STATISTICAL ANALYSIS PLAN
for
Protocol: NTMT-03-B

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

Version 4.0

DATE: 20 May 2021

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Study Title:	A Phase III randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia type 2
Protocol Number Code:	NTMT-03-B
Development Phase:	Phase III
Name of Investigational Product:	NT-501 implant
Form/Route:	Surgical implantation of device in study eye
Indication Studied:	Macular telangiectasia type 2
Sponsor:	Neurotech Pharmaceuticals Inc. 900 Highland Corporate Drive Suite 101 Cumberland, RI 02864 Phone: 401-333-3830
Clinical Trial Initiation Date:	November 17, 2017
Clinical Trial Completion Date:	August 2022 (estimated)
SAP Authors:	Robin Bliss, PhD
Date of the Analysis Plan:	20 May 2021
Version Number:	4.0

This study was performed in compliance with Good Clinical Practice, including archival of essential study documents.

STATISTICAL ANALYSIS PLAN

Sponsor Name:	Neurotech Pharmaceuticals, Inc. Product: NT-501
Protocol No.:	NTMT-03-B
Protocol Title:	A Phase III randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia type 2
Prepared by:	Veristat
SAP Version:	4.0
Version Date:	20 May 2021

APPROVAL SIGNATURES

The signatures below indicate approval of the Statistical Analysis plan for this study.

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05/21/2021
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
BCVA	Best-corrected visual acuity
CNTF	Ciliary Neurotrophic Factor
CRC	Central Reading Center
CSR	Clinical study report
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
Emmes	The Emmes Company, LLC
ETDRS	Early Treatment of Diabetic Retinopathy Study
EZ	Ellipsoid Zone
GCP	Good Clinical Practice
FA	Fluorescein angiography (angiogram)
HFM	Hollow Fiber Membrane
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	Investigational Product
IS/OS	Inner Segment – Outer Segment Junction Line
mITT	Modified Intent-to-treat
MacTel	Macular Telangiectasia Type 2

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NT-501	NT.501.6A.02 ECT (nominal dose of CNTF 20ng device/day)
OCT	Optical coherence tomography (tomogram)
ONL	Outer Nuclear Layer
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis Systems
SD-OCT	Spectral domain-optical coherence tomography (tomogram)
SRNV	Sub-retinal neovascularization
TEAE	Treatment-emergent adverse event
VA	Visual Acuity
VFQ-25	(National Eye Institute) Visual Functioning Questionnaire 25
WPM	Words read per minute

1 PREFACE

This statistical analysis plan (SAP) is for the data collected through the Month 24 time point in the clinical study protocol titled "A Phase III randomized, sham controlled, study to determine the safety and efficacy of NT-501 in macular telangiectasia type 2" (NTMT03-A). This SAP describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, figures, and listings planned for the final analyses in the Clinical Study Report (CSR).

This SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety endpoints, and a list of proposed tables, figures, and listings. If revisions to this SAP are needed, the document will be amended. All SAP amendments will be finalized prior to the database lock. All deviations from the analyses described in the final SAP will be noted in the CSR.

Neurotech Pharmaceuticals, Inc or a designated Contract Research Organization (CRO) will perform he statistical analysis of the efficacy and safety data; SAS version 9.1.3 or higher will be used to generate all statistical outputs (tables, figures, listings and datasets). The SAP will be finalized and approved prior to the final clinical data lock for the study.

The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2 INTRODUCTION

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

The natural course is a gradual progressive bilateral loss of vision with the progression of the EZ loss, occasionally accompanied by sub-retinal neovascularization, leading to severe vision loss [1]. Functional impairment may be mild with no or only slight reduction in binocular best-corrected visual acuity in the early stages of MacTel type 2. However, loss of visual acuity in at least one eye is a frequently reported complaint [3, 4]. Notably, even in the presence of deep paracentral scotomata and

reduced reading ability, distance visual acuity may be relatively preserved [5, 6]. However, a decrease in visual acuity may eventually occur with disease progression. There appear to be essentially two different factors contributing to the decline of visual acuity[7, 8]. Initially, there may be a slow drop in visual acuity usually not below 20/50 which may be due to structural foveal changes, e.g. a low-grade chronic vascular leakage or hypo-reflective cavities in the inner retina. The second and more important factor for a decline in visual acuity is atrophy of the foveal photoreceptors which may result in eccentric fixation and a visual acuity of around 20/200. Such photoreceptor dropout initially occurs temporal to the foveola causing the characteristic deep paracentral scotomata and may later spread centrally. If a relatively faster drop in visual acuity is observed, an associated macular hole, the development of a retinal pigment epithelial hypertrophy, or neovascular complex may be suspected. Visual acuity below 20/200 is rarely observed but there may be marked functional impairment in very late disease stages with large central areas of photoreceptor atrophy or due to the development of a larger neovascular complex [4, 9].

