



STATISTICAL ANALYSIS PLAN

STUDY SPONSOR: Neurotech Pharmaceuticals, Inc.

SPONSOR REPRESENTATIVE: Thomas Aaberg
Chief Medical Officer

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

PROTOCOL NUMBER: NTMT-02b

PROTOCOL VERSION AND DATE: Version 4: 21 January 2022
Version 3: 16 July 2021
Version 2: 18 March 2021
Version 1: 20 Jan 2021

NAME OF TEST DRUG: NT-501

PHASE: Phase II

METHODOLOGY: Multicenter, Open-label

ANALYSIS PLAN DATE: 14 July 2022

ANALYSIS PLAN VERSION: Version 1.0

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Confidentiality Statement

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APPROVAL SIGNATURE PAGE

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

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Protocol Number: NTMT-02b

Document Date / Version: 14 July 2022 / Version 1.0

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Sponsor Signatory:**Sponsor Approval**

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

| Approval Signature | Job Title |
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|------------|---|
| Ab | antibodies |
| AE | adverse event |
| AREDS | Age-Related Eye Disease Study |
| AMD | age-related macular degeneration |
| BCVA | best-corrected visual acuity |
| CFR | Code of Federal Regulations |
| CNTF | ciliary neurotrophic factor |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| DHFR | dihydrofolate reductase |
| DSMC | data and safety monitoring committee |
| eCRF | electronic case report form |
| ECT | encapsulated cell therapy |
| EDC | electronic data capture |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| EZ | ellipsoid zone |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HFM | hollow fiber membrane |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IDE | investigational device exemption |
| IEC | independent ethics committee |
| IND | investigational new drug |
| IOP | intraocular pressure |
| IRB | institutional review board |
| IReST | International Reading Speed Texts |
| IS/OS | inner segment/outer segment junction line |
| MacTel | macular telangiectasia type 2 |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Nab | Neutralizing antibodies |
| NEI-VFQ-25 | National Eye Institute Visual Function Questionnaire-25 |

| | |
|----------------------|---|
| NHOR | Natural History and Observation and Registry Study of Macular Telangiectasia Type 2 |
| OCT | optical coherence tomography |
| ONL | outer nuclear layer |
| PET yarn | polyethylene terephthalate yarn |
| PSNS | parasympathetic nervous system |
| RP | retinitis pigmentosa |
| RPE | retinal pigment epithelium |
| SAE | serious adverse event |
| SD-OCT | spectral-domain optical coherence tomography |
| SE | standard error |
| SOE | Schedule of events |
| SRNV | subretinal neovascularization |
| SUSAR | serious unexpected suspected adverse reaction |
| TEAEs | treatment-emergent AEs |
| US, USA | United States |
| VLDLR | very low-density lipoprotein receptor |
| Vldlr ^{-/-} | very low-density lipoprotein receptor knockout (mouse) |

1. INTRODUCTION AND OBJECTIVES

1.1. Introduction

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

There is significant evidence to support the use of ciliary neurotrophic factor (CNTF) as a potential therapy for retinal degenerative diseases. Histopathologic studies in naturally occurring and genetically engineered animal models of photoreceptor dysfunction and death that phenotypically model retinitis pigmentosa (RP), have indicated the promise of CNTF as an effective therapeutic agent for reducing photoreceptor loss associated with degeneration of the cells of the outer retina. CNTF is one of several neurotrophic factors that are produced endogenously by neurons or Müller cells. CNTF has been demonstrated to be effective in retarding photoreceptor neuron loss in animal models of retinal degeneration of various forms, including environmental light stress.

Although CNTF is an attractive therapeutic candidate for neurodegenerative diseases, it is significantly handicapped by its extremely short half-life. Neurotech Pharmaceuticals, Inc. has developed the NT-501 implant to treat retinal degenerative diseases. The NT- 501 implants are positioned into the vitreous cavity with a surgical procedure that may be performed under local/monitored anesthesia care. These implants consist of a sealed semipermeable hollow fiber membrane (HFM) capsule surrounding a scaffold of 6 strands of polyethylene terephthalate yarn, which have been loaded with CNTF-secreting NTC-201.6A cells. The NT- 501 implants are positioned into the vitreous cavity with a surgical procedure that may be performed under local/monitored anesthesia care. These implants consist of a sealed semipermeable hollow fiber membrane (HFM) capsule surrounding a scaffold of 6 strands of polyethylene terephthalate yarn, which have been loaded with CNTF-secreting NTC-201.6A cells.

