Photoreceptor Structure in a Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor (CNTF) for Participants with Retinitis Pigmentosa Using Rates of Change in Cone Spacing and Density as the Primary Outcome

Neurotech USA, Inc.

Protocol Designation: CNTF/UCSF

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Investigator(s):	Jacque Duncan, MD
Institution(s):	University of California, San Francisco
Trial Sponsor:	Neurotech USA, Inc.
Chief Medical Officer:	Charles Johnson MB ChB
Date of Issue:	26 October 2015
Version:	2.0

Study Administrative Structure

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Contract Research Organization:	N/A
Clinical Investigator:	Jacque Duncan, MD

Sponsor Protocol Approval Signature

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Protocol Designation: CNTF/UCSF

Authorized Sponsor Representative Signature

Signature: 

Date: 27 October 2015

Name: Charles Johnson MB ChB

Title: Chief Medical Officer

Principal Investigator Signature Page

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I confirm that my staff and I have carefully read and understand this protocol. I agree to conduct this study according to this attached protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) International Conference on Harmonization (ICH) guidelines, and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board (IRB) and any other institutional requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB.

I have read, understand, and agree to abide by all conditions and instructions contained in this protocol. I confirm that I am qualified by training and experience as an appropriate expert to participate as principal investigator in this clinical study. I will provide copies of the study protocol and access to all study-related information to the study personnel at my site who are involved with this protocol. I will discuss with them this material and the material in the Investigator's Brochure to ensure that they are fully informed about the study agent and understand the protocol. All documents will be kept in the confidence.

Signature

Signature: _____

Date: _____

Name: Jacque Duncan, MD
University of California, San Francisco
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Protocol Summary

Protocol Title:	Photoreceptor Structure in a Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor (CNTF) for Participants with Retinitis Pigmentosa Using Rates of Change in Cone Spacing and Density as the Primary Outcome
Protocol Designation:	CNTF/UCSF
Test Article:	NT-501 Encapsulated cell intraocular implant; releasing CNTF.
Primary Endpoint(s):	The primary efficacy variable is the rate of change in cone spacing and cone density from baseline to 30 months.
Secondary Endpoints(s):	Secondary efficacy variables will include: mean change from baseline value in Humphrey Visual Field Sensitivity (VFS) from baseline to 24 months, mean change in "5-point" VFS from baseline to 24 months (using the 5 retinal points with greatest average change), mean change from baseline in Best Corrected Visual Acuity (BCVA) at 12, 18, 24, 30 and 36 months, and changes in ERG, Optical Coherence Tomography (OCT), clinical grades of inflammation (anterior chamber cell and vitreous haze grades), and vision-related quality of life (NEI-VFQ25) at each visit.
Safety Endpoint(s):	Safety variables will include the incidence of adverse events, changes in vital signs, marked changes in clinical laboratory data, ECG abnormalities, and findings during physical examinations through 36 months
# of Clinical Sites:	This is a single investigator study; Retinal Degenerations Clinic at the University of California, San Francisco
# of Study Subjects:	Approximately 30

Inclusion Criteria:

1. Participant must be between 18 and 55 years of age.
2. Participant must have a diagnosis of retinitis pigmentosa or Usher syndrome type 2 or 3.
3. Participant must understand and sign the protocol informed consent. If the participant's vision is impaired to the point where he/she cannot read the informed consent document, the document will be read to the participant in its entirety.
4. Best-corrected visual acuity must be no worse than 20/63 (at least 59 letters).
5. Participants must have clear natural lenses.
6. Participants must have less than 6 diopters myopia.
7. Participants must be medically able to undergo ophthalmic surgery for the NT-501 device insertion and able to undergo all assessments and tests associated with the protocol.

8. Females of childbearing potential (women with last menses ≤1 year prior to screening**)** must agree to use an effective form of birth control from study onset until they complete the study.
9. Participants must have reproducible baseline AOSLO image montages at 2 baseline imaging sessions with quality suitable to identify a minimum of 7 regions of interest (ROIs) at which reliable cone spacing and/or density measures can be made over the central 5.7 degrees.
10. Participants must have interocular symmetry of disease severity as measured by cone spacing, with a difference of less than 2 standard deviations in average cone spacing z-scores at the selected ROIs between the 2 eyes.
11. Participant's clinical diagnosis must be consistent with retinal degeneration in the set of retinitis pigmentosa (RP) dystrophies characterized by the following features:
    a) clinical evidence of progressive photoreceptor cell dysfunction and degeneration of the outer retina;
    b) intraretinal 'bone-spicule'-like pigment observed on clinical examination;
    c) peripheral visual field constriction documented on standard testing;
    d) symptomatic night blindness;
    e) reduction of both rod and cone electroretinogram (ERG) responses.

For purposes of this study, individuals diagnosed with Retinitis Pigmentosa or Usher Syndrome Type 2 or Type 3 (without profound deafness or cochlear implants) who meet the inclusion criteria will be considered as potential candidates for this study. A maximum of 4 Usher Syndrome Type 2 or Type 3 participants may be enrolled in this trial.

Exclusion Criteria:

1. Participant is medically unable to comply with study procedures or follow-up visits.
2. Participant who has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 3, or a nuclear opacity > standard 3 as measured on the AREDS clinical lens grading system; or participant is pseudophakic or aphakic.
3. Participant has history of corneal opacification or lack of optical clarity.
4. Participant has undergone LASIK surgery or other refractive surgery for either eye.
5. Participant has nystagmus.
6. Participant has greater than 6 diopters myopia.
7. Participant has cystoid macular edema with cysts present within 4 degrees of the foveal center.
8. Participant has fewer than 7 ROIs present on 2 baseline AOSLO image montages.
9. Participant has retinal vascular disease such as diabetic retinopathy or prior retinal vascular occlusive disease.

10. Participant has chronic requirement (e.g., ≥ 4 weeks at a time) for ocular medications or has disease(s) that in the judgment of the examining physician are vision threatening, toxic to the lens, retina, or optic nerve or may affect the primary outcome.
11. Participant has a requirement of acyclovir and/or related products during study duration. To be eligible for this study, the participant must discontinue use of these products prior to enrollment and must not continue with the products until after they have completed the study.
12. Participant is receiving systemic steroids or other immunosuppressive medications.
13. Participant is currently participating in or has participated in any other clinical trial of a drug by ocular or systemic administration within the last 6 months.
14. Participant has previous exposure to an intra-ocular device or implant into the eye (excluding intra-ocular lens).
15. Participant has uveitis or other retinal inflammatory disease.
16. Participant has a history of myocardial infarction within the last 12 months.
17. Participant is pregnant or lactating.
18. Participant is considered immunodeficient or has a known history of HIV. A laboratory test for HIV will be performed, and a positive result is also an exclusion criterion.
19. Participant with a history of ocular herpes zoster.
20. Participant is on chemotherapy.
21. Participant has a history of malignancy, except study participant with cancer treated successfully ≥5 years prior to inclusion in the trial.
22. Participant with severe hearing disabilities in both ears.
23. Participant who has been diagnosed and treated for amblyopia as an infant.
24. Participant who, in the opinion of the study doctor, will not be a good study subject.

Visit Schedule of events and participant procedures is provided in Table 1

Table 1: Visit Schedule

SCHEDULED VISIT WEEK	Baseline 1 (Screening)[1]	Baseline 2 (Screening)[1]	Baseline 3 (<4 days pre-op)[2]	Implant Surgery	1 Day Post-Op	1 Week (+ 3 days)	1 Month (± 3 days)	6 Months (±7 days)	12 months (± 14 days)	18 Months - (± 14 days)	24 Months - (± 14 days)	30 Months - (± 21 days)	36 Months - (± 21 days)
GENERAL ASSESSMENTS													
Informed consent	X												
Medical history, brief PE, and systems review	X				X	X	X	X	X	X	X	X	X
Vital signs (BP, respiratory rate, temperature)	X		X[3]		X	X	X	X	X	X	X	X	X
ECG			X[3]										
AE assessment					X	X	X	X	X	X	X	X	X
Implant site clinical examination					X	X	X	X	X	X	X	X	X
NEI-VFQ25 questionnaire	X						X	X	X	X	X	X	X
VISUAL SYSTEM EXAMS													
Manifest Refraction	X						X	X	X	X	X	X	X
Best Corrected Visual Acuity, IOP	X	X			X	X	X	X	X	X	X	X	X
Slit lamp exam and dilated fundus exam	X	X			X	X	X	X	X	X	X	X	X
AOSLO	X[5]	X[5]						X	X	X	X	X	X
Axial length, anterior chamber depth, corneal curvature measurement [a-scan]	X								X		X	X	X
Humphrey 10-2 Visual Field	X[4]							X	X	X	X	X	X
Dark Adapted Fundus-Guided Microperimety	X[4]							X	X	X	X	X	X
Infrared Fundus Photographs	X[4]							X	X	X	X	X	X
Spectral domain OCT	X[4]							X	X	X	X	X	X
ERG		X[4]							X		X		
STUDY THERAPY													
Implant Surgery				X									
LABORATORY													
Serum chemistry , hematology, urinalysis			X[3]						X		X		X
Urine Pregnancy[6]			X[3]						X		X		X
HIV testing			X[3]										
Genetic testing through eyeGENE			X[7]										
Serum for antibody/CNTF concentration			X						X		X	X	X

[1] Baseline 1 Screening will occur within 7 weeks of implant surgery; Baseline 2 Screening will occur within 4 weeks of Baseline 1.
[2] Baseline 3 will occur < 4 days prior to implant surgery
[3] ECG and pre-op laboratory testing should be performed within the timeframe mandated by the OR.
[4] Measurement or exams should be taken at any point within 7 weeks preceding implant surgery.
[5] Measurement at Baseline 1 must establish a minimum of 7 ROI's; measurement at Baseline 2 must verify a minimum of 7 of the previously established ROI's for measurement throughout the study period.
[6] Urine pregnancy test will only be performed on premenopausal women.
[7] Genetic testing will be offered to patients with diseases for which eyeGENE offers testing. Separate consent is required and patients can refuse to submit blood for genetic testing but still participate in the present study.

