, vitreous floaters occurred only in eyes that received the NT-501 implant (13/117 study eyes; 11.1%) and all events were considered mild in intensity. Likewise, across all 6 combined Mac Tel studies (Pool 2) vitreous floaters occurred mostly in the NT-501 group vs the Sham group (24/220 eyes; 24%, and 2/162 eyes; 1.2%, respectively), with the majority of events considered mild in intensity in both the NT-501 and sham groups (21/220 eyes; 9.5%, and 1/162 eyes; 0.6% respectively). The only event of severe vitreous floaters occurred in one subject in the NT-501 group (1/220 eyes; 0.5% of Pool 2. Thus, the LMRI safety review finding of 1 implanted respondent with floaters (requiring a vitrectomy) is not a new safety signal.

3.1.3 CATARACT SURGERY

LMRI reported that overall, 26 respondents reported undergoing cataract extraction surgery since exiting the Neurotech NT-501 trials. LMRI also reported that some respondents have been evaluated for, and are currently awaiting, cataract extraction surgery. LMRI stated that data were not collected regarding previous cataract extraction surgery prior to enrolling in, or before exiting from the NT-501 trials.

- **In Phase 3A:** 13 total participants had cataract extraction
 - For NT-501 Group: 10 participants had cataract extraction
 - For Sham Group: 3 participants had cataract extraction
- **In Phase 3B:** Of the 5 implanted participants who had cataract extraction:
 - For NT-501 Group: 3 participants had cataract extraction
 - Fellow eye: 2 participants had cataract extraction.
 - For Sham Group: 2 participants had cataract extraction.
- **Phase 2:** 6 total participants had cataract extraction
 - For NT-501 Group:5
 - Fellow eye:1

Cataract formation is listed as a potential risk in the sponsor's pharmacovigilance plan and this safety concern is labeled in sections 5.7, 6.1 and 17 of the proposed USPI (see additional details in Section 7.2.1 Cataract formation in this memo).

The remainder of the LMRI NT-501 Safety Report pertains to questions posed to respondents related to vision, quality of life issues, newly reported systemic disorders, and deaths. Vision related events reported by the respondents included decreased vision (self-reported), increased eye pain /irritation, delayed dark adaptation, change in pupil size, and metamorphopsia.

Reviewer comment: Except for metamorphopsia, the vision related events reported by respondents in the LMRI NT-501 Safety Report are labeled in Table 1 of the Encelto USPI, and therefore do not represent new safety signals. Metamorphopsia occurred infrequently in the original Phase 3 pivotal studies with lower rates of occurrence in the NT-501 implant group versus the sham group (0.9%; 1/117 eyes, vs 3.6%; 4/111 eyes respectively). Although the LMRI Safety Report suggests that metamorphopsia occurred equally between implant and sham group respondents ("approximately one-half of all participants reported experiencing metamorphopsia or visual disturbances in both the implant and sham groups in all study phases") the specific number of respondents answering this question was not enumerated. Therefore, estimates of frequency for the occurrence of metamorphopsia are difficult to assess.

The Safety Report stated an Improvement in vision was reported by 11.5% (7/61) of sham respondents compared to 30% (30/100) implant respondents. The nature of those were self-perceived stability of vision (n=7), self-perceived improvement of vision (n=10) and experiencing less distortion (n=4). Other improvements included decreased headaches, smaller "black spot" in central vision, and improved dark adaptation.

Reviewer comment: The Safety Report states that visual improvement occurred more frequently (30%) in implant respondents versus sham respondents (11.5%), but the specific visual improvements that occurred are not identified by treatment group. Since delayed dark adaptation occurred only in implanted eyes in the original Phase 3 pivotal studies, it can be assumed that reports of improved dark adaptation occurred in respondents with the implant.

The Safety Report states that in all three studies, quality of life issues reported by respondents included (1) decreased reading ability (in half of the respondents, and reported equally in both the implant and sham groups); (2) decreased ability to read fine print, or use the computer (reported by similar proportions of implant and sham respondents); (3) No change in driving ability for most respondents regardless of treatment group. For those noting a change, night driving was noted to be more difficult.

