Clinical Trial Protocol

Protocol Title:	A Phase 2, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray in Subjects with Neurotrophic Keratopathy (the Olympia Study)
Protocol Number:	OPP-102
Study Phase:	2
Product Name:	OC-01 (Varenicline) Nasal Spray
IND Number:	138645
Indication:	Neurotrophic Keratopathy
Investigators:	Multi-Center
Sponsor:	Oyster Point Pharma, Inc. 202 Carnegie Center, Suite 109 Princeton, NJ 08540

	Date
Original Protocol:	24 November 2020
Amendment No. 1	08 February 2021
Amendment No. 2	16 March 2021
Amendment No. 3	06 May 2021
Amendment No. 4	22 Nov 2021
Amendment No. 5	03 Jun 2022
Amendment No. 6	17 Jun 2022
Amendment No.7	10 Nov 2022

Confidentiality Statement

SPONSOR PERSONNEL

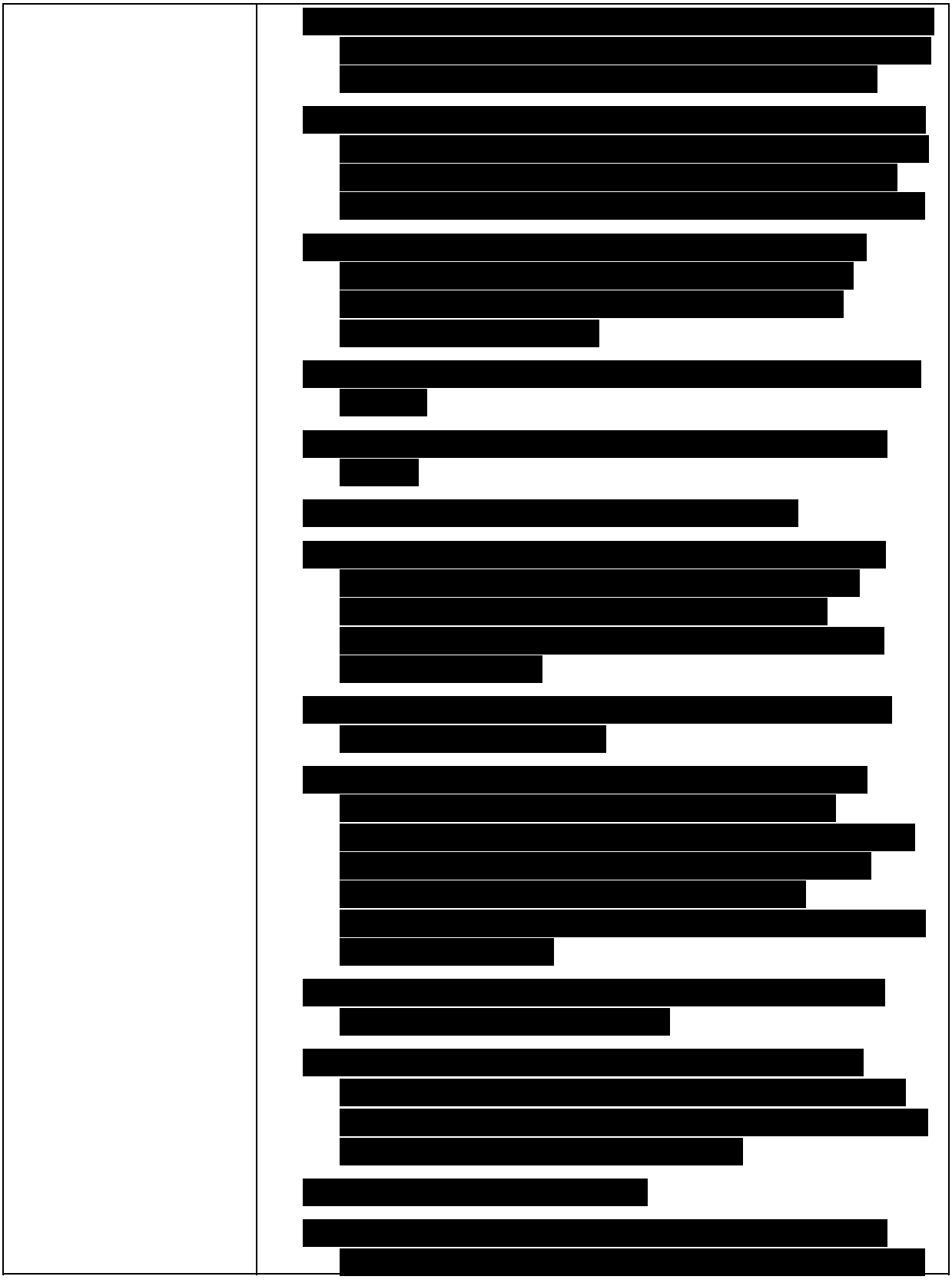
[redacted]	[redacted]
[redacted]	[redacted]

SYNOPSIS

Protocol Title:	A Phase 2, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray in Subjects with Neurotrophic Keratopathy (the Olympia Study)
Protocol Number:	OPP-102
Investigational Product:	OC-01 (varenicline) nasal spray, 1.2 mg/mL
Study Objective:	The objective of this study is to evaluate the safety and effectiveness of OC-01 (varenicline) nasal spray as compared to placebo nasal spray for mean change from baseline in corneal fluorescein staining in subjects with Stage 1 (corneal epithelial hyperplasia/punctate keratopathy) neurotrophic keratopathy (NK) in one or both eyes.
Overall Study Design	
Structure:	A Phase 2, multicenter, randomized, controlled and double-masked study
Duration:	Treatment: 8 weeks Follow-up: 1 Week post treatment and 6 months post treatment
Control:	Placebo (vehicle control) nasal spray
Dosing Regimen:	Subjects will receive OC-01 (varenicline)/ nasal spray or placebo nasal spray for 8 weeks three times daily (TID) as follows: • OC-01 (varenicline) nasal spray, 1.2 mg/mL • Placebo (vehicle control) nasal spray
Summary of Visit Schedule:	Visit 1- Day 1 - Screening and Randomization Visit 2 (Week 1) - Day 7 ± 2, corneal assessment. Visit 3 (Week 2) - Day 14 ± 2, corneal assessment. Visit 4 (Week 4) - Day 28 ± 2, corneal assessment. Visit 5 (Week 6) - Day 42 ± 2, corneal assessment. Visit 6 (Week 8) - Day 56 ± 2, corneal assessment. Visit 7 (Week 9) - Day 63 ± 7, phone follow-up. Visit 8 (Week 24) - Day 168 ±7, safety follow-up

Measures Taken to Reduce Bias:	This is a randomized and double-masked study
Study Population Characteristics	
Number of Subjects:	Approximately 100 subjects (50 subjects per treatment arm)
Condition/Disease:	Neurotrophic Keratopathy (NK)
Inclusion Criteria:	**Subjects must:** 1. Be at least 18 years of age at Visit 1. 2. Patients with Stage 1 (corneal epithelial hyperplasia/punctate keratopathy) NK in one or both eyes[1], as defined by the Mackie Criteria. 3. Evidence of decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) in at least 1 corneal quadrant. 4. Schirmer's test without anesthesia ≥3 mm/ 5 minutes in the affected eye [redacted] 12. If a female is of childbearing potential, they must: use an acceptable means of birth control (acceptable methods of contraception include hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a

	diaphragm or condom, IUD, or surgical sterilization of partner), and have a negative urine pregnancy test on Day 1. [1] [redacted].
Exclusion Criteria:	**Subjects must not:** 1. Have Stage 2 or Stage 3 NK affecting one or both eyes. 2. Have ocular graft versus host disease or Stevens-Johnson syndrome. 3. Have any active ocular infection (COVID-19 conjunctivitis, bacterial, viral, fungal, or protozoal) or active ocular inflammation not related to NK in the affected eye. [redacted] 6. Be currently receiving autologous serum tears, amniotic membrane, cenegermin, Fresh Frozen plasma or cord blood derived tears. 7. Have severe blepharitis and/or severe meibomian gland disease in the study eye. [redacted]



	[redacted]
Study Formulations:	Subjects will be randomized 1:1 to receive as a 50 microliter (µL) spray in each nostril: • OC-01 (varenicline) nasal spray, 1.2 mg/mL • Placebo (vehicle control) nasal spray
Randomization:	Subjects who meet the eligibility requirements will be randomly assigned to 1 of 2 treatment groups. The randomization will be stratified by:: • Pre-procedure (baseline) non-anesthetized Schirmer's score (≤5, >5) measured at the screening/randomization visit. A central randomization list will be created using block randomization. Sites will be assigned entire blocks as needed.
Evaluation Criteria	
Efficacy Measures:	**Primary Endpoint** • Mean change from baseline in corneal fluorescein staining in subjects with Stage 1 NK at Week 8. **Secondary Endpoints** • Mean change from baseline in visual acuity at Week 8 •
Safety Measures:	• Adverse event (AE) query • Intranasal exam

	• Slit lamp biomicroscopy
[redacted]	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of covariance
BCDVA	Best corrected distance visual acuity
CAE®	Controlled adverse environment
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGF	Epidermal Growth Factor
ETDRS	Early Treatment Diabetic Retinopathy Study
HGF	Hepatocyte Growth Factor
HIPAA	Health Information Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
NEI-VFQ	National Eye Institute Visual Function Questionnaire
Mg	Milligram
NGF	Nerve Growth Factor
NK	Neurotrophic Keratopathy
mL	Milliliter
µL	Microliter
Mm	Millimeter
PED	Persistent Epithelial Defect
PDGF	Platelet Derived Growth Factor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
STS	Schirmer's Test Score
TEAE	Treatment-emergent adverse event
TID	Three times daily
US	United States
VAS	Pain Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor