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

In Type 2 Macular Telangiectasia (MacTel), leakage occurs during fluorescein angiography with manifest retinal capillary dilatation but without retinal thickening. This is the most common group of patients with macular telangiectasia. These people typically are diagnosed in their fifth or sixth decade of life although it is likely there are clinical manifestations of the disease at much earlier times that are not detected because the patients remain asymptomatic. Both genders are affected. This disorder is characterized by minimal exudation, superficial retinal crystalline deposits, retinal opacification and right-angle venules. As the disease progresses, intra-retinal pigment plaques and sub-retinal neovascularization may develop.

As noted previously, the natural history study of MacTel type 2 has demonstrated that photoreceptor loss is intrinsic to this disorder. Although anti-VEGF therapy reduced the vascular permeability, it does not influence the progression of photoreceptor cell loss or functional loss. A mouse model in which the very low density lipoprotein receptor has been knocked out (VLDLR-/-) mimics many of the characteristics of the human disease including focal disruption of photoreceptors coincident with the abnormal outer retinal-penetrating vessels [10]. The new vessels observed in the human disease and the VLDLR-/- mouse exhibit relatively mild permeability defects and are accompanied by glial activation and disruption of the RPE. Thus, in the absence of clinically significant leakage or hemorrhage, we observe neuronal cell death due to increased oxidative stress caused by proximity to the abnormal vessels. Using the Vldlr-/- mouse model Dorrell et al have demonstrated that targeted delivery of a neurotrophic factor, Neurotrophin-4, to sites of abnormal NV significantly reduced photoreceptor degeneration and protected against visual dysfunction in Vldlr-/- mice even in the face of persistent microvascular abnormalities in these mice [11].

Imaging using OCT has recently demonstrated a neurodegenerative process in MacTel, with photoreceptor damage mapped to loss of vision. Similarly, adaptive optics scanning laser

ophthalmoscopy (AOSLO) reveals unique dark regions in the cone mosaic and decreased cone density associated with decreased vision, even in areas with normal vasculature, which suggests that this feature represents early neuronal changes involved in the pathogenesis of MacTel [12]. These studies, taken together with the clinical observations of MacTel, support the concept that delivery of neurotrophic molecules, such as CNTF, may prevent photoreceptor degeneration in diseases with outer retinal vascular abnormalities such as MacTel. Thus, we believe we have an established rationale for using CNTF delivered by NT-501 to treat MacTel.

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

2.1 Purpose of the Analyses

This SAP describes the statistical methodology required to assess the endpoints of interest. These analyses will assess the efficacy and safety of the NT-501 implant that delivers a daily dose of CNTF in comparison to sham surgery with no implant, in participants with confirmed MacTel. The analyses described will be included in the CSR.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

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

3.1.1 Primary Objective

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

3.1.2 Secondary Objective

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

3.2 Study Endpoints

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

3.2.1 Primary Endpoint

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

3.2.2 Secondary Endpoints

3.2.2.1 Secondary Efficacy Endpoints

- Mean change in aggregate sensitivity of microperimetry within the EZ line break area from the Baseline Visit through the Month 24 Visit

- Mean change in reading speed from the Baseline Visit through the Month 24 Visit
- Mean change in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) near activities subscale score from the Baseline Visit through the Month 24 Visit

3.2.2.2 Secondary Safety Endpoints

- Number and proportion of participants with a loss in BCVA of 15 or more letters from the Baseline Visit through the Month 24 Visit in the study eye using the ETDRS distance chart
- Number and proportion of participants with at least 1 treatment-emergent serious adverse event (SAE) from the Baseline Visit through the Month 24 Visit

3.3 Study Definitions and Derived Variables

The near activities subscale score from the NEI-VFQ-25 questionnaire and the reading speed from the IReST are the only calculated measurements analyzed. A description of the scoring for the NEI-VFQ-25 questionnaire is in Section 4.4.1 below.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase III, prospective, multi-center, masked, sham-controlled study of approximately 112 study participants with MacTel. All participants will be followed through the 24-Month Visit where 1 month is defined as 30 days. A subset of participants will be followed through the 36-Month Visit and/or the 48-Month Visit, based on the date of the surgical procedure. The study will have a common end date which will be the date when the last enrolled participant completes 24 months of follow up, approximately August 2022. Therefore, not all participants will complete the 36- and/or 48-Month Visit.

