CLINICAL RESEARCH PROTOCOL

DRUG:	NT-501
STUDY NUMBER:	NTMT-02B
PROTOCOL TITLE:	Phase II, Multicenter, Open-label Safety Study of Bilateral NT-501 in Participants with Macular Telangiectasia Type 2
IND NUMBER:	10931
SPONSOR	Neurotech Pharmaceuticals, Inc
PROTOCOL VERSION	Version 4.0
DATE	January 21, 2022 (US and AUS)

CLINICAL PROTOCOL APPROVAL FORM

Phase II, Multicenter, Open-label Safety Study of Bilateral NT-501 in Participants with Macular Telangiectasia Type 2

Study No: NTMT-02B

Protocol Version/Date:

Version 1.0 / 20 January 2021

Version 2.0 / 18 March 2021 (US and AUS)

Version 3.0 / 16 July 2021 (US and AUS)

Version 4.0 / 21 January 2022 (US and AUS)

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:

1. The current risk-benefit evaluation of the investigational product
2. 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: Thomas Aaberg, MD Chief Medical Officer Neurotech Pharmaceuticals, Inc.	Thomas Aaberg I am approving this document.	01/21/2022 01:18 PM EST
CRO Representative: Joseph Sliman, MD Global Medical Monitor, The Emmes Company, LLC	Joseph Sliman Joseph Sliman I am approving this document.	01/21/2022 10:40 AM EST

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 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

PROTOCOL SYNOPSIS

Title of Study:	Phase II, Multicenter, Open-label Safety Study of Bilateral NT-501 in Participants with Macular Telangiectasia Type 2
IND Number:	10931
Sponsor:	Neurotech Pharmaceuticals, Inc.
Study Compound:	NT-501 is a combination of a sealed semipermeable hollow fiber membrane (HFM) capsule surrounding a scaffold of 6 strands of polyethylene terephthalate (PETP) yarn, and Ciliary Neurotrophic Factor (CNTF) secreting NTC-201.6A cells that adhere to the polyethylene terephthalate (PET) yarn. Using a surgical procedure, this implant is positioned into the vitreous and anchored to the sclera
Study Objectives	
Primary Objective:	Assess the incidence and severity of adverse events following bilateral ocular implantation of NT-501. Ocular safety will be assessed using ocular examinations, as well as best corrected visual acuity (BCVA) measurements using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol. Systemic safety will be assessed based on the incidence and severity of systemic adverse events (AE)
Secondary Objectives:	Assess serum levels of CNTF, the immunogenicity of NT-501 with quantification of antibodies (Ab) to CNTF, neutralizing antibodies (Nab) to CNTF, and Ab to NTC-201.6A cells, as well as Ab to dihydrofolate reductase (DFHR), in samples collected at the Baseline, Month 1, Month-3 and Month-6 study visits.
Study Design:	
Clinical Study Sites:	Participants will be recruited from up to 10 clinical study sites. Clinical sites must have participated in the multicenter Phase 1/2 extension study, NTMT-01/02E, or the Phase 3 (NTMT-03) study of NT-501 in participants with Macular Telangiectas Type 2 (MacTel).
Number of Participants:	The goal is to have a minimum of 30 evaluable participants
Structure:	Multicenter, Open-Label
Visit Schedule:	There will be a maximum of 7 visits over a study period of up to 7 months. These visits will include Visit 1, Screening (Day -28 to Day -1); Visit 2, Surgery; Visit 3, Post-Surgery Day 1; Visit 4, Post-Surgery Week 1; Visit 5, Post-Surgery Month 1; Visit 6, Post-Surgery Month 3; Visit 7, Post-Surgery Month 6 and Exit Visit.
Duration:	The study duration will be approximately 7 Months (screening period of up to 28 days plus a follow-up period of 6 months).

Study Description:	This is a multicenter, open-label, study to evaluate the safety of bilateral NT-501 implants in a minimum of 30 study participants with MacTel type 2. All study subjects who have received a NT-501 implant in one eye through participation in the Phase 1/2 extension study, NTMT-01/02E, or the Phase 3 (NTMT-03) study and meet the eligibility criteria, will receive a NT-501 implant in their fellow eye and will be followed for 6 months following the NT-501 implantation.
Inclusion Criteria:	Study eligibility is to be assessed at Visit 1 (Screening). To participate in this study, the potential participant must meet all the following criteria:

General Inclusion Criteria:

1. Participants from the Phase 3 study must have completed the Month-24 visit
2. Participant in the MacTel Phase 1/2 extension study or the Phase 3 study must exit these studies prior to entering the Bilateral Implant safety study (NTMT-02B)
3. Participant must be willing and able to follow the study instructions and be willing and able to complete all required study procedures and visits
4. Participant must be willing and able to provide a signed Informed Consent, as well as written documentation in accordance with the relevant country and local privacy requirements, e.g., written data protection consent
5. Females of childbearing potential must consent to and complete a pregnancy test during the screening visit
6. A participant's refusal to allow the collection of blood samples for Ciliary neurotrophic factor (CNTF), Ab to CNTF, Nab to CNTF, Ab to NTC-201.6A cells, and Ab to DFHR will not exclude the participant from study participation

Ocular Inclusion Criteria

1. Participant must have a positive diagnosis of MacTel type 2, 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 in their study eyes
2. Participant must have steady fixation in the foveal or parafoveal area in the study eye and sufficiently clear media for good quality photographs
3. Participant must have a NT-501 implant in one eye and have completed the Phase 1/2 extension study (NTMT-01/-2E) or the Month 24-visit of the Phase 3 study (NTMT-03)

Exclusion Criteria

Unless otherwise stated, eligibility assessments are to be performed at Visit 1 (Screening). The following criteria will exclude participant from entry into the study.

