CLINICAL RESEARCH PROTOCOL

DRUG:	NT-501
STUDY NUMBER(S):	NTMT-03-A
PROTOCOL(S) TITLE:	A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia Type 2
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CLINICAL PROTOCOL APPROVAL FORM

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

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	Version 5.0:	12 October 2020 (Global)
	Version 6.0.	26 March 2021 (Global)
	Version 6.1	12 April 2021 (Global)
	Version 7.0	31 August 2021 (Global)

This study protocol was subject to critical review by the sponsor's appropriate protocol review committee, and the signatures below document approval. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice as described in the Code of Federal Regulations (CFR 21, parts 50, 54, 56, and 312), and according to applicable local requirements

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature	Date
Sponsor Representative: John Pollack, MD Chief Medical Officer Neurotech Pharmaceuticals, Inc.	John S. Pollack I am approving this document. John Pollack	09/02/2021 07:56 PM EDT
Medical Monitor Representative: Joseph Sliman, MD Medical Monitor, The Emmes Company, LLC	Joseph Sliman I am approving this document. Joseph Sliman	08/31/2021 11:18 AM EDT

NTMT-03-A

A PHASE 3, MULTICENTER, RANDOMIZED, SHAM-CONTROLLED, STUDY TO DETERMINE THE SAFETY AND EFFICACY OF NT-501 IN MACULAR TELANGIECTASIA TYPE 2

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to NT-501 are the confidential and proprietary information of Neurotech Pharmaceuticals, Inc., and except as may be required by federal, state, or local laws or regulations, may not be disclosed to others without prior written permission of Neurotech Pharmaceuticals, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my personnel to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonisation guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Neurotech Pharmaceuticals, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about NT-501 and the study.

Principal Investigator Name (printed)	Signature
Date	Site Number

STUDY SUMMARY

Title:	A Phase 3 Multicenter, Randomized, Sham-Controlled Study to Determine the Safety and Efficacy of NT-501 in Macular Telangiectasia Type 2
Rationale:	Preliminary findings suggest that employing NT-501 in participants with macular telangiectasia type 2 (MacTel) has the potential to provide benefit with an acceptable risk profile.
Target Population:	Participants with a confirmed diagnosis of MacTel
Number of Participants:	Approximately 112 participants
Objectives:	The overall objective of this study is to evaluate the efficacy and safety of NT-501 for the treatment of MacTel. Primary objective: • To determine the rate of change in the ellipsoid zone (EZ; inner segment/outer segment [IS/OS]) area loss over 24 months, as measured by study eye spectral-domain optical coherence tomography (SD-OCT) in participants with MacTel Secondary objective: • To evaluate the safety of NT-501 in participants with MacTel
Study Design:	Phase 3, prospective, multicenter, masked, sham-controlled study
Inclusion Criteria:	To participate in this study, the potential participant and at least 1 of their eyes **must meet** all of the following criteria: 1. Participant must have at least 1 study eye with a positive diagnosis of MacTel with evidence of fluorescein leakage typical of MacTel and at least one of the other features that include hyperpigmentation that is outside of a 500 micron radius from the center of the fovea, retinal opacification, crystalline deposits, right-angle vessels, or inner/outer lamellar cavities 2. Participant must have an IS/OS PR break and EZ (area of IS/OS loss) as measured by SD-OCT between 0.16 and 2.00 mm^2 3. Participant's best-corrected visual acuity (BCVA) is 54-letter score or better (20/80 or better) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at screening 4. Participant must have steady fixation in the foveal or parafoveal area and sufficiently clear media for good quality photographs 5. Participant must be greater than 21 years of age or less than 80 years of age at screening 6. Participant must be able to provide written informed consent to participate in the study, in accordance with the International Conference on Harmonisation Good Clinical Practices guidelines, and local regulations, before initiating any study-related procedures

7. Women of childbearing potential must agree to use highly effective contraception (Germany and France only)

Exclusion Criteria:

To participate in this study, the potential participant **must not meet** any of the following criteria. The ocular exclusion criteria are related to the study eye (unless indicated for either eye):

1. Participant is medically unable to comply with study procedures or follow-up visits
2. Participant received intravitreal steroid therapy for non-neovascular MacTel within the last 3 months
3. Participant has ever received intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye OR has, within the past 3 months, received intravitreal anti-VEGF therapy in the fellow eye at randomization
4. Participant has evidence of ocular disease other than MacTel that, in the judgment of the examining physician, may confound the diagnosis, procedures, or outcome of the study (eg, glaucoma, severe nonproliferative or proliferative diabetic retinopathy, uveitis)
5. Participant has a chronic requirement (eg, ≥ 4 weeks at a time) for ocular medications and/or has a diagnosed disease that, in the judgment of the examining physician, may be vision threatening or may affect the primary outcome (artificial tears are permitted)
6. Participant has evidence of intraretinal neovascularization or subretinal neovascularization (SRNV), as evidenced by hemorrhage, hard exudate, subretinal fluid or intraretinal fluid in either eye
7. Participant has evidence of central serous chorio-retinopathy in either eye
8. Participant has evidence of pathologic myopia in either eye
9. Participant has significant corneal or media opacities in either eye
10. Participant has had a vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
11. Participant has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the Age-Related Eye Disease Study (AREDS) clinical lens grading system
12. Participant has undergone lens removal in the previous 3 months or YAG laser within 4 weeks
13. Participant was a participant in any other clinical trial of an intervention (drug or device) within the last 6 months
14. Participant is on chemotherapy
15. Participant is pregnant or breastfeeding
16. Participant has a history of malignancy that would compromise the 24-month study survival
17. Participant with a history of ocular herpes virus in either eye

18. Participant has, in the opinion of the investigator, any physical or mental condition that would increase the risk of participation in the study or may interfere with the study procedures, evaluations, and outcome assessments
19. Participant has evidence of intraretinal hyperreflectivity by OCT

Primary Efficacy Endpoint:

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

Secondary Efficacy Endpoints:

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

Secondary Safety Endpoint:

- Number and proportion of participants with a loss in BCVA of 15 or more letters from baseline in the study eye using the ETDRS distance chart
- Number and proportion of participants with at least 1 treatment-emergent serious adverse event

Measures of Interest:

MacTel is a progressive disease. The natural history of MacTel suggests that patients will deteriorate markedly in near visual function and visual acuity over time and that this progression of the disease is evidenced by the increased loss of photoreceptors reflected in the increasing size of the area of EZ break.

SCHEDULE OF EVENTS

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

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

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

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

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

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

[e] Urine pregnancy tests are required for premenopausal female participants only

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

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

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

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

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LIST OF ABBREVIATIONS

AE	adverse event
AREDS	Age-Related Eye Disease Study
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CI	confidence interval
CNTF	ciliary neurotrophic factor
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DSMC	data and safety monitoring committee
eCRF	electronic case report form
ECT	encapsulated cell therapy
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	ellipsoid zone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HFM	hollow fiber membrane
ICF	informed consent form
ICH	International Conference on Harmonisation
IDE	investigational device exemption
IEC	independent ethics committee
IND	investigational new drug
IOP	intraocular pressure
IRB	institutional review board
IReST	International Reading Speed Texts
IS/OS	inner segment/outer segment junction line
ITT	intention-to-treat
MacTel	macular telangiectasia type 2
MAIA	Macular Integrity Assessment
MedDRA	Medical Dictionary for Regulatory Activities

NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
NHOR	Natural History and Observation and Registry Study of Macular Telangiectasia Type 2
OCT	optical coherence tomography
ONL	outer nuclear layer
PP	per protocol
PSNS	parasympathetic nervous system
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SE	standard error
SRNV	subretinal neovascularization
SUSAR	serious unexpected suspected adverse reaction
TEAEs	treatment-emergent AEs
US, USA	United States
VEGF	vascular endothelial growth factor
VLDLR	very low density lipoprotein receptor
Vldlr$^{-/-}$	very low density lipoprotein receptor knockout (mouse)

1. INTRODUCTION AND RATIONALE

1.1 BACKGROUND

Idiopathic macular telangiectasia type 2 (MacTel) is a bilateral neuro/vascular/glial degenerative condition of unknown etiology with characteristic neurosensory atrophy and perifoveal telangiectatic vessels that leak on fluorescein angiography [1]. Other characteristic lesions include loss of retinal transparency, crystalline deposits, a decrease or absence of macular pigment, and hyperplasia of the retinal pigment epithelium (RPE) in the macular area. Spectral-domain optical coherence tomography (SD-OCT) assessments show disruption of the photoreceptor inner segment/outer segment junction line (IS/OS line) or ellipsoid zone (EZ) [2], and hyporeflective cavities in both the inner and outer retina.

The natural course of MacTel is a gradual bilateral loss of vision with the progression of EZ loss, occasionally accompanied by subretinal neovascularization (SRNV), leading to severe vision loss [1]. Functional impairment may be mild with no impairment or only a slight reduction in binocular best-corrected visual acuity (BCVA) in the early stages of MacTel. However, loss of visual acuity in at least 1 eye is a frequently reported complaint [3, 4]. Notably, even in the presence of deep paracentral scotomata and reduced reading ability, distance visual acuity may be relatively preserved [5, 6]. However, a decrease in visual acuity may eventually occur with disease progression. There appear to be essentially 2 different factors contributing to the decline of visual acuity [7, 8]. Initially, there may be a slow drop in visual acuity, usually not below 20/50, which may be due to structural foveal changes, eg, a low-grade chronic vascular leakage or degenerative hyporeflective cavities in the inner retina. The second and more important factor for a decline in visual acuity is atrophy of the foveal photoreceptors, which may result in eccentric fixation and a visual acuity of around 20/200. Such photoreceptor dropout initially occurs temporal to the foveola causing the characteristic deep paracentral scotomata and may later spread centrally. If a relatively faster drop in visual acuity is observed, an associated macular hole, the development of a retinal pigment epithelial hypertrophy, or neovascular complex may be suspected. Visual acuity below 20/200 is rarely observed but there may be marked functional impairment in very late disease stages, with large central areas of photoreceptor atrophy or due to the development of a larger neovascular complex [4, 9].

