Clinical Trial Protocol: DDES001/18-110-0002

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of Topical Naltrexone Ophthalmic Solution on the Signs and Symptoms of Dry Eye in Diabetic Subjects
Protocol Number:	DDES001/18-110-0002
Study Phase:	2
Investigational Product Name:	Naltrexone Ophthalmic Solution
IND/IDE/PMA Number:	IND 103,624
Indication:	Dry Eye Disease
Investigator / Sponsor:	Dr. Eugene McLaurin Single-center
Funder:	Ocunova, Inc. 225 Market St. Suite 500 Harrisburg, PA 17101
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673 USA

	Date
Original Protocol:	30 March 2018
Amendment 1:	21 June 2018

Confidentiality Statement

FUNDER PERSONNEL

Funder:	Ocunova, Inc. Tel: 610-733-0446 Fax: 484-367-7958
Funder CEO	Mike Shine Tel: 610-733-0446 Fax: 484-367-7958

ORA PERSONNEL

Department Vice President:	George Ousler Tel: (978) 685-8900 x 9481 Fax: (978) 689-0020 gousler@oraclinical.com
Department Director:	Michael Watson Tel: (978) 685-8900 x 9446 Fax: (978) 849-7371 mwatson@oraclinical.com
Project Manager:	Phoebe Carter Tel: (978) 685-8900 x9496 Fax: (978) 849-7371 pcarter@oraclinical.com

SYNOPSIS

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of Topical Naltrexone Ophthalmic Solution on the Signs and Symptoms of Dry Eye in Diabetic Subjects
Protocol Number:	DDES001
Investigational Product:	1) Naltrexone Ophthalmic Solution, 0.002% 2) Placebo Ophthalmic Solution
Study Phase:	2
Primary Objective(s):	The objective of this exploratory study is to determine the safety and efficacy of 0.002% Naltrexone Ophthalmic Solution, compared to placebo for the treatment of the signs and symptoms of dry eye in diabetic subjects.
Secondary Objective(s):	To assess the tolerability of twice daily administered 0.002% Naltrexone Ophthalmic Solution, eye drops vs placebo
Overall Study Design:	
Structure:	Single-center, double-masked, randomized, placebo-controlled study
Duration:	An individual subject's participation is estimated to be approximately 38 days
Controls:	Placebo (vehicle minus active) Ophthalmic Solution
Dosage/Dose Regimen/ Instillation/Application/Use:	Screening: During a 10-day study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally BID for 29 days (from Visit 2 to Visit 5).

	1) Naltrexone Ophthalmic Solution, 0.002% 2) Placebo Ophthalmic Solution (Vehicle)
Summary of Visit Schedule:	5 visits over the course of approximately 6 weeks: • Visit 1 = Day -10 ± 1, Screening • Visit 2 = Day 1, Confirmation / Baseline • Visit 3 = Day 8 ± 1, One Week Follow-Up • Visit 4 = Day 15 ± 1, Two Week Follow-Up • Visit 5 = Day 29 ± 2, Four Week Follow-Up and Study Exit
Measures Taken to Reduce Bias:	This is a randomized treatment assignment, double masked study.
Study Population Characteristics:	
Number of Subjects:	60 (30 per treatment arm) subjects
Condition/Disease:	Diabetic subjects with Dry Eye Syndrome

Inclusion Criteria:	**Subjects must:** a. Be at least 18 years of age; b. Provide written informed consent; c. Have a diagnosis of type 1 or type 2 diabetes mellitus prior to Visit 1; d. Have a reported history of dry eye for at least 6 months prior to Visit 1; e. Have a history of use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1; f. Have a corneal fluorescein staining score of ≥ 2 in any region (inferior, superior, or central regions) in at least one eye at Visits 1 and 2 (must be the same eye at Visits 1 and 2); g. Have at least one of the following at Visits 1 and 2: 1. A total lissamine green conjunctival score of ≥ 2 in at least one eye, based on the sum of the temporal and nasal regions at Visits 1 and 2 (must be the same eye at Visits 1 and 2); 2. Report an OSDI score ≥ 20 at Visits 1 and 2.
Exclusion Criteria:	**Subjects must not:** a. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters; b. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1; c. Have concurrent neurotrophic keratopathy from a source other than diabetes (h/o HSV keratitis, h/o HZO with ocular manifestations, or CN VII palsy or other condition resulting in lagophthalmos); d. Have active diabetic foot ulcers;