General Exclusion Criteria

1. Females of childbearing potential (those who are not surgically sterilized or post-menopausal, i.e., absence of menstruation for 12 months or longer) may not participate in the study if any of the following conditions exists:
    - Pregnant (positive pregnancy test at Visit 1 or intend to become pregnant during the study)
    - Nursing (lactating)
    - Do not agree to use adequate birth control methods for the duration of the study and until 90 days after the last administration of study drug

(adequate birth control methods are: hormonal – oral, implantable, transdermal or injectable contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm, intrauterine device [IUD] or surgical sterilization of partner, or total sexual abstinence)

2. Participant is too ill to likely complete the entire study, based on the investigator's assessment
3. Participant, in the opinion of the investigator, is not suitable for study participation
4. Participant has any screening laboratory result (serum chemistry, hematology, urinalysis) that in the opinion of the investigator is not suitable for study participation
5. History or current evidence of severe hypersensitivity to the NT-501 implant
6. Participant has a history or current evidence of a medical condition (systemic or ophthalmic disease, metabolic dysfunction, physical examination finding or clinical laboratory finding) that may in the opinion of the investigator preclude the safe administration of the NT-501 or adherence to the scheduled study visits, safe participation in the study or affect the results of the study (e.g., unstable or progressive cardiovascular, cerebral vascular, pulmonary, Parkinson's, liver or renal disease, depression, cancer, or dementia)

Ocular Exclusion Criteria

1. Participant has a history or evidence of the following surgeries/procedures in the study eye, as assessed at Visit 1, including:
   - Submacular surgery
   - Vitrectomy
   - Retinal detachment
   - Incisional glaucoma surgery
   - Trabeculectomy or trabeculoplasty
   - Cataract surgery or laser-assisted in situ keratomileusis (LASIK) performed in the previous 6 months
2. Participant has uncontrolled glaucoma; or ocular hypertension, i.e., IOP ≥ 25 mmHg in the study eye
3. Participant has evidence of intraretinal or subretinal neovascularization or central serous chorio-retinopathy in the study eye
4. Participant has evidence of ocular disorder(s) in the study eye of a severity that could confound the interpretation of study results, compromise visual acuity or require medical or surgical intervention during the study period, including retinal vascular occlusion, severe non-proliferative or proliferative diabetic retinopathy, retinal detachment, macular hole, geographic atrophy, intraretinal or subretinal neovascularization, central serous chorio-retinopathy, pathological myopia
5. Participant has a vitreous hemorrhage in the study eye at Visit 1 (Screening)
6. Participant has the spherical equivalent of refractive error in the study eye demonstrating more than 8 diopters of myopia
7. Participant has a history or evidence of penetrating ocular trauma in the study eye
8. Participant has an anticipated need for cataract extraction in the study eye within 6 months of Visit 1 (Screening) such as 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

9. Participant has uveitis, history of uveitis in either eye or history of ocular herpes virus in either eye
10. Participant has undergone major surgery within the last 6 months (systemic or ocular in either eye) or participant who is likely to require major surgery within 6 months of Visit 1 (Screening)
11. Participant has a periocular or ocular/intraocular infection or inflammation in either eye (such as infectious conjunctivitis, keratitis, scleritis, endophthalmitis) within 3 months prior to Visit 1 (Screening)
12. Participant has ocular hypotension in either eye (<6 mmHg) that in the opinion of the Investigator would interfere with the NT-501 implantation
13. Participant has a history of scleritis, scleral thinning, periocular, ocular, or intraocular infection or inflammation, cicatrizing conjunctival diseases any other ocular conditions in the study eye that could interfere with the administration of NT-501

Response Measures

Safety Assessments:

- Adverse Events after NT-501 Implantation Surgery
- General Physical Exam
- Vital Signs
- Pregnancy Test
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP)
- BCVA
- SD-OCT
- Serum chemistry, hematology, and urinalysis
- Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR (serum)
- Blood sample collection for analysis of serum levels of CNTF

Safety Endpoints

Number and proportion of adverse events from day of surgery through post NT-501 implantation follow-up

Number and proportion of severe adverse events from day of surgery through post NT-501 implantation follow-up

Number and proportion of ocular adverse events from day of surgery through post NT-501 implantation follow-up

Number and proportion of non-ocular adverse events from day of surgery through post NT-501 implantation follow-up

General Statistical Methods and Types of Analyses

Formal sample size calculations were not performed. The number of participants was chosen based on feasibility and is considered sufficient to meet the study objectives.

	The general analytical approach for all endpoints is descriptive. No formal statistical hypothesis testing will be conducted.
Analysis Populations	*Safety Population*: Defined as participants who have a NT-501 implant in both eyes. This population will be used for all safety analysis.
Safety Analysis	The primary objective of the study is to assess the safety and tolerability of bilateral NT-501 implants. Tolerance and safety will be based on the incidence and severity of treatment-emergent adverse events (TEAEs).
Sample size Calculations	Formal sample size calculations were not performed. The number of participants was chosen based on feasibility and is considered sufficient to meet the study objectives

Figure 1. Study Design

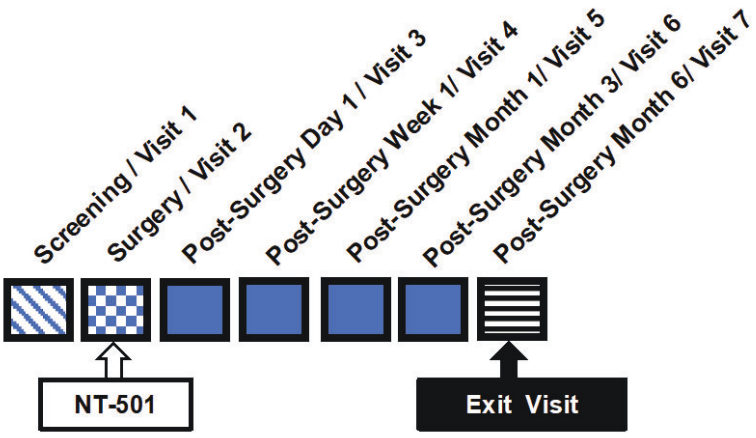

Table 1: Schedule of Visits and Procedures in the Assessment of Safety in Participants with Bilateral NT-501 Implants