Photoreceptor Structure in a Phase 2 Study of Encapsulated Human NTC-201 Cell Implants Releasing Ciliary Neurotrophic Factor (CNTF) for Participants with Retinitis Pigmentosa Using Rates of Change in Cone Spacing and Density as the Primary Outcome

1 Background and Rationale

Retinitis Pigmentosa (RP) is a group of hereditary disorders whose common feature is a progressive deterioration of the rod and cone photoreceptors in the retina, which results in the reduction and loss of both peripheral and central vision. Histopathologic studies in naturally occurring and genetically engineered animal models of photoreceptor dysfunction and death in the condition termed retinitis pigmentosa (RP) have indicated the promise of ciliary neurotrophic factor (CNTF) as an effective therapeutic agent for reducing photoreceptor loss associated with degeneration of the cells of the outer retina. CNTF is one of several neurotrophic factors that are produced endogenously by neurons or supporting glial cells and has been demonstrated to be highly effective in retarding photoreceptor neuron loss in 12 animal RP models with various forms of retinal degeneration.

One of the major challenges in the treatment of RP is to deliver therapeutic macro-molecules such as CNTF to the retina. The blood-retinal barrier effectively prevents the passage of large therapeutic molecules from the bloodstream into the tissues of the eye thus limiting systemic treatment approaches. Neurotech developed a form of encapsulated cell technology (ECT) specifically to overcome this challenge. This technology enables the controlled, continuous and long-term delivery of therapeutic macro-molecules, including a wide variety of neurotrophic factors and other proteins and compounds, directly into the vitreous cavity inside the eye.

Due to RP's slow progression and standard clinical imaging techniques that have, until recently, been unable to visualize individual photoreceptors due to optical imperfections in living eyes, it has been challenging to evaluate CNTF's potential to treat RP. Natural history studies of retinal degeneration predict that significant changes in visual function may be measured reliably only after greater than 7 years, suggesting that significant photoreceptor loss is necessary before changes in visual function can be measured reliably (Fishman et al, 2007; Grover et al, 1997; Iannaccone et al, 2004). However, adaptive optics (AO) ophthalmoscopy, including adaptive

optics scanning laser ophthalmoscopy (AOSLO), can produce images of individual cone photoreceptors non-invasively in living eyes (Liang et al, 1997; Roorda et al, 2002; Zhang et al, 2006). Direct visualization of cones allows comparison of cone spacing and density, and in ideal situations, tracking of individual cones longitudinally. Cone spacing and density have been used to characterize normal eyes and eyes with retinal degeneration (Choi et al, 2006; Duncan et al, 2007; Rossi et al, 2010). In addition, dark-adapted fundus-guided microperimetry has been used to study visual function reliably and provides insight into the function of both rods and cones in the macula of patients with retinal degeneration (Crossland et al, 2010).

Preliminary studies using AOSLO to image cones in patients with retinal degenerations showed reduced rates of cone loss in eyes treated with CNTF compared to contralateral eyes that received sham treatment over 24-32 months, despite no significant changes in visual acuity or visual field (Talcott et al, 2010). These studies suggest that CNTF may be effective in slowing the rate of photoreceptor loss in eyes with retinitis pigmentosa and Usher syndrome, but that measures of visual function including visual acuity and visual field sensitivity are not sufficiently sensitive to identify a treatment effect over 24 months.

2 Scientific Rationale

2.1 Encapsulated Cell Technology

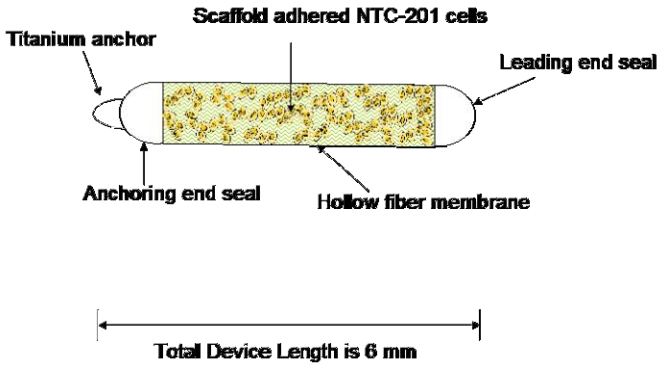
Encapsulated cell implants (NT-501) consist of cells encapsulated within supportive matrices and surrounded by a semi-permeable polymer membrane. The NT-501 implants consist of encapsulated NTC-201 cells**.** The NTC-201 cells[1], which produce ciliary neurotrophic factor (CNTF) in the NT-501 device, are derived by genetically modifying the NTC-200 cells using a proprietary plasmid vector containing the CNTF gene. The NTC-200 cells are derived from a human retinal pigment epithelial cell line, ARPE-19 (ATCC # CRL-2302). This cell line is diploid, non-tumorigenic and meets established criteria for safety and freedom from microbial contaminants and adventitious viruses (Investigational New Drug Application BB-IND-10931).

Two implant dosage forms, high (NT-501-6A.02) and low (NT-501-10.02) CNTF-secreting implants, were developed and employed in phase 1 and phase 2 studies to allow for the

[1] A spontaneously immortalized human retinal pigment epithelial line derived from the ARPE-19 line (ATCC No. CRL-2302).

evaluation of different CNTF dosing regimens and their respective safety profiles in patients with RP. Implants appeared identical, but differed in that they were loaded with either a high output (NTC-201-6A) or low output (NTC-201-10) CNTF-secreting cell line. The CNTF-specific productivity rate of the NTC-201-6A cell line is 800 ng CNTF per $1x10^6$ cells per day. The NTC-201-6A cells are used to produce the CNTF secreting NT-501 implant that releases CNTF at 20 ng/day. The NTC-201-10 cell line is a lower output line at 250 ng CNTF per $1x10^6$ cells per day are used to produce the CNTF secreting NT-501 implant that releases CNTF at ~5 ng/day.

Figure 1 Schematic Representation of the NT-501 Implants



2.2 Rationale of ECT in Participants with RP

Currently, there are no treatments available for retinal degenerative disorders, and the clinical course for RP is very poor. RP symptoms usually manifest in patients between the ages of 7-30 and the rate of progression varies among them. Most RP patients are legally blind by age 40. It has been hypothesized (Seiving et al, 2006) that CNTF implants improved the visual acuity of some of these participants who had both advanced RP and atrophic macular degeneration.

2.3 Rationale for Use of Sham Surgery

This Phase 2 study will explore the effect on cone spacing and cone density over a 24-month period of CNTF release by the NT-501 intravitreal device to establish whether CNTF delivered in this manner can improve cone photoreceptor survival or lessen the decline in cone density relative to the contralateral control eye. Measures of change in visual acuity, visual field sensitivity and disease modification will be collected over a total of 24 months as secondary

outcomes. Given this observation period to reach the primary outcome and the relatively small, absolute magnitude of improvement expected, a control sham treatment with minimal risk to the fellow eye is justified to qualify the chance that any observed differences are a result of a participant effort rather than from the treatment itself.

2.4 Rationale for Excluding Participants Under 18 or Above 55 Years of Age

The age limits were selected to maximize the homogeneity of the RP population under study. Participants younger than 18 or older than 55 may have a different clinical course of disease.

3 Study Objectives

The objective of this study is to investigate whether CNTF improves or lessens the rate of cone photoreceptor loss, measured as increased cone spacing or decreased cone density, relative to the fellow control eye in participants with Retinitis Pigmentosa and Usher Syndrome types 2 and 3.

4 Study Design and Methods

This is a prospective, randomized, double-masked, sham-controlled trial of approximately 30 study participants with reduced vision in both eyes due to RP and Usher Syndrome types 2 and 3. This trial will be conducted at the Retinal Degenerations Clinic at the University of California, San Francisco. The surgeon designated by the Principal Investigator will not be masked as to which eye received the implant and which eye received the sham. The participants and the technicians will be masked regarding the sham versus implant eye.

All participants will receive the implant after successfully completing baseline examinations during which participant's eligibility to participate in the trial will be determined (see section 4.6.1).

Although implants containing the "high output" CNTF-secreting cell line are the intent of the study, a cohort of "low output" implants will also be studied: The initial 9 participants will receive the high output implant; the subsequent 6 participants will receive the "low output" implant, and the remainder of subjects will receive the "high output" implant.

Initial implantation of the investigational devices will be staggered over a 3-month period in order to permit a review of patient safety data by the SMC. The 3-month staggered enrollment

will occur as follows. Here, references to days, weeks and months are relative only to the first surgical procedure:

- The first patient will undergo surgical implantation of the investigational product on day 1 of week 1.
- The one day, one week and one month post implant safety findings for the first patient will be forwarded to the Chairman of the SMC for review of the safety findings. Communicating the outcome of the SMC review will be accomplished prior to week 5.
- Assuming a recommendation to continue enrollment results from the SMC's review of safety data (up to one month post implant), the second patient will undergo surgical implantation of the investigational product during day's 1 – 5 of week 5.
- The 2-month post implant safety data for patients 1 and the one-month post-implant safety data for patient 2 will be supplied to the chairman of the SMC at the beginning of week 9.