Reviewer comment: The specific number of respondents answering these questions was not enumerated, therefore estimates of frequency for occurrence of quality-of-life issues are difficult to assess.

The Safety Report stated there was a low incidence of all surveyed systemic diseases in all study phases, no differences between groups and none attributed to the NT-501 implant. Lastly, the Safety Report stated there were 10 deaths since the beginning of the NT-501 trials and none of these deaths were related to the NT-501 implant.

Reviewer comment: The LMRI NT-501 Safety Report did not provide any additional information pertaining to the 10 deaths reported. In Neurotech’s 120-Day Safety Update, the sponsor reported 2 deaths in participants after exiting the NT-501 trials (see previous discussion in this memo under Pool 1 Non-Ocular deaths)bringing the total number of deaths experienced in the 6 Mac Tel studies to 8 participants. DPV asked the sponsor (IR #34) to provide information pertaining to the two additional deaths cited in the LMRI NT-501 Safety Report. The IR response from Neurotech (125798/0.52, received on October 21, 2024) confirmed the total number of deaths as 10 and acknowledged FDA’s observation of two unaccounted deaths mentioned in the LMRI 120-Day Safety Report. The response from LMRI (125798/0.51, received on October 21, 2024) regarding the two participant deaths (subjects (b) (6)) which occurred after exiting the NT-501 clinical trials, was that the information pertaining to the deaths came via the LMRI Safety Report (i.e. the NHOR study) and that the NHOR registry study does not collect information about a participant’s cause of death and does not have a mechanism to determine the cause of death.

6 SPONSOR’S PHARMACOVIGILANCE PLAN

The sponsor submitted a pharmacovigilance plan (BLA 125798/0, submitted on May 8, 2024) proposing routine pharmacovigilance activities (adverse event reporting and signal detection), a Phase 3 extension study, and focused patient surveys from the Natural History Observation Registry (NHOR) study in order to conduct safety monitoring of NT-501 in the post-marketing setting.

*Reviewer comment: The sponsor did not originally include a pharmacovigilance plan in their BLA (# 125798/0) for NT-501, submitted to the FDA on April 18, 2024. Therefore, DPV sent IR #1 (dated April 23, 2024) to the sponsor requesting for a Pharmacovigilance Plan detailing the important identified risks, important potential risks, and missing information regarding their product. The sponsor was also asked to describe routine pharmacovigilance planned for the post market setting should their product be approved. The sponsor responded on May 8, 2024, by submitting the proposed Pharmacovigilance Plan described in **Table 11** below, which DPV found acceptable.*

Table 11. Sponsor’s Proposed Pharmacovigilance Plan*

Type of Concern	/ Concern	Proposed Action
Identified	Suture related complications	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Identified	Device Extrusion	Routine pharmacovigilance

		Phase 3 extension sham dosing NHOR patient survey
Identified	Delayed Vitreous Hemorrhage	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Identified	Delayed Dark Adaptation	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Identified	Miosis	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Potential	Cataract formation	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Potential	Cataract surgery related complications	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Potential		Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Potential		Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Missing	Long term safety	Routine pharmacovigilance Phase 3 extension sham dosing NHOR patient survey
Missing	Pregnancy/Lactation	Routine pharmacovigilance Phase 3 extension sham dosing

*Adapted from Table 2, Summary of Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern, Version 1.0 STN 125798/0 (submitted on May 8, 2024)

Reviewer comment: Should this product be approved; FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary at this time to ensure the benefits of NT-501 outweigh its risks. Thus, NTMT4: NT501 Extension Trial in Mac Tel

and the NHOR Study are voluntary risk minimization strategies undertaken by the sponsor.