1.2. Study Objectives

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

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.3. Study Design

1.3.1. Synopsis of Study Design

This is a multicenter, open-label study to evaluate the safety of bilateral NT-501 implants in a minimum of 30 study participants with MacTel type 2. All study subjects who have received a NT-501 implant in one eye, completed either the Phase 1/2 extension study (NTMT-01/02E) or the Month-24 visit of the Phase 3 study (NTMT-03) and meet the eligibility criteria, will receive a NT-501 implant in their fellow eye and will be followed for 6 months following NT-501 implantation.

Study participants will have a screening period of up to 28 days. Participants who meet the inclusion/exclusion criteria will have implant surgery within 30 days of the Screening Visit. After the surgery, subjects receiving a NT-501 implant will return to the clinical center for assessments performed on Day 1, Week 1 (\pm 2 days), Month 1 (\pm 7 days), Month 3 (\pm 14 days) and Month 6 (\pm 14 days). Upon completion of the 6-month visit, these participants will exit the study. These participants may elect to be followed for safety and disease progression in a nested substudy of the existing Natural History and Observation and Registry Study of Macular Telangiectasia Type 2 (NHOR).

1.3.2. Randomization Methodology

No randomization will be performed for this study. All subjects will receive an additional NT-501 implant in their study eye.

1.3.3. Stopping Rules and Unmasking

There are no formal stopping rules. This is a single-arm, open label study thus unmasking of subjects or study personnel to study treatment is not a concern.

1.3.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments

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

| Procedures | Screening Day -28 to -1 | Surgery Day 0 | Post- Surgery Day 1 | Post- Surgery Week 1 | Post- Surgery Month 1 | Post- Surgery Month 3 | Post- Surgery Month 6 |
|---|-------------------------------|------------------|---------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Visit Window | | | | ±2 days | ±7 days | ± 14 days | ±14 days |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| NT-501 implantation surgery | | X | | | | | |
| Post NT-501 implant assessment | | | SE | SE | OU | O U | OU |
| External photograph of conjunctiva over implant | | | | | OU | O U | OU |
| Complete Exit Form | | | | | | | X |

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

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

1.3.5. Safety Parameters

Safety will be evaluated by monitoring AEs and SAEs, complete ophthalmic exam (consisting of an external examination of the eye and adnexa, screening for pupil responsiveness, slit lamp biomicroscopy, dilated fundus examination, indirect ophthalmoscopy, and IOP), and measurement of BCVA.

All AEs will be captured whether or not considered to be related to the surgical procedure, implant, or CNTF. An attempt will be made to differentiate between treatment-related AEs and AEs considered to be part of normal progression of the disease. In addition, for treatment-related AEs, an attempt will be made to differentiate those that the investigator believes are due to the implant itself, to CNTF, or to the implant procedure.

Safety will be assessed as noted in the Schedule of Events (SOE). The following assessments will be performed at the time points indicated in the SOE.

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

1.3.6. Primary Safety Parameters

Safety evaluations that will be performed during the study include physical examinations, measurement of vital signs, clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, and monitoring of adverse events and concomitant medications. Serum chemistry, hematology, and urinalysis will be performed only at baseline.

Primary safety endpoints are:

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

1.3.7. Secondary Safety Parameters

Secondary safety endpoints are:

- Number and proportion of participants with a loss in BCVA of 15 or more letters from baseline in the study eye using the Early Treatment Diabetic Retinopathy Study (ETDRS) distance chart
- Number and proportion of participants with at least 1 treatment-emergent serious adverse event (SAE)
- Detectable serum levels of CNTF at Months 1, 3 and 6 post-implantations of NT-501
- Number and proportion of participants with serum Ab or Nab to CNTF, Ab to NTC-201.6A cells and Ab to DFHR at Baseline and Months 1, 3 and 6 post-implantation of NT-501

2. SUBJECT POPULATION

2.1. Population Definitions

All analyses will be performed using the Safety Population.