There is a large body of evidence to support the use of ciliary neurotrophic factor (CNTF) as a potential therapy for retinal degenerative diseases [10, 11]. Histopathologic studies in naturally occurring and genetically engineered animal models of photoreceptor dysfunction and death that phenotypically model retinitis pigmentosa (RP), have indicated the promise of 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 Müller cells. CNTF has been demonstrated to be highly effective in retarding photoreceptor neuron loss in animal models of retinal degeneration of various forms, including environmental light stress. In 2 preclinical animal studies conducted by Neurotech Pharmaceuticals, Inc., CNTF-producing cells have been shown to have a protective effect on the photoreceptors in the outer nuclear layer (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 had 5 to 6 layers of photoreceptors in the ONL compared with 1 to 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 had 5 to 6 layers in the ONL compared with 2 to 3 layers in the untreated eyes [12].

Although CNTF is an attractive therapeutic candidate for neurodegenerative diseases, it is significantly handicapped by its extremely short half-life. Neurotech Pharmaceuticals, Inc. has developed the NT-501 device to treat retinal degenerative diseases. Human safety data is available from studies in participants with MacTel, RP, atrophic age-related macular degeneration (AMD), and glaucoma. The NT-501 devices are implanted into

the vitreous cavity with a simple surgical procedure performed under local anesthetic. These devices consist of a sealed semipermeable hollow fiber membrane (HFM) capsule surrounding a scaffold of 6 strands of polyethylene terephthalate yarn, which have been loaded with CNTF-secreting NTC-201.6A cells.

Safety data from approximately 250 participants implanted with the NT-501 device (nominal dose 20 ng/24 hours) suggest that adverse events (AEs) are generally limited to those related to the implant procedure. A number of participants have reported miosis, which is believed to be directly related to CNTF. During early development, a number of participants developed inflammation following implantation. This was subsequently related to impurities in the membrane. Trace to mild inflammation is seen postoperatively in a minority of participants and typically clears by 3 months. In the Phase 2 study, one episode of delayed inflammation (grade 3) was noted at 6 months and resolved by 12 months.

Studies of NT-501 in RP and AMD did not demonstrate any potential benefit. However, in the NTMT-02 study of 67 participants (99 eyes randomized 1:1) with MacTel, there was a statistically significant reduction in the rate of progression of MacTel in the eyes implanted with NT-501 as compared with the eyes that underwent the sham procedure. The mean (standard error [SE]) area of EZ break increased by 0.218 (0.049) mm^2 in the implanted eyes and by 0.270 (0.050) mm^2 in the sham eyes. The difference between groups in the increase of the MacTel lesion (0.052 mm^2) was statistically significant ($p = 0.039$, 1-sided). The mean change in retinal sensitivity as measured by microperimetry was not different between the treated and sham eyes. However, when the aggregate retinal sensitivity (dB) was compared with the corresponding area affected by MacTel, a difference between treated and sham eyes was detected. This difference was consistent with the slower growth of the MacTel lesion in the treated eyes. There was a significant difference between treatment groups in reading speed at 24 months (13.5 words read per minute, $p = 0.016$). Specifically, the implanted eyes had not deteriorated from baseline (0.03 words read per minute), but the sham eyes showed impairment in reading speed relative to baseline (-13.5 words read per minute). The mean (SE) macular thickness was significantly increased in the treated population when compared with the sham group (NT-501: +5.45 [3.02] μ; sham: -4.97 [2.85] μ; $p = 0.007$). The mean (SE) pupil size was also significantly reduced in the implanted eyes as compared with the sham eyes (difference between groups: 0.922 [0.13] mm, $p < 0.0001$).

As of September 2019, a total of 64 participants (94 study eyes) were consented in the Phase 2 Extension Study, and of those, 92 study eyes had EZ break grading at 36 months and 86 had EZ break grading at 48 months. The mean (standard error [SE]) area of EZ break at 36 months was 0.149 (0.035) mm^2 in the implanted eyes and 0.241 (0.032) mm^2 in the sham eyes. The difference between groups in the increase of the MacTel lesion (0.092 mm^2) was statistically significant ($p = 0.022$, 1-sided). The mean (standard error [SE]) area of EZ break at 48 months was 0.211 (0.059) mm^2 in the implanted eyes and 0.208 (0.056) mm^2 in the sham eyes. The difference between groups in the increase of the MacTel lesion (0.077 mm^2) did not meet statistical significance ($p = 0.488$, 1-sided). There was not a statistically significant difference between treatment groups in reading speed at 36 months (10.6 words read per minute, $p = 0.093$), or 48 months (5.4 words read per minute, $p = 0.202$). The mean (SE) pupil size for all NTMT-02 Extension Study participants was reduced in the implanted eyes as compared with the sham eyes at 36 months (difference between groups: 0.805 [0.14] mm, $p < 0.0001$) and 48 months (difference between groups: 0.844 [0.15] mm, $p < 0.0001$).

Consistent with the experience of the NT-501 device in studies of RP and dry AMD, the device was generally well tolerated in the Phase 2 study. No participant had the implant removed during the course of the study. The AEs considered related to the device could be grouped into those resulting from the procedure and those related to the parasympathetic agonistic effect of CNTF. One participant (2 eyes) reported an ophthalmic serious adverse event (SAE) of an extended hospital stay (1 day) because of blurred vision immediately following the procedure. This event resolved without sequelae.

In the current study, participants with a confirmed diagnosis of MacTel and an EZ break area of at least 0.16 mm^2 and no greater than 2.00 mm^2 will be randomly assigned to 1 of 2 treatment groups: implantation of the NT-501 device or sham surgery with no implant. A single device will be inserted into the study eye for the 24 to 48-month duration of the study.

The study will be conducted in full compliance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa), the guidelines set forth by the International Conference on Harmonisation (ICH), current Good Clinical Practice (GCP), and in compliance with local regulatory requirements and all of the applicable United States (US) Code of Federal Regulations (CFR), 21 CFR parts 50 and 312.

1.2 STUDY RATIONALE

Historically, MacTel has been considered a vascular disorder of the retina. This concept was largely based on clinical observation and limited histopathology. With the initiation of a natural history study including over 700 participants followed for more than 5 years, it has become apparent that MacTel may, in fact, not be primarily a retinal vascular disease but, rather, one involving photoreceptor and glial cell abnormalities as well. The primary objectives of the MacTel natural history study are to enroll participants with MacTel and to document structural and functional changes over time using multiple real-time imaging modalities and functional assessments.

The most common group of patients with MacTel has leakage that occurs during fluorescein angiography with manifest retinal capillary dilatation but without retinal thickening. These individuals typically are diagnosed in their fifth or sixth decade of life, although it is likely that there are clinical manifestations of the disease at much earlier times that are not detected because the patients remain asymptomatic. Both sexes are affected. 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 SRNV may develop.

As noted previously, the natural history study of MacTel has demonstrated that photoreceptor loss is intrinsic to this disorder. Although antivascular endothelial growth factor therapy reduced the vascular permeability, it did not influence the progression of photoreceptor cell loss or functional loss. A mouse model in which the very low density lipoprotein receptor (VLDLR) has been knocked out (ie, $Vldlr^{-/-}$ mice) mimics many of the characteristics of the human disease, including focal disruption of photoreceptors coincident with the abnormal outer retinal-penetrating vessels [13]. The new vessels observed in the human disease and the $Vldlr^{-/-}$ mouse exhibit relatively mild permeability defects and are accompanied by glial activation and disruption of the RPE. Thus, in the absence of clinically significant leakage or hemorrhage, neuronal cell death due to increased oxidative stress caused by proximity to the abnormal vessels is observed. Using the $Vldlr^{-/-}$ mouse model, it has been demonstrated that targeted delivery of a neurotrophic factor, neurotrophin-4, to sites of abnormal neovascularization significantly reduced photoreceptor degeneration and protected against visual dysfunction, even in the face of persistent microvascular abnormalities in these mice [14].

Two postmortem donor eyes from elderly individuals with MacTel were analyzed histopathologically and immunohistochemically [15, 16]. Both eyes had extensive disruption of foveal anatomy and substantial reduction in Müller glial cell marker expression, as well as many other neural and glial abnormalities. Based on this observation, a knockout mouse was evaluated, in which Müller glial cells were depleted leading to photoreceptor apoptosis, vascular telangiectasis, blood-retinal barrier breakdown and, later, intraretinal neovascularization [17]. In the mature retina, Müller glia are a major source of CNTF. Intravitreal CNTF had no effect on wildtype retinas, but significantly reduced both the area of cone outer segment loss and the number of apoptotic cells in the ONL between 7 and 10 days after tamoxifen-induced Müller cell ablation in transgenic mice. Functional rescue after CNTF administration was not assessed in this study.

Imaging using SD-OCT has recently demonstrated a neurodegenerative process in MacTel, with photoreceptor damage mapped to loss of vision. Similarly, adaptive optics scanning laser ophthalmoscopy (AOSLO) reveals unique dark regions in the cone mosaic and decreased cone density associated with decreased vision, even in areas with normal vasculature, which suggests that this feature represents early neuronal changes involved in the pathogenesis of MacTel [18]. These studies, taken together with the clinical observations of MacTel, support the concept that delivery of neurotrophic molecules, such as CNTF, may prevent photoreceptor degeneration in diseases with outer retinal vascular abnormalities such as MacTel. Thus, we believe we have an established rationale for using CNTF delivered by NT-501 to treat MacTel.

1.2.1 Pharmacokinetics

CNTF is not detectable in the serum of participants with an intravitreal NT-501 device in situ. Pharmacokinetic sampling of the vitreous is invasive and potentially harmful to participants.

1.2.2 Preclinical Pharmacology

The half-life of CNTF is extremely short and is measured in minutes[19].

1.2.3 Potential for Drug-Drug Interactions

None.

1.2.4 Clinical Adverse Event Profile

Most AEs in the clinical studies of NT-501 have been related to the implantation procedure and were generally mild and well tolerated. The majority of these events resolve within a few days. A small proportion of participants have reported miosis. No discontinuations due to this event have been reported in the MacTel clinical studies.

1.2.5 Elevations in Liver Function Tests

No changes in aspartate aminotransferase, alanine aminotransferase, or serum bilirubin were seen in early studies of NT-501 in RP or atrophic AMD.