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

The implant surgery/sham procedure in the study eye should be completed within 4 weeks of randomization and/or up 58 days from screening. Only 1 study-eligible eye of each participant will be designated as the study eye. Participants will be randomized (1:1) to receive the NT-501 implant or to undergo the sham procedure in the study-eligible eye. The implant surgery/sham procedure will occur on Day 0. Participants will be assessed on Day 1, Week 1 (± 2 days), Month 1 (± 7 days), Month 3 (± 14 days), Month 6 (± 30 days), Month 12 (± 30 days), Month 16 (± 30 days), Month 20 (± 30 days), and Month 24 (± 30 days). Note that, in regions other than France, a telephone contact will be made at Month 1 (± 7 days) and Month 3 (± 14 days) instead of a clinic visit. A subset of participants, based on the date of the surgical procedure, will be assessed at Month 36 (± 30 days) and Month 48 (± 30 days).

Participants who will reach the Month 36 and/or Month 48 timepoint will be required to provide additional informed consent. Upon completion of the 24, 36, or 48-month observation, all participants will be followed for safety and disease progression in a nested substudy of the existing Natural History and Observation and Registry Study of Macular Telangiectasia Type 2 (NHOR) [13]. Study data will be recorded on electronic Case Report Forms (eCRFs).

4.2 Selection of Study Population

Approximately 112 participants will be accrued for the study from identified patients with confirmed MacTel who meet the inclusion/exclusion criteria.

Please refer to the current study protocol for the current, comprehensive list of inclusion and exclusion criteria.

4.3 Investigational Products

4.3.1 Investigational Products Administered

The study device is the NT-501 implant, NTC-201-6A ECT (delivering a nominal CNTF dose of 20 ng/device/day), which will be implanted per randomization and will remain in situ for the duration of the study. There are no plans to remove the device, except in the case of participant intolerance or complications such as infection or inflammation.

4.3.2 Identity of Investigational Product

NT-501 implant:

Active compound:	Ciliary neurotrophic factor (CNTF)
Formulation:	Encapsulated cell therapy (ECT)
Strength:	20 ng/device/day
Container:	
Manufacturer:	Neurotech Pharmaceuticals, Inc (USA)
Trade name:	NT-501 implant
Storage requirements:	Room temperature, not to exceed 55°C (131°F) or fall below −20°C (−4°F),
Composition:	Certificate of Analysis to be supplied by the Sponsor

4.3.3 Method of Assigning Participants to IP Groups (Randomization)

One eye of eligible participants will be randomized (1:1) to receive the implant with a nominal dose of CNTF 20 mg device/day or sham procedure. If both eyes qualify for the study, the study eye will be chosen as part of the centralized randomization process. The eye is deemed eligible only after the reading center has reviewed all baseline images.

4.3.4 Selection of Doses in the Study

Only one configuration of the NT-501 implant will be used in this study with a nominal dose of CNTF 20ng per device/day.

4.3.5 Selection and Timing of Dose for Each Participant

A single NT-501 implant is surgically positioned into the vitreous once and remains in situ for the duration of the study.

4.3.6 Masking

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

4.3.7 Prior and Concomitant Therapy

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

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

4.4 Efficacy and Safety Variables

4.4.1 Efficacy Variables

The efficacy variables in this study include EZ area (i.e., area of IS/OS loss) measured by SD-OCT, retinal sensitivity measured by Macular Integrity Assessment (MAIA) microperimetry, reading speed using the International Reading Speed Texts (IReST) Worksheets developed by the IReST Study Group [14], and participant responses to the NEI-VFQ-25 questionnaire, which is described below.

International Reading Speed Texts (IReST)

The International Reading Speed Texts (IResT) consists of paragraphs of text (approx. 130 words per text) - according to the everyday life reading demands with the same difficulty, content and linguistic characteristics in the different languages. It consists of a set of ten equivalent texts in each language for repeated measurements and international studies and was already evaluated in 425 normal young

subjects. Reading speed is calculated as the number of words read per minute.

Visual Function Questionnaire-25

The Visual Function Questionnaire-25 (VFQ-25) is a reliable 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). The survey measures health-related quality of life relevant to participants with vision disorders. The test is designed to capture the influence of vision on emotional well-being and social functioning dimensions. Response category for each item ranges from either 1 to 5 or 1 to 6. Each item will then convert to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score (e.g., a score of 50 represents 50% of the highest possible score). Then, items within each sub-scale are averaged together to create the 12 sub-scale scores. The following table indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not considered when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the sub-scale that the respondent answered.