1. INTRODUCTION

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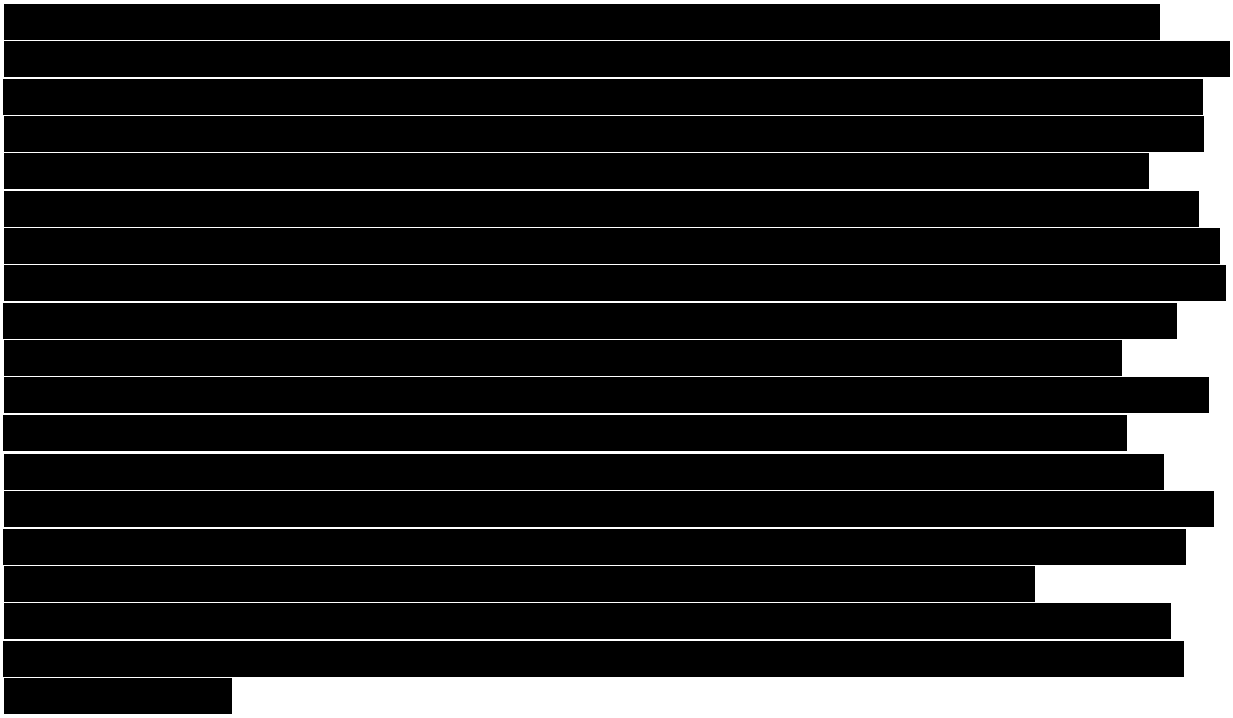


2. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of OC-01 (varenicline) nasal spray as compared to placebo for mean change from baseline in corneal fluorescein staining in subjects with Stage 1 (corneal epithelial hyperplasia/punctate keratopathy) NK in one or both eyes.

3. CLINICAL HYPOTHESES

This study is testing the hypothesis that OC-01 (varenicline) nasal spray is superior to placebo nasal spray in treating subjects with Stage 1 NK.

4. OVERALL STUDY DESIGN

Protocol OPP-102 is a Phase 2, multicenter, randomized, controlled, double- masked study designed to evaluate the safety and efficacy of OC-01 (varenicline) nasal spray in subjects with NK. Approximately 100 subjects at least 18 years of age with a physicians' diagnosis of Stage 1 NK, as defined by the Mackie Criteria and meeting all other study eligibility criteria will be randomized 1:1 and will receive OC-01 (varenicline)/ nasal spray or placebo nasal spray for 8 weeks three times daily (TID) as follows:

- OC-01 (varenicline) nasal spray, 1.2 mg/mL
- Placebo (vehicle control) nasal spray

All doses will be delivered as a 50 microliter (μL) nasal spray.

Subjects who terminate early during the application period will be asked to complete safety and/or efficacy assessments (if the subjects agree) prior to study exit. Subjects who are terminated early from the study will not be replaced.

5. STUDY POPULATION

5.1. Number of Subjects

Approximately 100 subjects (approximately 50 per arm) will be enrolled in approximately 40 sites in the US.

5.2. Study Population Characteristics

All subjects must be at least 18 years of age, of any gender and race and must meet all inclusion criteria and none of the exclusion criteria.

5.3. Inclusion Criteria

Subjects must:

1. Be at least 18 years of age at Visit 1.
2. Patients with Stage 1 (corneal epithelial hyperplasia/punctate keratopathy) NK- in one or both eyes[1], as defined by the Mackie Criteria.
3. Evidence of decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) in at least 1 corneal quadrant.
4. Schirmer's test without anesthesia >3 mm/ 5 minutes in the affected eye

[redacted]

[1] [redacted]

[redacted]

12. If a female is of childbearing potential, they must: use an acceptable means of birth control (acceptable methods of contraception include hormonal – oral, implantable, injectable, or transdermal contraceptives, mechanical – spermicide in conjunction with a barrier such as a diaphragm or condom, IUD, or surgical sterilization of partner), and have a negative urine pregnancy test on Day 1.

5.4. Exclusion Criteria

Subjects must not:

1. Have Stage 2 or Stage 3 NK affecting one or both eyes.
2. Have ocular graft versus host disease or Stevens-Johnson syndrome.
3. Have any active ocular infection (COVID-19 conjunctivitis, bacterial, viral, fungal, or protozoal) or active ocular inflammation not related to NK in the affected eye.

[redacted]

6. Be currently receiving autologous serum tears, amniotic membrane, cenegermin, Fresh Frozen plasma or cord blood derived tears.
7. Have severe blepharitis and/or severe meibomian gland disease in the study eye.

[redacted]

[redacted]

5.5. Withdrawal Criteria

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from treatment, but will be followed for safety for the duration of the study, unless they refuse to attend follow-up visits.

Additionally, if a subject should progress to Stage 2 NK while receiving the study drug, the subject should remain in the study and receive treatment. If a subject should progress to Stage 3 NK while receiving study treatment, the subject may be withdrawn from treatment at the discretion of the Investigator. The subject will continue to be followed for safety unless the subject refuses to attend the follow-up visits.

A subject may withdraw consent from the study at any time.

The Sponsor and/or the Investigator may discontinue any subject from study treatment for non-compliance or for any valid medical reason during the study (see Section 8.6.2).

6. STUDY PARAMETERS

6.1. Efficacy Measures

6.1.1. Primary Efficacy Measure

The following primary endpoints will be tested:

- Mean change from baseline in corneal fluorescein staining in subjects with Stage 1 NK at Week 8.

6.1.2. Secondary Efficacy Measure

The following secondary endpoints will be tested:

- Mean change from baseline in visual acuity at Week 8

6.2. Safety Measures

- Adverse events
- Intranasal exam
- Slit lamp biomicroscopy

6.3. Other Measures

- Urine pregnancy test (Visit 1, Visit 4 and Visit 6)

7. STUDY MATERIALS

7.1. Study Drug

7.1.1. Regimens

The study drug will be delivered as a 50 microliter (µL) nasal spray in each nostril TID:

- OC-01 (varenicline) nasal spray, 1.2 mg/mL
- Placebo (vehicle control) nasal spray

7.1.2. Dispensation Schedule

At Day 1, qualified subjects will be screened and randomized and the first dose of study drug will be administered in the clinic. The remaining administrations will happen at home after the clinic visit.

Between clinic visits, subjects will self-administer OC-01 (varenicline) nasal spray as a 50 µL dose in each nostril.

At Visit 2, the study drug/placebo nasal spray will be administered in the clinic to reinforce the proper use of the nasal pump. The remaining administrations will happen at home.

At Week 8, the final study drug/placebo nasal spray administration will occur in the clinic.

Subjects will self-administer OC-01 (varenicline) nasal spray as a 50 µL dose in each nostril up to 8 weeks.

7.1.3. General Appearance

OC-01 (varenicline)/placebo nasal spray will be formulated at the desired concentration in sodium phosphate buffers and sodium chloride as an aqueous solution and presented in a multi-use preservative-free nasal pump.

The product is preservative-free and intended for intranasal use only. The product should not be used if cloudy or if particulate matter is present.

OC-01 (varenicline) solution must be administered without dilution.

8. STUDY METHODS AND PROCEDURES

8.1. Subject Entry Procedures

8.1.1. Overview

Subjects as defined by the criteria in Section 5.2, Section 5.3 and Section 5.4 will be considered for entry into this study.

8.1.2. Informed Consent

Prior to a subject's enrollment in the trial (i.e., prior to any study-related procedures), the study will be discussed with each potential subject and subject wishing to participate must be administered and provide written informed consent using an Institutional Review Board (IRB)-approved informed consent form (ICF). The ICF must be the most recent version that has received approval by a properly constituted IRB.

8.1.3. Washout Intervals

Prohibited medications, treatments, and activities are outlined in the Exclusion Criteria (Section 5.4).

8.1.4. Procedures for Final Study Entry

Subjects must meet all inclusion criteria and none of the exclusion criteria.

8.1.5. Methods for Assignment to Treatment Groups

Each subject who enters the screening period for the study (defined as the point at which the subject signs the informed consent form (ICF) receives a unique subject identification number before any study-related activities/procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study.