1.2.6 Potential Risk of Testicular Injury

There is no evidence from previous clinical trials or from preclinical toxicology studies to suggest a risk of testicular injury.

1.2.7 Potential Risk to Fetal Development

No embryo-fetal/teratogenicity studies have been conducted for the development of NT-501. Studies to support the systemic use of human CNTF from the treatment of amyotrophic lateral sclerosis were performed in rats and rabbits (Syntex Discovery Research, Palo Alto, USA). At doses up to 300 µg/kg/day, no effects were seen on fertility in male and female rats. At doses up to 1000 µg/kg/day in rats and 10 µg/kg/day in rabbits, there was no evidence of fetal abnormality. The risk of these events in this trial is considered to be low given the fact that the CNTF produced by the NTC-201-6A cell line is of human origin. There is no detectable CNTF in patient plasma. CNTF has been extensively studied in animal and human neurological models and is considered a neuroprotectant.

1.2.8 Dosing Regimen

A single device is implanted once and remains in situ for the duration of the study. Only one configuration of the NT-501 device will be used in this study that delivers a nominal dose of CNTF 20 ng/device/day.

2. STUDY OBJECTIVES

The overall objective of this study is to evaluate the efficacy and safety of NT-501 for the treatment of MacTel.

Primary objective:

- To determine the rate of change in the EZ (IS/OS) area loss over 24 months, as measured by study eye SD-OCT in participants with MacTel

Secondary objective:

- To evaluate the safety of NT-501 in participants with MacTel

3. STUDY ENDPOINTS

Measures of efficacy have been determined on the principle that treatment will modulate deterioration of function or delay the increase in structural abnormalities.

3.1 PRIMARY ENDPOINTS

The primary efficacy endpoint will be the rate of change in the EZ (IS/OS) area loss from the Baseline visit through the Month-24 Visit, as assessed in the study eye of subjects with MacTel using SD-OCT

3.2 SECONDARY ENDPOINTS

3.2.1 Secondary Efficacy Endpoints

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

3.2.2 Secondary Safety Endpoints

- Number and proportion of participants with a loss in BCVA of 15 or more letters from baseline in the study eye using the Early Treatment Diabetic Retinopathy Study (ETDRS) distance chart
- Number and proportion of participants with at least 1 treatment-emergent serious adverse event (SAE)

4. STUDY PLAN

4.1 STUDY DESIGN

This is a Phase 3, prospective, multicenter, masked, sham-controlled study of approximately 112 study participants with MacTel.

All participants are to be followed through the 24-Month Visit, where 1 month is defined as 30 days. Originally the subset of participants enrolled early into the study were to be followed through a 36-Month Visit and/or a 48-Month Visit, based on the date of the surgical procedure. The rate of change in the EZ (IS/OS) area loss over the Month-36 and Month 48 time points were identified as secondary endpoints. A decision has been made to discontinue the Month-36 and Month 48 study visits because the limited number of subjects completing these

visits does not provide sufficient statistical power to demonstrate a treatment effect for these secondary endpoints. The Sponsor decision to terminate this study early is not related to any safety or any adverse event related to the study treatment or surgical procedures related to the implantation.

With the current protocol amendment, the changes to the study visit schedule include the following:

(1) Subjects who will complete the Month-24 visit after 01 December 2021 will not complete their scheduled Month-36 and/or their Month-48 study visits. These study participants will exit the study when they complete the Month-24 visit.

(2) Subjects who have completed the Month-24 visit and have Month 36 and/or Month 48 visits scheduled before or on 01 December 2021 will exit from the study after completing these scheduled visits.

(3) Subjects who have completed the Month-24 visit and have Month 36 and/or Month 48 visits scheduled after 01 December 2021 will not complete these visits but will complete a safety check-in call and exit the study by 01 December 2021.

With the current study design, all participants will have a screening period of up to 30 days. During that time, a single baseline image of the EZ lesion will be taken to establish eligibility and the study baseline. The EZ line break area for eligibility will be determined by the reading center. Images will be reviewed for quality and may be repeated if necessary and obtained within the screening period (30 days). Two independent masked readers will determine lesion area from a single acceptable image. If the 2 estimates of area are within 10% and at least 1 measure is ≥ 0.16 and ≤ 2.0 mm^2, the MacTel lesion will be deemed eligible. If the 2 readings differ by more than 10%, an arbitrating reader will estimate the area. If the third reading is within 10% of either of the first 2 estimates, then the third and selected primary readings will be used to establish eligibility. Baseline EZ area will be the mean of the 2 qualifying estimates.

The implant surgery/sham procedure in the study eye should be completed within 30 days of randomization and/or up to 58 days from screening. Only 1 study-eligible eye of each participant will be designated as the study eye. Participants will be randomized (1:1) to receive the NT-501 implant or to undergo the sham procedure in the study-eligible eye. The implant surgery/sham procedure will occur on Day 0. Participants will be assessed on Day 1, Week 1 (± 2 days), Month 1 (± 7 days), Month 3 (± 14 days), Month 6 (± 30 days), Month 12 (± 30 days), Month 16 (± 30 days), Month 20 (± 30 days), and Month 24 (± 30 days). Note that, in regions other than France, a telephone contact will be made at Month 1 (± 7 days) and Month 3 (± 14 days) instead of a clinic visit. A subset of participants, based on the date of the surgical procedure, will be assessed at Month 36 (± 30 days and Month 48 (± 30 days). Upon completion of the 24, 36, or 48-month observation, all participants will be followed for safety and disease progression in a nested substudy of the existing Natural History and Observation and Registry Study of Macular Telangiectasia Type 2 (NHOR) [20].

4.1.1 Efficacy Variables

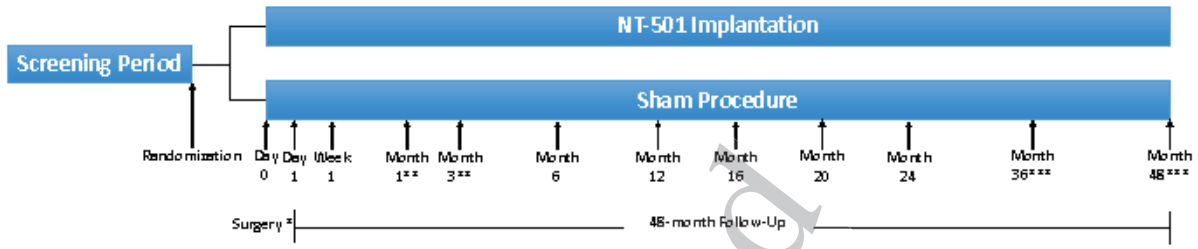
The efficacy variables in this study include EZ area (ie, area of IS/OS loss) measured by SD-OCT, retinal sensitivity measured by Macular Integrity Assessment (MAIA) microperimetry, reading speed using the International Reading Speed Texts (IReST) Worksheets developed by the IReST Study Group [21], and participant responses to the NEI-VFQ-25.

4.1.2 Safety Variables

Safety will be evaluated by monitoring AEs and SAEs, results of ophthalmic examinations (including slit-lamp biomicroscopy and dilated fundus parameters, as well as measurements of BCVA and intraocular pressure [IOP]).

All AEs will be captured whether or not considered to be related to the surgical procedure, implant, or CNTF. The incidence of reported AEs will be compared between the treated and sham participants, particularly with respect to ocular AEs. 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 that the investigator believes are due to the device itself, to CNTF, or to the implant/sham procedure.

4.1.3 Study Schematic



* The implant surgery/sham procedure in the study eye should be completed within 4 weeks of randomization and/or up to 58 days from screening.
** In regions other than France, a telephone contact will be made at Month 1 (± 1 week) and Month 3 (± 2 weeks). In France, at these time points, participants will be assessed at clinic visits.
***A subset of participants, based on the date of the surgical procedure, will be assessed at Month 36 (± 4 weeks) and Month 48 (± 4 weeks).

5. POPULATION

This study is open to all persons with confirmed MacTel who meet the inclusion/exclusion criteria.

5.1 NUMBER OF PARTICIPANTS

This study will enroll approximately 112 participants with confirmed diagnosis of MacTel. Enrolled participants will be those who have received either a NT-501 implant or undergo the sham procedure.

5.2 INCLUSION CRITERIA

No persons shall be excluded on the basis of gender, race, or ethnicity.

To participate in this study, the potential participant and at least 1 of their eyes **must meet** all of the following criteria:

1. Participant must have at least 1 study eye with a positive diagnosis of MacTel with evidence of fluorescein leakage typical of MacTel and at least one of the other features that include hyperpigmentation that is outside of a 500 micron radius from the center of the fovea, retinal opacification, crystalline deposits, right-angle vessels, or inner/outer lamellar cavities
2. Participant must have an IS/OS PR break and EZ (area of IS/OS loss) as measured by SD-OCT between 0.16 and 2.00 mm^2
3. Participant's BCVA is 54-letter score or better (20/80 or better) as measured by the ETDRS chart at screening
4. Participant must have steady fixation in the foveal or parafoveal area and sufficiently clear media for good quality photographs

5. Participant must be greater than 21 years of age or less than 80 years of age at screening
6. Participant must be able to provide written informed consent to participate in the study, in accordance with the ICH GCP guidelines, and local regulations, before initiating any study-related procedures
7. Women of childbearing potential must agree to use highly effective contraception (Germany and France only)

5.3 EXCLUSION CRITERIA

To participate in this study, the potential participant **must not meet** any of the following criteria. The ocular exclusion criteria are related to the study eye (unless indicated for either eye):