	e. Have a corneal sensitivity score ≤ 1.5 cm as measured by Cochet-Bonnet at Visit 1; f. Report an OSDI score > 75 at Visits 1 and 2; g. Have worn contact lenses within 21 days of Visit 1 or anticipate using contact lenses during the study (no contact lens wear during study); h. Have used any eye drops within 2 hours of Visit 1; i. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 24 months; j. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 45 days of Visit 1; k. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 12 months; l. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1; m. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study); n. Have corrected visual acuity greater than or equal to logMAR +0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in either eye at Visit 1; o. Have concurrent autoimmune disease causing dry eye (e.g., rheumatoid arthritis, Sjogren's, GVHD, Steven's Johnson, Grave's); p. Have Fuchs endothelial dystrophy; q. Have recurrent corneal erosion syndrome or anterior basement membrane dystrophy; r. Be a woman who is pregnant, nursing, or planning a pregnancy; s. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman

	who is permanently sterilized (i.e., has had a hysterectomy or bilateral tubal ligation), or is post-menopausal (without menses for 12 consecutive months); t. Be a woman of childbearing potential who is not using 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. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, they must agree to use adequate birth control as defined above for the remainder of the study; u. Have a known allergy and/or sensitivity to the test article or its components; v. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study; w. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; x. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1; y. Be unable or unwilling to follow instructions, including participation in all study assessments and visits. z. Be currently using a systemic opioid antagonist (e.g., Naltrexone or Naloxone) or have used a systemic opioid antagonist in the previous 90 days
Study Formulations and Formulation Numbers:	• Naltrexone Ophthalmic Solution, 0.002% • Placebo Ophthalmic Solution

Efficacy Measures and Endpoints:	**Efficacy Measures:** • Fluorescein staining; regions: inferior, superior, central, corneal sum, temporal, nasal, conjunctival sum, total eye; • Lissamine green staining; regions: inferior, superior, central, corneal sum, temporal, nasal, conjunctival sum, total eye; • Tear film break-up time (TFBUT); • Conjunctival redness; • Schirmer's Test (without anesthesia); • Cochet-Bonnet Corneal Sensitivity • Tear Osmolarity; • MMP-9; • Total Ocular Surface Disease Index (OSDI); • Ocular discomfort (0-4 scale); • Ocular discomfort, dryness, grittiness, burning and stinging (0-5 scale); • VAS.
Safety Measures:	• Visual acuity; • Slit-lamp biomicroscopy; • Adverse event query; • IOP; • Dilated fundoscopy.

General Statistical Methods and Types of Analyses

Analysis Populations

- Modified Intent-to-Treat Population – The modified intent-to-treat (mITT) population includes all randomized subjects with at least one post visit 2 study assessment. Efficacy analysis will be performed on the mITT population. Subjects in the mITT population will be analyzed as randomized.

- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and all efficacy data will be performed for the mITT population.

Sample Size:

As an exploratory study, the study is not powered to show statistical differences for any of the efficacy endpoints.

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

Multiplicity Consideration:

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

Safety Variables:

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, corneal sensitivity, dilated fundoscopy, intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye may be summarized separately.

Summary of Known and Potential Risks and Benefits to Human Subjects

The previous human experience with topical naltrexone administered to the eyes of healthy volunteers and the nonclinical safety studies conducted have indicated that topical naltrexone appears to be well tolerated. Nevertheless, patients will be closely monitored for safety-related issues.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
BCVA	best-corrected visual acuity
BID	twice daily
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
DED	dry eye disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug application
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
ITT	intent to treat
KCS	keratoconjunctivitis sicca
LASIK	laser in situ keratomileusis
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
Mg	microgram
µL	microliter
Mm	millimeter

NDA	new drug application
NEI	National Eye Institute
OD	right eye
OS	left eye
OSDI	Ocular Surface Disease Index
OU	both eyes
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
TF	tear film
TFBUT	tear film break-up time
VA	visual acuity