Subjects who meet the eligibility requirements will be randomly assigned to 1 of 2 treatment groups.

The randomization will be stratified by:

- Pre-procedure (Baseline) non-anesthetized Schirmer's score ($\leq$5, >5) measured at the screening/randomization visit.

A central randomization list will be created using block randomization. Sites will be assigned entire blocks as needed.

8.2. Concomitant Therapies

The use of any concurrent medication, prescription or over the counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study during the treatment period is not permitted. Any investigational therapies taken after the treatment period of the study must be recorded on the eCRF.

Subjects on topical ophthalmic medications must have a stable medication regimen for at least 2 weeks prior to enrollment and the regimen must remain unchanged during the treatment period of the study.

8.2.1. Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined below:

- No concomitant use of a nicotinic acetylcholine receptor agonist [Nicoderm®, Nicorette®, Nicotrol NS® (nicotine), Tabex®, Desmoxan® (cytisine), and Chantix® (varenicline)] during the treatment period (baseline to Day 56) of the study.
- Topical ophthalmic medications, including preservative free artificial tears must not be utilized for 1 hour pre and post study drug administration.
- Other nasal sprays, including nasal steroids must not be utilized for 1 hour pre and post study drug administration
- Autologous serum tears, amniotic membrane, cenegermin, Fresh Frozen plasma or cord blood derived tears during the study treatment period.

8.2.2. Escape Medications

If a subject should progress to Stage 2 NK while receiving the study drug, the subject should remain in the study and receive treatment. If a subject should progress to Stage 3 NK while receiving the study drug, the subject may be withdrawn from the study treatment at the discretion of the Investigator.

8.2.3. Special Diet or Activities

No special diets or activity is required for this study.

8.3. Examination Procedures

8.3.1. Procedures to be Performed at Each Study Visit with Regard to Study Objectives(s)

The following procedures will be performed (see Appendix 2 for description)

Visit 1 (Day 1): Screening and Randomization

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical history, prior medication (s), and ocular history
- Eligibility criteria
- Urine pregnancy test (if applicable)
- NEI-VFQ-25 questionnaire
- Pain Visual Analog Scale (VAS)
- Best corrected distance visual acuity (BCDVA)
- Slit lamp biomicroscopy (prior to Schirmer's Test)

- Corneal fluorescein staining (prior to Schirmer's Test)
- Slit lamp (cornea) photography (prior to Schirmer's Test)
- Corneal sensitivity (prior to Schirmer's Test)
- In-vivo Confocal Microscopy (prior to Schirmer's Test) (select centers)
- Schirmer's Test without anesthesia (pre- treatment)
- Schirmer's Test with anesthesia (concurrent with treatment)
- Intranasal examination (pre- and post- treatment)
- Randomization
- Administration of the study drug/placebo nasal spray (concurrent with Schirmer's test with anesthesia)
- Dispense the study drug/placebo nasal spray
- Concomitant medications
- AE query

Visit 2 (Week 1) - Day 7 ±2: 1 Week: Corneal Assessment

- Slit lamp biomicroscopy
- Corneal fluorescein staining assessment
- Slit lamp (cornea) photography
- NK staging per Mackie Criteria
- Schirmer's Test with anesthesia (concurrent with treatment)
- Intranasal examination
- Administration of the study drug/placebo nasal spray (concurrent with Schirmer's test)
- Dispense the study drug/placebo nasal spray
- Concomitant medications
- AE query

Visit 3 (Week 2) - Day 14 ±2: 2 Week Corneal Assessment

- VAS
- Slit lamp biomicroscopy
- Corneal fluorescein staining
- Slit lamp (cornea) photography
- Intranasal Examination

- NK staging per Mackie Criteria
- Dispense the study drug/placebo nasal spray
- Concomitant medications
- AE query

Visit 4 (Week 4) - Day 28 ± 2: 4 Week Corneal Assessment

- NEI-VFQ-25 questionnaire
- Urine pregnancy test (if applicable)
- NK staging per Mackie Criteria
- VAS
- BCDVA
- Slit lamp biomicroscopy
- Corneal fluorescein staining
- Slit lamp (cornea) photography
- Corneal sensitivity
- Intranasal Examination
- Dispense the study drug/placebo nasal spray
- Concomitant medications
- AE query

Visit 5 (Week 6) - Day 42 ± 2: 6 Week Corneal Assessment

- VAS
- Slit lamp biomicroscopy
- Intranasal Examination
- NK staging per Mackie Criteria
- Dispense the study drug/placebo nasal spray
- Concomitant medications
- AE query

Visit 6 (Week 8) - Day 56 ± 2: corneal assessment

- NEI-VFQ-25 questionnaire
- VAS
- Urine pregnancy test (if applicable)

- NK staging per Mackie Criteria
- BCDVA
- Slit lamp biomicroscopy (prior to Schirmer's Test)
- Corneal fluorescein staining (prior to Schirmer's Test)
- Slit lamp (cornea) photography (prior to Schirmer's Test)
- Corneal sensitivity (prior to Schirmer's Test)
- In-vivo Confocal Microscopy (prior to Schirmer's Test) (select centers)
- Intranasal examination
- Schirmer's Test with anesthesia (concurrent with treatment)
- Administration of the study drug/placebo nasal spray (concurrent with Schirmer's test)
- Concomitant medications
- AE query

Visit 7 (Week 12) - Day 63 ± 7 Phone Visit Follow up

- Concomitant medications
- AE query

Visit 8 (Week 24) _Day 168 ± 7: Safety Follow up

- Intranasal Examination
- Concomitant medications
- AE query

Early Termination

- Urine pregnancy test (if applicable)
- NEI-VFQ-25 questionnaire
- VAS
- BCDVA
- Slit lamp biomicroscopy (prior to Schirmer's Test)
- Corneal fluorescein staining (prior to Schirmer's Test)
- Slit lamp (cornea) photography (prior to Schirmer's Test)
- Corneal sensitivity (prior to Schirmer's Test)
- In-vivo Confocal Microscopy (prior to Schirmer's Test) (select centers)

- NK staging per Mackie Criteria
- Schirmer's Test with anesthesia
- Intranasal examination
- Administration of the study drug/placebo nasal spray (concurrent with Schirmer's test if subject agrees)
- Concomitant medications
- AE query

8.4. Schedule of Visits, Measurements and Dosing

8.4.1. Scheduled Visits

Refer to Appendix 1 for a schedule of visits and measurements.

8.4.2. Unscheduled Visits

These visits may be performed to ensure subject safety. All procedures performed at an unscheduled visit will be recorded in the source documents and on the Unscheduled Visit eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Unscheduled Visit include:

- Slit lamp biomicroscopy
- BCDVA
- Intranasal examination
- Assessment of AEs
- Assessment of concomitant medications and/or treatments
- Any other assessments needed in the judgment of the Investigator.

8.5. Compliance with Protocol

Subjects will be instructed on the proper use and storage of the study drug and provided with written instructions upon dispensation of their study drug at Visit 1.

8.6. Subject Disposition

8.6.1. Treatment Completed Subjects

A Treatment Completed Subject is one who has completed 8 weeks of study visits (Visit 6).

8.6.2. Safety Follow up Completed Subjects

A Safety Follow up Completed Subjects is one who has completed all study visits up to Month 6 (Visit 8).

8.6.3. Discontinued Subjects

Subjects may be discontinued from treatment, or from involvement in the study at any time prior to their completion of the study due to:

- Non-fatal adverse event
- Protocol violations
- Disease progression
- Lost to follow-up.
- Physician decision
- Subject non-compliance
- Death
- Study terminated by the Sponsor
- Withdraw by subject (e.g., withdrawal of consent); and
- Other

Note: In addition, any subject may be discontinued from treatment or from study involvement from any sound medical reason at the discretion of the Investigator (after consultation with the Sponsor) or the Sponsor.

Notification of a subject discontinuation and the reason for discontinuation will be made to the Sponsor and will be clearly documented on the eCRF.

If a subject discontinues from treatment, the subject will be asked to be followed for safety for the duration of the study, unless they refuse to attend follow-up visits. A subject will be asked to attend Visit 8 and have all scheduled assessments performed as per the Schedule of Visits and Measurements (Appendix 1)

Discontinued subjects will not be replaced.

8.7. Study Termination

The study may be stopped at any time by the Investigator and/or Sponsor, with appropriate notification.

8.8. Study Duration

An individual subject's participation will involve 8 visits over 6 months.

8.9. Monitoring and Quality Assurance

[redacted]

[redacted]

9. SAFETY DEFINITIONS, MONITORING AND REPORTING

9.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether the event is considered drug related or not. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the subject started dosing with the study drug, without any judgment about causality. Any pre-existing medical condition that worsens after administration of the study drug/placebo nasal spray will also be considered a new AE.

AE collection will start following the first administration of the study drug/placebo nasal spray until the last follow up visit of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the Investigator or reported by the subject upon indirect questioning.

9.1.1. Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

9.1.2. Relationship to Study Drug

The relationship of each AE to the investigational product should be determined by the Investigator (in a blinded manner) using these explanations:

- *Definite:* When there are good reason and sufficient documentation to demonstrate a direct causal relationship between investigational product and AE

- *Probable:* When there are good reasons and sufficient documentation to assume a causal relationship in the sense of plausible, conceivable, likely but not necessarily highly probable
- *Possible:* When there is sufficient information to accept the possibility of a causal relationship in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example, due to missing data or insufficient evidence.
- *None:* When there is sufficient information to accept a lack of a causal relationship, in the sense of impossible and improbable.
- *Unclassified:* When the causal relationship is not assessable for whatever reason due to insufficient evidence, conflicting data, or poor documentation.