- Safety Population: All subjects who receive a NT-501 implant in the study eye and have at least 1 safety measurement. No participant (or data) will be excluded from the safety population because of protocol violations that occur during the study.

2.2. Protocol Violations

The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Veristat and the data monitoring group as applicable; this file will include a description of the protocol violation. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

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

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of surgical implantation of the NT-501 device in the fellow eye which is designated as Day 0. The preceding day is Day -1, the day before that is Day -2, etc. Post-surgical study days are numbered relative to the last dose and are designated as Day 1, Day 2, etc.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

This study is primarily descriptive in nature; therefore, there are no formal statistical hypothesis tests planned. Data will be presented by subject and summarized overall.

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 or later

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to surgical implantation of the NT-501 device in the study eye. Prior to enrollment into the NTMT-02B study, all subjects previously received an implant as part of their participation in either the Phase 1/2 extension study (NTMT-01/02E) or the Phase 3 study (NTMT-03). As a result, participants' fellow eyes in the prior studies will be the study eye in the current study.

3.5. Methods of Pooling Data

Pooling of data is not applicable to this study.

3.6. Adjustments for Covariates

No statistical analyses or statistical models that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

There are no tests of hypotheses. Data will be analyzed descriptively.

3.8. Subpopulations

No analyses of subject subgroups are planned.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are withdrawn or discontinue from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form will be included in data listings that will accompany the clinical study report.

When tabulating adverse event data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the CRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

No interim analyses are planned for this study.

4. STUDY ANALYSES

4.1. Subject Disposition

Subject disposition will be tabulated and include the total number screened, the total number treated, the number who withdrew prior to completing the study and reason(s) for withdrawal..

A by-subject data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographics, baseline characteristics, medical history, ophthalmic history, vital signs, hematology, chemistry, and urinalysis will be displayed descriptively and through listings. Demographic characteristics (age, sex, body mass index [BMI], and race), and baseline characteristics (Number of correct letters on BVCA by both eyes, spectral domain coherence tomography by both eyes, and baseline CNTF serum level).

Number of subjects, mean, SD, median, minimum, and maximum will be presented for continuous measures; number and percentage of subjects will be presented for categorical measures. The Safety population will be used. No formal statistical comparisons will be performed.

Subjects who report multiple races will be counted for each race reported.

Medical history will include the overall incidence of any finding. Details will be provided in a listing.

4.3. Evaluation of Primary Safety Endpoints

All analyses will be conducted using the safety population.

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using system organ class (SOC) and preferred term.

Analyses of adverse events will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined as any adverse event with onset after the day of surgical implantation through the end of the study (Month 6 ± 14 days post surgery), or any event that was present at baseline but worsened in intensity or was subsequently considered study-related by the Investigator through the end of the study.

Adverse events are summarized by subject incidence rates. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

The number and percent of subjects will be tabulated overall, by SOC and preferred term within SOC for the following endpoints.

- Treatment-emergent adverse event (TEAE)
- Treatment-related TEAE
- Ocular TEAE occurring in the study eye
- Ocular TEAE occurring in the fellow eye
- Treatment-related Ocular TEAE
- TEAE by maximum grade
- Serious Adverse Events
- TEAEs leading to discontinuation

No formal hypothesis-testing analysis of adverse event incidence rates will be performed.

By-subject listings also will be provided for the following: subject deaths, serious adverse events, and adverse events leading to withdrawal.

4.4. Evaluation of Secondary Safety Endpoints

4.4.1. Serum CNTF Levels

Descriptive statistics will be tabulated for Serum levels of CNTF at Months 1, 3, and 6 post surgery. The number of records, mean, standard deviation, geometric mean, 95% confidence intervals of the mean, median, minimum, maximum, geometric mean, geometric standard deviation of CNTF serum levels will be displayed. The confidence interval of the mean will be based on the t-distribution and the confidence interval for the geometric mean will be based on the log-normal distribution.