6.1 Enhanced Pharmacovigilance

The ocular adverse event of delayed dark adaptation occurred more frequently in the NT-501 group vs Sham group in Pool 1 Phase 3 studies (23.1%; 27/117 eyes and 2.7%; 3/111 eyes, respectively) and Pool 2 Mac Tel combined studies (19.1%; 42/220 eyes, and 3.1%; 5/162 eyes, respectively). In addition, the majority of these events had not resolved by the end of the studies. Thus, due to the high incidence and lack of resolution associated with this event, the OTP clinical team and DPV pharmacovigilance team discussed potential enhanced pharmacovigilance strategies applicable to the AE of delayed dark adaptation and agreed to have the sponsor include signal analysis of delayed dark adaptation in their periodic safety reports for 3 years upon approval of their study product. This expectation was conveyed to the sponsor in IR # 34 (dated October 10, 2024). The sponsor's response (125798/0.52, received October 21, 2024) indicated they were in agreement with the request and, in addition, would include monitoring for delayed dark adaptation as part of the long-term safety evaluation in their planned Phase 4 extension clinical study (NTMT-04). OTP indicated they planned on asking the sponsor to add delayed dark adaptation analysis in the ongoing Phase 3 NT-501 Extension Study (later referred to by the sponsor as the Phase 4 extension clinical study, NTMT-04). OTP planned to request the sponsor to conduct a voluntary sub-study, under the extension study, to include psychological testing of a subset of patients, possibly using data from the Mac Tel NHOR study as a control. Please see clinical review memo. OBPV defers to OTP for review of the Phase 4 extension clinical study NTMT-04, and for follow-up of clinical trial participants under NHOR registry.

Additionally, Neurotech stated they will include a dedicated table in all periodic safety reports, providing an aggregate safety assessment for delayed dark adaptation events, incorporating data from both the Phase 4 clinical extension study and post-market pharmacovigilance.

Therefore, in collaboration with the OTP clinical team, DPV sent the following IR (# 29) to the sponsor (September 16, 2024) requesting additional information about their pharmacovigilance plan:

Our review of the submission STN 125798/0 is ongoing. We have the following questions:

1. Your Pharmacovigilance Plan submitted under STN 125798/0.2 specifies in section 1.2.2.2 an additional proposed study, "designated as an extension of the

Phase 3 Mac Tel registration clinical trials.” Please provide details of the extension study and when the protocol will be submitted.

2. The pharmacovigilance plan also describes an ongoing natural history observational study (NHOR) through the Lowry Medical Research Group in patients with Mac Tel. Please submit the following:
 - A summary of any information (patient reports and psychophysical and/or electrophysiologic testing) related to the complaint of delayed dark adaptation, that might have been obtained during this Natural History Observation Study.
 - A protocol synopsis for the NHOR study.

A response to DPV’s IR (#29) was received on September 25, 2024, from Neurotech (STN 125798/0.40) and Lowry Medical Research Institute (STN 125798/0.39).

In response to Question # 1 above, Neurotech replied they are currently developing a Phase 4 extension protocol (NTMT4: NT-501 Extension Trial in Mac Tel) which will be submitted to the FDA for review on October 21, 2024. The sponsor anticipates participant enrollment will begin in the early second quarter of 2025. A protocol synopsis (version 1.0) was submitted to FDA. As this study is a continuation of the phase 3 studies and will have efficacy endpoints, after discussion with OTP they stated they will be the primary review office.

In response to Question # 2 above, Lowry Medical Research Institute (LMRI) replied that no information related to the adverse event of delayed dark adaptation was obtained during the NHOR enrollment visit or annual assessments. LMRI states that during the NT-501 Study 120-day Safety Review, NHOR participants who were also previous participants in the NT-501 clinical trials, were asked the question of whether they have experienced increased difficulty with dark adaptation, and if so, in one or both eyes? LMRI states this was a subjective question that was added to the data collection form because it was related to quality of life and a similar question was asked at post-op visits during the clinical trials.