The SMC's recommendation was to continue enrollment following the SMC review of safety data (up to two month post implant). The remaining patients will undergo surgical implantation of the investigational product in accordance with enrollment.

Devices will not be explanted except in instances where it is medically advised due to an adverse event. An examination for safety will occur one day following surgical implant and periodically thereafter.

All participants will be followed clinically for 30 months.

4.1 Outcomes

Primary Outcome:

The primary outcome is rate of change in cone spacing and rate of change in cone density as determined using AOSLO images of regions of interest (ROIs) preselected at baseline in eyes treated with CNTF compared to contralateral eyes treated with sham surgery over 30 months. Cone spacing and density will be measured by 3 independent graders who will remain fully masked to the treatment assignment throughout the duration of the trial. We will compare rates of change in cone spacing and cone density between CNTF-treated and contralateral sham-treated eyes through 30-months using pooled linear regression.

Secondary Outcomes:

Secondary outcome measures will involve comparing rates of change in standardized measures of visual function between CNTF- and sham-treated eyes. Secondary outcomes will include the following functional and structural assessments: mean and median change in best spectacle-corrected visual acuity (BCVA) using the ETDRS protocol, changes in visual field sensitivity and foveal sensitivity in decibels (dB) using automated static perimetry using the Humphrey visual field 10-2 protocol and rod and cone-mediated fundus-guided microperimetry using a modified Nidek MP1, changes in thickness of the outer nuclear layer (ONL) and outer segment plus RPE (OS+) layer thickness as measured using spectral-domain optical coherence tomography (SD-OCT), and changes in full-field ERG scotopic and photopic standard a- and b-wave amplitudes and timing from baseline to 36 months. All parameters except full-field ERG will be measured at 6, 12, 18, 24, 30 and 36 months after implant surgery; standard full-field ERG will be performed according to ISCEV standards at baseline, 12, and 24 months.

Safety Outcomes:

Safety of the NT-501 ECT technology implant has been demonstrated in prior Phase 1 and Phase 2 trials of the implant. Separately from efficacy outcomes which demonstrate a reduction or increase in function, safety parameters will continue to be collected and assessed by the following outcomes (occurrence of these outcomes does not necessarily require explant):

- Rejection or extrusion of the NT-501 device.
- Protocol-related abnormal findings from serum chemistry, hematology, and urinalysis (those abnormal findings that are determined to be clinically significant by the Principal Investigator).
- Peri-implant fibrosis, which either blocks the visual axis of the implanted eye or affects the lens or retina (minor/moderate fibrosis around the implant and/or the attachment point is an expected possibility and will be considered safe on ocular function). Attention should focus on fibrosis that may detach the retina.
- Development of choroidal neovascularization (CNV) in the implanted eye, in which case it may be considered a safety event and explant will be considered.

- Adverse events affecting ocular function, which are different from those expected in the normal course of RP or Usher Syndrome, which are thought to be potentially related to the implant.
- Local or systemic toxicities considered serious adverse events that are potentially related to the implant.

There are risks associated with the surgeries to implant and explant the device and with the sham surgery. In general, the risks of intra-ocular surgery are very small. Some side effects could occur locally in the eye and could affect the participant's vision. There may be pain or infection, a small amount of bleeding, cataract, vitritis, and/or mild astigmatism. A retinal detachment could also possibly occur. Participants may experience a transient red eye from superficial bleeding and itching or a foreign body sensation in the corner of the eye from irritation of the suture itself. These side effects are usually temporary and generally clear up in two weeks or less. In many cases, topical antibiotics and topical steroids can treat minor degrees of inflammation or infection. More serious infection or inflammation may require further surgery on the eye, likely with removal of the implant.

In addition, all adverse events will be collected regardless of severity or potential relationship to the implant, CNTF, or surgical procedure.

4.2 Inclusion Criteria

1. Participant must be between 18 and 55 years of age.
2. Participant must have a diagnosis of retinitis pigmentosa or Usher syndrome type 2 or 3.
3. Participant must understand and sign the protocol informed consent. If the participant's vision is impaired to the point where he/she cannot read the informed consent document, the document will be read to the participant in its entirety.
4. Best-corrected visual acuity must be no worse than 20/63 (at least 59 letters).
5. Participants must have clear natural lenses.
6. Participants must have less than 6 diopters myopia.
7. Participants must be medically able to undergo ophthalmic surgery for the NT-501 device insertion and be able to undergo all assessments and tests associated with the protocol.

8. Females of childbearing potential **(women with last menses ≤1 year prior to screening)** must agree to use an effective form of birth control from study onset until they complete the study.
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4.3 Exclusion Criteria

1. Participant is medically unable to comply with study procedures or follow-up visits.
2. Participant who has any of the following lens opacities: cortical opacity > standard 3, posterior subcapsular opacity > standard 3, or a nuclear opacity > standard 3 as measured on the AREDS clinical lens grading system; or participant is pseudophakic or aphakic.
3. Participant has history of corneal opacification or lack of optical clarity.

4. Participant has undergone LASIK surgery or other refractive surgery for either eye.
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11. Participant has a requirement of acyclovir and/or related products during study duration. To be eligible for this study, the participant must discontinue use of these products prior to enrollment and must not continue with the products until after they have completed the study.
12. Participant is receiving systemic steroids or other immunosuppressive medications.
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15. Participant has uveitis or other retinal inflammatory disease.
16. Participant has a history of myocardial infarction within the last 12 months.
17. Participant is pregnant or lactating.
18. Participant is considered immunodeficient or has a known history of HIV. A laboratory test for HIV will be performed, and a positive result is also an exclusion criterion.
19. Participant with a history of ocular herpes zoster.
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21. Participant has a history of malignancy, except study participant with cancer treated successfully ≥5 years prior to inclusion in the trial.
22. Participant with severe hearing disabilities in both ears.
23. Participant who has been diagnosed and treated for amblyopia as an infant.
24. Participant who, in the opinion of the study doctor, will not be a good study subject.

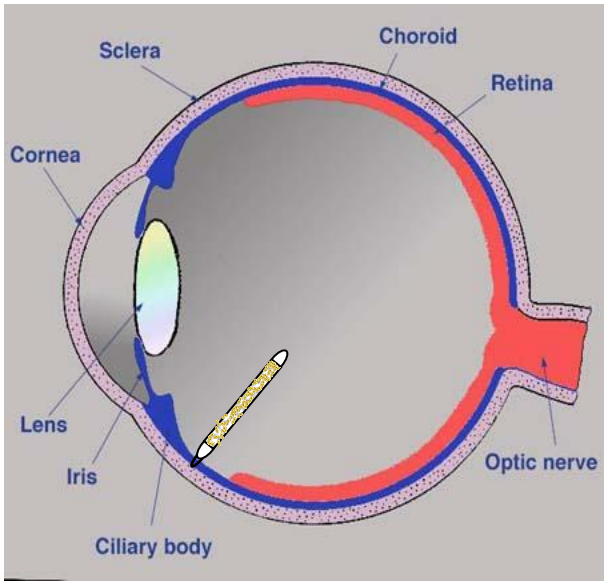
4.4 Study and Concomitant Therapy Administration

Study Treatment

Each participant will be randomized to determine the study eye. The fellow eye will receive sham surgery and serve as the control. The surgeon will determine whether the sham or the implant surgery occurs first but it is recommended that the implant surgery be done first.

The surgical procedure involves a small incision at the pars plana through the sclera, which is generally closed with three sutures. The titanium loop will be sutured beneath the sclera (using the Vitrasert technique) with the insertion site at the *pars plana* (Figure 2).

Figure 2 NT-501 (not to scale) with titanium anchor sutured beneath the sclera, secured by three sutures through the sclera (Vitrasert technique). Illustration shows site of device insertion through the pars plana, anterior to the neural retina, in the vitreous.



Study/Follow-up Visit and Assessments

The Schedule of visits and procedures is provided in Table 1 (within the Protocol Summary).

Prohibited Medications/Therapy

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Neurotech should be notified before the prohibited medication/treatment is administered.

The use of systemic steroids and intraocular steroids in the study eye are prohibited unless required for the safety of the patient and should not be administered without consultation with the Sponsor, if possible.

Administration of subconjunctival or intravitreal antibiotics is prohibited unless treating a sight-threatening condition. Administration of gentamicin or other aminoglycosides is prohibited topically, periocularly or by injection unless treating a sight-threatening condition and no other alternatives are appropriate. Systemic administration of aminoglycosides should also be avoided, if possible. Aminoglycosides are known to be toxic to RPE cells and could harm the cells in the NT-501 investigational product.

4.5 Investigational Product Packaging, Labeling, and Handling at Study Site

All study therapy required for completion of this study will be provided by Neurotech Pharmaceuticals, Inc. The recipient will acknowledge receipt of the product indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study product dispensed, used and returned will be maintained.

The NT-501 implant is seated in a primary, sterile, inner container, called the primary package, which is protected by a secondary outer container, called the secondary package. The primary package is comprised of a sealed lower compartment that holds the maintenance medium and NT-501 implant, separated by a dry upper compartment allowing for access and ease of the removal of the implant from the lower compartment. The implant is suspended within the maintenance medium by a titanium clip that, in turn, is held in position by a luer locking cap that is twisted onto the flange of the packaging baffle, sealing and separating the lower from the upper compartment of the primary package. The primary and secondary packages are each hermetically sealed with a foil laminate barrier. The contents of the finished product package are sterile.