9.1.3. Expectedness

The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:

- *Unexpected:* An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- *Expected:* An AE that is listed in the IB at the specificity and severity that has been observed.
- *Not Applicable:* Any AE that is unrelated to the study drug.

AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the drug under investigation are to be considered unexpected.

The Investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's determination.

9.2. Serious Adverse Events

An AE is considered a serious adverse event (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include emergency room visits; outpatient/same day/ambulatory procedures; observation/short stay

units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

Note: Planned hospital admissions or surgical procedures for an illness or disease that was present before the patient received any study drug are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier than planned).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer, or damage to the optic nerve).

- A congenital anomaly/birth defect in an offspring of a study subject.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs are collected at the time the subject signs the Informed Consent Form until the last follow up visit of the study.

9.3. Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to the Sponsor, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1. Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to the Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

9.3.2. Reporting a Serious Adverse Event

To ensure subject safety, all SAEs, regardless of relationship to the study drug, must be reported within 24 hours of the Investigator's knowledge. All information relevant to the SAE must be recorded on the appropriate CRFs. The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the CRF. All subjects experiencing a SAE must be followed up and the outcome reported.

In the event of a SAE, the Investigator must obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject; provide the Sponsor with a complete case history, which

includes a statement as to whether the event was or was not suspected to be related to the use of the study drug; and inform the IRB of the SAE within their guidelines for reporting SAEs.

An SAE will be reported through the electronic data capture (EDC) system. If the EDC system is unavailable to the site staff to report the serious adverse event, the information is to be reported to the sponsor via the SAE Form and submitted to safety@oysterpointrx.com. The data must be entered into the EDC system when the system is again available. If requested, medical records may be provided at safety@oysterpointrx.com.

9.4. Procedures for Unmasking of Study Drug

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regards to treatment assignments. When medically necessary, the Investigator may need to determine what treatment regimen has been assigned to a subject. When possible (i.e., in non-emergent situations), the Sponsor should be notified before unmasking study drug. Unmasking will be performed utilizing the randomization system. The unmasked subject will continue the study if warranted by the Investigator in consultation with the Medical Monitor.

9.5. Type and Duration of the Follow-up of Subjects after Adverse Events

The Investigator will follow unresolved AEs to resolution until the subject is lost to follow-up or until the AE is otherwise classified. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-ups will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

New information relating to a previously reported serious adverse event must be submitted. All new information for serious adverse events must be submitted within 24 hours following the investigator's knowledge of new information. The investigator may be asked to provide additional follow-up information, which may include discharge summary or extracts from the medical record.

10. STATISTICAL ANALYSIS

Statistical considerations and methods of analyses for this study are provided below; the accompanying Statistical Analysis Plan (SAP) contains complete details of the planned analyses.

10.1. Primary and Secondary Endpoints

10.1.1. Primary Endpoint

- Mean change from baseline in corneal fluorescein staining in subjects with Stage 1 NK at Week 8.

10.1.2. Secondary Endpoints

- Mean change in baseline in visual acuity at Week 8

10.2. Analysis Populations

[redacted]

10.2.2. Per Protocol

The per-protocol (PP) population will include all ITT subjects with baseline corneal fluorescein staining ≥2 in subjects with Stage I (corneal epithelial hyperplasia/punctate keratopathy) NK in one or both eyes. Analysis using the PP population will group subjects according to the treatment to which they were randomized.

10.2.3. Safety Population

The safety population will include all randomized subjects who received at least one dose of the study drug. Analysis on the safety population will group subjects according to the treatment received.

10.3. Statistical Hypotheses

Let μ_h, and μ_p denote the mean change in corneal fluorescein staining from baseline to Week 8 (1.2 mg/mL OC-01 and placebo, respectively) in subjects with Stage 1 NK

H_0: $\mu_h - \mu_p = 0$

H_1: $\mu_h - \mu_p \neq 0$

10.4. Sample Size and Power Considerations

[redacted]

10.5. Statistical Analysis

This section briefly outlines the planned efficacy analyses. The statistical analysis plan (SAP) describes the methods to be used in detail. If the SAP and the protocol disagree, the details and methods of the SAP will prevail.

10.5.1. Randomization and Stratification

Subjects will be randomized 1:1 to receive either OC-01 nasal spray or vehicle control.

The randomization will be stratified by:

- Pre-procedure (Baseline) non-anesthetized Schirmer's score (<5, >5) measured at the screening/randomization visit

A central randomization list will be created using block randomization. Sites will be assigned entire blocks as needed.

10.5.2. General Considerations

Quantitative variables will be summarized using the number of subjects (n), mean, SD, median, 25th and 75th percentiles, and minimum and maximum. Qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group. Summaries will be provided for demographics, medical history, concomitant medications, and subject disposition.

For the summaries, medical history, concomitant medications, and AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization Drug dictionaries, as appropriate.

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 1 screening.

10.5.3. Unit of Analysis

[redacted]

For safety endpoints, both eyes will be analyzed.

10.5.4. Subject Demographics and Baseline Characteristics

Continuous summary statistics will be generated for age in years by treatment group and for all subjects. Discrete summary statistics will be generated for the following qualitative demographic variables: age category, gender, ethnicity, race, and other baseline intranasal examination results, tabulated by treatment group and for all subjects. Individual subject data listings will support the summary tables.

10.5.5. Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed on the [redacted] comparing the treatment group to placebo with the randomization strata, Baseline Schirmer's Test Score as the covariate and Mackie Classification Stage as an independent variable. The primary endpoint will be the mean change from baseline in corneal fluorescein staining at Week 8. The analysis using the PP population will be treated as the primary analysis.

10.5.6. Secondary Efficacy Analysis

The secondary efficacy endpoints are as follows:

- Mean change from baseline in visual acuity at Week 8

The secondary efficacy endpoint will be analyzed on the PP population using an analysis of covariance model comparing the treatment group to placebo with randomization strata, baseline Schirmer's Test Score and the baseline ETDRS visual acuity as covariates.

10.5.7. Safety Analysis

All safety analyses will be performed on the safety population.

The safety of OC-01 (varenicline) will be assessed primarily by the incidence of AEs. An AE will be considered a treatment-emergent AE (TEAE) if it occurs or worsens on or after initiation of treatment. An overall summary of TEAEs will be presented including the number of events and the number of subjects with events (along with percentages) by treatment group for TEAEs in several categories base on seriousness, relationship to treatment, and severity.

Other safety endpoints including visual acuity, slit lamp bio microscopy and intranasal examination will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will be summarized where appropriate. For assessments performed by eye, study eye and fellow eye will be summarized separately.

The SAP will present methods of analysis of these defined parameters in detail.

10.5.8. Interim Analysis

No interim analysis is planned for this study.

11. COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with this protocol, Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1. Protection of Human Subjects

11.1.1. Subject Informed Consent

Informed consent/assent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent/assent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Sponsor prior to submission to the governing IRB and that it is read, signed and

dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Sponsor and provided in writing by Sponsor prior to the consent process.

11.1.2. Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations [U.S. 21 Code of Federal regulations (CFR) Part 56.103]. The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB-approved version of the informed consent form will be used.

11.2. Ethical Conduct of Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3. Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions so as to ensure the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of the Sponsor, the IRB approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the above listed individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4. Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as photographs, X-rays, laboratory tests, and electrocardiograms. The Investigator's copy of the CRFs serves as the Investigator's record of a subject's study-related data.

11.4.1. Retention of Documentation

All study related correspondence, subject records, consent forms, record of the distribution and use of all study drug and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the study drug. These

documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.5. Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

11.5.1. Labeling/Packaging

The study drug/placebo nasal spray will be provided in multi-use intranasal applicator that will be assigned at randomization for use during study.

11.5.2. Storage of Study Drug/Placebo Nasal Spray

The study drug/placebo nasal spray must be stored in accordance with the pharmacy manual for this study, which contains detailed information regarding the storage and administration.

11.5.3. Accountability of Study Drug

The study drug/placebo nasal spray is only prescribed by the principal Investigator or his/her named sub investigator(s) and is to only be used in accordance with this protocol. The study drugs must only be distributed to subjects properly qualified under this protocol to receive study drug. The Investigator must keep an accurate accounting of the study drugs by maintaining a detailed inventory. This includes the amount of study drugs received by the site, amount dispensed to subjects, amount returned to the site by the subjects, and the amount returned to the Sponsor upon the completion of the study.

11.5.4. Return or Disposal of Study Drug

You may be requested to destroy study drug or study drug kits on-site that are expired, not acceptable for use due to a temperature deviation, or at the end of the study. If site regulations do not permit destruction, study drugs will be returned to the Sponsor or their designee for destruction.

11.6. Recording of Data on Source Documents and Electronic Case Reports Forms

All subject data will be captured in the subject source documents which will be transcribed in the eCRFs. The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, source documents, and all study-related materials. All study data should also be attributable, legible, contemporaneous, and original. A recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make

clear who made the correction and when, by adding to the correction his/her initials as well as the date of the correction.

Data entry of all enrolled and randomized subjects will use software that conforms to 21 CFR Part 11 requirements and will be performed only by staff who have been trained on the system and have access to the system. Minimal data will be entered for screen failure subjects. An audit trail will be maintained within the electronic system to capture all changes made within the eCRF database. After the end of the study and database lock, electronic copies of all applicable subjects' eCRFs will be provided to each Investigator Site to be maintained on file by the Investigator.

11.7. Handling of Biological Specimens

Not applicable.