1 INTRODUCTION

1.1 Dry Eye Disease (DED)

Dry Eye Disease (DED) is defined by the International Dry Eye Workshop (DEWS) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (DEWS II Definition and Classification 2017). As many as 5 - 35% of patients visiting ophthalmic clinics report dry eye symptoms, making it one of the most common conditions seen by ophthalmic specialists (McCarty CA, *et al*. 1998; Lin PY, *et al*. 2003). Estimates range from 20 million people in the United States (US) being affected with mild to moderate dry eye, to a high of as many as one out of every five Americans. Prevalence is greater in females and the elderly. Schaumberg *et al*. reported prevalence rates ranging from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older, while an increased rate from 5.7% in women younger than 50 years to 9.8% in women >75 years was observed (Schaumberg DA, *et al*. 2003). Prevalence is affected by geographical parameters and appears to be higher in Asian populations. Dry eye can be related to external factors, such as the low humidity of air conditioned offices, winter heating, a dusty or windy outdoor environment, prolonged computer use, or wearing contact lenses, as well as to internal factors, such as hormonal imbalance, autoimmune disease, the presence of many widely prescribed systemic medications, anatomical changes or trauma, and aging. Symptoms result in mildly decreased quality of life at a minimum, and with increasing severity, loss of function and productivity, pain, light sensitivity, and the misery that accompanies significantly impaired vision and decreased quality of life. With the aging population in the United States and other countries of the developed world, and with increasing computer use, DED is expected to continue to become more prevalent and finding a treatment is becoming more important (Schaumberg DA, *et al*. 2009).

STUDY TREATMENT

Researchers at Pennsylvania State University/Hershey Medical Center have been exploring the role of the Opioid Growth Regulatory System (OGRS), which includes Opioid Growth Factor (OGF), and its receptor, OGFr, in the health and healing of the corneal epithelium for nearly 20 years. These studies included evaluating the impact of the OGRS on healthy corneal epithelium and the healing of wounded corneal epithelium utilizing cell and organ culture. Experiments have been performed in living animals. Additionally, cell and organ culture experiments were performed utilizing human eye bank corneas not suitable for transplantation. These studies have demonstrated the safety and efficacy of topically applied naltrexone in expediting the healing of corneal epithelial wounds in normal and diabetic rats. This research led to an investigational drug study entitled: “Topical Application of Naltrexone to the Ocular Surface of Healthy Volunteers: A Tolerability Study” (Liang et al., Volume 32 (2), 2016, pp 127-132; DOI: 10.1089/jop.2015.0070). It was concluded that topical naltrexone was well tolerated in healthy human subjects after 1 or 4 eye drops of naltrexone at dosages up to ~3.76 μg administered over a 24-h treatment period and observed for 1 week.

2 STUDY OBJECTIVES

The objective of this study is to compare the safety and efficacy of Naltrexone Ophthalmic Solution, 0.002% to placebo for the treatment of the signs and symptoms of dry eye in diabetic subjects.

3 CLINICAL HYPOTHESIS

The clinical hypotheses for this exploratory study is that Naltrexone Ophthalmic Solution has a beneficial effect compared to vehicle in improving the signs and symptoms of DED.

4 OVERALL STUDY DESIGN

This is a Phase 2, single-center, double-masked, randomized, placebo-controlled study to compare the safety and efficacy of Naltrexone Ophthalmic Solution, 0.002% to placebo for the treatment of the signs and symptoms of dry eye in diabetic subjects. Subjects eligible to be randomized will receive one of the following treatments to be administered bilaterally BID for 29 days (from Visit 2 to Visit 5): Naltrexone Ophthalmic Solution, 0.002% or Placebo Ophthalmic Solution (Vehicle). During a 10-day study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID. Participants who terminate early during the application period will be asked to complete safety assessments (if the participants agree) prior to study exit. Participants who are terminated early from the study will not be replaced. A chart illustrating the study's structure is below.

Visit 1 Day -10 ± 1 day Screening	• Informed consent/Health Information Portability and Accountability Act (HIPAA) consent • Demographic data, medical/medication, and ocular history • Urine Pregnancy Test (if applicable) • Ocular Surface Disease Index (OSDI) • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • VAS • Best Corrected Visual Acuity (BCVA) • Slit lamp biomicroscopy • Ora Calibra® Conjunctival redness; • Corneal sensitivity (Cochet-Bonnet) • TFBUT;

	• Fluorescein staining (Ora Calibra® scale); regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score • Lissamine green staining (Ora Calibra® scale); regions: inferior, superior, central, temporal, nasal, corneal sum, conjunctival sum, and total eye score) • Review inclusion and exclusion criteria • Run-in (vehicle) dose • Dispense vehicle to all qualifying patients for BID dosing until Visit 2 • Dispense dosing diary • Adverse Event Query • Schedule Visit 2
↓	
Approximate 10-Day Run-In Period with Vehicle	
↓	
Visit 2 Day 1 Confirmation/Baseline	• Run-in and diary collection • Medical/medication update • Adverse event query • Ocular Surface Disease Index (OSDI) • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • VAS • BCVA • Slit lamp biomicroscopy • Ora Calibra® Conjunctival redness • Corneal Sensitivity (Cochet-Bonnet) • Tear Osmolarity • InflammaDry® (MMP-9) testing • Tear film break-up time (TFBUT) • Corneal and conjunctival fluorescein staining

