Extension Study of NT-501 Ciliary Neurotrophic Factor (CNTF) Implant for Macular Telangiectasia (MacTel)

Neurotech Pharmaceuticals, Inc.

Protocol Designation: NTMT-01/02E

IND – 10,931

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Statement of Compliance

This study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to 45 CFR 46 (Human Subjects Protection, 21 CFR 312 (Investigational New Drug [IND]), and 21 CFR 56 (Institutional Review Board [IRB]).

SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol. I understand and am aware of my responsibilities as an investigator as described in the applicable GCP regulations.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the IRB responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, Part 312.64.

_____

Principal Investigator Name (Print)

_____ _____

Principal Investigator Signature Date

IND SPONSOR SIGNATURE

The signatures below document the review and approval of this protocol and the attachments (e.g., investigator brochure) and provide the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. Code of Federal Regulations and ICH guidelines.

Martin Friedlander MD President CMNT

Sponsor Representative's Name (Print) Sponsor Representative's Title

Sponsor Representative's Signature

04OCT16

Date

Charles Johnson CMO, Neurotech.

Sponsor Representative's Name (Print) Sponsor Representative's Title

Sponsor Representative's Signature

05 OCT 2016

Date

Study Summary

Protocol Number: NTMT-01/02E

Title: Extension Study of NT-501 Ciliary Neurotrophic Factor (CNTF) Implant for Macular Telangiectasia (MacTel)

Short Title: MacTel NTMT-01/02 Extension Study

Sponsor: Neurotech Pharmaceuticals, Inc.
900 Highland Corporate Drive
Cumberland, RI 02864
Tel: 401-333-3880

Study Phase: 2

Objectives:

- To investigate long term safety and efficacy of the NT-501 implant in participants previously enrolled in the NTMT-01 and NTMT-02 protocols.
- To investigate the change in the ellipsoid zone (area of [inner/outer segment] IS/OS loss) in participants previously enrolled in the NTMT-01 and NTMT-02 protocols, as measured by en face imaging by spectral domain optical coherence tomography (SD-OCT) in study eye(s).

Study Design: Two participant cohorts will be enrolled in this study:

Cohort 1 - Prospective, multi-center, open label safety and tolerability study. All participants will have been enrolled (undergone a NT-501 implant) in the *Protocol for Extended Follow-up of a Phase 1 Multicenter Open Label Safety and Tolerability Clinical Trial of Ciliary Neurotrophic Factor (CNTF) in Patients with Macular Telangiectasia Type 2 (MacTel NTMT-01)* protocol and have agreed to continue in this follow-up study.

Participant visits will occur at Months 72, 84, 96 and 108 (+/- 1 month) following the date of the surgical procedure for NTMT-01.

Cohort 2 - Prospective, multi-center, single-masked sham-controlled study. All participants will have been enrolled (undergone a NT-501 implant and/or sham procedure) in the *A Phase 2 Multicenter Randomized Clinical Trial of Ciliary Neurotrophic Factor (CNTF) for Macular Telangiectasia Type 2 (MacTel NTMT-02)* protocol and have agreed to continue in this follow-up study.

In the event that the NTMT-02 study is positive, Cohort 2 participants who received sham only may be eligible for active treatment in the control/non-treated eye.

Participant visits will occur at Months 36, 48, 60 and 72 (+/- 1 month) following the date of the surgical procedure for NTMT-02.

Sample Size:

Cohort 1 - 7 participants (7 study eyes) – previously enrolled in NTMT-01 protocol

Cohort 2 – 66 participants (98 study eyes) – previously enrolled in NTMT-02 protocol

Diagnosis and Key Eligibility Criteria: Previously enrolled in NTMT-01 or NTMT-02 protocols

Investigational Product: NT-501 implant

Duration of Treatment:

Cohort 1 - Visits to continue until Month 108 from date of study procedure, with annual analyses at Months 72, 84, 96, and 108.

Cohort 2 - Visits to continue until Month 72 from date of study procedure, with annual analyses at Months 36, 48, 60, and 72.

Number of Centers: 8 sites in the United States and 3 sites in Australia

Study Outcomes:

Cohort 1: The following efficacy outcomes as outlined in the NTMT-01 Protocol will continue to be analyzed to investigate the efficacy of Ciliary Neurotrophic Factor (CNTF) produced by NT-501 (all changes relative to NTMT-01 baseline measurements):

- Change in the ellipsoid zone (area of IS/OS loss) from baseline to Months 72, 84, 96 and 108.
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 72, 84, 96 and 108.
- Proportion of study eyes with a 35% or more increase from baseline in the ellipsoid zone (area of IS/OS loss) at Months 72, 84, 96 and 108.
- Change in best corrected visual acuity (BCVA) from baseline to Months 72, 84, 96 and 108.
- Proportion of study eyes with 15 or more letter loss from baseline in BCVA at Months 72, 84, 96 and 108.
- Proportion of study eyes with 10 or more letter loss from baseline in BCVA at Months 72, 84, 96 and 108.

Cohort 2: The following efficacy outcomes as outlined in the NTMT-02 Protocol will continue to be analyzed to investigate the efficacy of Ciliary Neurotrophic Factor (CNTF) produced by NT-501 (all changes relative to NTMT-02 baseline measurements):

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

Assessment/Examination Schedule

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

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List of Abbreviations and Definition of Terms

Abbreviation	Term
AE	Adverse event
AOSLO	Adaptive optics scanning laser ophthalmoscope
BCVA	Best corrected visual acuity
CFR	Code of Federal Regulations
CNTF	Ciliary neurotrophic factor
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data Safety and Monitoring Committee
eCRF	Electronic case report form
ECT	Encapsulated cell technology
EDC	Electronic data capture
ERG	Electroretinogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
IS	Inner segment
MacTel	Macular Telangiectasia Type 2
MOP	Manual of Procedures
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical coherence Tomography
SD-OCT	Spectral Domain-Optical Coherence Tomography
ONL	Outer nuclear layer
OS	Outer segment
RP	Retinitis pigmentosa
SAE	Serious adverse event
VEGF	Vascular endothelial growth factor

1 Précis

Macular telangiectasia type 2 (MacTel), a bilateral degenerative condition of the macula that may cause progressive loss of vision, is estimated to have an incidence of 1:22,000 (Lamoureux et al. 2011). A recent study (Chew 2015) correlating visual field defects detected by microperimetry with optical coherence tomography shows that the defects are closely associated with cavitation of the outer retina with gaps in the inner-/-outer-segment junction, indicating that loss of vision in MacTel is caused by loss of photoreceptors. Current evidence implies that photoreceptor cell loss is intrinsic to the disorder rather than being consequent upon blood vessel changes. Photoreceptor abnormality occurs early in the disorder and progression of photoreceptor cell loss is not influenced by modulation of blood vessel changes using anti-VEGF treatment. To date, there is no effective treatment for MacTel.