Change in CNTF from baseline to 1, 3, and 6 months post-surgery will be calculated. At each of these time points, the number of records, mean change, standard deviation, minimum change, maximum change and the 95% confidence interval for the mean change will be tabulated.

4.4.2. BCVA

The number and percent of subjects with a loss in BCVA of 15 or more letters from baseline in the study eye at any follow-up study visit and by each study visit and the associated 95%

confidence intervals will be tabulated. Confidence intervals will be based on the Clopper-Pearson method.

4.4.3. Serology and Antibody

The number, proportion of participants with positive serum antibody to CNTF and the associated 95% confidence intervals will be tabulated at Baseline, Months 1, 3, and 6 post-surgery. The 95% confidence interval for the proportion will be estimated using the Clopper-Pearson method.

Geometric means, geometric standard deviations and the associated 95% confidence interval for the serum Ab titers will also be calculated. Confidence intervals will assume serum antibody titers are distributed according to a log-normal distribution.

The geometric mean fold-rise (GMFR) from baseline to Months 1, 3, and 6 post surgery and the associated 95% confidence intervals will be calculated. GMFRs will be calculated as the anti- \log_{10} of the mean of the \log_{10} transformed fold rise values. Confidence intervals will be calculated based on exponentiation of the \log_{10} transformed fold-rise values from the t-distribution.

Analyses of neutralizing antibodies to CNTF, antibodies to NTC-201.6A cells, and antibodies to DFHR will be performed using the same approach described above for the analyses of serum antibody to CNTF.

4.4.4. Ophthalmic Exam

The ophthalmic exam consists of an external exam of the eye and adnexa, screening for eyelid and pupil responsiveness, slit lamp biomicroscopy, indirect ophthalmoscopy and intraocular pressure. Ophthalmic exams of study and fellow eyes will occur at baseline, Months 1, 3, and 6 post-surgery; additional exams of study eyes only will occur 1 day and 1 week post-surgery.

Ophthalmic exam results will be provided in data listings.

4.5. Evaluation of Additional Safety Assessments

Additional safety assessments will be conducted using the Safety population.

4.5.1. Study Drug Exposure

Study drug exposure will be calculated as the number of subjects who received the NT-501 implant in their study eye.

The number and percent of subjects who had an implant removed prior to the Month 6 visit will be calculated. By-subject listings will be generated for these subjects noting which implant(s),

either from the current study or received during previous studies, was removed and the reason for removal.

4.5.2. Laboratory Data

Clinical laboratory values will be expressed in reported units or SI units. Serum chemistry, hematology, and urinalysis are performed only at baseline.

The actual value will be summarized for each clinical laboratory parameter. In the event of repeat values, the last non-missing value per study day/time will be used.

All laboratory data will be provided in data listings.

A subset listing will be presented for all abnormal laboratory values.

4.5.3. Vital Signs and Medical Examination

Vital signs are collected at baseline only. Actual values will be summarized using descriptive statistics and measurements will be presented for each subject in a data listing.

Medical examinations will occur at screening or baseline only and are standard for any surgical procedure. All findings will be presented in a data listing.

4.5.4. Concomitant Medications and Non-study Procedures

Concomitant medications will be coded using the WHO Drug Dictionary and Non-study procedures. Concomitant medications will be tabulated by anatomic therapeutic class (ATC) and preferred term. Non-study procedures will be tabulated by SOC and preferred term.

Any medications that did not end prior to date of surgical implantation will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications will be included in a by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan.

6. REFERENCES

Charbel Issa P, Gillies MC, Chew EY, Bird AC, Heeren TF, Peto T, et al. Macular telangiectasia type 2. *Prog Retin Eye Res.* 2013;34:49-77.

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(Required)

Signature Adoption: Pre-selected Style

Signature ID:

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Thomas Aaberg



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