Label: The product label for NT-501 will appear on the top of the finished package, centered on the top polymer-foil. The label will identify the implant investigational product is for clinical use only (CAUTON statement), the protocol number, lot number, and will comply with all regulatory requirements. The label will indicate the single use package contains 1 intraocular implant NT-

501, is sterile if package is unopened, the intraocular implant is for surgical implantation only, to use only as directed by the study protocol, and storage temperature.

Documentation: The Neurotech shipping/product receipt form is to be completed, and the product is inspected and documented, prior to use in accordance with Neurotech instructions. The completed form is to be provided to Neurotech. The investigational product is to be stored in the shipping box until surgery. The IP must be used within the "Use By" date.

All study therapy must be kept in a secure place under adequate storage conditions. The Investigator has overall responsibility for ensuring that study therapy is stored in a safe limited access location under the specified appropriate storage conditions. The Investigator or designee will record dispensing of the study medication on a study medication accountability record. These records should include dates, quantities, lot numbers, expiration dates, and the unique code number assigned to the investigational product. This record will be made available to clinical monitoring personnel for the purpose of accounting for the clinical study medication supply. A study medication supply inspection for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Neurotech Pharmaceuticals, Inc and a plan for resolution will be documented.

Following surgical implantation, all unused product will be destroyed and documentation of destruction recorded.

4.6 Surgical Procedure

All procedures must be performed by qualified retinal surgeons. All study surgeons will be trained by the Sponsor Neurotech. A general overview is provided below. Neurotech will provide surgical tools (ie, Sapphire Spearpoint Blade and incision dilators in an instrument tray). Additional information regarding the tools is provided in Appendix 13.

4.6.1 *Subject Preparation, Implant and Sham Surgery*

NT-501 Preparation Prior to Implantation

1. Prior to scrubbing, perform a visual inspection of the implants. Note that in most cases, > 1 implant will be available for every study subject undergoing the implant procedure. Note the package labeling, expiration/Use By date and overall integrity of each of the implants including their packaging and media color. Choose one to open onto sterile field.
2. Once in the sterile field, open the inner package and prepare to secure the implant for suturing.

3. Closely inspect the device for damage not visible while inside the package. If there is concern, discard and open the second device.
4. **Drying of the device must be minimized by limiting air exposure to < 2 minutes. BSS rinse can be applied if needed to maintain the device moist.**

Patient Preparation Prior to Implantation Procedure

1. Prior to transfer to the surgical suite, the participant's general condition will be recorded.
2. Establish an IV line for administration of medications.
3. Dilate pupils with a minimum of two drops each of phenylephrine hydrochloride (2.5%) and cyclopentolate hydrochloride (1%).
4. Transfer the study subject to the operating room and onto the operating table in a supine position.
5. Monitor the participant for oxygen saturation, heart rate, temperature, blood pressure and ECG throughout the implant and sham procedures.
6. It is recommended that the implant eye surgery will be performed prior to sham surgery.

NT-501 Implant Surgery

1. The surgeon has the option of bilateral peribulbar or subtenon anesthesia. If the option of peribulbar is used, administer the block to the implant eye at this point using bupivacaine 0.5% with lidocaine 2% 1:1.
    - Prep with anesthetic and iodine-based solution(s) and drape in standard sterile fashion. For example, scrub/prep the periocular region with 10% iodophor and the exposed surface of the eye and the conjunctiva will be rinsed with 5% iodophor solution.
    - Placing corneal shield or alternative to avoid direct illumination of the macula is recommended
2. Secure sterile drapes.
3. Retract the eyelids with a lid speculum.
4. Under microscopic visualization, perform an inferior limbal conjunctiva peritomy using scissors.
5. If the option of subtenon injection is selected, then administer the subtenon injection to the implant eye at this point using bupivacaine 0.5% with lidocaine 2% 1:1.

6. Make a 2.0 mm sclerotomy 3.75 mm posterior to the limbus in the inferotemporal quadrant. An alternative quadrant may be selected if the vitreo-retinal surgeon determines that the implant should not be inserted in the inferotemporal quadrant.
7. Using the custom dilator tool, dilate the opening made by the scleral incision.
8. Remove the NT-501 implant from its packaging. NOTE: **Drying of the device must be minimized by limiting air exposure to < 2 minutes. BSS rinse can be applied if needed to maintain the device moist.** Rinse the implant with a stream of sterile BSS and insert the implant into through the scleral incision and into the vitreous, being careful the keep the titanium loop visible above the sclera.
9. Release the device from the titanium clip using forceps or needle holders.
10. Feed the 9-0 Prolene suture through the implant's titanium clip and secure it with 2 single knots.
11. Pass each arm of the suture through either side of the wound at a depth of nine-tenths thickness through the sclera. Anchor the implant to the sclera with a triple throw knot followed by 2 single throws. It is important to leave the tails of the suture long to facilitate the following steps.
12. Place interrupted 9-0 nylon sutures over the tails of the anchoring suture to ensure closure of the wound; an attempt to bury the knots will be made for comfort. The tails on the anchoring sutures can be left slightly long, but should be trimmed so that they lie flat on the sclera. If necessary, additional 9-0 sutured knots may be used to further close the incision site.
13. Close or reappose the conjunctiva with 7-0 vicryl suture for complete coverage of the wound.
14. Examine the eye with an indirect ophthalmoscope to confirm placement of the device into the vitreous. Sterile bacitracin will be applied and the eye will be patched during the post surgical observation period.
15. Examine the eyes with an indirect ophthalmoscope to confirm placement of the device into the vitreous
16. Day of Surgery Wound Care Recommendations:
    1. At the end of surgery, administer subconjunctival dexamethasone (2mg/0.5 ml (4mg/ml), or comparable; *If the case is complicated and excess inflammation is*

anticipated in the opinion of the investigator, a higher dose of dexamethasone (0.5cc of 10mg/ml or comparable) may be used.

2. Apply Vigamox® (moxifloxacin) to eye prior to patching
3. Patch eye during the post surgical observation period as deemed necessary

Post-Op Implant Wound Care: Starting the next day, the participant will self-administer the following medications is provided in section 4.6.3

Sham Implant Surgery

1. These instructions assume that the surgeon completed the implant eye surgery first and operates on the sham eye immediately upon completion of the implant surgery.
2. If the peribulbar anesthesia was used in implant surgery, either administer the peribulbar block to the sham eye at this point using bupivacaine 0.5% with lidocaine 2% 1:1, or perform a small skin puncture using small gauge needle, to simulate the skin puncture in the fellow eye, without the actual block being placed.
3. Prep with anesthetic and iodine-based solution(s) and drape in the usual sterile fashion. For example, scrub/prep the periocular region with 10% iodophor and rinse the exposed surface of the eye and the conjunctiva with 5% iodophor solution. Note that the sham eye may be scrub prepped at the time of implant eye preparation.
4. Placing corneal shield or alternative to avoid direct illumination of the macula is recommended
5. Secure the sterile drapes.
6. Retract the eyelids with a lid speculum.
7. Perform an inferior limbal conjunctiva peritomy under microscopic visualization using scissors.
8. If a subtenon block will be used, then apply it at this point to the sham eye using bupivacaine 0.5% with lidocaine 2% 1:1 (unless the surgeon prefers the peribulbar block (see above)).
9. Apply pressure for two seconds at 3.75 mm posterior to the limbus in the inferotemporal quadrant. Select an alternative quadrant if the vitreo-retinal surgeon determines that the pressure should not be applied in the inferotemporal quadrant.
10. Close the conjunctiva with 7-0 vicryl suture.
11. Day of Surgery Wound Care Recommendations:

a. At the end of surgery, administer subconjunctival dexamethasone (2mg/0.5 ml (4mg/ml), or comparable; *If the case is complicated and excess inflammation is anticipated in the opinion of the investigator, a higher dose of dexamethasone (0.5cc of 10mg/ml or comparable) may be used.*

b. Apply Vigamox® (moxifloxacin) to eye prior to patching

c. Patch eye during the post surgical observation period as deemed necessary

Post-Op Implant Wound Care: Starting the next day, the participant will self-administer the following medications is provided in section 4.6.3

12. Examine the eye will with an indirect ophthalmoscope.

    At the completion of the exampatch the eyes for the post surgical observation periodas deemed necessary.

4.6.2 *Post Surgical Observation Period*

1. After the post surgical observation period, send the participant with instructions to return to the clinic for examinations and evaluations the next day and at one week (+3 days).
2. Provide post-operative care instructions to the study subject and instruct him/her to contact the center in the event of any adverse event.
3. Provide post operative wound care medications to self administer per section 4.6.4.
4. Perform routine post-surgery check-ups 1 day, 1 week, and 1 month after the implantation (visual acuity, IOP, slit lamp exam, indirect ophthalmoscopy, and AE assessment per the Visit Schedule in Table 1).

4.6.3 *Post-Op Implant Wound Care Recommendations*

Starting the next day, the participant will self-administer the following medications as follows:

1. Vigamox (moxifloxacin) one drop 4 times a day to both eyes for 7 days
2. PredForte to both eyes
   - *1 drop every 2 hours for 5 days (while awake)*
   - *Then 1 drop 4 times a day for 7 days*
   - *Then 1 drop 3 times a day for 7 days*
   - *Then 1 drop 2 times a day for 7 days*
   - *Then 1 drop daily for 7 days*

4.6.4 *Removal of Device*

The NT-501 implant may be explanted for significant safety or tolerability concerns, but should not be removed without prior consultation with the sponsor, if possible. Once removed, the implant is to be returned to the sponsor if possible, using handling and shipping instructions provided by the sponsor prior to explantation.