1. Participant is medically unable to comply with study procedures or follow-up visits
2. Participant received intravitreal steroid therapy for non-neovascular MacTel within the last 3 months
3. Participant has ever received intravitreal anti-vascular endothelial growth factor (VEGF) therapy in the study eye OR has, within the past 3 months, received intravitreal anti-VEGF therapy in the fellow eye at randomization
4. Participant has evidence of ocular disease other than MacTel that, in the judgment of the examining physician, may confound the diagnosis, procedures, or outcome of the study (eg, glaucoma, severe nonproliferative or proliferative diabetic retinopathy, uveitis)
5. Participant has a chronic requirement (eg, ≥ 4 weeks at a time) for ocular medications and/or has a diagnosed disease that, in the judgment of the examining physician, may be vision threatening or may affect the primary outcome (artificial tears are permitted)
6. Participant has evidence of intraretinal neovascularization or SRNV, as evidenced by hemorrhage, hard exudate, subretinal fluid or intraretinal fluid in either eye
7. Participant has evidence of central serous chorio-retinopathy in either eye
8. Participant has evidence of pathologic myopia in either eye
9. Participant has significant corneal or media opacities in either eye
10. Participant has had a vitrectomy, penetrating keratoplasty, trabeculectomy, or trabeculoplasty
11. Participant has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 2, or a nuclear opacity > standard 3 as measured on the Age-Related Eye Disease Study (AREDS) clinical lens grading system
12. Participant has undergone lens removal in the previous 3 months or YAG laser within 4 weeks
13. Participant was a participant in any other clinical trial of an intervention (drug or device) within the last 6 months
14. Participant is on chemotherapy
15. Participant is pregnant or breastfeeding
16. Participant has a history of malignancy that would compromise the 24-month study survival
17. Participant with a history of ocular herpes virus in either eye
18. Participant has, in the opinion of the investigator, any physical or mental condition that would increase the risk of participation in the study or may interfere with the study procedures, evaluations, and outcome assessments

19. Participant has evidence of intraretinal hyperreflectivity by OCT

5.4 PARTICIPANT SCREENING

Potential participants will be consented prior to initiation of any screening procedures. All screening procedures may be completed in 1 visit or may take place on more than 1 day if convenient for the participant or clinical site. All screening procedures should be completed within 30 days.

5.5 DEVIATION FROM INCLUSION/EXCLUSION CRITERIA

No deviations from the stated inclusion/exclusion criteria will be allowed.

5.6 MASKING

There are different levels of masking within the study. The participant is masked to treatment assignment throughout the study. The refractionist, visual acuity examiner, and photographers/imagers must be masked to treatment assignment (implant or sham procedure) for all follow-up visits. The ophthalmologist, surgeon, and clinic coordinator will be unmasked to treatment assignment. To ensure that the participant remains masked to the randomized assignment, the ophthalmologist, surgeon, and clinic coordinator are to not discuss the treatment received with the participant. All personnel at the image reading center will be masked to whether the participant received the implant or sham in the study eye.

6. STUDY CONDUCT

All participants will have a screening period of up to 30 days. The implant surgery/sham procedure in the study eye should be completed within 30 days of randomization and/or up to 58 days from screening. Only 1 study-eligible eye per participant will be allowed in this study. Participants with 1 study eye that meets the inclusion criteria will be randomized (1:1) to receive the NT-501 implant or sham procedure in the study-eligible eye. If both eyes qualify for the study, the study eye will be chosen as part of the centralized randomization process. The eye will be deemed eligible only after the reading center has reviewed all baseline images.

6.1 STUDY PROCEDURES BY TIME POINT

Study eyes will receive the NT-501 implant or undergo the sham procedure on Day 0 and will be assessed on Day 1, Week 1 (± 2 days), Month 1 (± 7 days), Month 3 (±14 days), Month 6 (± 30 days), Month 12 (± 30 days), Month 16 (± 30 days), Month 20 (± 30 days), and Month 24 (± 30 days). Note that, in regions other than France, a telephone contact will be made at Month 1 (± 7 days) and Month 3 (± 7 days) instead of a clinic visit. A subset of participants, based on the date of their surgical procedure, will be assessed at Month 36 (± 30 days) and Month 48 (± 30 days). Participants who will reach the Month 36 and/or Month 48 timepoint will be required to provide informed consent at the start of their next visit. At baseline, SD-OCT and fluorescein angiography will be performed to confirm diagnosis and to exclude SRNV. Participants will be followed at regular intervals in the first and second years of follow-up, where 1 month is defined as 30 days. All SD-OCT, microperimetry, fluorescein angiogram, autofluorescence and fundus photographic images will be read centrally at the reading center by masked, trained readers.

Beginning in February 2020 in European and Australian sites and March 2020 in U.S. sites, planned assessment visits were delayed due to the COVID-19 pandemic. To account for such delays, sites were instructed to perform the assessments at the earliest availability following the scheduled timepoint. For visits impacted by COVID-19, the acceptable time windows were adjusted for select visits as follows: Month 12 (-30 days / +119 days), Month 16 (+119 days), Month 20 (+119 days), Month 24 (+119 days).

In the event of extenuating circumstances of the COVID pandemic whereby an in-clinic follow-up visit cannot be conducted within the designated visit window, a Safety Check-In call should be performed, and an out of window in-clinic visit should be performed as soon as possible. However, if the out of window visit cannot be performed within 119 days of the originally scheduled visit, i.e prior to the start of the subsequent protocol designated visit window, the missed visit should not be performed. Following a missed or out of window visit, every effort should be made to return the participant to the original protocol-specified visit schedule.

7. DESCRIPTION OF STUDY PROCEDURES

7.1 STUDY PROCEDURES

The following are examinations to be performed at the times indicated in the schedule of study procedures, where 1 month is defined as 30 days. Additional information related to these examinations is provided in the procedure specific instructions. All ocular evaluations/procedures will be completed bilaterally unless otherwise indicated.

- Medical evaluation, as would be standard for any surgical procedure or anesthesia (the tests to be performed will be site-specific)
- Complete ophthalmic examination including:
    - Manifest refraction
    - BCVA (This test will be performed using the ETDRS chart by a masked certified technician who was not involved in the implant or sham surgery.)
    - Goldmann applanation tonometry
    - Measurement of undilated pupil diameter
    - Slit-lamp biomicroscopy
    - Dilated fundus examination
    - Ophthalmic assessments including:
        - Microperimetry
        - SD-OCT
        - Fluorescein angiography
        - Color digital fundus photography
        - Fundus autofluorescence imaging
- Urine pregnancy test for premenopausal female participants
- NEI-VFQ-25
- Reading Speed
    - Monocular reading speed will be assessed using the IReST cards developed by the IReST Study Group 21, and will be used to document the participant's functional status with an important everyday visual task.

Goldmann applanation tonometry, measurement of undilated pupil diameter, slit-lamp biomicroscopy, dilated fundus examination, and urine pregnancy testing will be performed following standard procedures at each site.

7.2 STUDY VISIT PROCEDURES

7.2.1 Screening/Baseline Procedures (Visit -1)

Screening procedures may be completed over more than 1 visit to accommodate schedules and to lessen participant burden. All screening evaluations should be completed within 30 days of the initial screening visit in order to be used to establish eligibility.

In the event that a participant is rescreened and the rescreening occurs within 6 months of the initial screening, fluorescein angiography, fundus autofluorescence imaging, and color fundus photography will not be repeated; the participant's initial screening results for each of these assessments will be used as their baseline.

Once the individual has indicated interest in participation, the principal investigator or appropriate designee must obtain the participant's written consent. Once the consent is obtained, the participant may initiate screening assessments. The results of all screening evaluations must be reviewed and the participant must be found eligible prior to randomization. Once a participant is determined to be eligible for the study, surgery should be completed within 4 weeks of randomization and/or up to 58 days from screening.

The screening examinations and imaging must include the following:

- Medical evaluation, standard for any surgical procedure or anesthesia (the specific tests to be ordered will be site-specific), may be performed on the day of surgery
- Demographics; medical and ophthalmic history
- Concomitant medications
- NEI-VFQ-25
- Reading speed
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Fluorescein angiography
- Fundus autofluorescence imaging
- Color digital fundus photography
- Urine pregnancy test for female participants of childbearing potential

The study investigator at each site, in conjunction with the reading center (SD-OCT, fluorescein angiography), will evaluate potential participants for study enrollment according to the inclusion and exclusion criteria as outlined in Sections 5.2 and 5.3.

7.2.2 Visit 0: Randomization and Surgery

If the participant meets all study criteria, including those determined by the reading center, and continues to agree to participate in the study, then the implant surgery/sham procedure date may be confirmed. ***The implant surgery/sham procedure in the study eye should be completed within 30 days of randomization and/or up to 58 days from screening.*** The study's electronic data capture (EDC) system will assign the randomization assignment. The participant study eye will be randomized using the EDC system prior to the implant surgery/sham procedure. The study eye will be randomized (1:1) to receive the NT-501 implant or to undergo the sham procedure. Only 1 eye per participant will be randomized. If both eyes qualify for the study, the study eye will be selected using the centralized randomization process.

On the date of the surgery, the investigator will confirm that no change in the participant's general condition has occurred that would exclude study participation.

The following evaluations/procedures will be conducted during this visit:

- If not already completed: medical evaluation, standard for any surgical procedure or anesthesia (the specific tests to be ordered will be site-specific)
- Any further medical/ophthalmic history
- Any additional concomitant medications
- AE assessment (from the time surgery begins)
- BCVA (may be performed within 1 week prior to the day of surgery)

7.2.3 Visit 1: 1 Day Postsurgery

Participants must return to the clinic 1-day postsurgery and will undergo the following procedures:

- AE assessment
- Review concomitant medications
- Goldmann applanation tonometry (study eye only)
- Slit-lamp biomicroscopy (study eye only)
- Dilated fundus examination (study eye only)
- Implant/sham site examination (study eye only)

7.2.4 Visit 2: One Week Postsurgery (± 2 Days)

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- Manifest refraction, only required if there is deterioration of 10 or more letters from baseline
- BCVA
- Goldmann applanation tonometry (study eye only)
- Measurement of undilated pupil diameter (study eye only)
- Slit-lamp biomicroscopy (study eye only)
- Dilated fundus examination (study eye only)
- Implant/sham site examination (study eye only)

7.2.5 Visit 3: 1 Month Postsurgery (± 7 Days)

In France only, the following evaluations/procedures will be conducted during this visit:

- AE assessment

- Review concomitant medications
- Manifest refraction, only required if there is deterioration of 10 or more letters from baseline
- BCVA
- Goldmann applanation tonometry (study eye only)
- Measurement of undilated pupil diameter (study eye only)
- Slit-lamp biomicroscopy (study eye only)
- Dilated fundus examination (study eye only)
- Implant/sham site examination (study eye only)

In regions other than France, telephone contact will be made with the participant to determine the following:

- AE assessment
- Review concomitant medications

7.2.6 Visit 4: 3 Months Postsurgery (± 14 Days)

In France only, the following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- Manifest refraction, performed if there is deterioration of 10 or more letters from baseline
- BCVA
- Goldmann applanation tonometry (study eye only)
- Measurement of undilated pupil diameter (study eye only)
- Slit-lamp biomicroscopy (study eye only)
- Dilated fundus examination (study eye only)
- Implant/sham site examination (study eye only)

In regions other than France, telephone contact will be made with the participant to determine the following:

- AE assessment
- Review concomitant medications

7.2.7 Visit 5: 6 Months Postsurgery (± 30 Days)

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

*7.2.8 Visit 6: 12 Months Postsurgery (± 30 Days)**

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- NEI-VFQ-25
- Reading speed
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

*7.2.9 Visit 7: 16 Months Postsurgery (± 30 Days)**

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

*7.2.10 Visit 8: 20 Months Postsurgery (± 30 Days)**

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

7.2.11 Visit 9: 24 Months Postsurgery (± 30 Days)

Participants who have a Month-24 study visit scheduled after 01 December 2021 will complete the visit and exit from the study at the M24 visit.