Procedures	Screening Day -28 to -1	Surgery Day 0	Post-Surgery Day 1	Post-Surgery Week 1	Post-Surgery Month 1	Post-Surgery Month 3	Post-Surgery Month 6
Visit Window				±2 days	±7days	±14 days	±14 days
Visit Number	1	2	3	4	5	6	7
STUDY DAY	**-28 to -1**	**0**	**1**	**7**	**30**	**90**	**180**
Informed Consent	X						
Demographics	X						
Medical & Ophthalmic History [a]	X	X					
Concomitant Medications and non-study procedures	X	X	X	**X**	X	X	X
Adverse Events		X	X	X	X	X	X
Vital Signs [b]	X						
Inclusion/exclusion criteria	X						
Eligibility Review	X	X					
Medical evaluation [c]	X	X					
Pregnancy Test [d]	X						
Serum Chemistry, Hematology & Urinalysis	X						
Visual Acuity (BCVA)	OU[e]	SE[f]		SE[f]	OU [e]	OU [e]	OU [e]
Measurement of pupil diameter	OU				OU	OU	OU
Complete Ophthalmic Exam [g]	OU		SE	SE	OU	OU	OU
Dilated Fundus Photography	OU						OU
SD-OCT [h]	OU			SE	OU	OU	OU
Fluorescein Angiography	OU						
Serum concentrations of CNTF, Ab or Nab to CNTF, Ab to NTC-201.6A cells; or Ab to DFHR (serum)	X				X	X	X
NT-501 implantation surgery		X					
Post NT-501 implant assessment			SE	SE	OU	OU	OU
External photograph of conjunctiva over implant					OU	OU	OU
Complete Exit Form							X

Abbreviations: BCVA= Best Corrected Visual Acuity; SD-OCT = spectral domain optical coherence tomography, OU = both eyes, SE = study eye

a Demographic data includes height, weight, eye color and smoking history
b Vital signs include body temperature, pulse rate, respiration rate and sitting blood pressure
c 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)
d Females of childbearing potential only; additional pregnancy tests may be performed at any time/day during study
e Manifest refraction will be performed prior to BCVA assessments except for the BCVA assessments performed prior to surgery and 1 week following surgery
f Best-corrected visual acuity must be performed within 1 week prior to the day of surgery
g Complete ophthalmic exam consists of an external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP assessment) Slit lamp biomicroscopy, indirect ophthalmoscopy and intraocular pressure (IOP). IOP measurements will be taken prior to pupil dilation. If possible, IOP measurements should take place at approximately the same time of the day at each visit and with the same equipment
h The same SD-OCT instrument should be used for an individual participant throughout the entire study

LIST OF ABBREVIATIONS

Ab	antibodies
AE	adverse event
AREDS	Age-Related Eye Disease Study
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CNTF	ciliary neurotrophic factor
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DHFR	dihydrofolate reductase
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
MacTel	macular telangiectasia type 2
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing antibodies
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
PET yarn	polyethylene terephthalate yarn
PSNS	parasympathetic nervous system
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
SAE	serious adverse event
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
VLDLR	very low-density lipoprotein receptor
$Vldlr^{-/-}$	very low-density lipoprotein receptor knockout (mouse)

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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, perifoveal telangiectatic vessels, and diffuse hyperfluorescence in the late phase of fluorescein angiography[1]. Other characteristic findings 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 development of a neovascular complex.[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 one eye is a frequently reported complaint[1,3,4]. Notably, even in the presence of deep paracentral scotomata and reduced reading ability, distance visual acuity may be relatively preserved.[1,5,6] However, a decrease in visual acuity may eventually occur with disease progression. There appear to be essentially two different factors contributing to the decline of visual acuity.[1,7,8]. Initially, there may be a slow drop in visual acuity, usually not below ~20/50, which may be due to structural foveal changes, e.g., 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 approximately 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.[1,4,9]

There is significant 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 effective in retarding photoreceptor neuron loss in animal models of retinal degeneration of various forms[12], including environmental light stress[13]. In two preclinical animal studies conducted by Neurotech Pharmaceuticals, Inc., CNTF-producing cells have been shown to have a protective effect on photoreceptors. In a rat model of RP, CNTF-producing cells delivered as an intravitreal injection appeared to have a protective effect on photoreceptors with treated eyes having 5 to 6 layers of photoreceptors in the ONL compared with 1 to 2 layers in the untreated eyes.[12] In a dog model of RP, the NT-501 implant was also observed to have a protective effect on 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 implant to treat retinal degenerative diseases. Human safety data is available from studies in participants with MacTel [13,14] RP[15], atrophic age-related macular degeneration (AMD)[16], and glaucoma (data on file). The NT-501 implants are positioned into the vitreous cavity with a surgical procedure that may be performed under

local/monitored anesthesia care. These implants 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 have been collected from approximately 250 participants with retinitis pigmentosa (RP), achromatopsia, age-related macular degeneration (AMD) and macular telangiectasia, type 2, who have received the NT-501 implant producing a nominal dose of 20 ng/24 hours). In these subjects, adverse events (AEs) were generally limited to those related to the implant procedure.[13,14,15,16] As noted previously, the natural history study of MacTel has demonstrated that photoreceptor loss is intrinsic to this disorder[17,18] Although anti-vascular endothelial growth factor therapy reduced the vascular permeability, it did not influence the progression of photoreceptor cell loss or functional loss.[19] A relatively small number of these participants have reported miosis , which is believed to be directly related to CNTF.[15] During early development, a number of participants developed inflammation following implantation. This was subsequently found to be related to impurities in the membrane of the implant, which has since been replaced with a new membrane with fewer impurities. Trace to mild inflammation was seen postoperatively in a minority of participants and typically cleared by 3 months. In the Phase 2 study MacTel 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. [15,16] 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.[14.] In the intent-to-treat population, 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, in a post hoc analysis of the per protocol population, when the aggregate retinal sensitivity (dB) was compared with the corresponding area affected by MacTel, a significant (P<0.002) difference between treated and sham eyes was detected. This difference was consistent with the slower growth of the MacTel lesion in the treated eyes. Additionally, 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), while 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] µm; sham: -4.97 [2.85] µm; 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 1/2 Extension Study, and of those, 92 study eyes had EZ break grading at 36 months and 86 had EZ break grading at 48-months (data on file). In post hoc analyses 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 implant in studies of RP and dry AMD, the implant was generally well tolerated in subjects with MacTel type 2. Of the 188 subjects receiving an NT-501 implant in the Phase 1, 2 and 3 studies, there have been 4 study participants who have undergone implant removal after completing the 24-month time point. In one of these subjects, the explant surgery was associated with a subsequent retinal detachment that was surgically reattached.