A sample of the vitreous will be collected if feasible during the explant procedure, to measure CNTF concentration. Surgical Explantation Procedure

The sponsor will review with the surgeon the instructions for surgical removal and handling of the ECT investigational product prior to the explants surgery. A general summary is provided.

Patient preparation:

- Prep with anesthetic and iodine-based solution(s) and drape in the usual sterile fashion
- After draping the eye, the eyelids will be retracted with a lid speculum.
- Under microscopic visualization a peritomy will be performed at the site of the previous implant.
- Placing corneal shield or alternative to avoid direct illumination of the macula is recommended
- Attention is then placed to implant removal. Bipolar wetfield cautery may be applied as needed to control bleeding
- The previously placed prolene sutures will be identified.
- The two lateral nylon sutures will be removed.
- A supersharpblade will then be used to create approximately a 1 mm sclerotomy on either side of the anchoring 9-0 prolene suture along the original incision.
- Bleeding from the pars plana sclerotomy will be controlled with a 23 gauge tapered bipolar cautery.
- Care will be taken to ensure the scleral wound lips are not cauterized. The edges of the sclerotomy will be gently spread and micro forceps will be used to grasp the anchoring loop on the implant.
- The sclerotomy may have to be enlarged to adequately visualize the implant.

Implant removal:

- Once grasped, the implant will be steadied while the sclerotomy is completed (joining adjacent sclerotomies) using the supersharpblade. The anchoring prolene knot will be transected by this maneuver.
- An attempt will then be made to gently remove the implant using the micro forceps.
- If resistance is encountered, the sclerotomy will be inspected and adhesions will be transected using thesupersharp blade or micro scissors.
- Handling instructions for the explanted ECT will be provided separately.
- A vitreous sample may be collected. Handling instructions will be provided separately.

Closure:

- Once the implant has been removed the sclerotomy will be closed with 7-0 vicryl suture and the retina inspected for tears or bleeding using indirect ophthalmoscopy.
- The conjunctiva will be closed.

4.7 Examination Requirements

At scheduled visits, participants will undergo a medical evaluation and an ophthalmic examination, which includes eye photography and vision measurements and laboratory tests. Scheduled visits are approximated with windows as defined in section 4.4.1 Study/Follow-up Visit and Assessment Schedule.

The following are examinations to be performed at the times indicated in section 4.4.1.

1. Medical evaluation including:
    - Demographic data
    - Medical history, including confirmation of RP diagnosis
    - Vital signs (blood pressure, respiration, and temperature)
    - Brief physical examination with body system review
    - Herpes zoster history
    - Adverse Event assessment
    - ECG (once prior to surgery)
2. Complete ophthalmic examination including:
    - Slit Lamp Exam including AREDS Clinical Lens Grading[2]
    - Implant site clinical examination
    - Ophthalmoscopic Exam
    - Manifest refraction
    - BCVA (using the ETDRS methods for refraction and EVA)
    - IOP
    - Humphrey 10-2 Visual Field Testing
    - Dark Adapted Fundus Guided Microperimetry using red and blue targets at 2 degree intervals across a horizontal line extending 10 degrees with a Goldmann V, 200 ms target using a 4-2-1 threshold strategy to assess rod and cone-mediated function

[2] The AREDS clinical lens grading protocol will be used for protocol scoring purposes (using slit lamp without any photographs).

- Full Field ERG using ISCEV standard protocol (Marmor et al, 2009)

3. Photography and measurements including:
    - Axial length, corneal curvature, anterior chamber depth measures using the IOL master (Carl Zeiss Meditech, Inc.)
    - Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO): AOSLO will be performed to image each eye of each subject at 2 baseline imaging sessions separated by no more than 1 month. During the first baseline session 37 fixation points will be imaged, each with a 1.2 degree field size, to yield a 5.7-degree diameter, roughly circular, montage of the central retina. The montage will be analyzed over the subsequent 2-3 weeks. Regions of interest (ROIs) in which unambiguous cone mosaics can be identified will be pre-specified in each eye, with the goal to identify at least 1 ROI per degree within 2.85 degrees radius of the anatomic fovea. Requirements for enrollment include the following:
        - At least 7 ROIs must be present in each eye of each patient,
        - ROIs must be located at similar distances from the fovea in each eye
        - There must be less than 2 standard deviations difference between average cone spacing z-scores (standard deviations from the mean at the eccentricity of the ROI) between the 2 eyes.
        - Cone spacing will be quantified in the ROIs by 3 independent graders, all of whom will remain fully masked to the treatment assignment throughout the duration of the study. A second baseline session performed within 1 month of the first session will focus exclusively on the ROIs identified at baseline visit 1. After at least 7 ROIs at 1 degree intervals within 2.85 degrees radius of the fovea in each eye have been identified on 2 baseline visits, the subject is eligible to enroll in the study. The PI will review AOSLO montages from each eye of each subject after each session to ensure the imaging features are indistinguishable before and after surgery between eyes randomized to receive CNTF and sham treatment. Although the PI will not be masked to treatment since she will be examining eyes post-operatively, the Co-Investigator and all study personnel responsible for AOSLO image processing and analysis will remain fully masked to

randomization and treatment assignment throughout the trial.

- Spectral Domain Optical Coherence Tomography (SD-OCT, 20 degree horizontal and vertical scans plus 20 x 15 degree volume scans; Spectralis HRA+OCT, Heidelberg Instruments, Inc.)
- Infrared Fundus photographs (Spectralis HRA+OCT, Heidelberg Instruments, Inc.)

4. Laboratory tests including:
    - Serum chemistry
    - Hematology with CBC, PTT, and APT
    - Urine pregnancy tests (females of childbearing age or potential only)
    - Urinalysis
    - HIV test
    - Whole blood collected for genetic testing through the eyeGENE research consortium, as applicable, for patients with autosomal dominant RP and other retinal degenerations that are included on the list of conditions tested by eyeGENE.

For consideration of eligibility, study participants will be screened to ensure eligibility. Some screening evaluations will not be completed on the initial screening day, however all screening evaluations, which are completed within 1 month of the initial screening visit, can be used to establish eligibility.

4.8 Enrollment, Randomization, Masking and Unmasking

Enrollment and Randomization:

To determine eligibility, prospective participants will be screened per the screening examination cited in Section 4 and Table 1 at the time of their routine visit for RP evaluation.

Participants will be enrolled and randomized in two stages. In the first stage, if the participant appears to be a likely candidate (based upon the patient's known medical history), the PI or a delegate will obtain the participant's informed consent. After receiving the participant's consent, the clinic will complete screening assessments during the Baseline 1 visit(s). AOSLO images will not be taken until the Principal Investigator or qualified designee has reviewed all non-AOSLO inclusion and exclusion criteria carefully. Once the patient is determined to be eligible

to participate based on all non-AOSLO criteria, a montage of AOSLO images will be acquired from the central 5.7 degrees surrounding fixation in each eye. AOSLO images will be analyzed and evaluated for selection of at least 7 ROIs in each eye, located at similar distances from the fovea and with less than 2 standard deviations difference between average cone spacing z-scores between the 2 eyes. The patient will return for a second baseline visit during which AOSLO images will be acquired again, but this time focusing on the ROIs that were identified during baseline visit 1. If the second set of AOSLO images of at least 7 ROIS are suitable for cone spacing and density measures in each eye (as determined by the Principal Investigator), and the patient continues to express interest to participate in the study, then the patient will be randomized. Upon randomization, the patient (now referred to as the "study subject" or "subject") is considered enrolled into the study and will then be qualified for surgery. The subject will proceed to the Baseline 2 and Baseline 3 visits prior to surgery. The timing for each Baseline visit is as follows:

- Baseline 1 will occur within approximately 7 weeks (21 days) of implant surgery;
- Baseline 2 will occur within approximately 4 weeks of Baseline 1;
- Baseline 3 will occur at the time of medical evaluation for surgery which will occur within ≤ 4 days before device surgical implant.

Masking:

The participants, vision examiners and AOSLO graders will be masked as to which eye receives the implant and which is the sham control eye. All other clinic staff will remain masked to the maximum extent possible. Personnel involved in AOSLO image acquisition and analysis, visual acuity and visual field examiners must not have access to implant surgery records, unless visual acuity is assessed by clinical coordinator for safety only. The surgeon designated by the Principal Investigator will be unmasked and will be responsible for performing the NT-501 and sham surgery procedures.

Unmasking:

Participants will be told which eye received the implant at the end of the study.

Unmasking prior to the end of study visit, or explant surgery visit (if necessary) should only be considered when knowing the randomization code would change the treatment decisions for a participant. Requests for unmasking should be referred to the Medical Monitor who will consult with the Safety Monitoring Committee (SMC) Chair prior to disclosing any treatment assignments. All incidences of premature unmasking without prior permission from the Medical Monitor and SMC Chair will be considered protocol deviations and should immediately be reported to the sponsor.

5 Safety Monitoring and Reporting

5.1 Safety Monitoring Committee

The SMC will be convened prior to trial initiation to review the protocol and will review accumulated data during the staggered implantation phase (see section 4.0) and on a regular basis during the trial. The Committee will also meet ad hoc to address any problems of significance related to participant safety brought to its attention. The committee will consider whether a protocol modification is indicated. If changes in the protocol are indicated, recommendations will be made to the sponsor who will act on such recommendations in a timely manner.

5.2 Adverse Experience Reporting

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

5.3 Obligations of Site Investigators

The Principal Investigator is obligated to promptly report to the sponsor any adverse event that may reasonably be regarded as caused by, or probably caused by the test article or study procedures. This protocol additionally requires the Investigator to report all other adverse events regardless of their severity or potential association with the test article or treatment procedures. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study test article or procedure.