The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- NEI-VFQ-25
- Reading speed
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Fundus autofluorescence imaging
- Color digital fundus photography
- Implant/sham site examination (study eye only)

7.2.12 Visit 10: 36 Months Postsurgery (± 30 Days)

Participants who have completed the Month 24 visit and have a Month-36 study visit scheduled before 01 December 2021 will complete the visit and exit from the study at the Month-36 study visit. Participants who have completed the Month 24 visit and have a Month-36 study visit scheduled after 01 December 2021 will not complete this visit. These subjects will complete a safety check-in call and exit the study by 01 December 2021. The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- NEI-VFQ-25
- Reading speed
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

7.2.13 Visit 11: 48 Months Postsurgery (± 30 Days)

Participants who have completed the Month-24 and Month-36 visits and have a Month-48 study visit scheduled before 01 December 2021 will complete the visit and exit from the study at the Month-48 study visit. Participants who have completed the Month-24 and Month-36 visits and have a Month-48 study visit scheduled

after 01 December 2021 will not complete this visit. These subjects will complete a safety check-in call and exit the study by 01 December 2021.
The following evaluations/procedures will be conducted during this visit:

- AE assessment
- Review concomitant medications
- NEI-VFQ-25
- Reading speed
- Manifest refraction
- BCVA
- Goldmann applanation tonometry
- Measurement of undilated pupil diameter
- Slit-lamp biomicroscopy
- Microperimetry
- Dilated fundus examination
- SD-OCT
- Implant/sham site examination (study eye only)

*During the COVID-19 pandemic, the acceptable visit window is extended to +119 Days from the original scheduled visit for Month 12, 16, 20, and 24 visits, as described in Section 6.1.

7.3 CLINICAL LABORATORY TESTS

All premenopausal female participants will undergo a urine pregnancy test at the screening visit.

7.4 PROTOCOL DEVIATIONS

Protocol deviations will be reported to the sponsor as they are discovered.

8. INVESTIGATIONAL PRODUCT MANAGEMENT

8.1 DESCRIPTION

8.1.1 Formulation

The study device is the NT-501 implant, NT501.6A.02 encapsulated cell therapy (ECT), delivering a nominal CNTF dose of 20 ng/device/day.

8.1.2 Storage

Storage of the shipping container is at room temperature, which is not to exceed 55°C (131°F) or fall below −20°C (−4°F) and must be used within the “use by” date. Storage of the box at temperatures outside this range could result in the internal temperature of the box and the implant exceeding the allowable range of 16°C to 37°C. If a planned implant surgical procedure is delayed such that the shipped investigational product will be in the shipping container for a period beyond the identified “use by” date, then Neurotech Pharmaceuticals Inc. must be notified and an alternate/replacement shipment will be provided.

8.2 PACKAGING AND SHIPMENT

The NT-501 device is contained within the primary packaging, which is comprised of a sealed clear plastic container that contains the transport medium. The NT-501 device is suspended within the transport medium by a titanium clamp which, in turn, is held in position by a luer cap that is twisted onto the flange of the primary packaging. The inner surfaces of the primary packaging, the transport medium, and all other component surfaces are sterile. In addition, as long as the secondary packaging remains sealed, the exterior of the primary packaging within the secondary packaging is maintained sterile. Product labeling is located on the exterior, nonsterile side of the secondary packaging seal. This container is protected in an insulated transport carton.

8.3 DOSE AND ADMINISTRATION

The study device is the NT-501 implant, NT501.6A.02 ECT (delivering a nominal CNTF dose of 20 ng/device/day), which will be implanted per randomization and will remain in situ for the duration of the study. There are no plans to remove the device, except in the case of participant intolerance or complications such as infection or inflammation.

8.4 ACCOUNTABILITY

All investigational product and supplies provided by the sponsor and used during this study must be maintained in a secure location. The investigator has overall responsibility for ensuring that the investigational product is stored in a safe, limited-access location under the specified appropriate storage conditions. Limited responsibility may be delegated to an unmasked nominated representative, but this delegation must be documented.

The investigator agrees not to supply any NT-501 device to any person not enrolled in this study or to any person not delegated to perform investigational product handling.

The investigator/recipient will acknowledge receipt of the investigational product, indicating shipment content and condition. A record of the TempTale® readings must be kept for each shipment. Damaged supplies will be reported to the sponsor. Accurate records will be kept for all investigational products supplied and received. The date of implantation will be recorded.

Investigational product will not be returned to the sponsor except in an instance of device inspection failure where the sponsor requests that the failed device or a portion thereof should be returned for investigation.

All investigational product not implanted per protocol into enrolled study participants must be destroyed on site as dictated by the appropriate biohazardous waste standard operating or study specific procedure at the participating institution (if appropriate). Investigational products should only be destroyed after investigational product accountability has been performed and all investigational products are accounted for. Duplicate devices provided at the time of surgery that are not required for implantation should be marked in large letters “NOT FOR HUMAN USE” following successful implantation of the original device until the time of destruction.

9. CONCOMITANT MEDICATIONS

Any concomitant medications a participant is receiving at the start of the study or given for any reason during the study (except for routine medications given for ocular procedures required by the protocol, such as a topical anesthetic), including over the counter, supplements and herbal formulas, must be recorded in the source document, including start and stop dates, dosing, route of administration, and indication information. Recording of concomitant medications on the case report forms (CRFs) must be done according to the instructions

provided in the study regulatory binder. In addition, all ocular and non-ocular procedures (excluding study surgery and procedures) must also be recorded in the source document, including start and stop dates. Recording of procedures on the CRFs must be done according to the instructions provided in the study regulatory binder.

9.1 PROHIBITED CONCOMITANT THERAPY

Ocular administration of subconjunctival or intravitreal antibiotics is prohibited unless treating a sight-threatening condition. The ocular administration of gentamicin or other aminoglycosides topically, peri-ocularly, or by injection is prohibited unless treating a sight-threatening condition for which no other alternatives are appropriate. Systemic administration of aminoglycosides should also be avoided. Aminoglycosides are known to be toxic to RPE cells and ocular administration could harm the cells in the NT-501 device.

10. ADVERSE EVENTS

An AE 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, ophthalmological assessments, etc., that is considered clinically significant by the study investigator and requires intervention is considered an AE. Medical conditions or diseases present before a participant starts study treatment are only considered AEs if they worsen after the participant starts study treatment (temporal association).

A suspected adverse reaction (related AE) is any event for which there is a reasonable possibility that the treatment caused the AE. A reasonable possibility implies that there is evidence that the treatment caused the event.

10.1 DOCUMENTING ADVERSE EVENTS

All AEs, either observed by the investigator or their medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported. Any AE regardless of severity or potential association with the NT-501 device, CNTF, or the study procedures must be documented in study records by the investigator and appropriately reported.

All AEs will be reported within the participant's records and in the EDC system. All AEs should be entered into the data system as soon as possible after identification by the site personnel. All AEs will be recorded from the time of surgery until the last study visit.

10.2 ASSESSMENT OF INTENSITY

Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an AE:

- 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

10.3 ASSESSMENT OF CAUSALITY

Guidelines for Determining Causality of an Adverse Event

The investigator will answer the following question when assessing causality of an AE 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 AE, the investigator will determine the causality in relation to the surgical procedure, to the device itself, and to CNTF.

Regarding relatedness of AEs, there are 3 possibilities. These include the following:

- Related to surgical procedure:
  Ocular events that occur immediately following the surgical procedure or later if they are directly related to the procedure
- Related to the device itself:
  These would include malposition of the device with impingement of the participant's visual field, inflammation of the vitreous, or visible deterioration of the device on inspection via the ophthalmoscope
- Related to CNTF:
  The known events related to CNTF release in the eye are clearly listed in the reference safety information of the investigator's brochure

10.4 ADVERSE EVENT FOLLOW-UP

Until the participant reaches the final scheduled follow-up visit, any new AEs, as well as follow-up information for ongoing AEs, must be recorded. For participants who withdraw prematurely, AEs should be followed until 30 days after last study visit.

10.5 REPORTING OF PREGNANCY

Pregnancy, in and of itself, is not regarded as an AE. A confirmed pregnancy in a participant (by urine or blood test) should be reported to the CRO as soon as the investigator has been made aware of the pregnancy. The decision on whether to remove the implant and withdraw 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 CRO as soon as possible.

The pregnancy should be followed until birth. The outcome of all such pregnancies (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed-

up on a form that will be provided by the CRO. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the CRO. 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 AEs.

11. SERIOUS ADVERSE EVENT

11.1 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received NT-501
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of Terms

Life-threatening: An AE is life-threatening if the participant is at immediate risk of death from the event as it occurred; ie, it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be reported as AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either serious or nonserious according to the usual criteria.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacity: An AE is disabling or incapacitating if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

11.2 REPORTING SERIOUS ADVERSE EVENTS

The investigators will report data on all SAEs within 24 hours of site awareness of the event. If there are technical difficulties when entering the event into the EDC system, the SAE will be reported to the contract

research organization (CRO) via fax communication or safety group email; the fax numbers and email address will be provided in the regulatory binder. All information reported by fax or email will need to be entered in the data system when it is available. All SAEs should be reported to local IRBs/independent ethics committees (IECs) per local IRB/IEC requirements.