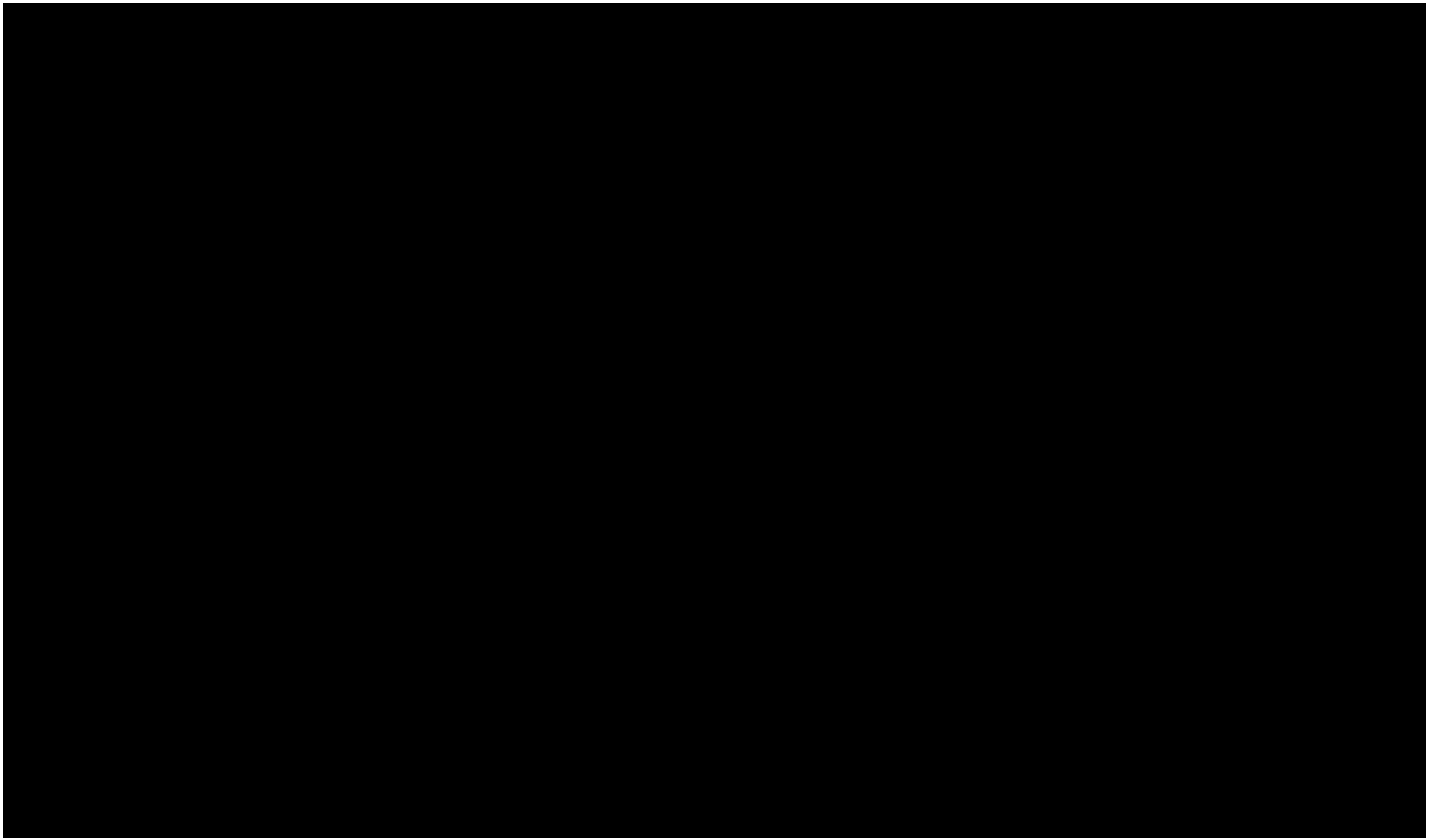
11.8. Publications

The study will be documented in a final report, which will contain appropriate statistical analysis and medical overview. No individual site or Investigator may publish or present any results from the study until the Sponsor completes a joint, multi-center publication of the trial results in conjunction with various participating Investigators and appropriate sites contributing data and comments. Subsequently, individual Investigators may request to publish or present results from the trial; however, approval will be at the sole discretion of the Sponsor. Should the foregoing language conflict with the language addressing publication in the clinical trial agreement, the language in the Clinical Trial Agreement will prevail.

12. REFERENCES

[redacted]

13. APPENDICES



APPENDIX 2: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

The following examination procedures, tests, equipment, and techniques are listed in this Appendix:

Table 1: Clinical Grading of Neurotrophic Keratopathy

Stage	Clinical Findings
I	Corneal epithelial hyperplasia and irregularity
	Scattered small facets of dried epithelium (Gaule spots)
	Superficial punctate keratopathy
	Rose bengal staining of inferior conjunctiva
	Increased viscosity of tear mucus
	Decreased breakup time
	Superficial neovascularization
	Stromal Scarring
	Dellen
II	Persistent corneal epithelial defect with smooth and rolled edges
	Descemet's membrane folds and stromal swelling
	Anterior chamber inflammatory reaction with hypopyon (rare)
III	Corneal ulcer
	Corneal perforation
	Corneal stromal melting

GUIDELINES FOR MEASURING VISUAL ACUITY TO THE STANDARD PROCEDURE DEVELOPED FOR THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY (ETDRS)

Visual Acuity Equipment and Facilities:

The procedure described in this section utilizes the following equipment:

- Set of three ETDRS Distance Visual Acuity Test charts which are modified ETDRS Charts 1, 2 and R for testing visual acuity at 4 meters
- Retro-illuminated box providing standardized chart illumination

Visual acuity testing is required at a distance of 4 meters and, for subjects with sufficiently reduced vision, at 1 meter. The 4-meter distance should be marked clearly and permanently. The 1-meter distance must be measured with a 1-meter stick when the subject is seated (see below)

Visual Acuity Charts

Charts 1 and 2 are used for testing the right and left eye, respectively, and Chart R is used for entering acuity measurements and refraction for each eye. The features of the charts are high contrast Sloan Letters in each of 14 lines, lines of equal difficulty, and a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution) from line to line. Charts 1, 2, and R have different letter sequences. Subjects should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins.

Visual Acuity Box

The dimensions of the light box are 24 ¾ inches by 7 inches. The box can be mounted on a wall or on a cylindrical stand. The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches long; two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied.

The light box should be mounted at a height such that the top of the third row of letters (0.8 log MAR) is 49 (2 inches +/-) from the floor. The rear of the box provides storage space for the two charts not being used.

Illumination

Most of the room lights should be turned off during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light

can have an adverse effect. With the light box off, the light box should appear uniformly dark with no specular reflections visible to the subject sitting in the examination chair.

The visual acuity light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and a ballast. Because the illumination of fluorescent tubes diminishes by 5% during the first 100 hours and by another 5% during the next 2,000 hours:

- New Tubes should be kept "on" for about 4 days (96 hours, does not have to be continuous). A note should be kept on the back of the light box, indicating the date and time when new tubes were replaced.
- No testing will be done with the light box during the initial 4-day period.
- All tubes should be replaced once a year.

Each tube is partly covered by a 14-inch fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube (4 3/16 inches) is left uncovered to the right and left of the sleeve. The openings in the backs of the sleeves should be oriented to point directly toward the back of the box (i.e., the sleeves should not be tilted up or down). Also, the lower sleeve has a cutout that should point toward the ballast.

4- and 1- Meter Visual Acuity Lanes

A distance of exactly 4 meters (13 feet and 1 1/2 inches, or 157.5 inches) is required between the subject's eyes and the visual acuity chart for the 4-meter test, and a distance of exactly 1 meter (39 and 3/8 inches) is required for the 1-meter test.

The room for visual acuity testing must have, in addition to the 4-meter lane, space for the visual acuity box (and possibly a stand) and space for the seated subject. Minimum room-length requirements vary according to how the box is mounted:

- Wall-mounted box: In addition to the 4-meter lane, 7 inches must be allowed for the depth of the box plus space for the seated subject.
- Stand-mounted box: In addition to the 4-meter lane, 13 inches must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the seated subject.

Marking the Distance

4 Meters

If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and no floor marks are needed to ensure the correct distance.

If the box is mounted on the wall but the subjects chair is not permanently affixed, the 4-meter distance of the subject's eye from the chart must be marked clearly and permanently.

The room lights should be reduced to a maximum of 15 foot-candles during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. With the light box off, the light box should appear uniformly dark with no specular reflections visible to the subject sitting in the examination chair.

If the box is mounted on a moveable stand, the 4-meter distance must be marked clearly and permanently on the floor. The location and orientation of the box must be rechecked each time a new chart is put in place. When the stand touches the rear wall of the room, two of the five casters should touch the wall.

1 Meter

The 1-meter distance is measured from the eye of the subject, seated comfortably in a chair with his or her back firmly placed against the back of the chair, to the center of the second or fourth letter on the third line of the chart. A non-flexible measuring device should be used for this measurement such as a yardstick, a dowel or a rod purchased at a local hardware store.

Refraction Technique

The technique described below is recommended for all study subjects whenever a manifest refraction and best-corrected visual acuity measurement is indicated by the protocol. Refraction Chart R must be used for determining the best lens correction in each eye. Charts 1 and 2 are not used for refraction, only for visual acuity testing. The right eye is refracted first and then the left eye. Chart 1 will be used to test visual acuity in the right eye, Chart 2 to test visual acuity in the left eye, and the Chart 1 will be also used to test binocular vision.