The class of molecules called “neurotrophic factors” has been demonstrated to reduce the rate of photoreceptor cell loss during retinal degeneration. One of these, ciliary neurotrophic factor (CNTF), was found to be effective in slowing vision loss from photoreceptor cell death in 12 animal models of outer retinal degeneration (e.g., rd/rd, rds/rds, 334ter-3 rats, 334ter-4 rats, P23H-1 rats, Rdy cats, rcd1 dogs, etc.). Similarly, delivery of a neurotrophic factor to the outer retina in a mouse model that shares many phenotypic MacTel characteristics has shown profound functional and anatomic photoreceptor cell rescue without correcting associated vascular abnormalities (Dorrell 2009). In addition, there is evidence that CNTF can cause regeneration of cone outer segment in rats with mutations in the rhodopsin gene (McGill 2007). Further, encapsulated cell delivery of CNTF has been tested in three human Phase 2 safety studies in the treatment of retinal dystrophies and atrophic age-related macular disease. Specifically, CNTF did not cause neovascularization in either disorder, both of which are recognized as being associated with the development of abnormal blood vessels. In these studies, there is some evidence of therapeutic benefit (Sieving 2005 and Talcott, 2010). The combined evidence from animal and human studies suggests that use of neurotrophic molecules may provide therapeutic benefit to patients with MacTel.

One major challenge is the delivery of this potential therapeutic CNTF agent to the back of the eye, and in particular, to the retina. The blood-retinal barrier prevents the penetration of a variety of molecules to the neurosensory retina from plasma in a manner similar to the action of the blood-brain barrier, which exists between the central nervous system and systemic circulation. To overcome this challenge, Neurotech Pharmaceuticals (Neurotech) developed

encapsulated cell technology (ECT), and specifically the NT-501 implant, to enable controlled, sustained delivery of therapeutic agents directly into the vitreous humor, thus providing direct access to the retina while restricting exposure of the growth factor outside the eye. ECT utilizes cells encapsulated within a semi-permeable polymer membrane that secretes therapeutic factors directly into the vitreous. Further, ECT devices can be surgically retrieved, providing an added level of safety.

Histopathologic studies of multiple forms of retinal neurodegenerative diseases have demonstrated the efficacy of CNTF as an effective treatment to reduce photoreceptor cell loss. Consequently, the use of the implanted NT-501 device, which secretes CNTF into the vitreous, may be beneficial in people with MacTel. A Phase 1 study is completed although we continue to follow these participants to accumulate further data on the effect of the intraocular NT-501 implant in 7 participants with bilateral MacTel. The primary outcome was the safety of the NT-501 implant and the associated surgical procedure. We found the implanting of the NT-501 was safe as demonstrated by the ERG findings and visual function results as measured by visual acuity and microperimetry (Chew 2015).

2 Background and Rationale

In 1982, Gass et al. published the seminal paper on macular telangiectasis (then called juxtafoveal or parafoveal telangiectasia). In further work, Gass et al. (Gass 1987 and Gass 1993) subdivided macular telangiectasia into three groups: Type 1: the telangiectasia is usually unilateral and associated with dilated retinal capillaries, leakage on fluorescein angiography and retinal thickening in mostly male patients. Type 2: Macular Telangiectasia (MacTel), leakage occurs during fluorescein angiography with manifest retinal capillary dilatation but without retinal thickening, and Type 3: 3 Macular Telangiectasis, capillary occlusion is suspected to cause telangiectasia. Mac Tel Type 2, the most common form of macular telangiectasia, is the disease evaluated in this study. This condition is typically diagnosed in the fifth or sixth decade of life in both sexes. This disorder is characterized by minimal exudation, superficial retinal crystalline deposits, retinal opacification and right-angle venules. As the disease progresses, intraretinal pigment plaques and intraretinal/subretinal neovascularization may develop.

In 2005, a prospective natural history study was initiated to define the clinical aspects of macular telangiectasia type 2 and to evaluate its progression. Several new features have now been described that alter our concept of the disorder’s pathogenesis. One of the earliest signs is

loss of luteal pigment centrally as manifested by fundus autofluorescence imaging using a confocal laser ophthalmoscope. Optical coherence tomography has shown abnormalities in photoreceptors early in the disease which is associated with significant loss of scotopic and photopic function beginning nasal to fixation (Charbel-Issa 2010). This gives rise to pre-fixational blindness. With adaptive optics imaging it has become evident that cone loss is an early characteristic of the disease (Ooto 2011). Thus, this photoreceptor loss is intrinsic to the disorder, occurs early in the evolution of disease and may precede vascular change. In addition, it has been shown that (1) anti-VEGF treatment causes reversal of the blood vessel changes but does not influence progression of photoreceptor cell loss or functional loss; (2) the retina is thinner than normal in MacTel, unlike other macular conditions such as diabetic retinopathy in which edema can lead to retinal thickening; and (3) there is leakage of dye during fluorescein angiography similar to the leakage around the perifoveal area found in the deeper retinal circulation associated with retinal degeneration. It is also evident that opacification of the retina occurs very early in disease that is not due to retinal edema. Histopathological examination of a single post mortem eye taken from a patient with long-standing MacTel shows an abnormality of Mueller cells that might explain the retinal opacification if they act normally as light guides, as has recently been suggested (Reichenbach 2010), and a second pair of post-mortem eyes also show similar results (data not published). The role of the Mueller dysfunction in this condition requires further clarification.