Scoring Key

Item Number	Response Category	Conversion (scores)
1, 3, 4, 15c	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0

Item Number	Response Category	Conversion (scores)
5, 6, 7, 8, 9,10, 11, 12, 13, 14,16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	Missing
17, 18, 19, 20, 21, 22, 23,24, 25	1	0
	2	25
	3	50
	4	75
	5	100

Sub-scales

Scale	Items to be averaged
General Health	1
General Vision	2
Ocular Pain	4, 19
Near Activities	5, 6, 7
Distance Activities	8, 9, 14
Social Functioning	11, 13
Mental Health	3,21,22,25
Role Difficulties	17, 18
Dependency	20, 23, 24
Driving	15c, 16, 16a
Color Vision	12
Peripheral Vision	10

The near activities subscale score is the measurement that will be used as a secondary outcome measure for the SAP.

4.4.2 Safety Variables

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

All AEs will be captured whether or not considered to be related to the surgical procedure, implant, or CNTF. The incidence of reported AEs will be compared between the treated and sham participants, particularly with respect to ocular AEs. An attempt will be made to differentiate between treatment-

related AEs and AEs considered to be part of the normal progression of the disease. In addition, for treatment-related AEs, an attempt will be made to differentiate those that the investigator believes are due to the device itself, to CNTF, or to the implant/sham procedure.

5 SAMPLE SIZE CONSIDERATIONS

Sample size calculation is based on the comparison of the 2 groups over 24 months (720 days) incorporating a longitudinal mixed effects model. The number of participants, N, in each of the 2 groups [15] is calculated as follows: We assume that, in the NT-501 implant group, the response of change in EZ area is as follows:

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

For the sham group the sham equation holds as follows:

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

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

The number of participants, m, in each of the 2 groups [15] is calculated as follows:

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

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

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

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

$$Y_{ij} = (\beta_0 + b_{0i}) + \beta_1 * TRT + \beta_2 * TIME + \beta_3 * TRT * TIME + \varepsilon_{ij}$$

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

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

5.1.1 Rationale for Parameters Used in Power Estimation

The NTMT-02 (Phase 2) allowed for the inclusion of both eyes in the study. If both eyes were eligible the right eye was randomized (1:1) to receive the NT-501 implant or sham procedure and the left eye received the alternative (surgery/sham). The sample size calculated above was based on estimates from an analysis incorporating NTMT-02 study design. Assuming independence between eyes the variance estimate (σ^2) is higher, yet the ρ is much higher with an estimate of power slightly higher 80%. Given the design of the NTMT-03A we assume similar estimates as those found in analysis assuming independence between eyes.

6 SUMMARY OF MODIFICATIONS

6.1 Modifications from the Approved Statistical Analysis Plan

This is the fourth version of the SAP for the Final Analysis. The major changes to this version include changes to the description of the secondary endpoints because of the addition or two study visits, Month 36 and Month 48, with amendment 5 of the study protocol. An additional change was made to the criteria for including in the per protocol analysis. This change has been added because of the marked increase in missed and out-of-window visits due to the COVID-19 pandemic.

7 GENERAL STATISTICAL CONSIDERATIONS

7.1 General Principles

All continuous variables at baseline and in terms of changes from baseline will be summarized using the following descriptive statistics: N (total number of participants in the population), n (total number of participants in the population with a given condition), mean, standard deviation (SD), median, maximum and minimum. Precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. If the measurements in the source (raw) data are integers, the corresponding mean and median will be presented in 1 decimal place and the SD in 2 decimal places; if the measurements are in 1 decimal place, the mean and median will be in 2 decimal places and the SD in 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision. The frequency and proportion of observed levels will be reported for all categorical measures. Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified in the statistical programming document for the study.

When appropriate, corresponding exact 95% confidence intervals will be included. In general, all data will be listed, sorted by site, treatment group and participant, and by visit number within participants when appropriate. All summary tables will be structured with a column or row for each treatment group. Descriptive summaries of study endpoints across each visit will be presented in tables by treatment group. Inferential summaries of study endpoints in which formal statistical testing is implemented will be performed and presented by treatment group. Descriptive graphical summaries of study endpoints will be presented by treatment group and visit. In general, all data will be listed, sorted by site, treatment and participant, and when appropriate by visit number within participant.

The baseline value will be defined as the most recent non-missing measurement collected during a screening visit. For example, if a participant was re-screened for the study, the baseline value will be the 2nd screening value. The change from baseline value will be defined as post-baseline value minus baseline

value. These definitions will apply to all analysis variables: demographics, background, baseline characteristics, efficacy and safety, unless otherwise specified.