In the ongoing Phase 3 studies, 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 were randomly assigned to 1 of 2 treatment groups: implantation of the NT-501 implant or sham surgery with no implant. A single NT-501 implant was inserted into the study eye for the duration of the study. The primary endpoint is 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).

The current study is an open-label safety study to assess the safety and tolerance of bilateral NT-501 implants in participants with MacTel. Eligibility is open to study participants who received a NT-501 implant in one eye and completed either the MacTel Phase 1/2 extension study (NTMT-01/02E) or the Month 24 visit of the Phase 3 (NRMt-03) study. Eligible participants who received an NT-501 in one eye and meet the eligibility criteria of the current study, NTMT-02B, will receive an NT-501 implant in the eye without an implant (study eye) and will be followed for 6-months after the surgical procedure.

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 the applicable United States (US) Code of Federal Regulations (CFR), 21 CFR parts 50 and 312.

1.1 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[17] including over 700 participants followed for more than 5 years, it has become apparent that MacTel may 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 retinal findings in patients with MacTel include retinal capillary dilatation associated with retinal vascular leakage, but without associated retinal thickening.[1] Additional findings include superficial retinal crystalline deposits, retinal opacification, and right-angle venules. As the disease progresses, intraretinal pigment plaques and neovascular complexes may develop. Although individuals with MacTel are typically diagnosed in their fifth or sixth decade of life, it is likely that onset of clinical manifestations occurs earlier but go undetected until they become symptomatic. Both sexes are affected by this disease.[1]

As noted previously, the natural history study of MacTel has demonstrated that photoreceptor loss is intrinsic to this disorder[17,18] Although anti-vascular endothelial growth factor (anti-VEGF) therapy has reduced the vascular permeability in subjects with MacTel type 2, anti-VEGF agents have not influenced the progression of photoreceptor cell loss or functional loss.[19] A mouse model in which the very low-density lipoprotein receptor (VLDLR) has been knocked out (i.e., $Vldlr^{-/-}$ mice) mimics many of the characteristics of the human disease, including focal disruption of photoreceptors coincident with the abnormal outer retinal-penetrating vessels[20]. 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.[21]

Two postmortem donor eyes from elderly individuals with MacTel were analyzed histopathologically and immunohistochemically[22, 23]. 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 these observations, 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.[24.] 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.[25] 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.

1.1.1 Pharmacokinetics

CNTF is not detectable in the serum of study participants implanted with a single NT-501 implant.

1.1.2 Preclinical Pharmacology

The half-life of CNTF in laboratory animals is extremely short and is measured in minutes.[26]

1.1.3 Potential for Drug-Drug Interactions

None.

1.1.4 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 resolved within a few days. Of the 188 subjects receiving an NT-501 implant in the Phase 1, 2 and 3 studies, there have been 4 study participants who have undergone implant removal after completing the 24-month time point, two from the NTMT-01/02 extension study and two from the NTMT-03 study. A small proportion of participants have reported miosis. No discontinuations due to this event have been reported in the MacTel clinical studies.

1.1.5 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.

1.1.6 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.

1.1.7 Potential Risk to Fetal Development

No embryo-fetal/teratogenicity studies have been conducted during 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 observed 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 low, given the fact that the CNTF produced by the NTC-201-6A cell line is of human origin and there is no detectable CNTF in patient plasma [13,15]. CNTF has been extensively studied in animal and human neurological models and is considered a neuroprotectant.

1.1.8 Dosing Regimen

Study participants with MacTel who have previously received a NT-501 implant in one eye will be implanted with a NT-501 implant in their fellow eye. Only one configuration of the NT-501 implant will be used in this study, the configuration that delivers a nominal dose of CNTF, 20 ng/implant/day.

2 STUDY OBJECTIVES

The overall objective of this study is to evaluate the safety and tolerability of the NT-501 implant, when implanted in both eyes of participants with MacTel type 2.

Primary objective:

- Assess the incidence and severity of adverse events following bilateral ocular implantation of NT-501. Ocular safety will be assessed using ocular examinations, as well as best corrected visual acuity (BCVA) measurements using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol. Systemic safety will be assessed based on the incidence and severity of systemic adverse events (AE)

Secondary objective:

- Assess serum levels of CNTF, the immunogenicity of NT-501 with quantification of antibodies (Ab) to CNTF, neutralizing antibodies (Nab) to CNTF, and Ab to NTC-201.6A cells, as well as Ab to dihydrofolate reductase (DFHR) in samples collected at the Baseline, Month 1, Month-3 and Month-6 study visits.

3 STUDY ENDPOINTS

Primary Safety Endpoints

- Number and proportion of adverse events from day of surgery through 6 months post implantation
- Number and proportion of severe adverse events from day of surgery through 6 months post implantation
- Number and proportion of ocular adverse events from day of surgery through 6 months post implantation
- Number and proportion of non-ocular adverse events from day of surgery through 6 months post implantation

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)
- Detectable serum levels of CNTF at Months 1, 3 and 6 post-implantations of NT-501
- Number and proportion of participants with serum Ab or Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR at Baseline and Months1, 3 and 6 post-implantation of NT-501

4 STUDY PLAN

4.1 Study Design

This is a multicenter, open-label, study to evaluate the safety of bilateral NT-501 implants in a minimum of 30 study participants with MacTel type 2. All study subjects who have received a NT-501 implant in one eye, completed either the Phase ½ extension study (NTMT-01/02E) or the Month-24 visit of the Phase 3 study (NTMT-03) and meet the eligibility criteria, will receive a NT-501 implant in their fellow eye and will be followed for 6 months following NT-501 implantation.