The promise of growth factors, neurotrophic factors and cytokines as therapy for neuro-degenerative retinal diseases has been demonstrated in many animal models. The results of these studies using CNTF are summarized in Table 1. CNTF may have the potential for the treatment of Mac Tel type 2.

Table 1: Animal Studies using CNTF for various neurodegenerative diseases

Animal Studies using CNTF for various neurodegenerative diseases					
Animal Models of Retinal Degeneration					
		CNTF protect from retinal degeneration	Increased ERG response		
LaVail 1992	12 animal models	+			
Chong 1999	334ter-3 rats, 334ter-4 rats P23H-1 rats, Rdy cats	+			
LaVail 1998	rds/rds mice	+			
Cayouette 1998	rds/rds/mice	+	+		
Tao 2002	rcd1 dog model	+			
Bush 2002	rcd1 dog model	+	No effect on ERG		
Studies of animal models of Amyotropic Lateral Sclerosis (ALS)					
	Animal models	Increased survival time	Improved behavioral studies	Improved Motor function	Histology: Reduction in motor neuron loss
Lindsay 1994	Several	Increased by 40%			
Sagot 1995	mouse		+	+	+
Aebischer 1995	mouse		+	+	+
Studies of animal models of Huntington's Disease					
	Animal model	Neuroprotective effect	Cognitive and motor function improvement		
de Almeida 2001	Rat	+			
Reguilier 2002	Rat	+			
Mittoux 2000	Rat	+	+		
Emerich 1996	Rat	+	+		
Emerich 1997	Primate	+	+		

Using the rapid retinal degeneration rat RP model (S334ter-3 rat), one eye was selected and given an intra-vitreal injection of either NTC-201 cells (which express CNTF) or NTC-200 cells (the parent line for NTC-201 that do not express CNTF). The contralateral eye served as a same-animal control. At the end of this study, eyes injected with NTC-201 cells had 5-6 layers of photoreceptors in the outer nuclear layer (ONL) while eyes injected with NTC-200 cells and untreated eyes had only 1-2 layers of photoreceptors in the ONL. These data suggested that CNTF delivered intra-ocularly from genetically engineered NTC-201 cells had a protective effect on the photoreceptors present in the ONL in this model.

Histopathologic studies in naturally occurring and genetically engineered animal models of photoreceptor dysfunction and death, phenotypically modeling retinitis pigmentosa (RP), have indicated the promise of ciliary neurotrophic factor (CNTF) as an effective therapeutic agent for reducing photoreceptor loss associated with degeneration of the cells of the outer retina. CNTF is one of several neurotrophic factors that are produced endogenously by neurons or Mueller cells. CNTF has been demonstrated to be highly effective in retarding photoreceptor neuron loss in 12 animal models of retinal degeneration of various forms, including environmental light stress. Neurotech has demonstrated in two preclinical animal studies that CNTF-producing cells have a protective effect on the photoreceptors in the ONL. A rat model of RP suggested that CNTF-producing cells delivered as an intravitreal injection had a protective effect on the photoreceptors in the ONL. The treated eyes in the rat study had 5-6 layers of photoreceptors in the ONL compared to 1-2 layers in the untreated eyes. In a dog model of RP, the NT-501 device was also observed to have a protective effect on the photoreceptors. The treated eyes in the dog study had 5-6 layers in the ONL compared to 2-3 layers in the untreated eyes.

3 Scientific Rationale

3.1 Encapsulated Cell Technology (ECT)

This study is designed to provide long term observation of the ongoing effect of CNTF as delivered continuously via the NT-501 implant in patients with MacTel type 2. MacTel type 2 is a slowly progressive condition which may take many years to develop clinical symptoms and signs.

The Phase II NTMT-02 trial was limited to 24 months of controlled observation. While it is anticipated that two years of controlled observation should be sufficient to determine efficacy, it is possible that a longer period is necessary to observe a meaningful separation between the groups. This extension study provides the opportunity for that continued observation.

Previous experience with the NT-501 implant in studies of participants with geographic atrophy or retinitis pigmentosa suggests that the implant is capable of delivering detectable CNTF for up to 66 months. Output of CNTF from explanted devices, along with vitreous levels of CNTF, is consistent with the histologic findings at these various time points; the cells remain healthy and productive within the membranes (capsules), and continue to produce and deliver CNTF. These data support the hypothesis that NT-501 will continue to provide similar levels of CNTF to the

study eyes during this prolonged follow up period. Mean duration of implantations together with explant and vitreous CNTF levels are shown in Table 2.

Table 2: Ex vivo production rates and vitreous CNTF concentrations at the time of NT-501 explantation

Implant Duration	Explant (ng/ day)	#	Vitreous (pg/mL)	#
6 months	1.54 ± 0.54	(5)	58 ± 0	(1)
12-13 months	2.09 ± 0.59	(11)	64 ± 0	(2)
18-20 months	1.78 ± 0.86	(7)	57 ± 0	(1)
24 months	1.08 ± 0.48	(11)	46 ± 0	(1)
30-33 months	1.10 ± 0.73	(6)	17 ± 0	(1)
45 months	1.25 ± 0.00	(1)	55 ± 0	(1)
54 months	0.70 ± 0.04	(2)	---	
66 months	1.16 ± 0.00	(1)	36 ± 0	(1)

The Phase I NTMT-01 trial designed to assess the safety and tolerability of the NT-501 implant in patients diagnosed with MacTel type 2 has completed enrollment (N=7) and follow-up continues. No serious adverse reactions have been reported to date. Preliminary data confirm that the progression of visual impairment is slow in MacTel type 2. This is consistent with the findings of Heeren et al (2015) who suggested that patients with MacTel type 2 require prolonged follow up for appropriate evaluation of functional loss.