The medical monitor will review each SAE report and will determine whether the SAE must be reported to the Food and Drug Administration (FDA)/regulatory authorities on an expedited basis. The final decision for disposition regarding reporting to the FDA and other 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 sponsor will ensure that the data and safety monitoring committee (DSMC; see Section 14.3) receives any safety report submitted to FDA/regulatory authorities. The CRO will maintain copies of any SAE reports submitted to FDA/regulatory authorities by the sponsor.

The CRO will provide expedited reports to the principal investigator at each individual site to submit to their respective IRB/IEC. Events that are serious, related to therapy, and unexpected (serious unexpected suspected adverse reaction [SUSAR]) will be reported to FDA/regulatory authorities within 15 days or within 7 days for deaths and for events deemed life-threatening by the investigator (per 21 CFR 312.32).

All 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. Every attempt must be made by the investigator to follow SAEs that are not resolved or medically stable within 30 days of the last study visit until they become resolved or medically stable.

11.3 NOTIFYING FDA/REGULATORY AUTHORITIES

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 1 of these 2 options:

- Standard reporting (report in the annual report). This option applies if the AE is classified as one of the following:

  Serious, expected, suspected adverse reaction (serious, expected, and related)

  Serious and not a suspected adverse reaction (serious and not related)

- Expedited reporting. This option applies if the AE is classified as SUSAR (serious, unexpected, and related).

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

- A single occurrence of an event that is uncommon and known to be strongly associated with study treatment
- One or more occurrences of an event that is not commonly associated with study treatment, but is otherwise uncommon in the population exposed to the study treatment
- Aggregate analysis of specific SAEs 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 study treatment) that indicates those events occur more frequently in the study 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

11.4 REPORTING SAES TO THE DSMC

The CRO will provide the DSMC with the data for all SAEs on an ongoing basis as described in the charter.

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.

12. STATISTICS

12.1 GENERAL PROCEDURES

This is a Phase 3 study to evaluate the efficacy and safety of NT-501 compared with the sham procedure for the treatment of MacTel.

One eligible study eye from each participant will be randomized in a 1:1 ratio as follows:

- Surgery to receive 1 NT-501 device implant delivering a nominal CNTF dose of 20 ng/device/day
- Sham surgery

Randomization: Two treatment assignments with a 1: 1 (NT-501 surgery: sham procedure) allocation scheme for each of the 2 protocols (Protocol A and Protocol B). The actual treatment assignment (NT-501 surgery or sham procedure) will be shown within Advantage eClinical. Randomization is unrestricted. One randomization list per protocol will be generated. There will be no stratification for prognostic factors.

The biostatistician will prepare detailed statistical procedures, listings, table shells and figures in a separate statistical analysis plan (SAP). The following key components will be considered, and a detailed description will be documented in the SAP:

- Descriptions of primary and secondary endpoints and how they will be measured
- Statistical methods and any applicable alternative methods (eg, model nonconvergence) used to analyze the endpoints
- Justifications for sample size calculations
- Multiple testing approaches
- Approaches to account for missing data

A biostatistician will perform statistical analyses as agreed with the sponsor according to the SAP. Any additional or supplemental data analyses performed independently by an investigator shall be submitted to the sponsor for review.

Analysis Populations:

The modified intention-to-treat (mITT) population will consist of all randomized participants who received surgery (NT-501 or sham surgery), all of whom will be analyzed in the treatment group to which they were assigned regardless of compliance or other protocol deviations.

The per-protocol (PP) population will be a subset of the mITT population and will include all available data from participants who follow the protocol without major protocol deviation. The PP population will be used for analyses of primary and key secondary efficacy variables. Participants will be analyzed according to the randomized treatment. The determination of all protocol violations and any data excluded from the efficacy analysis will be made prior to locking the final database.

The safety population will include the data from all randomized participants who receive any treatment and have at least 1 safety measurement. Participants will be analyzed in the group according to the treatment received, and no subjects (or data) will be excluded from this dataset because of protocol violations that occur during the study.

The efficacy analysis will be conducted on the mITT population and on the PP population. Safety analyses will be performed using the safety population. The handling of participants with missed visits or visits occurring outside the specified windows will be considered in the SAP.

If both eyes of a participant qualify for the study, the study eye will be selected using the centralized randomization process.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum), and categorical variables will be summarized using the count and percentage of participants in each category.

Significance Level:

A significance level, α, of 0.05 will be used for statistical testing of the primary and secondary endpoints.

A hierarchical testing procedure will be applied to secondary efficacy analyses to control the overall type I error rate. In the case that the primary efficacy analysis is statistically significant at a 2-sided type I error rate of 0.05, the secondary efficacy endpoints will be tested at a 2-sided type I error rate of 0.05 in the order listed below. If any of the secondary endpoints are found to be not statistically significant at the 2-sided 0.05 level, the hypothesis testing will stop. Later endpoint(s) after a non-statistically significant result will be summarized descriptively and p-values may be produced for descriptive purposes only.

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

Accounting for Missing Data:

Every attempt will be made to collect data per the protocol and to avoid missing data. As such, dropouts and missing data are expected to be minimal, but can inevitably occur. For cases with unavoidable missing data, no imputation will occur.

As the efficacy endpoints in this study are longitudinal, measured over the course of multiple observations over time, the minimum requirement for completion of the study is to have measurements at Baseline and Month 24, plus at least one interim visit for the primary efficacy endpoint. Imputation methods may be implemented for sensitivity assessments of primary and secondary efficacy analyses should the dropout rate and proportion of missing values be higher than expected or should there be missing data due to an identifiable cause unrelated to study procedures or treatments (e.g. delayed visits due to COVID-19).

Covariates and Subgroups:

There are no plans to adjust the primary efficacy analysis for baseline characteristics and disease status. Exploratory analyses will be conducted to assess the potential contribution of a number of baseline disease characteristics as well as study site on the likelihood of a response to treatment.

Exploratory analyses will be performed to assess the potential impact of various prognostic factors on efficacy. Appropriate statistical models will be fit with these factors as covariates and the effect of treatment will be assessed after adjusting for other significant risk factors. Risk factors will include, but are not limited to age, race, sex, and baseline EZ area.

12.2 SAMPLE SIZE

Sample size calculation is based on the comparison of the 2 groups over 24 months incorporating a longitudinal mixed effects model. The number of participants, N, in each of the 2 groups [22] is calculated as follows: We assume that, in the NT-501 group, the response of change in EZ area is as follows:

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

For the sham group the sham equation holds as follows:

$$Y_{ij} = \beta_{0\,Sham} + \beta_{1\,Sham} x_{ij} + \varepsilon_{ij}, \quad j = 1, \dots, n; i = 1, \dots, m$$

Both groups have the same number of participants (m), $x_{ij} = x_j$ represents the duration between the first and the jth visit in which case $\beta_{1\,Sham}$ *and* $\beta_{1\,NT-501}$ represents the rates of change in Y for Sham and NT-501, respectively, and each person is measured at the same time points, and each participant has n repeated observations of EZ area at baseline, 12, 16, 20 and 24 months (where months will be converted to years).

The number of participants, m, in each of the 2 groups [22] is calculated as follows:

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

where $d = \beta_{1\,Sham} - \beta_{1\,NT-501}$ and s_x^2 is the within-subject variance of x_j.

Using the above equation with a Type 1 error rate of 0.05 (2-sided); σ^2= 0.0256; ρ = 0.6; s_x^2 = 0.47 and n = 5 (baseline and 12, 16, 20 and 24 months) we have 80% power with a sample size of 50 participants per treatment group to detect a difference in rate of change 0.037 mm^2/year in the EZ area in the NT-501 group versus the sham group. The sample size will be increased to 56 participants per treatment group (112 total participants) to provide adequate power in the analysis of the population evaluable for efficacy.

The statistical model will be a random intercept model as follows:

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

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

$$H_o: \beta_3 = 0 \ \ versus \ H_1: \beta_3 \neq 0$$

12.3 STATISTICAL METHODS

12.3.1 Primary Endpoint(s)

The primary hypothesis is that NT-501 will slow the rate of change in the EZ (IS/OS) area loss. The primary efficacy endpoint will be analyzed using the mITT population (main analysis) but restricted to only those participants with at least 3 visits recorded. Baseline, Month 24, and at least one of Month 12, 16, or 20. A similar analysis will also be conducted with the PP Population.

The primary efficacy variable will be the rate of change that will be determined by using values from the EZ area as measured by SD-OCT. EZ area will be defined as the mean of 2 independent readings of the single eligible SD-OCT enface image taken at baseline and Months 12, 16, 20, and 24. A longitudinal mixed model will include EZ area as the dependent variable, a random intercept term to account for within subject variability, treatment group, time as a continuous variable, and the interaction between treatment and time. Time will be captured as the relative study day (defined as days since date of surgery) of the respective efficacy assessment and will include the days corresponding to the Baseline, Month 12, 16, 20, and 24 visits. The difference in the rate of change in EZ area over 24 months (to be computed by including baseline and Months 12, 16, 20, and 24 EZ measurements will be compared using a random intercept model and the corresponding 95% confidence interval (CI), SE, test statistic, and p-value of the difference between treatment group parameters by computing the parameter estimate for the treatment by time interaction term. An Unstructured covariance structure will be implemented as with continuous time there will be a single parameter each for between and within participant variability.

12.3.2 Secondary Endpoint(s)

The secondary endpoints will be analyzed using the mITT population and the PP population to test for superiority of NT-501 over sham. The secondary endpoints are listed below:

- Mean change in aggregate sensitivity of microperimetry within the EZ line break area through 24 months
- Mean change in reading speed from baseline through 24 months
- Mean change in the NEI-VFQ-25 near activities subscale score from baseline through 24 months

Continuous secondary outcomes will be analyzed using a longitudinal mixed effects model and the corresponding 95% CI, SE, test statistic, and p-value of the difference between treatment group means at the 24-month time point will be computed. For the mixed effects model, fixed effects will include the treatment group (between-participant factor) and the visit (within-participant factor). The unstructured covariance matrix is preferred for this analysis. If the model does not converge, the "best" covariance structure will be chosen based on Akaike's Information Criteria [23].