Study participants will have a screening period of up to 28 days. Participants who meet the inclusion/exclusion criteria will have implant surgery within 30 days of the Screening Visit. After the surgery, subjects receiving a NT-501 implant will return to the clinical center for assessments performed on Day 1, Week 1 (± 2 days), Month 1 (± 7 days), Month 3 (± 14 days) and Month 6 (± 14 days). Upon completion of the 6-month visit, these participants will exit the study. These participants may elect to 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).[17]

4.2 Safety Variables

- Safety will be evaluated by monitoring AEs and SAEs, complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP), and measurement of BCVA.
- All AEs will be captured whether or not considered to be related to the surgical procedure, implant, or CNTF. An attempt will be made to differentiate between treatment-related AEs and AEs considered to be part of 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 implant itself, to CNTF, or to the implant procedure.

4.3 Safety Assessments:

The following safety assessments will be performed at the indicated timepoints:

- Adverse Events
- Vital Signs
- Pregnancy Test
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, BCVA and IOP)
- SD-OCT
- Serum chemistry, hematology, and urinalysis
- Ab or Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR (serum)
- Serum levels of CNTF

5 POPULATION

All study subjects must have a diagnosis of bilateral MacTel type 2 in both eyes to be eligible for enrollment.

5.1 Number of Participants

The study will enroll a minimum of 30 participants who meet the inclusion and exclusion criteria.

5.2 Inclusion Criteria

Eligibility to participate in the NTMT-02B study is limited to participants with an NT-501 implant in one eye and have completed and exited from the NTMT-01/02 extension study or the Month 24 visit of the Phase 3 study (NTMT-03). No persons shall be excluded based on gender, race, or ethnicity. Study eligibility is to be assessed at Visit 1 (Screening). To participate in this study, the potential participant must meet all the following criteria:

General Inclusion Criteria

1. Participants from the Phase 3 study must have completed the Month-24 visit
2. Participant in the MacTel Phase 1/2 extension study or the Phase 3 study must exit these studies prior to entering the Bilateral Implant safety study (NTMT-02B)
3. Participant must be willing and able to follow the study instructions and be willing and able to complete all required study procedures and visits
4. Participant must be willing and able to provide a signed Informed Consent, as well as written documentation in accordance with the relevant country and local privacy requirements, e.g., written data protection consent
5. Females of childbearing potential must consent to a pregnancy test before entering the study
6. A participant's refusal to allow the collection of blood samples for analysis of serum CNTF, serum Ab or Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR levelsin one eye will not exclude the participant from study participation

Ocular Inclusion Criteria

1. Participant must have a positive diagnosis of MacTel type 2 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 in the study eye
2. Participant must have steady fixation in the foveal or parafoveal area in the study eye and sufficiently clear media for good quality photographs

5.3 Exclusion Criteria

Unless otherwise stated, eligibility assessments are to be performed at Visit 1 (Screening). The following criteria will exclude participant from entry into the study.

General Exclusion Criteria

1. Females of childbearing potential (those who are not surgically sterilized or post- menopausal, i.e., absence of menstruation for 12 months or longer) may not participate in the study if any of the following conditions exists:
    - Pregnant (positive pregnancy test at Visit 1 or intend to become pregnant during the study)
    - Nursing (lactating)
    - Do not agree to use adequate birth control methods for the duration of the study and until 90 days after the last administration of study drug (adequate birth control methods are: hormonal – oral, implantable, transdermal or injectable contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm, intrauterine device [IUD] or surgical sterilization of partner, or total sexual abstinence)

2. Participant is too ill to likely complete the entire study, based on the investigator's assessment
3. Participant, in the opinion of the investigator, is not suitable for study participation
4. Participant with any screening laboratory finding (serum chemistry, hematology, urinalysis) that in the opinion of the investigator is not suitable for study participation
5. Participant has a history or current evidence of severe hypersensitivity to the NT-501 implant
6. Participant has a history or current evidence of a medical condition (systemic or ophthalmic disease, metabolic dysfunction, physical examination finding or clinical laboratory finding) that may in the opinion of the investigator preclude the safe administration of the NT-501 implant or adherence to the scheduled study visits, safe participation in the study or affect the results of the study (e.g., unstable or progressive cardiovascular, cerebral vascular, pulmonary, Parkinson's, liver or renal disease; depression, cancer, or dementia

Ocular Exclusion Criteria

1. Participant has a history or evidence of the following surgeries/procedures in the study eye, as assessed at Visit 1, including:
   - Submacular surgery
   - Vitrectomy
   - Retinal detachment
   - Incisional glaucoma surgery
   - Trabeculectomy or trabeculoplasty
   - Cataract surgery or laser-assisted in situ keratomileusis (LASIK) performed in the previous 6 months
2. Participant has uncontrolled glaucoma; or ocular hypertension, i.e., IOP ≥ 25 mmHg in the study eye
3. Participant has evidence of intraretinal or subretinal neovascularization or central serous chorio-retinopathy in the study eye
4. Participant has evidence of ocular disorder(s) in the study eye of a severity that could confound the interpretation of study results, compromise visual acuity or require medical or surgical intervention during the study period, including retinal vascular occlusion, severe non-proliferative or proliferative diabetic retinopathy, retinal detachment, macular hole, geographic atrophy, intraretinal or subretinal neovascularization, central serous chorio-retinopathy, pathological myopia
5. Participant has a vitreous hemorrhage in the study eye at Visit 1 (Screening)
6. Participant has a spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
7. Participant has a history or evidence of penetrating ocular trauma in the study eye
8. Participant has an anticipated need for cataract extraction in the study eye within 6 months of Visit 1 (Screening) such as 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