For any serious or unexpected adverse event, the sponsor must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below (see Section 5.2.1.1). Adequate information must be collected with supporting documentation to complete a standard MedWatch Form FDA 3500A for submission to the sponsor.

For adverse events considered non-serious, expected or routine and where the specific event type is explicitly tracked on study case report forms, timely recording is considered acceptable when the data are reported on the schedule established for regular case report forms in the study Manual of Procedures.

If the participant reaches the final scheduled follow-up visit, any new adverse events, as well as follow-up information for ongoing adverse events, must be recorded. For participants who withdraw prematurely, adverse events should be followed until resolved or 30 days after the final study visit. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study visit must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days).

5.3.1 **Expedited Reporting Responsibilities of the Site**

When expedited reporting of a serious adverse event (SAE) is required (or expected to be required) for event types described in Sections 5.2.3.1 or 5.2.3.2, the Investigator (or the Study Coordinator) will promptly:

- Notify the medical monitor and SMC chair of any SAE within 24 hours of the knowledge of the occurrence of the SAE and fax a SAER Form to the medical monitor at 401-333-3881.
- Assess and report the causality of the event.
- If applicable, provide the Medical Monitor with immediate follow-up information necessary to make an initial assessment of the event, in order to meet reporting obligations.

- Provide the medical monitor with subsequent follow-up information to finalize the SAE (in the form of a follow-up SAER, answered SAE query form, discharge summary, laboratory reports, etc. as applicable).

5.3.2 **Submitting an Expedited Safety Report to the Local IRB**

Once the medical monitor receives all supporting documentation for the reported event, the Medical Monitor will determine if the safety report is eligible for expedited review. The medical monitor will log the initial event within 1 day after initial receipt. The Medical Monitor will complete the review of the event and will create a MedWatch form. This form, as well as other supporting documentation, will be forwarded to the Medical Monitor for review. The Medical Monitor will finalize the report for distribution within 2 days after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A, and any additional pertinent information recommended by the sponsor, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the local IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

5.3.3 **Submitting Adverse Events Report to IRBs**

When the Principal Investigator receives an expedited safety report from the medical monitor or the sponsor detailing adverse events occurring under this protocol or in other studies using the same test article, it must be promptly submitted to the site's IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB.

5.3.4 **Contacting the Medical Monitor**

When contacting the medical monitor, the protocol number and location of the study should be clearly noted. If necessary, back-up personnel and procedures are in place to assure adverse events are adequately handled and reported correctly. Neurotech Safety contact is provided on the protocol cover page.

5.4 Obligations of Study Sponsor

Neurotech is the IND holder with the FDA and hence is the legal sponsor of this study. The protocol was designed by the sponsor in collaboration with participating study investigators.

Neurotech must immediately investigate each reported adverse event. The sponsor has 15 days to submit a report to the FDA of any reported adverse experience that is associated with the use of the test article that is both serious and unexpected.

5.5 Adverse Events Defined

An adverse event includes any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the investigational product or device.

Medical conditions or diseases present before a participant starts study treatment are only considered adverse events if they worsen after the participant starts study treatment (temporal association).

For adverse events that result in persistent or significant disability/incapacity, disability/incapacity refers to a substantial disruption of a participant's ability to carry out normal life functions.

Non-serious adverse events that are expected according to previous experience with the test article (as described in the protocol, investigator's brochure and consent materials) can be collected in a routine manner using case report forms. If an expected event is observed to occur during the study at a greater frequency or severity than previously described, it may become an unexpected event that requires further investigation and reporting as an unexpected adverse event. Serious or unexpected adverse events, or any other events not specifically listed on case report forms as expected events, must be promptly reported to the Medical Monitor as noted above. This permits immediate investigation by the Medical Monitor and sponsor to determine the reporting requirements to regulatory authorities.

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

5.5.1 **Serious Adverse Events Defined**

A serious adverse event (SAE) [may also be termed a Serious Suspected Adverse Drug Reaction – Serious SADR; or in device studies, a serious unanticipated device effect – Serious UADE] is defined for this protocol as an adverse event or experience that meets one or more of the following criteria:

A. A death occurring during the study or which comes to the attention of the Investigator within 6 months of the end of the protocol-defined follow-up period, whether considered treatment-related.
B. A life-threatening event.
C. An adverse event requiring in-patient hospitalization or prolonged hospitalization due to the adverse event.
D. An adverse event resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function or structure, physical activities or quality of life. As part of the outcome-measure of these studies, any progression in disease will be identified through routine scheduled visual assessments. Natural progression of disease alone (e.g., worsening of vision) is not to be considered a serious adverse event (SAE). Any disease progression that is deemed by the Investigator as beyond the natural progression of disease will be reported as an SAE.
E. A congenital anomaly or birth defect, where exposure to the test articles prior to conception or during pregnancy is suspected in resulting in an adverse outcome in the child.
F. An event that otherwise required a medical or surgical intervention to preclude permanent impairment or damage (excluding unrelated elective or cosmetic procedures).

Hospitalization scheduled before a participant enrolls in the study is not the result of a treatment-emergent AE, and therefore events leading to such hospitalization will not be considered study

AEs or SAEs. During the study, if a participant has elective surgery for a pre-existing condition and the condition did not worsen during the study, the reason for elective surgery (and resulting hospitalization, if applicable) should not be considered or reported as an SAE. Surgery or hospitalization should always be reported as an outcome of an adverse event. In the case of surgery for a pre-existing condition, the surgery or hospitalization itself does not merit an SAE report.

5.5.2 **Unexpected Events Defined**

An unexpected event is any adverse drug experience or unanticipated adverse device effect, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the test article, the Investigator's Brochure, or as described in the clinical protocol and consent materials. This includes an increase in the frequency or severity of a previously reported adverse event that is significantly above the rates known from previous experience with the test article.

5.5.3 **Relatedness of Event to Test Article or Procedure**

The Investigator (or an authorized study physician) must submit an attribution for the relatedness of the reported adverse event to the test article or procedure.

The attribution should take into account both the temporal association and any known physical, physiological or toxicological information regarding the test article that could reasonably infer causality. Relatedness should only be considered for the experimental test article and not for any standard study examination or diagnostic procedures. The five attribution categories are:

- Definite—*Clearly related* to test article or procedure.
- Probable—*Likely related* to test article or procedure.
- Possible—*May be related* to test article or procedure.
- Remotely—*Unlikely related* to test article or procedure.
- Unrelated—*Clearly NOT related* to test article or procedure.

5.6 Withdrawal Criteria

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

If a participant withdraws from the study completely, they should return for a safety visit at least 1 month after withdrawing. All 30-month assessments/examinations should be included in the safety visit.

6 Statistical Considerations

6.1 Description of Trial

10 subjects will be enrolled into the study. Both eyes of each participant will be evaluated in this study. There are, thus, a minimum of 10 participants and a minimum of 20 eyes in the trial. One eye of each participant will be randomly assigned to receive CNTF, and the fellow eye will receive sham surgery. AOSLO montages will be acquired at baseline 1 covering the central 5.7 degrees to identify at least 7 ROIs where unambiguous cone mosaics are visualized. AOSLO images will be acquired at Baseline 2 within 1 month of Baseline 1 and focused on the ROIs. Humphrey visual field sensitivity of each eye will be measured at baseline, month 6, month 12, month 18, month 24 and month 30. The total score for the entire retina, averaged across replicates, will serve as the unit of analysis for baseline qualifications and efficacy outcomes. In addition, the 5 points of the visual field with the greatest change during treatment will serve as a key secondary efficacy variable. Pupil size will be recorded during HVF assessment.

6.2 Analysis Populations

Efficacy and safety analyses will be based on all randomized patients, in accordance with the intent-to-treat principle. Secondary analyses will be performed in the subgroup of patients who are in full compliance with protocol, have a favorable surgical outcome and no evidence of cataracts at 30 months.

6.3 Efficacy and Safety Variables

The primary efficacy variable is the rate of change in cone spacing and cone density from baseline to 24 months. Secondary efficacy variables will include: mean change from baseline value in Humphrey Visual Field Sensitivity (VFS) from baseline to 24 months, mean change in "5-point" VFS from baseline to month 24 (using the 5 retinal points with greatest average change), mean change from baseline in Best Corrected Visual Acuity (BCVA) at 12, 18, and 24 months, and changes in ERG, Optical Coherence Tomography (OCT), clinical grades of

inflammation (anterior chamber cell and vitreous haze grades), and vision-related quality of life (NEI-VFQ25) at each visit.

The mean change in VFS will be calculated using the sum of all points at baseline and each follow-up visit. Likewise, the 5 points with greatest change from baseline will be selected for each patient based on the average score per point across replicates at baseline and at month 24; the mean of these 5 points will be used to compute the change from baseline in "5-point" VFS.

Safety variables will include the incidence of adverse events, changes in vital signs, marked changes in clinical laboratory data, ECG abnormalities, and findings during physical examinations.

6.4 Sample Size Rationale

The primary analysis will compare the mean rate of change in cone spacing and cone density between CNTF-treated and control eyes over the 24-month study period using pooled linear regression. With a minimum 10 patients the sample size will provide in excess of 80% power to detect a difference of 0.084 arcminutes in cone spacing (twice the effect reported per year in preliminary studies (Talcott et al, 2010), assuming a within-region standard deviation of 0.11 (based on preliminary data, and using a paired-subjects t-test as a basis for power calculations).