7 ANALYSIS OF SPONSOR’S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Suture Related Complications

Suture related complication was the most frequently reported ocular adverse event in the combined Phase 3 pivotal studies [Pool 1] that occurred in at least 2 study eyes in either the NT-501 group or the Sham group (18/117eyes; 15.4% vs 3/111 eyes; 2.7%, respectively) and was considered related to the study surgery. In addition, this event was also the most frequently reported ocular SAE in implanted eyes in the Pool 1 studies (5 /117 eyes; 4.3%) which in all instances was also considered related to surgery and did not result in NT-501 removal. The important identified risk of suture

related complications will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is labeled in the following sections of the proposed USPI:

- Section 5.5, Suture Related Complications
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information.

***Reviewer comment:** The sponsor's proposed pharmacovigilance plan is adequate to monitor the important identified risk of suture related complications.*

7.1.2 Device Extrusion

In the Phase 3 pivotal studies, only one participant (subject (b) (6) in the NT-501 group experienced the ocular adverse event of device extrusion (1/117 eyes; 0.9%). The event was considered serious (medically important) but mild in severity. The study device was surgically repositioned and did not require removal. The important identified risk of device extrusion will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is labeled in the following sections of the proposed USPI:

- Section 5.4, Device Extrusion
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

***Reviewer comment:** The sponsor's proposed pharmacovigilance plan is adequate to monitor the important identified risk of device extrusion.*

7.1.3 Delayed Vitreous Hemorrhage

In the Phase 3 pivotal studies, vitreous hemorrhage occurred only in participants in the NT-501 group at a frequency of 8.5% (10/117). Most cases occurred within 90 days after surgical implantation of the study device and resolved spontaneously. Of note, late onset (i.e., after 365 days post-surgery) occurred in 3 implanted eyes (2/6%) and 1 of these events, occurring after the Month 24 visit, was serious and occurred in 1 participant (subject (b) (6) in the NT-501 group (of NTMT-03-A). The event occurred in the study eye on Day 846. The SAE was considered to be related to the surgical procedure, was moderate in intensity, and resulted in NT-501 being removed on Day 912. The participant was subsequently discontinued from the study on Day 1101. The important identified risk of vitreous hemorrhage will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is labeled in the following sections of the proposed USPI:

- Section 5.3, Vitreous Hemorrhage
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

***Reviewer comment:** The sponsor's proposed pharmacovigilance plan is adequate to monitor the important identified risk of delayed vitreous hemorrhage.*

7.1.4 Miosis

In the Phase 3 pivotal studies, miosis occurred only in participants in the NT-501 group at a frequency of 15.4% (18/117) with most events occurring within 365 days post-surgery. These events were mostly mild in intensity, did not lead to NT-501 removal, and had not resolved by the end of the study. Miosis was attributed to the NT-501 device in 2 implanted eyes (1.7%) and to CNTF in 18 implanted eyes (15.4%). The sponsor has stated in the label that if miosis occurs, it is expected to continue for the duration that an eye retains the implant. The important identified risk of miosis will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is labeled in the following sections of the proposed USPI:

- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The sponsor's proposed pharmacovigilance plan is adequate to monitor the important identified risk of miosis.

7.1.5 Delayed Dark Adaptation

In the Phase 3 pivotal studies, the adverse event of delayed dark adaptation was one of the AEs reported at the 3 highest frequencies in the NT-501 group (23.1%; 27/117 eyes) and occurred at a frequency $\geq 5\%$ higher than in the sham group (2.7%; 3/111 eyes). Delayed dark adaptation was attributed to the NT-501 device in 4 implanted eyes (3.4%) and to CNTF in 24 implanted eyes (20.5%). The sponsor has stated in the label that if delayed dark adaptation occurs, it is expected to continue for the duration that an eye retains the implant. The important identified risk of delayed dark adaptation will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. In addition, the sponsor will monitor this risk through enhanced pharmacovigilance for 3 years upon approval of the study product, to include a dedicated table in all periodic safety reports, providing an aggregate safety assessment for delayed dark adaptation events, incorporating data from both the Phase 4 study and post-market pharmacovigilance.