12.3.3 Analysis of Safety

Safety analyses will be performed on all participants who underwent either implant surgery or the sham procedure. The assessment of safety will be based on the summary of ocular and nonocular treatment-emergent AEs (TEAEs) and ophthalmic examinations. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs.

The TEAEs will be presented by treatment group (NT-501 versus sham). Summaries for TEAEs include the following: all TEAEs regardless of causality, treatment-related TEAEs, ocular TEAEs, treatment-related ocular TEAEs, TEAEs by intensity, SAEs, and TEAEs leading to discontinuation from the study.

The number and proportion of participants with a loss in BCVA of 15 or more letters from baseline in the study eye will be tabulated and presented by treatment group.

Detailed methods for the analysis of all endpoints will be outlined in the SAP.

12.3.4 Demographic and Baseline Characteristics

Participant demographic and baseline characteristics will be summarized for the ITT analysis population. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual participant data listings.

12.4 INTERIM ANALYSIS

No interim analysis for efficacy is planned for this study.

Prior to the completion of the study and database lock, summaries of the distribution of timing of efficacy visits (excluding any efficacy variables themselves) will be compared between treatment arms to determine if the pattern of visit attendance is comparable between treatment arms.

In addition, masked summaries of the overall results will be analyzed to determine appropriate parameterization of time as a continuous or categorical variable for the primary efficacy analysis. The determination of non-linearity will be concluded if the observed pattern of EZ area loss response over time follows a distinctly non-linear trend. Assessment will be made through an overall linear regression goodness-of-fit analysis, including review of a residual plot from a simple linear regression.

The analysis will be limited in scope and will not reveal unmasked results. No type I error adjustment will be made.

13. STUDY RISKS

Studies of intravitreal CNTF delivered by ECT have been performed in human participants with RP, atrophic AMD, and MacTel. A total of 180 human participants have been exposed to the 20 ng/day dose in randomized clinical studies. This is the same dose that will be tested in the proposed Phase 3 trial. A further 59 participants were exposed to a lower dose and in this group, miosis and change in dark adaptation were not reported.

Miosis: In the controlled clinical studies of AMD, RP, and MacTel (Phase 1 and Phase 2 studies), 40 of 180 (22.2%) participants reported miosis as an AE. These events were reported by participants. The prevalence of these findings was confirmed by the DSMC in their review of the data. The DSMC in their review of these data confirmed that the potential benefit outweighed the risk of this event.

The intracellular mechanisms through which the trophic factor CNTF regulates cholinergic development were examined in sympathetic neuron cultures [24]. Treatment with CNTF increased levels of choline acetyltransferase activity significantly, thus confirming the parasympathetic agonist effect of CNTF. Stimulation of the parasympathetic nervous system (PSNS) results in constriction of the pupillary muscles. Constriction of the

pupil occurs when the circular muscle, controlled by the PSNS, contracts. This is the most likely mechanism for CNTF causing miosis. At lower doses in the Phase 2 studies of RP, this effect was not observed.

In addition, in the Phase 2 study of MacTel, pupil size was measured routinely throughout the duration of the study in all participants. The majority of eyes that received the implant had a reduction in the size of the pupil of approximately 1 mm. This effect was not seen in sham eyes but was present in over 90% of all treated eyes. The reason that only approximately 20% of the participants complained about the miosis is possibly related to the lack of any clinical symptoms and of noticeable effect for the participants. Certainly, no participant asked to have the device removed as a result of noting this well-described drug effect.

Delayed Dark Adaptation: This AE has only been reported in study participants with MacTel with 11 cases out of the 55 (22%) implanted eyes in the Phase 1 and 2 studies. In the studies of participants with RP and atrophic AMD, this AE was not reported. The cause of the delayed dark adaptation is not well understood, but a plausible explanation is that it is related to either miosis and/or the observed effect on photoreceptors following treatment with CNTF [10]. CNTF treatment results in a change in rod photoreceptor nucleus phenotype, featuring an increase in euchromatin and an increase in nuclear size. Chronic stimulation of retinal cells with CNTF has been shown to affect gene expression in photoreceptors including reduction of phototransduction genes such as rhodopsin in animal models [25]. As rod photoreceptors are more light sensitive than cone cells and are almost entirely responsible for night vision, it is possible that the CNTF-mediated changes in the rod photoreceptors may affect the participant's ability to adapt to the dark. The reason why this AE is limited to a small subpopulation of the participants with MacTel is not well understood.

An increase in retinal thickness is observed in the majority of all eyes treated with CNTF at the dose proposed for study in Phase 3. Taken together, the preclinical data in dogs and the fact that macular thickening is seen only in the treated eyes, suggest that the AE of delayed dark adaptation may well be a direct consequence of CNTF treatment.

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

- 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.
- 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.
- In rare instances, the cornea may be abraded during measurement of IOP or the 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 associated with the procedures required for participants in this study. The fluorescein angiogram requires injection of dye in the participant's arm. Local subcutaneous infiltration of dye may create discomfort and temporary staining of the skin (< 5% risk). There is a chance of fainting, ecchymosis at the site of injection, and a remote possibility of cellulitis from the needle track. After the dye injection, some participants (< 5%) may experience nausea that usually passes after a few seconds, and rarely, participants vomit.

Allergic reactions to fluorescein are uncommon; reactions may cause hives and itching. These reactions are usually treated with oral or injectable antihistamines as needed. Anaphylaxis from fluorescein is extremely rare and may be life-threatening. Fluorescein dye routinely causes a yellowing/orange color to the skin and urine that generally passes in 24 hours.

Imaging using OCT is an FDA-approved technique, which is not associated with any AEs.

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

There are also risks associated with the operations to implant and explant the device and with the sham procedure. 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, all of which can be readily treated without any functional changes or any other permanent structural changes.

The risks of the sham procedure include: the risk of pre-operative sedation, the risk of the local anesthetic, and the risk of the superficial conjunctival incision and suture.

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

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

Surgery to remove the NT-501 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 treatment with a laser or surgery on the eye. A small sample (about 0.1 mL) of the vitreous along with the device may be collected and shipped back to the sponsor for analysis.

14. ETHICS AND RESPONSIBILITIES

Although disease progression of MacTel appears to be slow when assessed with standard methods, some participants report worsening visual function despite stable visual acuity measures. Functional evaluation of participants with MacTel using fundus-controlled perimetry (microperimetry) reveals characteristic small, deep, paracentral scotomata; these do not necessarily affect performance on single optotype visual acuity testing, [5] but may affect reading and other visual tasks that require an intact paracentral visual field. Indeed, more pronounced reading disability than would be expected from distance visual acuity testing alone correlate with such paracentral focal loss of macular sensitivity [6]. Moreover, longitudinal data from a recent interventional study showed progressive paracentral visual function loss in a subset of participants while visual acuity remained stable [7, 26].

Currently there is no known therapy for MacTel. Previous clinical experience with the NT-501 device in human participants suggests that the device is generally well tolerated. Importantly, the device can be readily removed with a simple procedure. Data from a significant number of human participants also suggest that the risks associated with NT-501 are limited to those expected with the surgical procedure. The use of a sham procedure

in the control participants is justified by the fact that potential bias of the placebo effect could invalidate the study results if a sham arm was not used.

While the placebo impact on the primary endpoint is minimized by the central masked reading of the area of the EZ break, the lack of a sham procedure could very well impact the outcome of the subjective endpoints of visual acuity, reading speed, and vision-related quality of life. The risks of the sham procedure are considered minimal and are clearly outlined in the informed consent form (ICF).

14.1 COMPLIANCE

This study will be conducted in compliance with the protocol, ICH guideline E6: GCP: Consolidated Guideline, and the applicable regulatory requirements from the US 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]).

14.2 GOOD CLINICAL PRACTICE

Participant medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (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. All active physician investigators are required to be experienced in the conduct of clinical trials and ophthalmologists with training in retinal surgery or retinal medicine. All physician investigators are trained specifically on the procedure for insertion of the device (or the sham procedure) and the handling of the investigational product.

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 site, if appropriate.

14.3 DATA AND SAFETY MONITORING COMMITTEE

An independent DSMC will operate according to the DSMC charter that will specify operations, roles and responsibilities, and communication with the sponsor. The committee will meet based on a timeline defined in the DSMC charter until completion of the study.

14.4 STEERING COMMITTEE

A steering committee composed of external experts and study personnel (sponsor and CRO) has been convened to design the protocol and oversee the execution of the study. The steering committee is accountable for ophthalmic medical and technical input and for advising on study execution.

14.5 INFORMED CONSENT

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 ICF, which must be obtained prior to enrollment. The participants will have an opportunity to review the ICF 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.

A template ICF will be provided to each site. The sponsor, or their designee, must review and approve any proposed deviations from the provided ICF template or any alternate consent forms proposed by the site (collectively, the "consent forms") before IRB/IEC submission. Participants must be reconsented per IRB/IEC requirements with the most current (updated) version of the respective consent form as applicable during their participation in the study. 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 person obtaining consent and 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 ICFs must remain in each participant's study file and must be available for verification by clinical research associates (CRAs) at any time.

The ICF should be revised whenever there are changes to the procedures outlined in the ICF or when new information becomes available that may affect the willingness of the participant to participate.

For any updated or revised ICFs, the case history for each participant shall document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study. The final revised IRB/IEC-approved ICF must be provided to the sponsor for regulatory purposes.

15. AUDITING AND MONITORING

This study will be conducted in accordance with 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.

15.1 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant and relevant supporting information must be submitted to the IRB/IEC by the principal investigator at 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 IND 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.

15.2 STUDY 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 personnel to discuss any findings/relevant issues. The principal investigator will permit the monitors, sponsor representatives, US FDA, other regulatory agencies, IRBs, and the respective national or local health authorities to inspect facilities and records relevant to this study.