Unscheduled measurements will be recorded as such and not attributed to a scheduled measurement time point, unless otherwise specified. Where applicable, visit windows for efficacy analysis are presented in the relevant section.

Incomplete/Missing data: Missing post-baseline values will not be imputed for the primary efficacy analysis conducted using longitudinal mixed effects methods, which make use of all available data even if a participant has missing data at some post-baseline visits. For some endpoints, sensitivity analysis including imputation may be conducted. Where applicable, these analyses have been indicated in Section 9.1.1.

For safety analysis, no imputation will be used. Missing data (e.g., dates) will remain as missing, and conservative conventions established, as required. These will be documented in the statistical programming document for this study.

No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Measurements recorded more than once at a certain time point are defined as replicate observations. If a measurement is replicated and both are valid, the first recorded measurement will be used for analysis. Replicated measurements are expected for the baseline MAIA.

Measurements recorded for the same participant at different time points are defined as repeated observations. If an assessment has planned repeated measurements, then statistical summaries will present all planned time points, as appropriate (e.g., EZ area loss).

7.2 Timing of Analyses

All final, planned analyses identified in this SAP will be performed only after the last participant has completed the Month 24 study visit and all relevant study data have been processed and integrated into the analysis database. In addition, no database may be locked or analyses completed until this SAP has been approved.

7.3 Populations

Assignment of participants to Populations will be done prior to the final data lock for the study. The following Populations will be defined: Population modified Intent to Treat (mITT) Set, Per Protocol Population Set, and Safety Population Set.

The analysis of baseline characteristics and efficacy endpoints will be performed on the mITT Population Set as defined below in Section 7.3.1. The primary efficacy analysis will also be performed on the Per Protocol Set as an additional sensitivity analysis. All safety analyses will be performed on the Safety Set.

7.3.1 Modified Intent-to-Treat Population

The Population mITT Set will include all randomized participants who received surgery (NT-501 implant or sham surgery) whether or not the participant adhered to the study protocol. Participants will be analyzed according to the treatment group to which they were randomized. All analyses of efficacy and non-safety (e.g., demographics) parameters will reference the mITT Population, as appropriate.

7.3.2 Per Protocol Population

The Per Protocol (PP) Population will be a subset of the mITT Population and will include all available data from participants who follow the protocol without major protocol violations(s). Major protocol violations are defined as deviations that may have a substantial impact on efficacy assessments. The criteria to be used for excluding participants from the PPS will be determined and documented before the final database lock. Participants will be analyzed according to the treatment group to which they were randomized. The PP Population will be used to perform supportive analyses of the primary and secondary endpoints.

7.3.3 Safety Set

The Safety Population will be defined as all participants who were randomized and received surgery (NT-501 implant or sham surgery) and have at least 1 safety measurement. Participants will be analyzed according to the group according to the treatment received, and no participants (or data) will be excluded from this dataset because of protocol violations that occur during the study. All analyses of safety will be conducted using the Safety Set.

7.3.4 Other Sets

Not applicable.

7.4 Covariates and Subgroups

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

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

7.5 Out of Window Visits for Primary and Secondary Variables

Every effort will be made to keep missing data at a minimum. Due to COVID-19, participants may not be able to attend their scheduled study visits within the protocol-specified visit window (+/- 30 days). To accommodate such delays, efficacy assessment visits delayed due to COVID-19 but conducted within -30 days of Month 12 visit or +119 days of the planned visit timepoints for Months 12, 16, 20, and 24 will be included in the analysis. To account for the variable timing of visits, the relative study day of assessments will be included in regression models as a continuous measure of Time where relative study day is defined as the number of days since surgery.

If time is included as a categorical variable (see Section 7.6), an estimated value for the scheduled visit endpoint will be computed from the raw data, adjusting the observed value to an estimated value at the targeted visit time, based on a linear trend since the previous observation. The estimated value for a participant-visit will be computed by determining the linear slope between the previous visit and the current visit. The estimated value will be the fitted value to that line at the targeted timepoint.

7.6 Interim Analyses

No formal interim analyses or early unmasking are planned.

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

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

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

7.7 Data and Safety Monitoring Committee

An independent DSMC will be established to monitor safety and the study conduct and will meet to review masked safety summaries prepared by the Coordinating Center. Members of the DSMC are external to the Sponsor and will follow a charter that outlines its roles and responsibilities. No interim analysis for efficacy is planned for this study.