This safety concern is labeled in the following sections of the proposed USPI:

- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The sponsor's proposed pharmacovigilance plan is adequate to monitor the identified risk of delayed dark adaptation.

7.2 Important Potential Risks

7.2.1 Cataract formation

In the Phase 3 pivotal studies, cataract formation (including preferred terms of cataract, cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities) occurred more frequently in the NT-501 group versus the Sham group (10.3%; 12/117 eyes vs 2.7%; 3/111 eyes, respectively) through the Month 24 visit. Of the 12 cataract AEs in the implanted eyes, 4 were considered related to the

NT-501 device and 3 were considered related to the study surgery procedure. The important potential risk of cataract formation will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is labeled in the following sections of the proposed USPI:

- Section 5.7, Cataract Formation
- Section 6.1, Clinical Trials Experience
- Section 17, Patient Counseling Information

Reviewer comment: The sponsor's proposed pharmacovigilance plan is adequate to monitor the important potential risk of cataract formation.

7.2.2 Cataract Surgery Related Complications

As is the case with any intraocular surgery, there may be related risks to the surgical removal of cataracts. The important potential risk of cataract surgery related complications will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is discussed in the following sections of the proposed USPI:

- Section 17, Patient Counseling Information.

Reviewer comment: The sponsor's proposed pharmacovigilance plan is adequate to monitor the important potential risk of cataract surgery related complications.

7.2.3 Risks associated with vitreoretinal surgery such as infections, endophthalmitis, retinal tear, retinal detachment.

Across the 6 Mac Tel studies, including the Phase 3 pivotal studies, no ocular adverse events of infectious endophthalmitis or retinal tear/detachment occurred in the NT-501 group. The important potential risks associated with vitreoretinal surgery (e.g., infections/endophthalmitis; retinal tear/detachment) will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. This safety concern is discussed in the following section of the proposed USPI:

- Section 5 Warnings and Precautions
- Section 5.1, Endophthalmitis
- Section 5.2 Retinal Tear and/or Detachment
- Section 17, patient Counseling Information

Reviewer comment: The sponsor's proposed pharmacovigilance plan is adequate to monitor the important potential risks associated with vitreoretinal surgery (such as infections/ endophthalmitis, and retinal tear/detachment).

7.2.4 Risks associated with intraocular devices such as dislocation of the NT-501, conjunctival retraction, conjunctival erosion, conjunctival bleb formation, mechanical complication of the implant, migration of the implant, wound dehiscence.

The most commonly reported ocular AEs across all 6 Mac Tel studies (Pool 2), including the Phase 3 pivotal studies, were those inherent to the implant surgery, which requires conjunctival incisions and conjunctival wound closure. The occurrence of AEs such as conjunctival bleb formation and wound dehiscence were infrequently reported in the 6 Mac Tel studies for the NT-501 group (0.5%; 1/220 eyes). The events of conjunctival retraction and erosion were not reported in any of the Pool 2 studies.

Generally, implanted devices can have a risk for migration, dislocation and/or mechanical complication. In the Pool 2 studies there were no event reports of implant migration (device extrusion is discussed in 7.1.2 of this memo). In the Pool 3 studies, one implanted eye (0.23%; 1/438 eyes) in a non-Mac Tel study, had a mild, non-serious AE of “device dislocation/ anterior displacement of tip of implant OS” on study day 187 that led to explantation of the device. The event was considered to be related to the study surgery and resolved. The important potential risks associated with vitreoretinal surgery (NT-501 migration/dislocation/mechanical complication of the implant; conjunctival retraction/erosion/bleb formation; and wound dehiscence) will be monitored through routine pharmacovigilance, a Phase 4 extension study and the NHOR patient survey. The safety concerns of implant dislocation/migration are generally referred to under Section 5.4 where the label states “*Monitor patients periodically to confirm proper positioning of ENCELTO.*” The safety concern of conjunctival erosion is mentioned under Section 5.5 where the label states: “*Suture tips and suture knots can irritate or erode through the conjunctiva.*” These safety concerns are discussed in the following sections of the USPI:

- Section 5.4 Device Extrusion
- Section 5.5 Suture Related Complications

Reviewer comment: The sponsor’s proposed pharmacovigilance plan is adequate to monitor the important potential risks associated with intraocular devices (such as NT-501 migration/dislocation/mechanical complication of the implant; conjunctival retraction/erosion/bleb formation; and wound dehiscence).