6.5 Statistical Analysis Plan

Prior to the statistical analysis of the data resulting from this study, the Statistical Analysis Plan (SAP) will be developed by an appropriate statistician, and approved by both the Principal Investigator and the Sponsor. The SAP will include, at a minimum, a discussion on the analysis and presentation of baseline and demographic data, efficacy analysis and safety analysis.

6.6 Interim Monitoring

The SMC will review safety summaries on a periodic basis throughout the trial. Data summaries will be provided by the study statistician in advance of all SMC meetings.

7 Human Participant Protection

All participants will receive a verbal explanation by the Principal Investigator or qualified designee, or as designated by state or local law in terms suited to their comprehension of the

purposes, procedures, and potential risks of the study. The participants must have the ability to understand and sign an informed consent form, which must be obtained prior to enrollment. The participants will have an opportunity to carefully review the consent and ask questions regarding this study prior to signing, and they will be informed that they may withdraw from the study at any time without prejudice to themselves.

The participants' names will not appear on any of the data forms reported to the sponsor. Participants will be identified by a name code and a study registration number. The information collected will remain confidential.

There are risks associated with the examination procedures required for participants in this study. However, these are all standard procedures that are performed as part of a normal eye and medical exam. The procedures associated with the implant/explant of the device employ standard surgical techniques but the device itself is experimental. Some of the discomforts associated with the ocular exam include the following:

1. Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur.
2. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available.
3. In rare instances, the cornea may be abraded during measurement of intra-ocular pressure or use of a contact lens (used for examination purpose only and not a contact lens used to correct one's refractive error). A corneal abrasion of this sort may be painful, but it heals quickly with no lasting effects.

There are also risks associated with the surgeries to implant and explant the device and with the sham surgery. In general, the risks of intra-ocular surgery are very small and are described below.

8 Study Risk and Precautions

8.1 NT-501 Device Implant and Sham Surgery

The risks associated with surgery to implant the NT-501 device are very small. They include pain, infection, bleeding and mild astigmatism. These side effects are usually temporary and generally resolve within two weeks. In many cases, topical antibiotics and topical steroids can treat minor degrees of infection or inflammation. More serious infection or inflammation may require further surgery on the eye and likely will include removal of the implant.

8.2 CNTF and CNTF Producing Cells

Based on data collected from NT-501 clinical trials, no serum levels of antibodies to NT501 or to CNTF have been demonstrated. In the rare event of a device rupture, surgery may be required to remove the implant. The NTC-201 cells are non-tumorigenic in nude mice, so it will not lead to tumor formation.

8.3 Dilation and Anesthetic Drops

Dilating or anesthetic drops may sting and can trigger an allergic reaction. An additional risk is a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. In the rare event that the drops are contaminated, an infection could also occur.

8.4 IOP Examination and ERG

In rare instances, the cornea may be abraded during measurement of intra-ocular pressure or use of a contact lens electrode. An abrasion like this may be painful, but it heals quickly with no lasting effects. In the event that a participant experiences a corneal abrasion, ointment should be administered and an eye patch or gauze should be placed over the eye.

9 Confidentiality and Access to Source Documents and Data

The Investigators and study staff must maintain the highest degree of confidentiality permitted for the information obtained from participants in this clinical study. Although medical and research records should be maintained in the strictest confidence, as part of the quality assurance and legal responsibilities of an investigator, the site must permit authorized representatives of the sponsor, SMC, and regulatory agencies to examine (and when permitted or required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and

evaluation of the study safety and progress. Unless required by the law, no copying of records with personally identifying information will be permitted. Only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information) or transmitted to the sponsor. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

10 Summary of GCP Compliance

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

10.1 Investigator Responsibilities

A Statement of Investigator (Form FDA-1572) including the names of the all sub-investigators and pertinent, key study personnel directly involved in the study will be completed and signed by the Principal Investigator;. The general responsibilities of the Investigator as acknowledged on the Form FDA-1572 are governed under the regulations in 21 CFR Parts 50, 54, 56, and 312. All study Investigators will be required to disclose all of their financial interests in the study test therapies or study sponsors per 21 CFR 54 – Financial Disclosure by Clinical Investigators, Subsection 4 – Certification and Disclosure Requirement. The investigational test article may be administered only in accordance with the approved protocol and under the supervision of the Investigator or a sub-investigator listed on this form. The Investigator must maintain accurate and complete study records, including records for disposition of the test article, and an accurate and complete record of all submissions made to and received from the IRB, including a copy of all reports and documents submitted. Adverse experiences that are reported to the FDA as IND Safety Reports or as described must be submitted promptly to the local IRB.

Progress reports must be submitted by the Investigator to the IRB at least once per year and to the study sponsor. The IRB must be promptly notified of completion or termination of the study.

The curriculum vitae (CV) or a résumé for each Investigator, sub-investigator, and key study personnel must also be supplied if named on the FDA Form 1572. This form and related CVs must be supplied to the sponsor prior to initiating the trial at each site. When necessary due to personnel changes, updated versions of the Form FDA-1572 must be forwarded to the sponsor and copies of all versions maintained in study records at each site. Any CV or résumé collected at the beginning of a study should be current. These documents should be updated in the event that substantial changes or additions are warranted (e.g., change of position or affiliation, certifications or licensure, or significant new publications relevant to the study protocol).

Institutional Review Board

The UCSF Institutional Review Board will operate in accordance with the regulations under 21 CFR Part 56 and authorized by the institution to review and approve materials for this trial. A list of IRB voting members, their titles or occupations, and their institutional affiliations, as well as a copy of the Assurance of Compliance, must be kept in the regulatory binder and made available by the institution for inspection and copying by authorized study monitors, auditors, and regulatory officials.

Review of Protocol, Consent and Recruitment Materials

The clinical protocol, consent materials and any participant recruitment materials specific to this study must be reviewed and approved by the IRB in accordance with local procedures and 21 CFR Parts 50, 56, and 312. Any amendments to the protocol or consent materials, or any revised materials used for the recruitment of participants in this study must also be approved in advance of their use by the local IRB/IEC. Before initiation of the study, the Investigator will develop a consent form in compliance with 21 CFR Part 50 for this trial that must be submitted for review and approved by the local IRB.

Written approval of the protocol and the consent form(s) must be obtained from the IRB/IEC and transmitted to the sponsor prior to enrollment of participants. Written approvals must specify which components (i.e., protocol, consent and/or recruitment materials) are being approved, and explicitly indicate the study title (or short title) and the protocol code number and date (and/or version number, if used) on the cover page of the protocol or any amendments. Written approvals should explicitly state the duration of the approval, or preferably the expiration date of

the approval, and the date when application for continuing approval is required. In accordance with 21 CFR Part 56, a written notification by an IRB that modifications are required to secure IRB approval for the protocol, consents or recruitment materials is not considered adequate documentation of final approval, even if the modifications have been made. In such a case, it is required that the site Principal Investigator receives written final approval from the IRB acknowledging the completion of the required modifications. At least once per year, the local IRB must review and give written approval to continue the study.

10.2 Data Handling and Record Keeping

The Principal Investigator is responsible for maintaining adequate clinical records documenting the medical history, condition, and test results for each study participant throughout the study. Source documentation may consist of written and/or electronic records and supporting data maintained by the Investigator and/or the institution. The preliminary case histories or medical records for each participant shall document that informed consent was obtained prior to participation in the study.

Case Report Forms:

Clinical data will be entered onto Case Report Forms (CRFs). Data on CRFs must correspond to and be supported by source documentation maintained at the investigational site. All study forms and records must carry only coded identifiers such that personally identifying information is not transmitted.

10.3 Protocol Amendments

The Investigator will not modify the protocol or alter the research activity without first obtaining permission from the local IRB and the sponsor. Protocol modifications that have an impact on participant safety, the scientific soundness or validity of the investigation, or the rights and welfare of study participants must be submitted in advance for approval by the SMC and approved by the local IRB and sponsor prior to implementation. The sponsor will forward protocol amendments and related documentation to all the participating sites, the SMC and the FDA as appropriate.

10.4 Monitoring Plan

The study sponsor, PI and UCSF will follow standard operating procedures for monitoring this study in accordance with GCP recommendations and FDA regulatory requirements. A monitoring plan will be developed prior to enrollment of the first study subject. This monitoring plan will describe, at a minimum, each of the items mentioned below.

Planned Site Visits:

Participating sites will have at a minimum a study site initiation visit, one or more annual routine monitoring visits and a study closeout visit conducted by experienced monitoring personnel from Neurotech, Inc. Additional monitoring visits may be performed for cause or if the volume of information to be reviewed cannot be easily completed in a single visit. Study visits will normally be scheduled well in advance so that necessary site staff and appropriate records will be available during the monitoring visit.

Items Reviewed at Site Visits:

Each monitoring visit will utilize a standardized checklist of elements to be reviewed at the site, tailored to the specific requirements of this study. Site monitoring visits will routinely review the participating site staff roster; study administrative and financial documents; required regulatory documentation; status of IRB/IEC approvals; changes or actions taken since any previous visit; participant recruitment status, screening, enrollment, and follow-up visit records; documentation of informed consent for each participant; review of adverse events; test article storage conditions, inventory, expiration dates and accountability; biological specimens or photographs awaiting transport or assessments; outstanding data clarifications and a review of selected data elements against source documentation. Site visits will follow standard procedures and a report will be prepared for study records.

Regulatory Binder:

Each site will maintain a confidential regulatory binder that contains site-specific and study-wide documentation. The Principal Investigator is required to maintain this documentation and make it available for review by authorized study monitors, auditors and regulatory authorities. Both current and outdated study documents must be maintained. The regulatory binder will contain all relevant information required for this trial in compliance with US regulations.