9. Participant has uveitis, history of uveitis in either eye or history of ocular herpes virus in either eye
10. Participant has undergone major surgery within the last 6 months (systemic or ocular in either eye) or who are likely to require major surgery within 6 months of Visit 1 (Screening)
11. Participant has periocular or ocular/intraocular infection or inflammation in either eye (such as infectious conjunctivitis, keratitis, scleritis, endophthalmitis) within 3 months prior to Visit 1 (Screening)
12. Participant has ocular hypotension in either eye (<6 mmHg) that in the opinion of the Investigator would interfere with the NT-501 implant insertion
13. Participant has a history of scleritis, scleral thinning, periocular, ocular, or intraocular infection or inflammation, cicatrizing conjunctival diseases any other ocular conditions in the study eye that could interfere with or complicate the surgery associated with NT-501implant insertion

5.4 Participant Screening

Subjects from the NTMT-01/02 extension and have completed the study and subjects from the NTMT-03 Phase 3 study who have completed the Month 24 visit and are interested in participating in the Bilateral Implant Safety Study, must exit from the these studies prior to participating in the Screening Visit for the Bilateral Implant Safety Study (NTMT-02B).

Potential participants will be consented prior to initiation of any screening procedures. All screening procedures may be completed in 1 day or may take place on more than 1 day if convenient for the participant or clinical site. All screening procedures should be completed within 28 days of signing the Informed Consent.

5.5 Deviation from Inclusion/Exclusion Criteria

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

5.6 Masking

Participant, as well as treating and assessing investigators are unmasked to treatment.

6 STUDY CONDUCT

All potential participants will have a screening period of up to 28 days. In subjects who meet the inclusion/exclusion criteria, the implant surgery procedure in the study eye should be completed within one month of the Screening visit.

6.1 Study Procedures by Time Point

Study eyes that receive a NT-501 implant will be assessed on post-operative Day 1, Week 1 (± 2 days), Month 1 (± 7 days), Month 3 (± 14 days), and Month 6 (± 14 days), where 1 month is defined as 30 days. At baseline, SD-OCT and fluorescein angiography will be performed to confirm diagnosis and to exclude presence of a neovascular complex. BCVA, complete ophthalmic exams, dilated fundus photography and photographic assessment of the site of the implant surgery will be performed intermittently to assess the safety of the implant surgery and participant tolerance of the implant.

6.2 Description of the Study Procedures

6.2.1 Study Procedures

The following examinations are 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 only in the study eye unless otherwise indicated.

- Medical evaluation, as would be standard for any surgical procedure and its associated anesthesia (the tests to be performed will be site-specific); evaluation may be performed during the screening period or on the day of surgery
- Complete ophthalmic examination including:
    - External examination of the eye and adnexa
    - Pupil responsiveness
    - Manifest refraction
    - Slit lamp biomicroscopy
    - Dilated fundus examination
    - Indirect ophthalmoscopy
    - Goldmann applanation tonometry
    - BCVA (this assessment will be performed using the ETDRS visual acuity procedure, administered by a certified technician)
    - Measurement of undilated pupil diameter
- Ophthalmic assessments including:
    - SD-OCT
    - Fluorescein angiography
    - Color fundus photography
    - External photograph of conjunctiva over implant
- Urine or blood pregnancy test for premenopausal female participants
- Serum chemistry, hematology, and urinalysis
- Serum analyses of CNTF, Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR

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

In the event of extenuating circumstances 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. Following a missed or out of window visit, every effort should be made to return the participant to the original protocol-specified visit schedule.

6.3 Study Visit Procedures

6.3.1 Visit 1: Screening/Baseline Procedures

Subjects who have completed the NTMT-01/02 extension study and have an NT-501 implant are eligible for screening. Subjects who have completed the Month-24 visit of the Phase 3 study and wish to be considered for entry into the Bilateral Implant Safety Study, must exit the Phase 3 study prior to participating in the Screening Visit for the Bilateral Implant Safety Study. Participants who sign the consent form and begin screening will be assigned a participant identification number by the Advantage eClinical system. Screening procedures may be completed over more than 1 day to accommodate schedules and to lessen participant burden. All screening evaluations should be completed within 28 days of signing the Informed Consent to establish eligibility.

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 investigator may initiate screening assessments. The results of all screening evaluations must be reviewed, and the participant must be found eligible prior to surgery. Once a participant is determined to be eligible for the study, surgery should be completed within approximately 30 days of the Screening visit.

The screening examinations and imaging must include the following:

- Informed consent
- Demographics; medical and ophthalmic history, including height, weight, eye color and smoking history
- Concomitant medications and non-study procedures
- Inclusion/exclusion criteria
- Vital signs (body temperature, pulse rate, respiration rate and sitting blood pressure)
- Medical evaluation, standard for any surgical procedure and its associated anesthesia (the specific tests to be ordered will be site-specific), may be performed during screening period or on the day of surgery
- Blood and urine sample collection for serum chemistry, hematology, urinalysis
- Urine or blood pregnancy exam for female participants of childbearing potential

- Blood sample collection for analysis of Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR
- Blood sample collection for analysis of serum levels of CNTF
- BCVA following manifest refraction (both eyes)
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, indirect ophthalmoscopy, and IOP) (both eyes)
- Measurement of undilated pupil diameter (both eyes)\
- Dilated fundus photography
- SD-OCT (both eyes)
- Fluorescein angiography (both eyes)
- Color dilated fundus photography (both eyes)

The study investigator at each site will evaluate potential participants for study enrollment during the Screening Visit according to the inclusion and exclusion criteria as outlined in Sections 5.2 and 5.3.

6.3.2 Visit 2: Enrollment and Surgery

If the participant meets all study criteria and agrees to participate in the study, then the implant surgery date should be identified. The implant surgery procedure should be completed within one month of the Screening visit.