15.3 RECORDS MANAGEMENT

The investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the sponsor, government regulatory bodies, and compliance and quality assurance groups of all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities (eg, pharmacy, diagnostic laboratory). All authorized personnel, including health authority inspector(s), sponsor and designees, monitor(s), and auditor(s) will be given direct access to source data and documentation (eg, medical records, laboratory results) for source data verification, provided that participant confidentiality is maintained in accordance with local requirements.

The unmasked staff at the CRO will maintain the randomization codes and procedures.

15.4 DATA QUALITY ASSURANCE

The CRO will have the primary responsibility for assuring that 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 major quality assurance features of the study are as follows:

- Standard data collection forms and procedures
- Common protocol for eligibility, examination, and follow-up of all participants at all sites
- Masked assessment of the primary outcome measure and secondary outcome measures
- Central masked grading of study images
- Data entry into EDC
- Central, computer driven data editing for missing, invalid, and suspect responses
- Regular reporting of performance of all sites
- Monitoring visits to all sites
- Certification of clinic personnel and of imaging equipment

15.5 SOURCE DOCUMENTATION

All data relating to study procedures will be entered by trained site personnel into the electronic case report form (eCRF) around the time of study assessment collection. The eCRF exists within an EDC system with controlled access managed by the sponsor or its designee for this study. Study personnel will be appropriately trained in the use of eCRFs before the start of the study and prior to being given access to the EDC system. Original data and any changes to data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail.

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

The investigator will attest that the information contained in the eCRFs is true by providing electronic signature within the EDC system prior to database lock. After database lock, the investigator will receive a copy of the participant data for archiving at the site. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRAs will perform ongoing site visits to confirm that critical protocol data (ie, 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 site must also allow inspection by applicable regulatory authorities.

When clinical observations are entered directly into the site's computerized medical record system (ie, 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 (eg, 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.

15.6 STUDY FILES AND RECORD RETENTION

The 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 ICFs, 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 US 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.

16. AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may only be made by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. The sponsor or their designee will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or the sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the participants, and/or has an impact on the participants' involvement in the trial, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for participants enrolled in the study and the new ICF signed before continued participation.

17. STUDY REPORT AND PUBLICATIONS

The sponsor or their designee is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements. The publication policy of the sponsor is discussed in the investigator's clinical research agreement.

18. STUDY DISCONTINUATION

Both the sponsor and the principal investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, the sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the principal investigator will inform the IRB/IEC of the same. If the decision is made to terminate the study, the sponsor and the principal investigator will assure that adequate consideration is given to the protection of the participants' interests.

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 noncompliance (eg, 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
- AE that is serious and unexpected
- Worsening condition
- Any other safety concerns

If a participant withdraws or is discontinued from the study before the Month-24 Visit, they should return for an exit visit. The schedule of assessments for this visit is the same as that for the 24 month.

18.1 PREMATURE DISCONTINUATION

Premature discontinuation is not anticipated to be a frequent event based on the history of previous clinical trials with this device. The investigator may discontinue a participant from the study if warranted and only after discussion with the medical monitor. If the participant discontinues study participation before completing the defined 24, 36 or 48 months of follow-up, the principal investigator and study coordinator of the study site for the NHOR will be notified to ensure long-term follow-up.

If a participant requests explantation and withdrawal from the study, this can be readily arranged. The investigator should contact the sponsor's medical monitor to discuss the reasons for the request and discuss the procedure for explantation. If a participant discontinues from the study they will not be replaced once recruitment is complete.

If a participant requests explantation but does not wish to withdraw from the study, this is also acceptable. The participant would continue in the study with all planned follow-up visits and assessments. For COVID-related out of window visits conducted less than 119 days beyond the protocol specified visit, an estimated value for the scheduled visit will be computed from the raw data and time using the actual out of window visit date, computed as month from surgery.

19. CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorized regulatory officials, IRB/IEC personnel, and the sponsor and its authorized representatives are allowed full access to the records.

The participants' names will not appear on any of the data forms reported to the CRO. Participants will be identified by a study number. The date of birth, or year of birth where applicable, of each participant will be collected in the data system.

20. REFERENCES

1. Charbel Issa P, Gillies MC, Chew EY, Bird AC, Heeren TF, Peto T, et al. Macular telangiectasia type 2. Prog Retin Eye Res. 2013;34:49-77.
2. Staurenghi G, Sadda S, Chakravarthy U, Spaide RF, International Nomenclature for Optical Coherence Tomography P. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN*OCT consensus. Ophthalmology. 2014;121(8):1572-8.
3. Gass JD, Blodi BA. Idiopathic juxtafoveolar retinal telangiectasis. Update of classification and follow-up study. Ophthalmology. 1993;100(10):1536-46.
4. Gass JD, Oyakawa RT. Idiopathic juxtafoveolar retinal telangiectasis. Arch Ophthalmol. 1982;100(5):769-80.
5. Charbel Issa P, Helb HM, Rohrschneider K, Holz FG, Scholl HP. Microperimetric assessment of patients with type 2 idiopathic macular telangiectasia. Invest Ophthalmol Vis Sci. 2007;48(8):3788-95.
6. Finger RP, Charbel Issa P, Fimmers R, Holz FG, Rubin GS, Scholl HP. Reading performance is reduced by parafoveal scotomas in patients with macular telangiectasia type 2. Invest Ophthalmol Vis Sci. 2009;50(3):1366-70.
7. Charbel Issa P, Finger RP, Kruse K, Baumuller S, Scholl HP, Holz FG. Monthly ranibizumab for nonproliferative macular telangiectasia type 2: a 12-month prospective study. Am J Ophthalmol. 2011;151(5):876-86 e1.
8. Heeren TF, Clemons T, Scholl HP, Bird AC, Holz FG, Charbel Issa P. Progression of Vision Loss in Macular Telangiectasia Type 2. Invest Ophthalmol Vis Sci. 2015;56(6):3905-12.
9. Yannuzzi LA, Bardal AM, Freund KB, Chen KJ, Eandi CM, Blodi B. Idiopathic macular telangiectasia. Arch Ophthalmol. 2006;124(4):450-60.
10. Bok D, Yasumura D, Matthes MT, Ruiz A, Duncan JL, Chappelow AV, et al. Effects of adeno-associated virus-vectored ciliary neurotrophic factor on retinal structure and function in mice with a P216L rds/peripherin mutation. Exp Eye Res. 2002;74(6):719-35.
11. Rhee KD, Nusinowitz S, Chao K, Yu F, Bok D, Yang XJ. CNTF-mediated protection of photoreceptors requires initial activation of the cytokine receptor gp130 in Muller glial cells. Proc Natl Acad Sci U S A. 2013;110(47):E4520-9.
12. Tao W, Wen R, Goddard MB, Sherman SD, O'Rourke PJ, Stabila PF, et al. Encapsulated cell-based delivery of CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2002;43(10):3292-8.
13. Heckenlively JR, Hawes NL, Friedlander M, Nusinowitz S, Hurd R, Davisson M, et al. Mouse model of subretinal neovascularization with choroidal anastomosis. Retina. 2003;23(4):518-22.
14. Dorrell MI, Aguilar E, Jacobson R, Yanes O, Gariano R, Heckenlively J, et al. Antioxidant or neurotrophic factor treatment preserves function in a mouse model of neovascularization-associated oxidative stress. J Clin Invest. 2009;119(3):611-23.
15. Powner MB, Gillies MC, Tretiach M, Scott A, Guymer RH, Hageman GS, et al. Perifoveal muller cell depletion in a case of macular telangiectasia type 2. Ophthalmology. 2010;117(12):2407-16.
16. Powner MB, Gillies MC, Zhu M, Vevis K, Hunyor AP, Fruttiger M. Loss of Muller's cells and photoreceptors in macular telangiectasia type 2. Ophthalmology. 2013;120(11):2344-52.
17. Shen W, Fruttiger M, Zhu L, Chung SH, Barnett NL, Kirk JK, et al. Conditional Mullercell ablation causes independent neuronal and vascular pathologies in a novel transgenic model. J Neurosci. 2012;32(45):15715-27.

18. Ooto S, Hangai M, Takayama K, Arakawa N, Tsujikawa A, Koizumi H, et al. High-resolution photoreceptor imaging in idiopathic macular telangiectasia type 2 using adaptive optics scanning laser ophthalmoscopy. Invest Ophthalmol Vis Sci. 2011;52(8):5541-50.

19. Dittrich F, Thoenen H, Sendtner M. Ciliary neurotrophic factor: pharmacokinetics and acute-phase response in rat. Ann Neurol. 1994;35(2):151-63.

20. Clemons TE, Gillies MC, Chew EY, Bird AC, Peto T, Figueroa MJ, et al. Baseline characteristics of participants in the natural history study of macular telangiectasia (MacTel) MacTel Project Report No. 2. Ophthalmic Epidemiol. 2010;17(1):66-73.

21. Trauzettel-Klosinski S, Dietz K, Group IRS. Standardized assessment of reading performance: the New International Reading Speed Texts IReST. Invest Ophthalmol Vis Sci. 2012;53(9):5452-61.

22. Diggle P, Heagerty P, Liang K-Y, Zeger S. Analysis of Longitudinal Data. Second ed. Oxford: Oxford University press; 2002. 346 p.

23. Akaike H. Information theory and an extension of the maximum likelihood principle. In. Proceedings of the 2nd International Symposium on Information Theory Budapest: Akademiai Kiado; 1973.

24. Kalberg C, Yung SY, Kessler JA. The cholinergic stimulating effects of ciliary neurotrophic factor and leukemia inhibitory factor are mediated by protein kinase C. J Neurochem. 1993;60(1):145-52.

25. Komáromy AM, Rowlan JS, Corr AT, Reinstein SL, Boye SL, Cooper AE, Gonzalez A, Levy B, Wen R, Hauswirth WW, Beltran WA, Aguirre GD. Transient photoreceptor deconstruction by CNTF enhances rAAV-mediated cone functional rescue in late stage CNGB3-achromatopsia. Mol Ther. 2013;21(6):1131-41.

26. Charbel Issa P, Troeger E, Finger R, Holz FG, Wilke R, Scholl HP. Structure-function correlation of the human central retina. PLoS One. 2010;5(9):e12864.