	• Corneal and conjunctival lissamine green staining • Unanesthetized Schirmer's Test • Intraocular Pressure (IOP) • Dilated fundoscopy • Review inclusion and exclusion criteria • Randomize qualifying subjects • Study treatment dose • Dispense study drug/placebo for BID dosing with active or placebo until Visit 5 according to randomization • Dispense dosing diary • Adverse Event Query • Schedule Visit 3
↓	
Visit 3 Day 8 ± 1 day 1-Week Follow-Up	• Study drug and diary collection • Medical/medication update • Adverse event query • OSDI • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • VAS • BCVA • Slit lamp biomicroscopy • Ora Calibra® Conjunctival redness • Corneal sensitivity (Cochet-Bonnet) • TFBUT • Corneal and conjunctival fluorescein staining • Corneal and conjunctival lissamine green staining • Unanesthetized Schirmer's Test • Dispense study drug • Dispense dosing diary • Adverse Event Query

	• Schedule Visit 4
↓	
Visit 4 Day 15 ± 1 day 2-Week Follow-Up	• Study Drug Collection • Medical/medication update • Adverse event query • OSDI • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • VAS • BCVA • Slit lamp biomicroscopy • Ora Calibra® Conjunctival redness • Corneal Sensitivity (Cochet-Bonnet) • TFBUT • Corneal and conjunctival fluorescein staining • Corneal and conjunctival lissamine green staining • Unanesthetized Schirmer's Test • Dispense study drug • Dispense dosing diary • Adverse Event Query • Schedule Visit 5
↓	
Visit 5 Day 29 ± 2 days 4-Week Follow-Up and Study Exit	• Study drug and diary collection • Medical/medication update • Adverse event query • Urine Pregnancy Test (if applicable) • OSDI • Ora Calibra® Ocular Discomfort Scale • Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire • VAS

	• BCVA • Slit lamp biomicroscopy • Ora Calibra® Conjunctival redness • Corneal sensitivity Cochet-Bonnet • Tear Osmolarity • InflammaDry® (MMP-9) testing • Tear film break-up time (TFBUT) • Corneal and conjunctival fluorescein staining • Corneal and conjunctival lissamine green staining • Unanesthetized Schirmer's Test • Intraocular Pressure (IOP) • Dilated fundoscopy • Blood Draw (optional) for enkephalin testing • Adverse Event Query • Study exit

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

Approximately 60 (30 per treatment arm) subjects will be enrolled in the study. The total number of expected participants, including screen failures, is approximately 120.

5.2 Study Population Characteristics

Approximately 60 subjects of either sex and of any race who are at least 18 years of age with a diagnosis of type 1 or type 2 diabetes mellitus and a subject-reported history of dry eye in both eyes and meeting all other study eligibility criteria will be randomized at 1 site in the US to receive treatment with Naltrexone Ophthalmic Solution, 0.002% or vehicle in a 1:1 ratio (approx. 30 subjects per treatment arm).

5.3 Inclusion Criteria

Each subject must:

a) Be at least 18 years of age;
b) Provide written informed consent;
c) Have a diagnosis of type 1 or type 2 diabetes mellitus prior to Visit 1;
d) Have a reported history of dry eye for at least 6 months prior to Visit 1;
e) Have a history or use or desire to use eye drops for dry eye symptoms within 6 months of Visit 1;
f) Have a corneal fluorescein staining score of ≥ 2 in any region (inferior, superior, or central regions) in at least one eye at Visits 1 and 2; must be the same eye at visits 1 and 2)
g) Have at least one of the following at Visits 1 and 2:
    i. A total lissamine green conjunctival score of ≥ 2 in at least one eye, based on the sum of the temporal and nasal regions at Visits 1 and 2; (must be the same eye at visits 1 and 2)
    ii. Report an OSDI score ≥ 20 at Visits 1 and 2.