The DSMC will review accumulating data for safety per the DSMC Charter. The DSMC will be responsible for monitoring data and safety and will exercise oversight of the clinical investigation independently from the study investigators. In addition, the DSMC will be responsible for reviewing the study design and, as appropriate, recommending safety design changes. More details on the DSMC role and responsibility for data monitoring can be found in the Charter.

Participants will be monitored during all study visits for AEs by the study investigators. The investigator will be responsible for the appropriate medical management of all AEs and for the personal safety and well-being of the participants. In case of an AE, the clinical investigator will initiate appropriate treatment per his/her medical judgment and will decide whether to continue treatment through full resolution of the event, discontinue the IP, or withdraw the participant from the study.

Regardless of severity or relationship to the IP, all AEs occurring during the study will be recorded in the participant's CRF. Any SAE will be reported immediately by entering the data into the EDC system within 24 hours of the investigator becoming aware of the occurrence of a serious or unexpected AE. This will notify the Coordinating Center which in turn will notify the Sponsor.

7.8 Multiple Comparisons/Multiplicity

The primary efficacy analysis involves a single hypothesis test at the 2-sided significance level of 5%. A hierarchical testing procedure will be applied to secondary efficacy analyses to control the overall type I error rate. In the case that the primary efficacy analysis is statistically significant, the secondary efficacy endpoints will be tested at a 2-sided type I error rate of 0.05 in the order listed below. If any of the secondary endpoints are found to be not statistically significant at the 2-sided 0.05 level, the hypothesis testing will stop. Later endpoint(s) will be summarized descriptively and p-values may be produced for descriptive purposes only.

- Mean change in aggregate sensitivity of microperimetry within the EZ line break area from the Baseline Visit through the Month 24 Visit
- Mean change in reading speed from the Baseline Visit through the Month 24 Visit

- Mean change in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) near activities subscale score from the Baseline Visit through the Month 24 Visit

P-values produced for safety analyses and treatment group comparisons of demographic and baseline characteristics will be considered descriptive statistics that support the results of the primary efficacy analysis and not as formal tests of hypotheses.

8 STUDY PARTICIPANTS

8.1 Disposition of Participants

Number and percentage of participants in the following categories will be summarized as appropriate:

- Randomized and received surgery (FAS)
- Randomized, Received Surgery and at least one safety measurement (Safety Set)
- Included in the PPS
- Prematurely discontinued in the study during the Treatment or Extension Periods and the reasons for discontinuations

A time to premature discontinuation analysis using the Kaplan-Meier method will be provided to assess the comparability of treatment groups in terms of premature discontinuation.

The disposition summary and discontinuation analysis will be based on the mITT Population.

8.1 Demographics and Baseline Characteristics

Demographic and ocular baseline characteristics (e.g., baseline EZ area) will be summarized. The demographics and baseline characteristics will be presented for both the mITT Population and the PP Population to allow review of characteristics of those included in the efficacy analysis, which will be based on these populations.

The medical and ophthalmic history data will be collected at the baseline visit including:

- Ongoing medical conditions
- Ocular history, ongoing ocular history, and confirmation of MacTel

Medical and ophthalmic history conditions will not be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Therefore, there will be no summary table, but all conditions will be provided in a participant listing for the FAS only.

8.2 Protocol Deviations

Protocol deviations will be provided as a participant data listing only. Major protocol violations will also be identified for analysis purposes.

8.2.1 Prior and Concomitant Medications

Frequency distributions and listings of concomitant medications will be shown by Anatomical Therapeutic Chemical (ATC) drug classification, drug name and treatment group. The medications will be shown separately for those starting before and after implant/sham surgery. All concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior and

concomitant medications will be summarized for the Safety population.

If medication start date is on or after date of dosing of study drug, then medication will be summarized as a concomitant medication regardless of whether medication end date is missing or not. If medication end date is before date of surgery, then medication will be summarized as prior medication regardless of whether medication start date is missing or not. Note that medication that started prior to surgery and continued after surgery will be summarized as prior medication and separately as a concomitant medication. Both prior and concomitant medications will be based on the FAS. If the data contain missing or partial medication start and stop dates which do not allow definitive classification as either a prior medication, concomitant medication, or both, a conservative rule will be implemented. This will be detailed in the statistical programming document for the study.

8.2.2 IP Exposure

IP for this study is the NT-501 implant that remains in place for the duration of the study, therefore the participant is not responsible for administering IP. An analysis of IP compliance is not measured, yet information will be provided on the number and percentage of participants based on the mITT Population who have the device removed during the study period.

9 EFFICACY EVALUATION

9.1 Primary Efficacy Analysis

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

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

Prior to the analysis, out of window visits will be incorporated as noted in Section 7.5. With a mixed effects model as the primary analysis model, no imputation of missing data will be done.