Beginning Approximate Refraction

The lens correction recorded should be the final correction in the trial frame at the end of refraction and spherical refinement in the visual acuity lane. Corrected aphakic patients, including those with intraocular lenses, should undergo subjective refraction as specified below. For uncorrected aphakic patients, a +10.00-diopter sphere should be added to the trial frame as the beginning approximate refraction.

The beginning approximate refraction is the result of the subjective refraction on the previous visit.

At Visit 1, if the visual acuity is 20/100 (2/10) or better, and the subject does not wear glasses for distance, the beginning approximate refraction is plano.

If he or she does wear glasses for distance, the beginning approximate refraction is the measured power of those glasses (using a lensometer).

Before the subjective refraction, visual acuity is measured using the beginning approximate refraction and Chart R.

If the subject's visual acuity is <20/200 (2/20) in either eye with the subject's present distance glasses (or without correction, if the subject does not have glasses), retinoscopy should be performed by an examiner proficient in this procedure.

An acceptable alternative is to use an automated refractor. The refraction steps below are recommended for visual acuities of 20/20 through 20/80 with the beginning approximate refraction. For visual acuities worse than 20/80, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (see Table 2) and follow a similar procedure using steps in power that are equal to the power of the lens being presented.

NOTE: Whenever the visual acuity improves to a higher range by improved correction, for example, from the 20/80 to 20/160 range to the 20/20 to 20/80 range, refinement should be performed with the smaller sphere and cylinder powers given for the better visual acuity.

Table 2: Refraction Protocol Summary

Vision with Best Correction (Refraction Distance)	**– Sphere**		**– Cylinder**			**– Sphere Refinement**	
	– Power	– Increment	– Axis	– Power	– Increment	– Power	– Increment
20/10-20/100 (4 meters)	+0.50 -0.37 +0.50	+0.50 -0.25 +0.50	0.50 JCC	0.25 JCC	+0.25 -0.25	+0.25 -0.37 +0.25	+0.25 -0.25 +0.25
<20/125-20/200 (4 meters)	+1.00 -0.75 +1.00	+1.00 -0.75 +1.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+0.50 -0.37 +0.50	+0.50 -0.25 +0.50
20/250 - 20/400 (4 meters)	+1.50 -1.00 +1.50	+1.50 -1.00 +1.50	1.00 JCC	1.00 JCC	+1.00 JCC	+0.75 -0.50 +0.75	+0.75 -0.50 +0.75
<20/400 (1 meter)	+2.00 -1.50 -2.00	+2.00 -1.50 +2.00	No Cylinder Test			No refinement	

Table 3: Axis Step Sizes for Refinement of Cylinder

Cylinder Power	Axis Step Sizes
<1.00 D	10º
1.00 - <2.00 D	5º
2.00 - <3.00 D	3º
3.00 - <5.00 D	2º
5.00 - <8.00 D	1º

Subjective Refraction

The trial frame is placed and adjusted on the subject's face so that the lens cells are level and parallel to the anterior plane of the orbits and centered in front of the pupils. The left eye is occluded (by lightly patching with an eye pad or folded tissue with tape) and the beginning approximate refraction, as determined above, is placed in the right lens cells with the cylindrical correction anterior. Chart R should be read at a distance of 4 meters.

Determination of Spherical Refraction

The visual acuity of the right eye is assessed and noted. A +0.50 sphere is then held in front of the right eye and the subject is asked if the vision is "better," "worse," or "no different" while he or she is looking at the smallest line read well.

- If vision is improved, the subject is requested to read the chart and if at least one more letter is read, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus. If vision is improved or there is no change, the sphere in the frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is held in front of the right eye again and the subject is asked again if the vision is "better", "worse" or "no different". This process of increasing the plus sphere in the trial frame is repeated until the subject says that the +0.50-sphere held in front of the trial frame makes the vision worse. When the subject responds that the vision is made "worse", the lens should be left in place for 10 to 15 seconds to evaluate whether the subject is accommodating (an unlikely situation in a population over age 60). If the vision clears during this period, the +0.50 sphere may be added again and succeeding attempts to evaluate additional plus lenses should be accompanied with a 10 to 15 second delay. If there is no evidence of unrelaxed accommodation, the delay period while assessing plus lenses is not necessary at any time further in the examination.

- Whenever the subject says that the vision is "worse" and remains worse, the +0.50 sphere is removed from in front of the trail frame.

By this process, the highest-plus or least-minus sphere that is tolerated without blurring the subject's vision is determined. After determining this highest-plus or least–minus sphere, the subject is asked to read the smallest line possible.

Next, a –0.37 sphere is held in front of the trial frame and the subject is asked if the vision is "better", "worse", or "no different".

- If vision is improved, the subject is requested to read the chart and if at least one more letter is read, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus.
- In certain situations, the subject may be unable to read more letters, but is convinced that the vision is improved. If the examiner believes this is the case, the additional minus lens can be added. At any stage in the examination, no more than 0.25 diopters of minus should be added without an increase in the number of letters read correctly. The additional minus lens should not be added if the subject reads fewer letters but states that the acuity is better. There is a general attempt in this refraction protocol to avoid "over-minusing" the subjects. However, when plus cylinders are in the refraction, one must be careful not to unnecessarily withhold minus which may be necessary for the subject to accept the needed plus cylinders later in the refraction. Minus spherical power is added in –0.25 diopter increments until the subject shows no further improvement in vision. If minus power is added, a +0.50 sphere is tried again to determine if more plus will be accepted.
- If the subject says the vision is "no different" or "worse", no minus power should be added, and the spherical determinations are completed.

Determination of Cylindrical Refraction

For purposes of this discussion only plus cylinder techniques are presented.

Cylinder axis determination

If the approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.37, or 0.50 diopter cross-cylinder, first with the positive axis 45 degrees to one side of the cylinder axis, and then with positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image, the subject is encouraged to select the position producing "less blur" while fixating on a single round letter on the line above the lowest line on the chart he or she is able to read when the cross-cylinder is not held up before the trial frame. If the subject cannot choose between the two positions of the cross cylinder at the beginning of this test, the axis of the cylinder is moved 5 to 15

degrees, first in one direction and then in the other, with the cross-cylinder being checked in each position to confirm that the original axis was indeed correct. If the subject prefers one position of the cross-cylinder to the other and the cylinder in the trial frame is plus the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder when it is in the position found to be less.

(When the power of the cylinder is low or if the subject's discrimination is poor; larger shifts will produce more clear-cut answers.) The cross-cylinder is tried again with the positive axis 45 degrees first to one side and then to the opposite side of the new cylinder axis to determine which position is producing less blur.

If the subject finds one position less blurry, the axis of the plus cylinder is moved toward the positive axis of the cross-cylinder. Testing for change of axis is repeated until the subject finds neither position better than the other.

Cylinder Power determination

Change in cylinder power is tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. For this test, the subject is requested to focus attention on a round letter on the lowest line on the chart he or she is able to read. If the subject prefers the position axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by an additional +0.25 diopter. If the subject prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the subject finds neither position definitely better than the other. As plus cylinders are added, the examiner should recognize that the spherical equivalent of the refraction is being changed. More minus spheres may be needed as plus cylinders are added. When using plus cylinders for every 0.50 diopter of cylinder power added, the sphere should be changed by –0.25 diopter. If, at any time, the preference with the cross-cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position. The axis should be refined, and the power should be tested again. If the beginning refraction is a "pure" sphere, the presence of astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having determined the highest-plus or least-minus sphere producing minimal blurring of vision, as described above. The refraction is then continued by using the cross-cylinder to test for cylinder axis and then cylinder power using the cross-cylinder technique outlined above. If, at any time, the preference with the cross-cylinder indicates that cylinder power should be removed entirely, the 0.25 cylinder should be rotated 90 degrees from its original position and the power should be tested again. At this point, if the subject prefers additional power, it should be added. If, on the other hand the subject prefers to remove the +0.25, it should be removed and the final refraction is then purely spherical. An example of this procedure follows:

Beginning refraction: -2.50 + 0.25 axis 37 degrees. Use of the cross-cylinder to check cylinder axis indicates that the subject prefers the 37-degree axis. If, upon using the cross-cylinder to check cylinder power, the subject wants the 0.25 cylinder removed, rotate the cylinder to 127 degrees and test for cylinder power again. If additional power is preferred, add it.

If the preference with the cylinder at 127 degrees is to remove the 0.25 cylinder, this should be done, and the resulting refraction is 2.50.

Minus cylinders may be used instead of plus cylinders to determine the best correction for the cylinder power and axis. If minus cylinders are used, the above procedure must be revised to reflect the change in sign (+ or -).

When using minus cylinder correcting lenses, the preferred orientation of the cross cylinder is determined in the same way as when using plus cylinder lenses. When determining cylinder axis however, the correcting minus cylinder axis is rotated toward the minus cylinder axis of the cross cylinder (not the cylinder axis as it is when a plus cylinder correcting lens is used). When determining cylinder power, the correcting minus cylinder power is increased when, in the preferred orientation, the minus axis of the cross cylinder coincides with the minus cylinder axis of the correcting lens.

Refining Final of Spherical Power

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and –0.37 sphere and changing the spherical power (see below). If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made.

This refraction protocol can be summarized as follows: First, having eliminated any possible accommodation with plus spheres, the best spherical equivalent power is found, which places the circle of least confusion on the retina. Then the cylinder power and cylinder axis are assessed. This process of checking sphere, cylinder axis, and cylinder power is repeated until there are no changes that result in an increased number of letters being read. Ideally, at the end of the refraction, the sphere is checked and the subject neither tolerates increased plus nor improves with increased minus spheres. Then the axis is checked and no change in axis is indicated. Finally, the cylindrical power is checked and no change in this is indicated. At this point, the refraction is completed. Sometimes this endpoint cannot be reached because there is an unending number of small corrections at each repetition of the process. When it becomes clear that these small changes are not resulting in an increased number of letters read correctly, the examiner may terminate the refraction.