5.4 Exclusion Criteria

Each subject may <u>not</u>:

a. Have any clinically significant slit lamp findings at Visit 1 that may include active blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergies that require therapeutic treatment, and/or in the opinion of the investigator may interfere with study parameters;
b. Be diagnosed with an ongoing ocular infection (bacterial, viral, or fungal), or active ocular inflammation at Visit 1;
c. Have concurrent neurotrophic keratopathy from a source other than diabetes (h/o HSV keratitis, h/o HZO with ocular manifestations, or CN VII palsy or other condition resulting in lagophthalmos;
d. Have active diabetic foot ulcers;
e. Have a corneal sensitivity score ≤ 1.5 cm as measured by Cochet-Bonnet at Visit 1;
f. Report an OSDI score > 75 at Visits 1 and 2;
g. Have worn contact lenses within 21 days of Visit 1 or anticipate using contact lenses during the study (no contact lens wear during study);
h. Have used any eye drops within 2 hours of Visit 1;
i. Have previously had laser-assisted in situ keratomileusis (LASIK) surgery within the last 24 months;
j. Have used cyclosporine 0.05% or lifitigrast 5.0% ophthalmic solution within 45 days of Visit 1;
k. Have any planned ocular and/or lid surgeries over the study period or any ocular surgery within the last 12 months;
l. Be using or anticipate using temporary punctal plugs during the study that have not been stable within 30 days of Visit 1;

m. Be currently taking any topical ophthalmic prescription (including medications for glaucoma) or over-the-counter (OTC) solutions, artificial tears, gels or scrubs, and cannot discontinue these medications for the duration of the trial (excluding medications allowed for the conduct of the study);
n. Have corrected visual acuity greater than or equal to logMAR +0.7 as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in both eyes at Visit 1;
o. Have concurrent autoimmune disease causing dry eye (rheumatoid arthritis, Sjogren's, GVHD, Steven's Johnson, Grave's);
p. Have Fuchs endothelial dystrophy;
q. Have recurrent corneal erosion syndrome or anterior basement membrane dystrophy;
r. Be a woman who is pregnant, nursing, or planning a pregnancy;
s. Be unwilling to submit a urine pregnancy test at Visit 1 and Visit 5 (or early termination visit) if of childbearing potential. Non-childbearing potential is defined as a woman who is permanently sterilized (e.g. has had a hysterectomy or tubal ligation), or is post-menopausal (without menses for 12 consecutive months);
t. Be a woman of childbearing potential who is not using 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. For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however, if the subject becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study;
u. Have a known allergy and/or sensitivity to the test article or its components;
v. Have a condition or be in a situation which the investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study;
w. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
x. Be currently using any medication known to cause ocular drying that is not used on a stable dosing regimen for at least 30 days prior to Visit 1;
y. Be unable or unwilling to follow instructions, including participation in all study assessments and visits.
z. Be currently using a systemic opioid antagonist (e.g. Naltrexone or Naloxone) or have used a systemic opioid antagonist in the previous 90 days.

5.5 Withdrawal Criteria (if applicable)

If at any time during the study the investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study in particular:

- the occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the investigator.
- the occurrence of an AE if discontinuation of trial drug is desired or considered necessary by the investigator and/or the subject.
- the occurrence of pregnancy.

Subjects may withdraw consent from the study at any time without reason.

The investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6).

The PI and Ora will regularly review the progress of the trial (semi-monthly) including a review of all adverse events noted during the period. In the event of a serious adverse event, the PI shall notify Ora (within 24 hours). Ora and PI will jointly determine whether any amendments to the trial are necessary or if the trial should be discontinued.

6 STUDY PARAMETERS

6.1 Efficacy Measures and Endpoints

6.1.1 Efficacy Measure(s)

- Fluorescein staining; regions: inferior, superior, central, corneal sum, temporal, nasal, conjunctival sum, total eye
- Lissamine green staining; regions: inferior, superior, central, corneal sum, temporal, nasal, conjunctival sum, total eye
- Tear film break-up time (TFBUT)
- Conjunctival redness
- Schirmer's Test (without anesthesia)
- Cochet-Bonnet
- Tear Osmolarity
- MMP-9
- Total Ocular Surface Disease Index (OSDI)
- Ocular discomfort (0-4 scale)
- Ocular discomfort, dryness, grittiness, burning and stinging (0-5 scale)
- VAS

6.2 Safety Measures

These evaluations will be performed in an effort to ensure subject safety throughout the trial:

- Visual acuity
- Slit-lamp biomicroscopy
- Adverse event query

- Intraocular Pressure (IOP)
- Dilated fundoscopy

6.3 Other Measures

- Urine Pregnancy Test at Visit 1 and Visit 5 (if applicable)
- Enkephelin levels

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatment

Naltrexone Ophthalmic solution will be formulated as a stable, sterile, topical, ophthalmic solution containing 21 µg/mL naltrexone hydrochloride in a multi-use container for topical administration to the eye. The study treatment will be delivered as a drop in each eye BID:

- Naltrexone Ophthalmic Solution, 0.002%
- Placebo Ophthalmic Solution

7.1.2 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s).