7.3 Important Missing Information

7.3.1 Long Term Safety

The long-term safety of NT-501 is unknown. The long-term safety of NT-501 will be monitored through a Phase 4 extension study and the NHOR study.

Reviewer comment: The sponsor’s proposed pharmacovigilance plan is adequate to address missing information for long-term safety.

7.3.2 Pregnancy/Lactation

Across the Mac Tel clinical program, no subject of childbearing potential who underwent urine pregnancy test during the screening period had a positive test result. In study NTMT-03-B, subject (b) (6) in the sham group, had a negative pregnancy test at screening; however, the subject subsequently reported a pregnancy that was electively

terminated. The sponsor states there is no data on the use of NT-501 in pregnant women. Likewise, there are no reports on the effects of CNTF on milk production or whether recombinant human (rh) CNTF will cause harm to the fetus when given at recommended doses. Of note, in animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of fetal harm at doses up to 2400 times the maximum potential human dose from the product (one implant per eye, both eyes treated). The sponsor proposes routine pharmacovigilance, and Phase 4 extension study, to monitor for exposure during pregnancy and lactation. The labeling also notes there is limited data in pregnant and breastfeeding women. Use in pregnancy is described in the following sections of the USPI:

- Section 8.1 Pregnancy
- Section 8.2 Lactation

***Reviewer Comment:** Pregnant and lactating women are generally excluded from most clinical studies. The sponsor had no reports of pregnancy and exposure during lactation for this product. The sponsor's proposed pharmacovigilance plan and labeling is adequate to address missing information in pregnancy and lactation.*

8 DPV ASSESSMENT

No new safety signals or adverse safety trends were observed during the pivotal Phase 3 studies (combined in Pool 1), across the 6 Mac Tel studies (combined in Pool 2) or across the 13 studies in multiple retinal degradation indications (combined in Pool 3). Important identified risks include suture related complications, device extrusion, delayed vitreous hemorrhage, miosis, and delayed dark adaptation. Important potential risks include cataract formation/cataract surgery related complications, risks associated with vitreoretinal surgery (such as infections/ endophthalmitis, retinal tear/detachment) and risks associated with intraocular devices (such as NT-501 migration/dislocation /mechanical complication; conjunctival retraction/erosion/ bleb formation, and wound dehiscence). Areas of important missing information include long term safety information and pregnant/lactating women. The sponsor proposes routine pharmacovigilance, a phase 4 extension study and the NHOR questionnaire to address these risks and areas of missing information. In addition, the sponsor proposes enhanced pharmacovigilance regarding delayed dark adaptation. There were no significant safety concerns from the clinical trials. The sponsor's safety specifications and pharmacovigilance actions are acceptable.

9 DPV RECOMMENDATIONS

Should the product be approved for the treatment of Mac Tel Type 2, the proposed PVP, version 1.0, dated 02-MAY-2024, is adequate to monitor postmarketing safety for NT-501 (ENCELTO).

Postmarketing safety monitoring for ENCELTO will include the following:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80.
- Enhanced pharmacovigilance: For 3 years following licensure, the sponsor will include a safety assessment for delayed dark adaptation events in periodic safety reports.

Follow up of clinical trial participants will continue in a Phase 4 extension clinical study NTMT-04 and the Natural History Observation and Registry. (OBPV defers to OTP clinical team for reviews related to follow-up of clinical trial participants in the above studies)..

The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post marketing requirement PMR). There is no agreed-upon postmarketing commitment (PMC) for a safety study for this product.