The lens corrections obtained in this way for the right eye are recorded on the BCdVA Assessment Form as the corrections obtained by subjective refraction for the right eye. The

entire process is repeated for the left eye, and these lens corrections are recorded on the BCdVA Assessment Form as the corrections obtained by subjective refraction for the left eye.

Refraction for Subjects with Poor Visual Acuity

If it is not possible to perform a subjective refraction at 4 meters because visual acuity is too poor and the patient reads less than 20 letters correct on the refraction chart at this distance, the refraction should be attempted at 1 meter. If the subjective refraction can be performed successfully at 1 meter, a +0.75 sphere should be subtracted from the results of the 1- meter refraction to make the correction appropriate for the 4-meter distance. This correction should be entered on the BCdVA Assessment Form in the space provided for distance subjective refraction. (NOTE: Visual acuity will be tested first at the 4-meter distance even if the subject cannot be refracted at this distance. If the patient reads less than 20 letters correctly at 4 meters, visual acuity must also be tested at 1 meter, in which case the +0.75 sphere should be added to the 4-meter refraction.)

Testing Best Corrected Visual Acuity

4-Meter Test

Testing of all eyes begins at 4 meters. First, the right eye is tested with Chart 1 and then the left eye is tested with Chart 2. Each Chart should remain hidden from view until the eye in question is ready for testing. For the binocular BCDVA testing the Chart 1 should be used.

The distance from the subject's eyes to the visual acuity chart must be exactly 4 meters (13 feet and 1 ½ inches, or 157.5 inches). The subject must sit for the 4-meter visual acuity test. As indicated previously, the subject should be seated comfortably with his or her back firmly placed against the back of the chair. The examiner should ensure that the subject is seated comfortably, that the head does not move forward or backward during the test, and that the subject's eyes remain at the 4- meter distance.

The testing procedure for visual acuity is based on the principle that the objective is to test visual acuity and not intelligence or the ability to concentrate or follow or remember instructions (although all of these factors are involved). The subject should be told that the chart has five letters in each line, and has letters only and no numbers. If the subject forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number.

The subject should be asked to read slowly (at a rate not faster than about one letter per second) to achieve the best identification of each letter and to not proceed until they have given a definite response. It may be useful for the examiner to demonstrate the letter-a-second place by reciting "A, B, C,…". If, at any point, the subject reads too quickly, he or she should be asked to stop and read slowly. If the subject loses his or her place in reading or the examiner loses his or her place (possibly because the letters are read too quickly), the

examiner should ask the subject to go back to where the place was lost. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test; instead, a sheet of white paper may be used to guide the subject to the proper location on the chart. Each letter is scored as right or wrong (see below). Once a subject has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the subject changes a response aloud (e.g., That was a "C", not an "O") before he or she has read aloud the next letter then the change should be accepted. If the subject changes a response after beginning to read the next letter, the change is not accepted.

When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two or more letters, he or she should be asked to choose one letter and if necessary, to guess even if the next letter has already been read. The examiner may suggest that the subject turn his or her head or eye in any manner if this improves visual acuity. If the subject does this, care must be taken to ensure that the fellow eye remains covered. If testing the right eye, the left eye must be occluded by lightly patching with an eye pad or a folded tissue with tape. The subject should be encouraged to read as many letters as possible.

There are several reasons for encouraging subjects to guess:

- Subject's statements that they cannot identify a letter are often unreliable.
  - Encouraging them to guess helps to maximize the subject's effort.
  - It helps to assure uniformity among procedures performed in different clinics.
  - It may help to prevent subject bias (malingering).

1-Meter Test

At 4 meters, if less than 20 letters on the chart are read correctly then visual acuity must also be tested at 1 meter. If the trial frame is to be removed when changing the test distance from 4 meters to 1 meter, the testing chart (Chart 1 and 2) should first be removed from view to prevent the subject from reading the chart with the fellow eye.

Before testing at 1 meter, a +0.75 sphere should be added to the 4-meter correction already in the trial frame to compensate for the closer testing distance. (As previously indicated, the subject should be seated comfortably with his or her back firmly placed against the back of the chair). The distance of 1 meter should be confirmed with a rigid measuring device. The avoidance of any head movement forward or backward is particularly important during the 1-meter test. The subject should be asked to read only the first six lines at 1 meter, making 30 the maximum score attainable at that distance.

After the test of the right eye is completed, switch the occlusion from the left to the right eye and replace Chart 1 by Chart 2. The test is repeated for the left eye, starting at 4 meters.

When testing of the left eye is completed Chart 2 should be removed from view. Once each eye, right eye and left eye, have been tested, then Chart 1 should be mounted again and, after giving a patient a rest of few minutes, then binocular vision with this Chart 1 should be undertaken.

Scoring Best-Corrected Visual Acuity

On the BCDVA Assessment Form, the total number of letters read correctly in each row of letters should be written down. Visual acuity will be measured once for each eye, using Chart 1 for the right eye, Chart 2 for the left eye, and Chart 1 for binocular vision testing. After each measurement of visual acuity, the visual score for the visit is calculated. The visual acuity score is defined as follows:

- If 20 or more letters are read correctly at the 4-meter test distance, the visual acuity score is equal to the numbers of letters read correctly at 4 meters, plus 30; or
- If less than 20 letters are read correctly at the 4-meter test distance, the visual acuity score is equal to the number of letters read correctly at 1 meter plus the number at 4 meters: or
- If no letters are read correctly at either the 4-meter distance or the 1-meter distance, the visual acuity score is 0.

Count Fingers Visual Acuity

If visual acuity is so poor that the subject cannot read any of the largest letters at 1 meter (i.e. number of letters read correctly at 1 meter is zero), count fingers vision (CF), the examiner's hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. If testing the right eye, the left eye must be occluded by lightly patching with an eye pad or a folded tissue with tape. A light should be shone directly on the hand from behind the patient. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the subject correctly identifies three of the five presentations, then count fingers (CF) is noted as "yes." If not, the subject should be tested for hand motion vision.

Hand Motion Visual Acuity

The examiner's hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The fellow eye should be occluded. If testing the right eye, the left eye must be occluded by lightly patching with an eye pad or a folded tissue with tape. A light should be shone directly on the hand from behind the subject. The examiner's hand should be moved in an up and down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per

second. The subject is instructed that the examiner's hand will be presented, and they will have to respond to the question: "What am I doing with my hand?" This should be repeated five times. Four out of five correct responses indicate that hand motion vision is present. If the subject does not correctly identify four of five, then light perception must be tested.

Light Perception and No Light Perception

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The fellow eye should be well occluded, ideally with a taped tissue behind the trial frame as well as the occlude lens in the trial frame. The indirect ophthalmoscope light should be in focus at 3 feet with the rheostat set at maximum voltage. From a distance of 3 feet, the beam should be directed in and out of the eye being examined at least four times, and the subject should be asked to respond when he or she sees the light. If the examiner is convinced that the subject perceives the light, vision should be recorded as "light perception"; if not, vision should be recorded as "no light perception."

When examiners conclude that the final visual acuity score is totally unreliable because of the subject's decreased mental ability, the visual acuity score must still be entered on the appropriate form.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible, during the entire study. If the same correction cannot be used (i.e., a subject broke his/her glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease defined as ≥ 3 lines (15 ETDRS letters) or from Visit 1 should be evaluated by the Investigator as a potential AE.

Slit Lamp Bio microscopy

Slit lamp bio microscopy will be performed during the study. Observations will be graded as *Normal* or *Abnormal*. Abnormal findings, which are clinically significant, will be described.

Cornea Photography

Details instructions will be provided in the photography manual.

Corneal Fluorescein Staining

The examiner should instill 5 μL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. Alternatively, corneal staining can be assessed using 1.0 mg sodium fluorescein strips. After moistening the tip of the strip with sterile buffered saline, the excess is shaken into a waste bin with a sharp flick. The lower lid is then

pulled down and the flat end of the tip should be gently applied to the inferior tarsal conjunctiva with the intent of not inducing reflex tearing and instilling a very small volume of dye.

The subject will be instructed to blink naturally several times without forced closure of the eyelid to distribute the fluorescein. To achieve maximum fluorescence, the examiner should wait at least two minutes after instillation before evaluating corneal fluorescein staining. A Wratten #12 yellow filter will be used to enhance the ability to grade fluorescein staining. The staining will be graded with the modified Oxford Grading Scale.

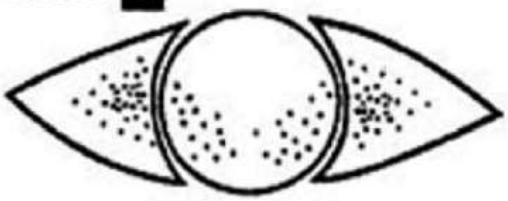
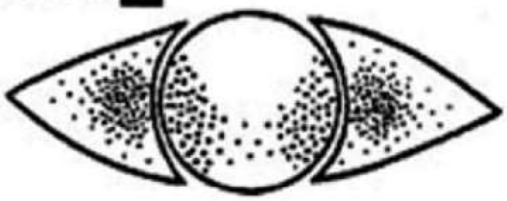
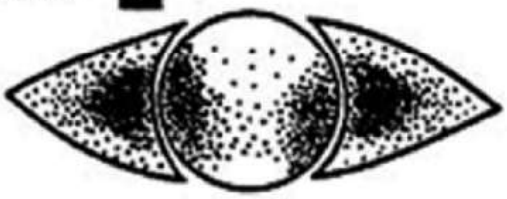
Modified Oxford Grading Scale

The examiner compares the overall appearance of the patient's corneal staining with the reference figure (below) and selects the appropriate grade that best represents the state of corneal staining.