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:

- Eligibility review
- Medical evaluation that is standard for any surgical procedure and its associated anesthesia (the specific tests to be ordered will be site-specific), unless the medical evaluation was performed during screening period
- Record any further medical/ophthalmic history
- Record any additional concomitant medications and non-study procedures
- Perform AE assessment (from the time surgery begins)
- Assess BCVA (may be performed within 1 week prior to the day of surgery or on the day of surgery, manifest refraction is not required)
- NT-501 implant surgery

6.3.3 Visit 3: 1 Day Post-surgery

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

- AE assessment
- Review concomitant medications and non-study procedures
- Complete ophthalmic exam of the study eye (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, indirect ophthalmoscopy, and IOP) \
- Implant site examination in study eye only

6.3.4 Visit 4: 1 Week Post-surgery (+/- 2 days)

Participants must return to the clinic 1-week post-surgery and will undergo the following procedures:

- AE assessment
- Review concomitant medications and non-study procedures
- BCVA in study eye only (manifest refraction is not required)
- Complete ophthalmic exam of study eye (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, indirect ophthalmoscopy, and IOP) in study eye only
- SD-OCT in study eye only
- Implant site examination in study eye only

6.3.5 Visit 5:1-Month Post-surgery (+/- 7 days)

Participants must return to the clinic 1-month post-surgery and will undergo the following procedures:

- AE assessment
- Review concomitant medications and non-study procedures
- Blood sample collection for analysis of Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR
- Blood sample collection for analysis of serum levels of CNTF
- BCVA following manifest refraction (both eyes)
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP) (both eyes)
- Measurement of undilated pupil diameter (both eyes)
- SD-OCT in both eyes
- Implant site examination (both eyes)
- External photograph of conjunctiva over implant (both eyes)

6.3.6 Visit 6: 3-Month Post-surgery (+/-14 days)

Participants must return to the clinic 3-months post-surgery and will undergo the following procedures:

- AE assessment
- Review concomitant medications and concurrent non-study procedures
- BCVA following manifest refraction (both eyes)
- Blood sample collection for analysis of Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR
- Blood sample collection for analysis of serum levels of CNTF
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP) (both eyes)
- Measurement of undilated pupil diameter (both eyes)
- SD-OCT in both eyes
- Implant site examination (both eyes)
- External photograph of conjunctiva over implant site examination (both eyes)

6.3.7 Visit 7: Six-Month Post-surgery (+/-14 days)

Participants must return to the clinic 6-months post-surgery and will undergo the following procedures:

- AE assessment
- Review concomitant medications and concurrent non-study procedures
- BCVA following manifest refraction (both eyes)
- Blood sample collection for analysis of Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR
- Blood sample collection for analysis of serum levels of CNTF
- Complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP) (both eyes)
- Measurement of undilated pupil diameter (both eyes)
- SD-OCT (both eyes)
- Implant site examination (both eyes)
- External photograph of conjunctiva over implant (both eyes)
- Color digital fundus photography (both eyes)

6.4 Clinical Laboratory Tests

All participants will undergo serum chemistry, hematology, and urinalysis examinations. In addition, premenopausal female participants will undergo a urine or blood pregnancy test at the screening visit and at other times if there is ever a question of possible pregnancy.

Blood for the chemistry and hematology analyses; and urine will be collected at the study site and analyzed at a local laboratory. Fasting prior to collection of these samples is not required. The results will be obtained by the investigator who will assess inclusion/exclusion criteria during the screening period and/or prior to surgery at Visit 2 on Day 0.

The following clinical laboratory analyses will be performed:

- Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocyte, eosinophils, and basophils) and quantitative platelet count
- Serum chemistries: blood urea nitrogen (BUN), serum creatinine, BUN/creatinine ratio, uric acid, cholesterol, triglycerides, albumin, total globulin, albumin/globulin ratio, total serum iron, total protein, serum electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium), phosphorus, glucose and the following liver function tests (LFT): serum aspartate transaminase (AST [SGOT]), serum alanine transaminase (ALT [SPGT]), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), total bilirubin, direct bilirubin, indirect bilirubin and lactate dehydrogenase (LDH), hemoglobin A1c
- Urinalysis: specific gravity, pH, color, protein, glucose, blood, ketones, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, crystals).

The investigator must review the results of the Screening visit clinical laboratory tests, including repeat analyses, prior to enrolling the participant into the surgical segment of the study. Participants with any clinically relevant laboratory values that may in the opinion of the investigator preclude the safe surgical implantation of the NT-501 implant, adherence to the scheduled study visits, safe participation in the study, or affect the results of the study, will not be eligible for study participation.

6.5 Study Laboratory Tests

All participants will undergo examinations of serum CNTF, Ab and Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR (serum). Serum samples will be collected at the Screening Visit (Visit 1), Visit 5 (Post-Surgery Month 1); Visit 6 (Post-surgery Month 3) and Visit 7 (Post-Surgery Month 6).

Blood collected for these assessments will be collected at the study site and will be shipped to a Neurotech central laboratory for analysis. The laboratory will enter the results into the electronic data capture system. Fasting prior to collection of these samples is not required.

6.6 Protocol Deviations

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

7 INVESTIGATIONAL PRODUCT MANAGEMENT

7.1 Description

7.1.1 Formulation

The study implant is the NT-501 implant, NTC-201.6A encapsulated cell therapy (ECT), delivering a nominal CNTF dose of 20 ng/implant/day.

7.1.2 Storage

The shipping container is to be stored at room temperature at the clinical or surgical center. Room temperature is not to exceed 55°C (131°F) or fall below −20°C (−4°F). The implant 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.

7.2 Packaging and Shipment

The NT-501 implant is contained within the primary packaging, which is comprised of a sealed clear plastic container that contains the transport medium. The NT-501 implant 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. 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.