Clinical Data:

Selected clinical data will be reviewed at monitoring visits according to the Monitoring Plan that will be developed and finalized prior to the enrollment of the first study subject. During a monitoring visit, data discrepancies noted by the monitor will be recorded and the list of discrepancies reported to the Principal Investigator and/or Coordinator. An audit of as much as 100% of study data elements may be performed for one or more participant records. Depending on the observed data discrepancy rate (number of discrepancies / total number of data elements reviewed), additional clinical data may be scrutinized at a more or less rigorous level than the initial plan, either during the same visit or at subsequent monitoring visits. Higher discrepancy rates will cause an increased level of review. All observed discrepancies will be corrected if possible during the monitoring visit. Any outstanding discrepancies may be resolved later and reported in accordance with standard procedures.

Monitoring Visit Report:

The monitor will prepare written reports for each monitoring visit. Reports will summarize the site administrative and regulatory status, detail data discrepancies observed and corrected, and list outstanding deficiencies that still require correction.

10.5 Retention of Records

The Principal Investigator is responsible for maintaining intact study records for a period of at least 2 years following the date of approval of a marketing application for the test article with the indication for which this study is conducted. If an application is not filed or approved for that indication, the Principal Investigator must maintain these records for at least 2 years after the investigation is discontinued and FDA is notified. Local policies for records retention may require longer periods, or the sponsor may request a longer retention period. When retention of trial-related records is no longer required, the study sponsor should inform the Investigator/institution in writing.

11 Certifications and Training Requirements

11.1 Certification for AOSLO Image Acquisition and Analysis

Quality control of AOSLO study data will be ensured with the following requirements. The exact field size and any scanning distortions will be carefully measured prior to each AOSLO imaging

session by recording a video of a model eye with a calibration scale in place of the retina. For each patient, trial lenses may be necessary to remove high refractive errors prior to AO correction. The exact location of the trial lenses with respect to the eye will be recorded for each session and additional corrections to the image scale will be made. After correction, scaling or field distortion errors are estimated to be < 1% across the image.

Metrics have been developed for quantitative cone assessment and all research assistants involved in the imaging and analyses have been trained and certified by the PI and/or appropriate delegate. The PI or delegate will evaluate the quality and selection of the ROIs at baseline visits 1 and 2 and will determine whether the subject is eligible for enrollment and randomization. All AOSLO images will be de-identified and coded. Trained readers will be fully masked to subject identifiers and treatment assignment. Three independent readers will analyze the coded AOSLO montage and obtain quantitative measures of cone parameters in each ROI according to the protocol described below:

Cone Identification: For cone density and spacing analyses, the cones are identified by hand. We have developed automated tools to aid in this process but final decisions on the cone locations are made manually. To confidently identify cones, images of cones must meet the following criteria:

1. Cones must form a close-packed array of distinct bright spots in the image;

2. An intact external limiting membrane and inner segment/outer segment junction must be present on SD-OCT images at that location.

Cone Spacing: To measure cone spacing, not all cones must be visualized, but a sufficient number ($\geq$ 30 cones) of neighboring cones must be identified within a ROI to yield an average cone spacing measurement. Cone spacing is a more conservative measure than cone density, and we anticipate that cone spacing at each ROI will be obtained at each visit.

Cone Density: To track cone density, ROIs in which all cones are visualized are required. We will require ROIs with a region of $\geq$ 50 cones in which every cone can be unambiguously identified for use in cone density measurements. Cone reflectivity is known to change over time, so high-resolution, high signal-to-noise images are required to see all cones, including those that

are weakly reflecting. Normal variation in image quality may result in fewer ROIs being used to track for cone density at all time points than can be used for cone spacing measures.

To ensure the cone spacing and density measures are made in an unbiased manner, each ROI will be evaluated by 3 independent graders masked to treatment assignment.

11.2 Certification for Humphrey Visual Field Testing

Specific certification in techniques for Humphrey Visual Field is required for this study. Certification involves a practicum and testing in the competent use of the equipment. Each person (e.g., physician, optometry professional, ophthalmic technician and/or nurse) that performs this testing on study participants must be certified. Training and certification for the Humphrey Visual Field Testing will be provided prior to study initiation.

11.3 Professional Licensure

All study physicians must provide evidence of current medical licensure applicable to the study location(s) if they are practicing medicine, diagnosing and/or treating participants. This includes physicians who perform the NT-501 implant / sham / explant surgeries. A physician who is a site Principal Investigator must also provide satisfactory evidence of ophthalmology training before study initiation.

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13 Appendix: NT-501 Implant Accessories: Surgical Tool Information

1.0 NT-501, 2.0 mm Sapphire Spearpoint Blade Tool

The NT-501 2.0 mm Sapphire Spearpoint Blade Tool is an ophthalmic knife used to create the incision for implantation of the NT-501 Implant. The knife is equipped with a spring-loaded retractable 2.0 mm Sapphire Spearpoint Blade on the distal end. The NT-501, 2.0 mm Sapphire Spearpoint Blade Tool is a Class I ophthalmic device per regulation 21 CFR 886.4350.

Materials
The handle of the NT-501, 2.0 mm Sapphire Spearpoint Blade is made of titanium. The 2.0 mm Sapphire blade is made of 9 Mohs hardness Sapphire. Both blade and handle are manufactured by Shaanxi Xingmao Industry Co., Ltd., an FDA registered medical device manufacturer.

Description of Use
The NT-501, 2.0 mm Sapphire Spearpoint Blade Tool is intended for use in ophthalmic surgical applications by trained physicians and personnel only. The knife is packaged in a sterilization container with the blade in the retracted position. The knife is to be cleaned and sterilized prior to use in accordance with NT-501 Surgical Instrument Handling Instructions provided to each investigator. Immediately prior to use, trained personnel should expose the blade from the handle by releasing the spring-loading mechanism on proximal end of the handle. The blade should be retracted immediately after use.
"Prior to each use, the blade should be thoroughly inspected for damage, sharpness and cleanliness. A blade showing signs of overuse, wear, damage or soil that cannot be removed with cleaning should be replaced."

Classifying Regulation and Product Code:
Regulation: 21 CFR 886.4350
FDA Classification Name: Knife, Ophthalmic
Product Code: HNN

Device Registration and Listing:
Device distributed by Robbins Instruments, Inc.
Registration number: 2221941
Neurotech Assigned Part Number (8.ZTC-186 Sapphire Spearpoint Blade Tool): 0346
Robbins Instruments Assigned Part Number: 8.ZTC-186
Device Manufactured by Shaanxi Xingmao Industry Co., Ltd.
Registration Number: 3004027120

Packaging
The NT-501, 2.0 mm Sapphire Spearpoint Blade Tool is packaged within a diamond knife plastic sterilization tray, 2 1/2" W x 6" L x 3/4" H, distributed by Ambler Surgical. The sterilization tray (RM 0334) is an off-the-shelf part that is etched with the Neurotech logo prior to use.

Packaging Registration and Listing Information:
Sterilization Tray Distributed by Ambler Surgical, LLC
Registration Number: 3005528784

2.0 NT-501 1.55mm Incision Dilator

The NT-501 1.55 mm Incision Dilator (RM 0347) is a manual ophthalmic instrument for use in maintaining a properly sized incision site for implantation of the NT-501 Implant. The dilator is a single instrument consisting of a 5.0mm long dulled point dilator of specified width (1.55 mm) connected via a widened, rounded chamfer to a proximal handle region. The NT-501 1.55 mm Incision Dilator is a Class I exempt investigational device.

Materials
The NT-501 1.55 mm Incision Dilator is made of ASTM F136 standard 6Al4V Titanium, received from AllVAC (Monroe, NC) per RM 0347 Material Certificate of Test.

Description of Use
NT-501 1.55 mm Incision Dilator is intended for use in ophthalmic surgical applications by trained physicians and personnel only. After an incision is made for implantation of the NT-501 Investigational Device using the NT-501 2.0 mm Sapphire Spearpoint Blade Tool, the 1.55 mm Incision Dilator is inserted within the incision site to dilate the scleral wound to adequately accommodate the NT-501 Investigational Device. Dilators should be cleaned and sterilized prior to use in accordance with NT-501 Surgical Instrument Handling Instructions, within the Manual of Procedures provided to each investigator.
"Prior to each use, dilator plugs should be thoroughly inspected for damage, surface roughness and cleanliness. If a dilator shows signs of wear, damage, surface roughness or soils that have not been removed with cleaning, it should not be used within the surgical field."

Classifying Regulation
Regulation: 21 CFR 886.4350
FDA Classification Name: Manual ophthalmic surgical instrument

Packaging
The NT-501 1.55 mm Incision Dilator is packaged within a diamond knife plastic sterilization tray, 2 1/2" W x 6" L x 3/4" H, distributed by Ambler Surgical. The sterilization tray (RM 0334) is an off-the-shelf part that is etched with the Neurotech logo prior to use.

Packaging Registration and Listing Information:
Sterilization Tray Distributed by Ambler Surgical, LLC
Registration Number: 3005528784

3.0 NT-501 Surgical Kit Assembly
Following release from quality management system, one NT-501, 2.0 mm Sapphire Spearpoint Blade Tool and one NT-501 1.55 mm Incision Dilator are fitted into one sterilization tray with cover (RM0334). The sterilization tray including one NT-501, 2.0 mm Sapphire Spearpoint Blade Tool and one NT-501 1.55 mm Incision Dilator is designated NT-501 Surgical Kit Assembly (RM 0343).