4 Study Objectives

- To investigate long term safety and efficacy of the NT-501 implant in participants previously enrolled in the NTMT-01 and NTMT-02 protocols.
- To investigate the change in the ellipsoid zone (area of [inner/outer segment] IS/OS loss) in participants previously enrolled in the NTMT-01 and NTMT-02 protocols, as measured by en face imaging by spectral domain optical coherence tomography (SD-OCT) in study eye(s).

5 Study Design and Methods

This is a prospective, multi-center, single-masked, sham-controlled follow-up study of the 7 participants that have completed 60 months of follow up in the open label NTMT-01 study (Cohort 1) and the 66 participants who completed 24 months of follow up in the NTMT-02 study (Cohort 2). All participants will be followed for an additional 48 months. Appendix 1 presents the scheduled examinations during the extended 48 month follow up period.

In the event that the NTMT-02 study is positive, Cohort 2 participants who received sham only may be eligible for active treatment in the control/non-treated eye.

6 Study Conduct

6.1 Efficacy Outcomes

Measures of efficacy have been determined on the principle that treatment will modulate deterioration of function or delay the increase in physical abnormalities. Analyses will be conducted separately for each cohort.

6.1.1 Cohort 1 Efficacy Outcomes

Efficacy outcomes to investigate the efficacy of CNTF produced by NT-501 include (all changes relative to NTMT-01 baseline measurements):

- Change in the ellipsoid zone (area of IS/OS loss) from baseline to Months 72, 84, 96 and 108.
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 72, 84, 96 and 108.
- Proportion of study eyes with a 35% or more increase from baseline in the ellipsoid zone (area of IS/OS loss) at Months 72, 84, 96 and 108.
- Change in BCVA from baseline to Months 72, 84, 96 and 108.
- Proportion of study eyes with 15 or more letter loss from baseline in BCVA at Months 72, 84, 96 and 108.
- Proportion of study eyes with 10 or more letter loss from baseline in BCVA at Months 72, 84, 96 and 108.

6.1.2 Cohort 2 Efficacy Outcomes

Efficacy outcomes to investigate the efficacy of CNTF produced by NT-501 include (all changes relative to NTMT-02 baseline measurements):

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

6.1.3 Safety Outcomes

The following ocular events (regardless of attribution) will be considered safety outcomes for both Cohorts if they occur:

- Rejection or extrusion of the NT-501 device.
- Development of peri-implant fibrosis, which either blocks the visual axis of the implanted eye or affects the lens or retina (minor/moderate fibrosis around the implant and/or the attachment point is an expected possibility and will be considered safe on ocular function). Attention should focus on fibrosis that may detach the retina.
- Development of choroidal or retinal neovascularization in the study eye.
- Adverse events affecting ocular function, which are different from those expected in the normal course of MacTel, which are potentially related to the surgical procedure, implant or CNTF including:
  - Endophthalmitis
  - Vitreal inflammation
  - Tractional retinal detachment

- Sectorial lens opacification
- Intraocular hemorrhage
- High or low Intraocular pressures
- Dry eye
- Self-reported change in dark adaptation
- Miosis
- Persistent chemosis
- Scleral leak

All adverse events (AEs) will be captured from the date of the Extension Study Consent whether or not considered to be related to the surgical procedure, NT-501 device, or CNTF. All adverse events occurring between the final NTMT-01 or NTMT-02 study visit will be considered part of the participants' Medical and/or Ophthalmic History.

An attempt will be made to differentiate between treatment-related AEs and AEs considered to be part of the normal progression of the disease. In addition, for treatment-related AEs, an attempt will be made to differentiate those the Investigator believes are due to the procedure, NT-501 device, or CNTF.

Analysis of safety events will be conducted separately for each Cohort.

6.2 Inclusion Criteria

To participate in this study, the potential participant **must meet** all of the following criteria:

1. Previously enrolled in the NTMT-01 or NTMT-02 protocol and received the NT-501 implant and/or underwent a Sham procedure.

2. Participant must be offered sufficient opportunity to review and to understand the informed consent form, agree to the form's contents and provide written informed consent.

6.3 Exclusion Criteria

There are no Exclusion Criteria.

6.4 Study Procedures

All study procedures will be carried out for both eyes at each visit. This will include both the study eye(s) and the fellow eye as applicable.

6.5 Concomitant Medications and Procedures

Any concomitant medications a participant is receiving at the start of the study or given for any reason during the study must be recorded in the source document, including start and stop dates and indication information. Recording of concomitant medications on the Case Report Forms (CRFs) must be done according to the instructions provided in the study Manual of Procedures (MOP). In addition, all ocular and non-ocular procedures must also be recorded in the Concurrent Procedures source document.

6.6 Prohibited Medications

Anti-herpetic nucleoside analogs (such as Acyclovir, Valaciclovir, Penciclovir and Famciclovir) or anti-cytomegaloviral nucleoside analogs (such as Ganciclovir or Foscarnet) are prohibited unless required for the safety of the participant and the infection is not expected to be self-limited without treatment. If used, these agents should only be used for the shortest possible duration. When possible, the sponsor, Neurotech, should be consulted prior to initiating treatment. Anti-influenza neuraminidase inhibitors (such as Zanamivir, Oseltamyvir) or other anti-influenza medications (such as Arbidol, Amantadine, Rimantadine) are permissible, if clinically indicated.

6.7 Masking

For participants in Cohort 2 there are different levels of masking within the study. The site staff refractionist, visual acuity examiner and photographers/imagers must remain masked to treatment assignment (NT-501 implant or sham procedure) for all visits. The Ophthalmologist, Surgeon and Clinic Coordinator will be unmasked to treatment assignment.

To ensure that the refractionist, visual acuity examiner and photographers/imagers remain masked to the randomized assignment, the Ophthalmologist, Surgeon and Clinic Coordinator are not to discuss the treatment received with the refractionist, visual acuity examiner and photographers/imagers.

All personnel in the Central Image Reading Center will be masked to whether the participant received the NT-501 implant or sham in a study eye(s).

Masking will remain as described above until all 66 participants in the NTMT-02 protocol have completed their original NTMT-02 Protocol Month 24 visit and data analysis has been completed. At that time, the Principal Investigators will be informed by the Sponsor that they

may unmask the participants. They may choose to do this at the participants' next scheduled visit or in a personalized communication to the participant. The sites will notify the Coordinating Center of the unmasking as outlined in the Manual of Procedures.