As stated in Section 7.6, it may be determined prior to study end and database lock that the most appropriate parameterization of time is as a categorical variable. If this occurs, the modification to the

above plan will be documented ahead of analysis. The model will proceed as described above with the exception that time will be included in the model with nominal visit labels for Months 12, 16, 20, and 24. The comparison between treatment groups will be assessed at Month 24. The preferred covariance structure is Unstructured. If the model does not converge, the covariance structure will be selected from one of the following: Variance Component, Compound Symmetry, or Auto-regressive covariance matrix through comparison of the Akaike Information Criterion [17].

9.1.1 Sensitivity Analysis of Primary Endpoint

The following sensitivity analyses of the primary variable will be performed to assess the robustness of the primary analysis:

- Categorical time model: The mixed model will be repeated with a categorical measure of time. In this model, a stochastic-adjusted EZ area will be computed for measured timepoints, as described in Section 7.5.

- Covariate adjusted model: An analysis as noted above will be conducted but will be adjusted for continuous baseline EZ area and continuous age at surgery. Other potential baseline characteristics may be considered and will be detailed in the in the statistical programming document for the study. The difference in rate of change will be defined as the parameter estimate for the treatment by time interaction term from a random intercept model.

- Exclusion of out of window visits: An analysis will be conducted excluding any out of window visits occurring more than +/- 30 days outside of the planned timepoints.

- Inclusion of all participants: An analysis will be conducted including all observed efficacy assessments, regardless of timing.

9.2 Secondary Efficacy Analysis

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

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

The observed change from Baseline visit to the Month-24 visit will be compared using t-tests. The analyses will be based on the actual values observed at the Baseline and the Month-24 visit efficacy assessment, regardless of timing of the visit as long as it occurs within +/- 30 days for pre-COVID period or within +119 days post-visit timepoint for COVID-related delays. The estimated mean treatment effect, a 95% confidence interval (CI), and a 2-sided p-value will be provided. No imputation of missing data will be done.

9.2.1 Sensitivity Analysis of Secondary Endpoints

- Exclusion of out of window visits: An analysis will be conducted excluding any out of window visits occurring more than +/- 30 days outside of the planned timepoints. Time-adjusted analysis: Time-adjusted analysis will be performed by adjusting the actual efficacy assessment results to the nominal timepoint, as described in Section 7.5.

9.3 Exploratory Efficacy Analyses

Any post hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices in the CSR. Any results from these unplanned analyses will also be clearly identified as such in the text of the CSR.

10 SAFETY EVALUATION

All safety analyses will be performed for the Safety population. Each analysis will consist of a summary of data within each treatment group and overall.

Safety analyses will be performed on all participants who underwent either implant surgery or the sham procedure. The assessment of safety will be based on the summary of ocular and non-ocular treatment-emergent AEs (TEAEs) and ophthalmic examinations.

Safety analysis will include the Month 24 safety analysis, i.e. the set of data associated with the period from surgery through the Month 24 Visit.

The overall safety profile of the NT-501 implant versus sham will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Visual acuity
- Intraocular Pressure (IOP)
- Pupil Size

10.1 Treatment-Emergent Adverse Events (TEAEs)

The collection period of adverse events, serious and non-serious, will begin after surgery and continue throughout the course of the participant's participation in the study. For analysis purposes, all adverse events will be classified as TEAE.

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

All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of TEAEs will be summarized for each treatment group by system organ class and preferred term. If a subject reports the same AE more than once, then that subject will only be counted once in the summary of that AE, using the most severe intensity.

AEs will be summarized through Month 24 and through the end of the trial/Month 48:

- All ocular TEAEs;
- All non-ocular TEAEs;
- All ocular TEAEs by intensity;
- All non-ocular TEAEs by intensity;
- All ocular TEAEs by relationship to surgical procedure/device/CNTF;
- All non-ocular TEAEs by relationship to surgical procedure/device/CNTF
- Ocular SAEs;
- Non-ocular SAEs;
- Ocular SAEs by relationship to surgical procedure/device/CNTF;
- Non-ocular SAEs by relationship to surgical procedure/device/CNTF;
- Deaths; and
- Ocular/Non-ocular TEAEs that led to explantation of IP.

All SAEs and TEAEs leading to premature withdrawal from the study will be listed.