Please see the final version of the package insert submitted by the sponsor for the final agreed upon language for the label.

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APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
Apr.18, 2024	Sponsor	STN125798/0	Module 1 Cover Letter (1.2) and Reviewer Guide (1.2)
Apr.18, 2024	Sponsor	STN125798/0	Module 1.12.17 Orphan Designation
Apr.18, 2024	Sponsor	STN125798/0	Module 1.14.1.3 Encelto Draft USPI
May 2, 2024	Sponsor	STN125798/0.2	Module 5.3.6 NT-501 Pharmacovigilance Plan
July 11, 2024	Sponsor	STN125798/0	Module 5 (section 2.7.4) Summary Clinical Safety and Integrated Summary of Safety (ISS)
July 11, 2024	Sponsor	STN125798/0	Module 5 Clinical Study Reports
July 11, 2024	Sponsor	STN125798/0	Module 5.2 Tabular Listing of All Clinical Studies
July 11, 2024	Sponsor	STN125798/0	Module 5.3 Clinical Study Reports
July 11, 2024	Sponsor	STN125798/0	Module 5.3.5.3 ISS tables, listings, figures and datasets
July 11, 2024	Sponsor	STN125798/0	Module 5.5.5.3 Integrated Summary of Safety
August 16, 2024	Lowy Medical Research Institute (LMRI)	STN 125798/0.22	120-Day Safety Update
August 16, 2024	Sponsor	STN 125798/0.23	120-Day Safety Update: Neurotech Safety Report
September 25, 2024	Sponsor	STN125798/0.40	Neurotech Phase 4 Extension Protocol (NTMT4: NT-501 Extension Trial in Mac Tel)
September 25, 2024	LMRI	STN 125798/0.39	Protocol Synopsis for NHOR Study
October 21, 2024	LMRI	STN 125798/0.51	LMRI response to IR # 34
October 21, 2024	Sponsor	STN 125798/0.52	Neurotech response to IR # 34

Table 8. Overview of Clinical Studies of NT-501 in Other Retinal Degeneration Indications

Study ID/ (Country)	Study Title	Study Design & Population	Study Procedure/Duration	Number Subjects/Eyes Evaluated for Safety (M/F, Age, Range of Randomized Subjects
CNTF-1 (US)	A Phase I Study of NT-501-10 and NT-501-6A.02, Implants of Encapsulated Human NTC-201 Cells Releasing Ciliary Neurotrophic Factor (CNTF), in Patients with Retinitis Pigmentosa	Open-label, nonrandomized, prospective, single center, dose escalation design Subjects with advanced RP	Dose escalation study to evaluate the safety of the NT-501-10 (low output) implant and the NT-501-6A (high output) implant in 10 subjects with advanced RP. Subjects each received a CNTF implant in 1 eye and were followed for 6 months, at which time the implant was to be removed. Safety follow-up occurred at 1 year.	10 subjects/eyes <u>NT-501 low dose:</u> 5 eyes <u>NT 501 high dose:</u> 5 eyes (2F/8M; 46-68 years)
CNTF-2 (US)	A Phase 2 Study of Implants of Encapsulated Human NTC-201 Cells Releasing Ciliary Neurotrophic Factor (CNTF), in Participants with Visual Acuity Impairment Associated with Atrophic Macular Degeneration	Double-masked, multicenter, randomized, sham controlled, parallel group design Subjects with atrophic AMD	Eligible subjects were randomized on a 2:1:1 basis to the higher CNTF output NTC-201-6A.02 implant, the lower CNTF output NTC-201-10.02 implant or to sham surgery. The implant could be removed from the eye after 12 months or earlier in case of AEs or at the subject's request. All subjects were to be followed clinically for 18 months.	53 subjects/eyes randomized (2 not treated) <u>NT-501 high dose:</u> 27 eyes <u>NT-501 low dose:</u> 12 subjects <u>Sham:</u> 12 eyes (28F/25M; 56-88 years)
CNTF 3 (US)	A Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic	Double-masked, multicenter, randomized, sham-controlled, parallel group design	Eligible subjects were randomized in a 2:1 allocation ratio to receive either the higher or lower output NT-501 implant in 1	67 subjects/eyes randomized (2 not treated) <u>NT-501 low dose</u> 22 eyes