6.8 Exam Requirements

The following are examinations to be performed at the times indicated in Appendix 1.

1. Informed Consent and Eligibility Criteria Review
2. Demographics and Participant Contact Information Review
3. Medical/Ophthalmic History Review (carried over from NTMT-01 or NTMT-02)
    - Adverse events noted during the NTMT-02 and NTMT-01 study period and up to the first Extension Study visit will be added as Medical/Ophthalmic History as applicable.
4. Adverse Event Assessment (from the date of the NTMT-01/02 Extension Study consent)
5. Concomitant Medications
6. Complete Ophthalmic Examination including:
    - Manifest refraction
    - BCVA (This test will be performed by a masked certified technician)
    - Goldmann applanation tonometry
    - Slit lamp biomicroscopy
    - Dilated fundus examination
    - Implant site clinical examination
7. Ophthalmic Assessments including:
    - Microperimetry
    - Spectral Domain Optical Coherence Tomography (SD-OCT)
    - Fundus Autofluorescence imaging
    - Digital Color Fundus photographs

- Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO), in selected participants
    - Participants who underwent AOSLO for NTMT-02 will undergo a separate consent process at the AOSLO Center if they agree to continue participating.

8. Reading Speed –NTMT-02 (Cohort 2) participants only

- Monocular and binocular reading speed will be assessed using IReST cards. Reading speed will be used to document the participant's functional status with an important everyday visual task.

6.9 Study Visit Procedures

Visits will occur annually for a total of 4 years following the below schedule with visit windows of +/- 1 month.

	Visit 1	Visit 2	Visit 3	Visit 4
Cohort 1	72 Months	84 Months	96 Months	108 Months
Cohort 2	36 Months	48 Months	60 Months	72 Months

The following study procedures will be completed only at Visit 1:

- If the participant agrees to continue in the Extension study, the Principal Investigator or appropriate designee will obtain the participant's consent
- Eligibility Criteria Review
- Demographics and Participant Contact Information Review
- Medical/Ophthalmic History Review (carried over from NTMT-01 or NTMT-02 study, including any AE's that have occurred since the last participant visit)

The following study procedures will be completed bilaterally at all visits for all participants unless otherwise noted:

- Adverse Event Assessment (only at Visits 2, 3, and 4)
- Concomitant Medications
- Manifest refraction
- Best Corrected Visual Acuity
- Goldmann applanation tonometry
- Microperimetry
- Slit lamp biomicroscopy

- Dilated fundus examination
- Implant site clinical examination
- SD-OCT
- Fundus Autofluorescence imaging
- Digital Color Fundus photographs
- Reading Speed – (Cohort 2 participants only)
- Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO), in selected participants

  Participants who underwent AOSLO for NTMT-02 will undergo a separate consent process at the AOSLO Center if they agree to continue participating

7 Monitoring Participants and Criteria for Withdrawal

7.1 Safety Plan

A Safety Plan will describe roles and responsibilities, adverse event reporting methods and requirements, communication and interaction with the Data and Safety Monitoring Committee (DSMC), grading the severity of adverse events and other safety monitoring processes. The plan will be based on the safety reporting requirements for investigational new drug applications (INDs) found in 21 CFR part 312 and other applicable regulatory authorities' regulations.

7.2 Adverse Experience Reporting

All adverse events (AEs) either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously or in response to direct questioning, will be reported. Any adverse event regardless of severity or potential association with the device or CNTF or study procedures must be documented in study records by the Investigator and appropriately reported.

AEs will be reported within the participant's records and in the AdvantageEDC^{SM} system. All AEs should be entered into the data system within 5 business days of identification by the site personnel. All AEs will be recorded from the date of obtaining informed consent until the last study visit.

Serious adverse events (SAEs) will be followed until resolution or until stability is reached. In rare instances, this may include following the participant after completion of the study.

All serious adverse events should be entered into the data system within 24 hours of identification. If there are technical difficulties when entering the event into the EDC system, the

SAE will be reported to the Coordinating Center by fax communication, and these numbers will be provided in the Manual of Operations. All information reported by fax will need to be entered in the data system when it is available. All SAEs should be reported to local Institutional Review Boards/Ethic Committees (IRBs/IEs) per local IRB/IEC requirements.

7.3 Definitions

An **adverse event** is any untoward medical occurrence in humans, whether or not considered treatment- or procedure-related, which occurs during the conduct of a clinical trial. Any change in clinical status, routine labs, ophthalmological assessments etc., that is considered clinically significant by the Study Investigator or designee and requires intervention is considered an AE. Medical conditions or diseases present before a participant starts study treatment are only considered adverse events if they worsen after the participant starts study treatment (temporal association).

Suspected adverse reaction (Related Adverse Event) is any adverse event for which there is a reasonable possibility that the treatment caused the adverse event. A reasonable possibility implies that there is evidence that the treatment caused the event.

Serious Adverse Events

A serious adverse event (SAE) as determined by the Investigator or the Sponsor is any event that results in any of the following outcomes:

1. Death
2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the Investigator or Sponsor, at immediate risk of death from the event as it occurred.)
3. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
4. Inpatient hospitalization or prolongation of existing hospitalization.
5. Congenital abnormality or birth defect.
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Note that the term “serious” is not a measure of severity, but speaks to a very specific definition as noted in 1-6 above.

A hospitalization for an elective or cosmetic procedure, scheduled prior to enrollment or during the course of the study, unrelated to the medical condition under study, is excluded from this definition of a serious adverse event.

Unexpected Adverse Event

An unexpected adverse event is an event where the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the test article or the Investigator's Brochure. This includes an increase in the frequency or severity of a previously reported adverse event that is significantly above the rates known from previous experience with the test article.