Summaries will be presented using frequency counts and percentages (i.e., the number and percentage of study eyes/participants with an event as well as the total number of events). Study eyes/participants with multiple occurrences of the same AE or a continuing AE will be counted once, and only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level in the relationship summaries. A separate table will summarize all TEAEs when each of them is considered unique, hereafter referred as AE count table. In addition, a listing containing individual participant adverse event data for all deaths and serious adverse events will be provided, separately. All adverse events will be presented in individual subject data listings.

10.2 Visual Acuity

Participants with 15 or more letters of vision loss from baseline in the study eye will be tabulated and presented by treatment group. A 2-sample test of proportions will be performed to determine if there is a significant difference in proportions between the treatment groups through Month 24.

10.3 Implant/Sham Site Examination

The number and percentage of study eyes with shifts deemed clinically significant in the implant surgical examination findings for the listed characteristics on the CRF from baseline to post-baseline will be tabulated by treatment group at each scheduled visit.

10.4 Surgical Medications

Surgical medications will be listed.

10.5 Ophthalmic Examination

Ophthalmic examination findings with attention to the presence or absence of retinal findings or grading of disease eye will be listed for the study eye for individual participants. Intraocular pressure (IOP), and pupil size, change in intraocular pressure and change from baseline pupil size at each study visit will be summarized using mean, SD, median, minimum and maximum by treatment group. Number and percent of participants with an IOP of 21 mm Hg or greater and an increase of 5 mm Hg or more from Baseline at post-operative visits will be summarized.

11 TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings. Additional statistical packages will be utilized as needed.

12 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes in the conduct of the study or planned analyses will be applied at this time.

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14 LIST OF APPENDICES

Appendix A: Schedule of Procedures
Appendix B: Overview of Planned Efficacy Analysis
Appendix C: Overview of Planned Safety Analysis

14.1 Appendix A: Schedule of Procedures

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

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

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

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

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

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

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

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

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

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

[i] External photographs should be stored in subject study file

14.2 Appendix B: Overview of Planned Efficacy Analysis

Efficacy Endpoint		Endpoint Type[1]	Population	Analysis Period	Subgroup Analysis	Sensitivity Analysis	Figure	Analysis Model
OCT	Rate of change in EZ Area Loss	1°	FAS, PPS	24	Yes[2]	Yes	Yes	Random Intercept Model
Microperimetry	Aggregate Sensitivity	2°	FAS, PPS	24	Yes[2]	Yes[3]	Yes	MMRM
IReST	Reading speed (words/min)	2°	FAS, PPS	24	Yes[2]	Yes[3]	Yes	MMRM
NEI-VFQ-25	Near activities subscale score	2°	FAS, PPS	24	Yes[2]	Yes[3]	Yes	MMRM

1 Indicates endpoint category, 1° = primary and 2° = secondary
2 Subgroup Analysis: Age at baseline, baseline endpoint measure
3 Sensitivity Analysis limited to impact of COVID-19

14.3 Appendix C: Overview of Planned Safety Analysis

Safety Endpoint		Analysis Period	Subgroup Analysis
AE	Ocular SOC and PT	24	No
	Non-Ocular SOC and PT	24	No
	Ocular by intensity	24	No
	Non-Ocular by intensity	24	No
	Ocular by relationship to surgical procedure/device/CNTF	24	No
	Non-Ocular by relationship to surgical procedure/device/CNTF	24	No
	Ocular SAEs	24	No
	Non-Ocular SAEs	24	No
	Ocular SAEs by intensity	24	No
	Non-Ocular SAEs by intensity	24	No
	Ocular SAEs by relationship to surgical procedure/device/CNTF	24	No
	Non-Ocular SAEs by relationship to surgical procedure/device/CNTF	24	No
	Deaths	24	No
	Explantation of IP	24	No

Safety Endpoint		Analysis Period	Subgroup Analysis
Visual Acuity	15 letter or more decrease from baseline	24	No
Ophthalmic Examination	Change in IOP	24	No
	Change in pupil size	24	No
Explant/Sham Site Examination	Development of CNV Shift	24	No
	Fluid leakage Shift	24	No
	Subconjunctival hemorrhage Shift	24	No
	Fibrosis Shift	24	No
	Extrusion of device Shift	24	No
	Vitreal inflammation Shift	24	No
	Tractional retinal detachment Shift	24	No
	Sectorial lens opacification Shift	24	No
	Intraocular hemorrhage Shift	24	No
	High or low intraocular pressures Shift	24	No
	Dry eye Shift	24	No
	Change in dark adaptation (per participant perception) Shift	24	No
	Miosis (per participant perception) Shift	24	No
	Persistent chemosis Shift	24	No
	Scleral leak Shift	24	No

Note: All safety analyses are descriptive in nature; analysis is based on the Safety Set.