	Factor (CNTF) for Participants with Retinitis Pigmentosa Using Visual Acuity as the Primary Outcome	Subjects with RP	eye and sham surgery in the fellow eye. Subjects had the option of having the implant removed after 12 months. All subjects were to be followed clinically for 18 months.	<u>NT-501 high dose:</u> 43 eyes <u>Sham:</u> 65 eyes (33F/34M; 17-67 years)
CNTF-4 (US)	A Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor (CNTF) in Participants with Retinitis Pigmentosa Using Visual Field Sensitivity as the Primary Outcome	Double-masked, multicenter, randomized, sham-controlled, parallel group design Subjects with RP	Eligible subjects were randomized in a 2:1 allocation ratio to receive either a higher or lower CNTF output implant in 1 eye (study eye). The study eye was randomly assigned. The fellow eye underwent a sham procedure. Following the Month 24 visit, subjects could request explant surgery to remove the CNTF implant. Explanted subjects were assessed through 6 months after explant surgery.	73 subjects/eyes randomized (5 not treated) <u>NT-501 low dose:</u> 20 eyes <u>NT-501 high dose:</u> 48 eyes <u>Sham:</u> 68 eyes (37F/36M; 17-59 years)
CNTF-5 [12-EI-0167] (US)	A Phase I/II Study of the NT-501 Intraocular Implant Releasing Ciliary Neurotrophic Factor (CNTF) in Participants with CNGB3 Achromatopsia	Single-center, single arm, open-label design Subjects with CNGB3 achromatopsia	One eye of each of the 5 subjects received a vitreous NT-501-6A.02 (high output) implant. All subjects were to be followed clinically for 3 years post-surgery.	5 subjects <u>NT-501 high dose:</u> 5 eyes (2F/3M; 26-35 years)
AOSLO-CNTF-FFB-01 (US)	Photoreceptor Structure in A Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor (CNTF) for Participants With Retinitis Pigmentosa Using Rates of Change in Cone Spacing and Density	Randomized, double masked, sham-controlled single-center design Subjects with early-stage RP or Usher syndrome (type 2 or 3)	One study eye from each subject was randomly assigned to receive a vitreous NT-501-6A.02 (high output) implant. The fellow eye underwent a sham procedure. All subjects were to be followed clinically for 30 months post-surgery.	22 subjects/eyes <u>NT-501 low dose:</u> 6 eyes <u>NT-501 high dose:</u> 16 eyes <u>Sham:</u> 22 eyes (9F/13M; 19-66 years)

201-CU-01RDD-2011 [CU-01] (US)	A Compassionate Use of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor for Participants with Retinal Degenerative Diseases	Compassionate use, open label Subjects with retinal degenerative diseases (RP,AMD, MacTel)	Subjects with reduced vision in both eyes due to RP, GA, or MacTel received a unilateral NT-501 implant within 7 weeks of initiating a baseline exam and assessments. Subjects followed for up to 36 months after the implant procedure.	9 subjects/eyes <u>NT-501 high dose:</u> 9 eyes (3F/6M; 37-76 years)
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Sponsor Table 2 (Module 2.7.4 Summary of Clinical Safety) reproduced.

AE = adverse event; AMD = age-related macular degeneration; CNTF = ciliary neurotrophic factor; F = female; GA = geographic atrophy; M = male; MacTel = macular telangiectasia type 2; RP = retinitis pigmentosa; US = United States
a Although each study included safety variables other than AEs, given the different populations, durations, and designs of these studies, and as per FDA request, only summaries of AEs are presented for Pool 3 that includes these studies. Also summarized is the number of subjects who lost ≥ 15 letters in vision from baseline.