Guidelines for Determining when Changes in Pre-Existing Conditions are Considered Adverse Events

Adverse events include illnesses with onset during the study or exacerbations of pre-existing illnesses. Exacerbation of pre-existing illness is defined as a clinically relevant increase in the severity of the illness as compared to the start of the study and should be considered when a participant requires new or additional treatment for that illness. Investigators should use the following guidelines to assess when an adverse event needs to be reported for a condition which results in a change to an ongoing medication and/or addition of a new medication:

- Addition of a new medication and/or change in ongoing medication due to an untoward (unfavorable and unintended) change in a participant's medical health for a disease/condition documented as ongoing at baseline.

- Addition of a new medication due to an untoward (unfavorable and unintended) change in a participant's medical health for a disease/condition not present at baseline.

Guidelines for Assessing Intensity of an Adverse Event

The Investigator should use the following definitions when assessing Intensity of an Adverse Event:

- MILD: Transient (< 48 hours) or mild discomforts, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities.

- MODERATE: Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required; hospitalization possible.
- SEVERE: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely.
- LIFE THREATENING: Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable.
- FATAL: Death

Guidelines for Determining Causality of an Adverse Event

The Investigator will answer the following question when assessing causality of an adverse event to study treatment: “Is there a reasonable possibility that the treatment caused the event?” A reasonable possibility implies there is evidence that the specific event was caused by the study treatment. An affirmative answer designates the event as a suspected adverse reaction, and the AE is therefore considered “related.” If the answer is no, then the AE is considered “unrelated.” For every related adverse event, the Investigator will determine the causality in relation to the surgical procedure - those related to the device itself, and the CNTF.

7.4 Obligations of Investigators

The Investigator is obligated to promptly report all adverse events. When submitting adverse event information, the Investigator may not delegate to someone other than a listed study physician the responsibility for reviewing the accuracy of the contents of an adverse event report. When reporting an adverse event, the Investigator must assign a severity grade to each event and also declare an opinion on the causality of the event relative to the study test article or procedure.

For any serious adverse event, the Coordinating Center and Sponsor must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Adequate information must be collected with supporting documentation to complete the standard electronic form set.

If the participant reaches the final scheduled follow-up visit, any new adverse events, as well as follow-up information for ongoing adverse events, must be recorded. For participants who

withdraw prematurely, adverse events should be followed until 30 days after last study visit. In any case, every attempt must be made by the Investigator to follow serious adverse events that are not resolved or medically stable within 30 days of the last study visit until they become resolved or medically stable.

7.5 Terminology for Adverse Event Descriptions

When reporting an adverse event, the event description should use the best matching terminology describing the event as found in the "Common Terminology Criteria for Adverse Events" (CTCAE, v 4.0). If an available CTCAE term fits the event well, no additional descriptors may be needed. However, any necessary descriptions should be used in order to clarify the event or to place it in an appropriate context. If an appropriate term matching the adverse event cannot be found in the CTCAE, the adverse event description should include a diagnosis, sign or symptom with additional information to facilitate subsequent categorization into MedDRA coding terms. Each reported event will be a single term or concept.

7.6 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an adverse event. A confirmed pregnancy in a participant (by urine or blood test) should be reported to the Coordinating Sponsor as soon as the Investigator has been made aware of the pregnancy. The decision on whether to remove the implant and terminate the participant from the study will be made by the Investigator and the participant following consultation with the Sponsor. The Investigator will use his/her expert judgment, based on an assessment of the potential benefit/risk to the participant, to determine if it is in the participant's best interest to continue participation in the study.

A pregnancy in the partner of a participant should also be reported to the Investigator who will in turn notify the Coordinating Center as soon as possible.

The pregnancy should be followed until birth. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be documented and followed-up on a form that will be provided by the Coordinating Center. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Coordinating Center. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study.

Elective abortion procedures, without complications, should not be considered as adverse events.

7.7 Notifying the Sponsor

The Investigators will provide the Coordinating Center with data of all SAEs as defined per the protocol on an ongoing basis. The Coordinating Center's Medical Monitor is responsible for notifying the Sponsor and will do so simultaneously with the reporting to the clinical database. As noted above, this should be within 24 hours of site awareness of the event. The Medical Monitor will review each SAE report and will determine whether the SAE must be reported to FDA/regulatory authorities on an expedited basis. The final decision for disposition regarding reporting to the FDA/regulatory authorities rests with the Sponsor or their designee. The IND Sponsor or their designee is responsible for submitting the SAE reports to FDA/regulatory authorities. The Coordinating Center will provide the DSMC with any safety reports submitted to FDA/regulatory authorities. The Coordinating Center will maintain copies of any SAE reports submitted to FDA/regulatory authorities by the Sponsor.

The Coordinating Center will provide these expedited reports to the individual site Investigators to submit to their respective IRB. Events that are serious, related to therapy and unexpected will be reported to FDA/regulatory authorities in 15 days or, for deaths and life threatening events, in 7 days (per 21 CFR 312.32).

7.8 Notifying FDA / Regulatory Authorities and the Data and Safety Monitoring Committee

After the SAE has been reported by the Principal Investigator and assessed by the IND Sponsor, the IND Sponsor or their designee must report the event to the appropriate regulatory authorities using one of these two options:

- Standard reporting (report in the annual report). This option applies if the AE is classified as one of the following:
    1. Serious, expected, suspected adverse reaction (serious, expected and related)
    2. Serious and not a suspected adverse reaction (serious and not related)
- Expedited reporting is required. This option applies if the AE is classified serious and unexpected suspected adverse reaction (serious, unexpected and related).

The Sponsor must report an adverse event as a suspected adverse reaction (related AE) only if there is evidence to suggest a causal relationship between the test article and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with test article.
- One or more occurrences of an event that is not commonly associated with the test article exposure, but is otherwise uncommon in the population exposed to the test article.
- Aggregate analysis of specific serious adverse events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of the test article therapy) that indicates those events occur more frequently in the test article treatment group than in a concurrent or historical control group.
- Any findings from clinical or epidemiological studies, analysis of data pooled across multiple studies, published or unpublished scientific papers or from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, General Investigational Plan section of the IND or other aspects of the overall conduct of the trial.