For subjects that progress to Stage 2, graders will assess the following:

- Lesion size
- Is any residual staining present (Yes/No)?
- If residual staining is present, is the staining persistent (Yes/No)?

The Grade 0 corresponds to none staining dots

PICTURE A 	EQUAL TO OR LESS THAN PICTURE A	GRADE 0.5
PICTURE B 	MORE THAN IN PICTURE A, EQUAL TO OR LESS THAN IN PICTURE B	GRADE 1
PICTURE C 	MORE THAN IN PICTURE B, EQUAL TO OR LESS THAN IN PICTURE C	GRADE 2
PICTURE D 	MORE THAN IN PICTURE C, EQUAL TO OR LESS THAN IN PICTURE D	GRADE 3
PICTURE E 	MORE THAN IN PICTURE D, EQUAL TO OR LESS THAN IN PICTURE E	GRADE 4
	MORE THAN IN PICTURE E	GRADE 5

Corneal Sensitivity

Cochet-Bonnet Aesthesiometer

Corneal sensation is measured in the affected eye of the patient at all applicable visits using a Cochet Bonnet aesthesiometer. The measurements taken from the affected eye are as follows:

Sensitivity in each of the 4 quadrants of the cornea:

- Superior nasal (cm)
- Inferior nasal (cm)
- Superior temporal (cm)
- Inferior temporal (cm)

Steps for using the handheld aesthesiometer:

Note: Cochet Bonnet aesthesiometer measurements MUST be performed prior to administration of Topical Anesthesia

- Sterilize the filament, by wiping only the tip with an alcohol pad, do not wipe the entire length of the filament or pull on the filament.
- Extend the filament to full length of 6 cm.
- Perform sensitivity in each of the 4 quadrants of the cornea:
- Superior nasal (cm)
- Inferior nasal (cm)
- Superior temporal (cm)
- Inferior temporal (cm)
- Retract the filament incrementally in 0.5 cm steps until the patient can feel its contact.
- Record the length (NOTE: The shorter the length indicates decreased sensation.)
- Compare the fellow eye cornea.
- Repeat steps 1-4 in each quadrant: superior nasal, inferior nasal, superior temporal, and inferior nasal.
- Sterilize the filament tip by gently wiping with an alcohol pad and retract back into the device to protect it from damage.

For Stage 1 subjects, corneal sensitivity is defined as the mean of the 4 quadrants (four measurements)

Intranasal Examination

Qualified subjects for the study must undergo an intranasal exam to make the final eligibility determination (e.g., severe nasal airway obstruction such as, severe septal deviation or inferior turbinate hypertrophy, or vascularized polyp seen on examination are reasons for exclusion). To monitor nasal mucosal integrity during the study for subject safety, an examination of the nasal cavities via an intranasal exam will be performed at Visit 1 (after all other screening procedures have been completed). This examination will be performed by an Ear Nose and Throat (ENT) specialist, otolaryngologist or other suitably qualified medical practitioner (i.e. one who has been trained to perform intranasal exam). Still images or video may be captured. The procedure used for the intranasal exam can be conducted either by endoscopic examination or nasal specula.

Schirmer's Test without Anesthesia

1. Excess moisture in the inferior fornix is gently removed with a sponge spear.
    - Schirmer's strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
    - Under ambient light, the subject will be instructed to look forward and to blink normally during the test. The test should be performed in a room with no direct air or sunlight on the subject's face.
    - The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.
    - After five minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the source document.

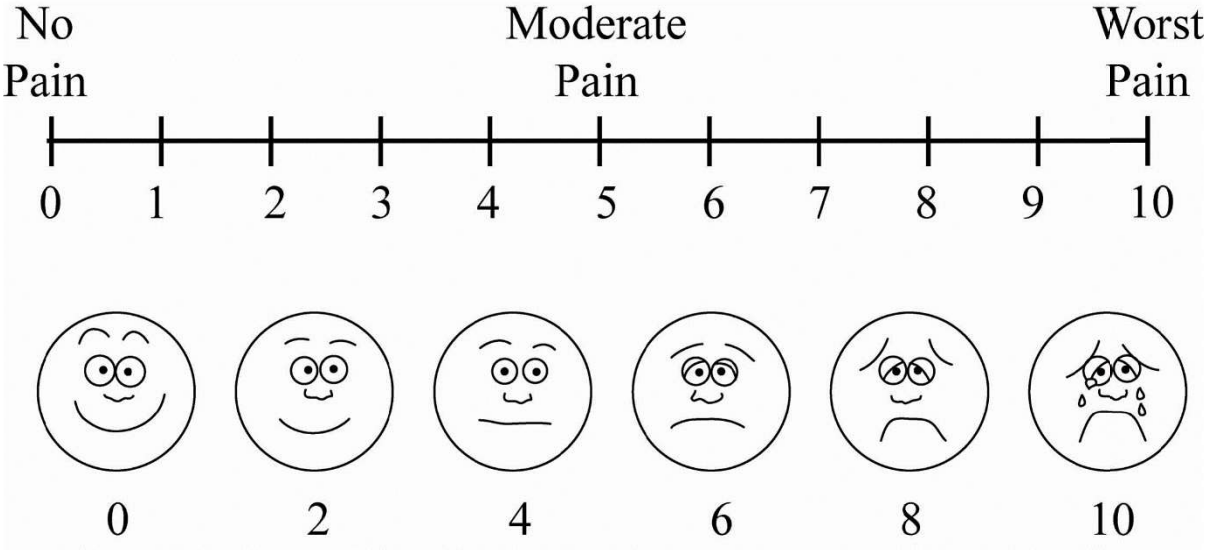
Schirmer's Test with Topical Anesthesia

The Schirmer's test will be performed concurrent with the study drug/placebo nasal spray treatment be used to assess tear production using the following steps:

1. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes of the subject.
    - The subject will be instructed to keep the eyes gently closed for one minute.

- After opening the eyes and allowing the eyes to recover for approximately one additional minute, excess moisture in the inferior fornix is gently removed with a sponge spear.
- Schirmer's strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
- Under ambient light, the subject will be instructed to look forward and to blink normally during the test. The test should be performed in a room with no direct air or sunlight on the subject's face.
- The Schirmer's strips should remain in place until five minutes have elapsed or both strips have reached maximum score.
- After five minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.

PAIN VISUAL ANALOG SCALE (VAS)



NATIONAL EYE INSTITUTE

Visual Functioning Questionnaire - 25

(NEI-VFQ-25)[2]

Version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question, please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge

about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

2. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

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3. Please answer every question (unless you are asked to skip questions because they don't apply to you).
4. Answer the questions by circling the appropriate number.
5. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.
6. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.
7. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	**1**
A little of the time	**2**
Some of the time	**3**
Most of the time	**4**
All of the time?	**5**

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	**1**
Mild	**2**
Moderate	**3**
Severe, or	**4**
Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**

Stopped doing this for other reasons or not interested in doing this 6

6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

8. How much difficulty do you have <u>reading street signs or the names of stores</u>?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty 3

Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

9. Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</u>?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</u>?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> you say?

(Circle One)

No difficulty at all 1

A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this..... 6

12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this.....6

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u> ?

(Circle One)

No difficulty at all..... 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty..... 4
Stopped doing this because of your eyesight..... 5
Stopped doing this for other reasons or not interested in doing this.....6

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

15. Are you <u>currently driving</u>, at least once in a while?

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you <u>never</u> driven a car or have you <u>given up driving</u>?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that <u>mainly because of your</u> <u>eyesight</u>, <u>mainly for some other reason</u>, or because of <u>both your</u> <u>eyesight and other reasons</u>?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have <u>driving during the daytime in familiar places</u>? Would you say you have:

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**

16. How much difficulty do you have <u>driving at night</u>? Would you say you have:

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16A. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**

Have you stopped doing this for other reasons or are you not interested in doing this..... 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for youthe statement is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
17. Do you accomplish less than you would like because of your vision?	**1**	**2**	**3**	**4**	**5**
18. Are you limited in how long you can work or do other activities because of your vision?.....	**1**	**2**	**3**	**4**	**5**
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	**1**	**2**	**3**	**4**	**5**

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	**1**	**2**	**3**	**4**	**5**
21. I feel frustrated a lot of the time because of my eyesight.	**1**	**2**	**3**	**4**	**5**
22. I have much less control over what I do, because of my eyesight.	**1**	**2**	**3**	**4**	**5**
23. Because of my eyesight, I have to rely too much on what other people tell me...	**1**	**2**	**3**	**4**	**5**
24. I need a lot of help from others because of my eyesight.	**1**	**2**	**3**	**4**	**5**
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	**1**	**2**	**3**	**4**	**5**

APPENDIX 3: SPONSOR APPROVALS

Protocol Title: A Phase 2, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (Varenicline) Nasal Spray in Subjects with Neurotrophic Keratopathy (the Olympia Study)

Protocol Number: OPP-102

APPENDIX 4: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Phase 2, Multicenter, Randomized, Controlled, Double-Masked, Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (varenicline) Nasal Spray in Subjects with Neurotrophic Keratopathy (the Olympia Study)
Protocol Number:	OPP-102

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed: _____ Date: _____

Name: _____

Title: _____

Site: _____

Address: _____

Phone Number: _____