7.3 Dose and Administration

The study implant is the NT-501 implant, NTC-201.6A encapsulated cell therapy (ECT), delivering a nominal CNTF dose of 20 ng/implant/day. This implant will be implanted in the fellow eye of participants who received a NT-501 implant in an eye in an earlier MacTel study. All implants will remain in situ for the duration of the study. There are no plans to remove the implant, except in the case of participant intolerance or complications such as infection or inflammation. NT-501 implants can also be removed if requested by the study participant.

7.4 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 a nominated representative, but this delegation must be documented.

The investigator agrees to not supply the NT-501 implant 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 implant inspection failure where the sponsor requests that the failed implant 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 implants 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 implant, until the time of destruction.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

8.1 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.

8.2 Concomitant Procedures

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.

8.3 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 implant. Anti-VEGF agents administered as intravitreal or intravenous injection are prohibited.

9 ADVERSE EVENTS

An AE is any untoward medical occurrence in humans, whether or not it is 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.

9.1 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 implant, 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 through completion of the last study visit.

9.2 Assessment of Severity

Guidelines for Assessing Severity of an Adverse Event

The investigator should use the following definitions when assessing severity 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

9.3 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 NT-501 implant 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 NT-501 implant itself:

  These would include malposition of the NT-501 implant with impingement of the participant's visual field, inflammation of the vitreous, or visible deterioration of the NT-501 implant 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

9.4 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.

9.5 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 in the EDC system 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 report in the EDC system as soon as possible.

The pregnancy should be followed until birth. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed-up in the EDC system. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported in the EDC system. 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.

10 SERIOUS ADVERSE EVENT

10.1 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.

10.2 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. The definition of a life-threatening AE 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 (e.g., 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.

10.3 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 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.

10.4 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

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

11 STATISTICS

11.1 General Procedures

This is an open-label Phase 2 study to evaluate safety of bilateral ocular NT-501 implants. The general analytical approach for all endpoints is descriptive. No formal statistical hypothesis testing will be conducted.

The safety population will include the data from all participants who receive a NT-501 implant in the study eye and have at least 1 safety measurement. No participant (or data) will be excluded from this dataset because of protocol violations that occur during the study.

11.2 Sample Size

Formal sample size calculations were not performed. The number of participants was chosen based on feasibility and is considered sufficient to meet the study objectives.

11.3 Statistical Methods

11.3.1 Analysis of Safety

Safety analyses will be performed on the safety population, which includes all participants who received an implant in the study eye. The assessment of safety will be based on the summary of ocular and non-ocular treatment-emergent AEs (TEAEs) and ophthalmic examinations. The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs.

Summaries for TEAEs will 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. Summary tables will be supported with individual participant data listings.
Assessments of safety will also include measurements of systemic levels of CNTF, as well as the number of participants and the titer of antibodies to CNTF, neutralizing antibodies to CNTF and antibodies to NTC-201.6A that are observed at the 3-month time point and persist through the 6-month time point.

Descriptive statistics will be displayed to provide an overview of the safety results. For categorical parameters, these consists of the number and percent of participants in each category. The denominator for the percentages will be based on the number of participants appropriate for the purpose of the analysis. For continuous parameters, descriptive statistics includes n, mean standard deviation (SD), median, minimum, and maximum. Participants who prematurely discontinued the study will be evaluated on the basis of data collected at each visit attended.

11.3.2 Interim Analysis

No interim analysis will be performed in the study.

12 STUDY RISKS

Studies of intravitreal CNTF delivered by ECT at a nominal daily dose of 20 ng/implant/day have been performed in human participants and is being tested in the ongoing Phase 3 trial in participants with MacTel.

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. 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. Miosis was not observed in 59 participants exposed to a lower dose of CNTF[15].

The intracellular mechanisms through which the trophic factor CNTF regulates cholinergic development were examined in sympathetic neuron cultures.[27] 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 implant 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[15] and atrophic AMD[16] this AE was not reported. Additionally, this AE was not observed in 59 participants exposed to a lower dose of CNTF[15]. 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.[28] 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 and for this bilateral implant study. 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 normal eye and medical examinations. 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; however, these 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 SD-OCT is an FDA-approved technique, which is not associated with any AEs.

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

NT-501 Implant Insertion or Removal Surgery:

There are risks associated with the eye surgery to insert or remove the NT-501 implant. Risks include pain, infection, bleeding, miosis (small pupil), retinal detachment, cataract, vitritis (inflammation inside the eye), a change in the curvature of the front of the eye (astigmatism), decreased vision, blindness, or loss of the eye. Topical antibiotics and topical steroids are used to treat minor degrees of inflammation or infection. More serious infection or inflammation or development of retinal detachment may require additional procedures or surgery on the eye and possibly the need to remove or replace the implant.

A small sample (about 0.1 mL) of the vitreous along with the implant may be collected and shipped back to the sponsor for analysis. The risks of this procedure are same as those previously described for the explant procedure.

13 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, 29].

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

14 COMPLIANCE

This study will be conducted in compliance with the protocol, ICH (International Council for Harmonization) 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]).

14.1 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 NT-501 implant 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.

14.2 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 (e.g., source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., 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 (e.g., medical records, laboratory results) for source data verification, provided that participant confidentiality is maintained in accordance with local requirements.

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
- 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

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 (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, memoranda, evaluation checklists, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, photographic negatives, magnetic media, and medico-technical departments involved in the clinical trial.

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

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

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

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 (e.g., missed visits), administrative reasons, or any other valid and ethical reasons.

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

- Investigator determination that it is not in the best interest of the participant to continue participation
- Intercurrent illness
- AE that is serious and unexpected
- Worsening condition
- Any other safety concerns
- If a participant withdraws or is discontinued from the study, they should return for an exit visit. The schedule of assessments for this visit is the same as that for the 6-month visit.

18.1 Premature Discontinuation

Premature discontinuation is not anticipated to be a frequent event based on the history of previous clinical trials with this implant. 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 6 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 explanation 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 explanation. If a participant discontinues from the study, they will not be replaced once recruitment is complete.

If a participant requests explanation 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.

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 of each participant will be collected in the data system.

20 REFERENCES

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