7.9 Reporting SAEs to the DSMC

The Coordinating Center will provide the DSMC with safety reports submitted to FDA/regulatory authorities as well as data on all SAEs on an ongoing basis.

The Investigator will ensure the timely dissemination of all AE information, including expedited reports and DSMC safety reviews, to the IRB and IEC in accordance with applicable local regulations and guidelines.

7.10 Early Termination or Participant Discontinuation

Participants may choose to withdraw from this study for any reason at any time without penalty or prohibition from enrolling in other clinical protocols.

The Investigator may discontinue a participant from the study if warranted. The Investigator and the Sponsor may also request the withdrawal of a participant because of non-compliance (e.g., missed visits), administrative reasons or any other valid and ethical reasons.

Reasons for participant discontinuation may include, but are not limited to, the following:

- Investigator determination that it is not in the best interest of the participant to continue participation
- Intercurrent illness
- Adverse event
- Worsening condition
- Any other safety concerns

If a participant withdraws or is discontinued from the study, they should return for an exit visit. The schedule of assessments for this visit is the same as that for the final visit.

The Sponsor may terminate the study earlier than planned for any reason. In the event of early termination, the Sponsor will notify the Investigators and IRBs of the decision and will provide all relevant information.

7.11Safety Monitoring

A medical monitor will be assigned to review safety information throughout the study. An independent Data and Safety Monitoring Committee (DSMC) will operate according to the DSMC Charter that will specify operations, roles and responsibilities and communication with the Sponsor.

8 Statistical Considerations

All analyses will be conducted separately for each Cohort.

8.1 Efficacy Outcomes

Cohort 1

Efficacy outcomes to investigate the efficacy of CNTF produced by NT-501 include (all changes relative to NTMT-01 baseline measurements):

- Change in the ellipsoid zone (area of IS/OS loss) from baseline to Months 72, 84, 96 and 108.
- Change in retinal sensitivity (dB) as measured by microperimetry from baseline to Months 72, 84, 96 and 108.
- Proportion of study eyes with a 35% or more increase from baseline in the ellipsoid zone (area of IS/OS loss) at Months 72, 84, 96 and 108.
- Change in BCVA from baseline to 72, 84, 96 and 108.

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

Cohort 2

The outcomes to investigate long term efficacy of CNTF or NT-501 include (all change relative to NTMT-02 baseline measurements):

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

8.2 Analyses in Support of the Efficacy Outcomes

Cohort 1

For continuous measures mean, median and distribution of change from baseline in BCVA, and enlargement of inner/outer segment discontinuity as measured by SD-OCT will be computed separately for study eyes and fellow eyes. For dichotomous outcomes proportions along with 95% confidence intervals will be computed separately for study eyes and fellow eyes.

Cohort 2

Continuous efficacy measures will be assessed using mixed effects models with an overall Type I error rate of 0.05 (no adjustments of the type I error rate will be made). Due to clustered data (data from two eyes for a percentage of the participants), the variability associated with the estimates of effect (mean difference) from a fixed effects model is likely to be biased, leading to

incorrect test statistics and confidence intervals. For example, if the correlation from paired eyes is ignored, the standard error for the treatment effect is likely to be overestimated when paired eyes from the same participant are in different treatment groups. For this reason, the unpaired t-test for the comparison of means between two treatment groups is not appropriate as it assumes that observations from the same cluster are independent. The appropriate statistical analysis of clustered data should take such correlation into consideration which can be accomplished for continuous outcome measures using a mixed effects model. The mixed effects model will incorporate both random (accounting for the correlation between eyes) and fixed effects (treatment) into the model and will be estimated with accompanying 95% confidence intervals and compared between treatment groups. For dichotomous outcomes, logistic regression incorporating the generalized estimation equation (GEE) methodology with accompanying 95% confidence intervals will be performed to determine if there are significant differences in the odds between the two treatment groups.

The efficacy analyses will be repeated to investigate the strength of potential predictors using multivariable mixed effects models or multiple logistic regression models. Examples of potential predictors include the following: baseline visual acuity, clinical site, participant's age at enrollment and gender.

8.3 Sample Size

A sample size of 66 participants, the number of participants enrolled in the NTMT-02 study and 7, the number of participants enrolled in the NTMT-01 study, will be eligible for enrollment.

8.4 Safety Analysis

Long term safety will be assessed through the summary of ocular and non-ocular adverse events, serious adverse events and pre-specified safety outcome as defined in Section 6.1.3 and will include frequency and descriptive tabulation. No formal statistical analysis will be employed. Safety analyses will include all participants who received the implant or sham.

8.5 Adverse Events

Adverse events will be tabulated by body system, high-level term and preferred term separately for each Cohort. Summaries of adverse events by severity will be provided. Separate summaries will be prepared for non-ocular and ocular adverse events, with events in the study eye(s) and fellow eye summarized separately for Cohort 1 and 2. Separate summaries of non-

ocular and ocular adverse events reported as related to the implant or the implant surgery will be prepared. Serious adverse events will be summarized similarly. Adverse events leading to discontinuation from the study will be listed and tabulated.

8.6 Data Quality Assurance

A Coordinating Center will have the primary responsibility for assuring that the quality of the data collected and reported in the study are of consistently high quality. Many factors contribute to the quality of the data, from the design and procedures of the trial to the analytic methods employed. The Coordinating Center works with the Reading Center on the design and implementation of a quality assurance program for grading images collected as part of the study.

The major quality assurance features of the study are:

- Standard data collection forms and procedures;
- Common protocol for eligibility, examination and follow-up of all participants in all clinical centers;
- **MASKED** assessment of the primary outcome measure and secondary outcome measures;
- Central masked grading of study images;
- Data entry into the study database and the Clinical Centers;
- Central, computer driven data editing for missing, invalid and suspect responses;
- Regular reporting of performance of all Clinical Centers;
- Monitoring visits to all Clinical Centers; and
- Certification of clinic staff and of imaging equipment.

9 Human Participant Protection

All participants will receive a verbal explanation from the Principal Investigator or his/her appropriate designee in terms suited to their comprehension of the purposes, procedures and potential risks of the study. In the opinion of the Principal Investigator or designee, the participants must be capable of comprehending the contents of the informed consent and able to sign an informed consent form, which must be obtained prior to enrollment. The participants will have an opportunity to review the consent form carefully and ask questions regarding this

study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves.

The participants' names will not appear on any of the data forms reported to the Coordinating Center. Participants will be identified by a study number. The date of birth of each participant will be collected in the data system. The information collected will remain confidential.

10 Study Risks

There are risks associated with the diagnostic procedures required for participants in this study. However, these are all standard procedures that are performed as part of a normal eye and medical exam. Some of the discomforts associated with the ocular exam include the following:

1. Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur.

2. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available.

3. In rare instances, the cornea may be abraded during measurement of intra-ocular pressure or use of a contact lens (used for examination purpose only and not a contact lens used to correct a participants' refractive error).

There are risks to the procedures required for participants in this study.

Optical Coherence Tomography is an FDA-approved imaging technique, which is not associated with any adverse events.

Fundus photography and autofluorescence are not associated with any adverse events, although some participants may experience mild discomfort due to the bright lights.

There are also risks associated with the operations performed during the NTMT-01 and NTMT-02 surgical visit to implant the device and/or perform the sham procedure. These risks will remain in the extension protocol in case any new procedure related adverse experiences are recorded. In general, the risks of intraocular surgery are very small. Some side effects could occur locally in the eye and could affect the participant's vision. There may be pain or infection, a small amount of bleeding, miosis, retinal detachment, cataract, vitritis and/or mild astigmatism.

In many cases, topical antibiotics and topical steroids can treat minor degrees of inflammation or infection. More serious infection or inflammation may require further surgery on the eye, likely with removal of the implant. The sham procedure of subconjunctival injection of lidocaine and inserting a final suture in the conjunctiva may be accompanied by subconjunctival bleeding, pain or infection which all can be readily treated without any functional changes or any other permanent structural changes.

A possible complication of the explant surgery, if necessary, to remove the NT-501 device is a retinal detachment. The probability of retinal detachment in the normal population is less than 1%. These other side effects are also possible (a probability of less than 1%):

- Bleeding in the eye
- Cataract
- Infection
- Inflammation inside the eye

Surgery to remove the device may result in pain, loss of vision or blindness in rare cases. Some of these side effects can be treated with medication either by mouth or injections in or around the eye. Some side effects may require laser or surgery on the eye to treat.

A small sample (about 0.1 mL) of the vitreous along with the device may be collected and shipped back to Neurotech for analysis.

If the participants have the NT-501 device removed, they will be invited to continue to participate in the Extension Study visits and assessments until the final Extension Study visit.

11 Investigator Requirements

This study will be conducted in accordance with Good Clinical Practice (GCP), using the guidance documents and practices offered by ICH and FDA, and in accordance with the Declaration of Helsinki. This study will also comply with the regulations 21 CFR Parts 50, 54, 56 and 312 under an IND application authorized by FDA.

11.1Informed Consent Form

A template Informed Consent Form will be provided to each site. The Sponsor, or their designee, must review and approve any proposed deviations from the provided Informed Consent template or any alternate consent forms proposed by the site (collectively, the

"Consent Forms") before IRB/IEC submission. The final IRB/IEC-approved Consent Forms must be provided to the Sponsor for regulatory purposes.

The Consent Forms must be dated and signed by the participant before his or her participation in the study. The case history for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the participant.

All signed and dated Consent Forms must remain in each participant's study file and must be available for verification by protocol monitors at any time.

The Informed Consent Form should be revised whenever there are changes to the procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the participant to participate. Participants must be re-consented with the most current (updated) version of the respective Consent Form during their participation in the study if deemed required by the Sponsor due to updated risks or new information becomes available that may affect the willingness of the participant to participate. This consent process must be documented in the case history.

11.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Forms, any information to be given to the participant and relevant supporting information must be submitted to the IRB/IEC by the Principal Investigator of each site for review and approval before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments and of any unanticipated problems involving risk to human participants or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, Investigators are required to promptly report to their respective IRB/IEC all unanticipated problems involving risk to human participants. Some IRBs/IECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study

treatments and are unexpected. Investigators may receive written IDE safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/IEC and archived in the site's Study File.

11.3Study Monitoring Requirements

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or their representative may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the Principal Investigator (and institution) must agree to grant the monitor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues. The Principal Investigator will permit the monitors, Sponsor representatives, US FDA, other regulatory agencies, Institutional Review Boards and the respective national or local health authorities to inspect facilities and records relevant to this study.

11.4Electronic Case Report Forms

Sites will receive training and a user's guide appropriate for electronic case report form (eCRF) completion. The eCRFs will be submitted electronically to the Coordinating Center and should be handled in accordance with instructions from the Coordinating Center.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate.

In addition, at the end of the study, the Investigator will receive participant data for his or her site in a readable format that must be kept with the study records.

11.5Source Data Documentation

Protocol monitors will perform ongoing site visits to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete and verifiable from source documents.

Source documents are where participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, memoranda, evaluation checklists, recorded data from automated instruments, copies of transcriptions that

are certified after verification as being accurate and complete, photographic negatives, magnetic media and medico-technical departments involved in the clinical trial.

To facilitate monitoring, the Investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits and IRB/IEC review. The investigational site must also allow inspection by applicable regulatory authorities.

11.6Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals, (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modifications of file), (3) protects the database from tampering and (4) ensures data preservation.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

11.7Disclosure of Data

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the participant, or unless permitted or required by law.

Medical information may be given to a participant's physician or other appropriate medical personnel responsible for the participant's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the US FDA and other regulatory agencies, national and local health authorities, Sponsor representatives and the IRB/IEC for each study site, if appropriate.

11.8Retention of Records

US FDA regulations (21 CFR §312.62[c]) and ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study, including eCRFs and consent forms, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a US IND/IDE, the Principal Investigator must comply with the record retention requirements set forth in the US FDA IND/IDE regulations and the relevant national and local health authorities.

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13 Appendix 1

Assessment / Examination Schedule

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