Selection of Dose:

Previous animal studies demonstrated that NTX dissolved in Vigamox® in the range of 10-5 M or 10-4 M was effective in reversing dry eye after 1 drop.

In the human study, the highest dosage of NTX was 5 x 10-5 M dissolved in Vigamox® and applied four times over a 24-hour period equaling 3.77 µg of NTX. The compound was prepared by Skip's Pharmacy, FL.

These molar dosages of NTX were converted by Bionex to yield a final formulation containing 20 µg/ml NTX, with each drop (0.028 ml) containing 0.56 µg NTX (assuming ~35.7 drops per ml). In the proposed clinical trial, drops will be applied twice daily yielding a total NTX dosage of 1.12 µg over a 24-hour period of time. This is one-third the clinical dosage shown to be safe for a 24-hour period of time.

Furthermore, the 20 µg/ml NTX dosage used in the bridge studies was shown to be consistently more effective in comparison to the NTX (5x 10-5 M) prepared in Vigamox®. Moreover, the 20 µg/ml NTX dosage was applied 4 times daily for a period of 30 days in both rats and rabbits and shown to be safe based on pathological assessment

by an outside veterinary ophthalmic pathologist (Yale University). The total amount of NTX applied to the rat or rabbit eye over a 30 day period was 120 µg.

7.1.3 Instructions for Use and Administration

Naltrexone will be formulated as a stable, sterile, topical, ophthalmic solution containing 21 µg/mL naltrexone hydrochloride in a multi-use container for topical administration to the eye.

a) During a 10-day study run-in period (for the purpose of subject selection) prior to randomization, all subjects will receive Placebo Ophthalmic Solution (Vehicle) bilaterally BID at home. After the run-in period, Subjects eligible to be randomized will receive one of the following treatments: Naltrexone Ophthalmic Solution, 0.002% or Placebo Ophthalmic Solution (Vehicle) to be administered at home bilaterally BID for 29 days (from Visit 2 to Visit 5). Subjects will be instructed not to administer drug/placebo before the appointment at home on the days they are scheduled for clinic visits.
b) All IP(s) must be stored in a locked container with access limited to the investigator and designated personnel. The temperature range for the IP is 2 to 25 degrees Celsius. Study drug will be delivered to the clinical site and stored refrigerated at the site. Once dispensed, subjects will be instructed to keep study drug at room temperature.
c) Subjects will receive one (1) bottle of run-in for at-home dosing between Visits 1 and 2. During the randomized dosing portion of the trial (Visits 2-5), subjects will be assigned two (2) study drug bottles. Subjects study drug bottles will be labeled with the subjects corresponding randomization number and A or B. The first bottle (A bottle) will be dispensed at Visit 2, re-dispensed at Visit 3, and collected at Visit 4. The second bottle (B bottle) will be dispensed at Visit 4 and collected at Visit 5.

7.2 Other Study Supplies

Urine Pregnancy tests, Sodium fluorescein, Lissamine green, Tear osmolarity cards, Tropicamide 1% ophthalmic solution, InflammaDry® cassettes, blood draw supplies.

8 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

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

8.1.2 Informed Consent

Prior to a subject's participation in the trial (i.e., changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent (and/or assent) using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC).

8.1.3 Washout Intervals

Prohibited medications and treatments are listed in the Exclusion Criteria (Section 5.4) with their respective washout intervals.

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 qualifies will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. If all inclusion and exclusion criteria are met at Visits 1 & 2, each qualifying subject will be assigned a randomization number at the end of Visit 2.

A masked randomization schedule will be provided to the investigational site. There will be an approximate equal number of subjects assigned to each of the two treatment arms at the site. Subjects will be randomized in sequential order staring with 3001. The site staff will dispense to the patient the randomized study drug bottles with the corresponding randomization number and "A" or "B". The randomization number will be recorded on the patient's source document and case report form (CRF). The Funder, Investigators, and study staff will be masked during the randomization process and throughout the study.

8.2 **Concurrent Therapies**

The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding case report form (CRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Disallowed medications and treatments are listed in the Exclusion Criteria (Section 5.4).

8.2.2 Escape Medications

No escape medications are required for this study.

8.2.3 Special Diet or Activities

No special diets or activities are required for this study.

8.3 Examination Procedures

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

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

Visit 1 = Day -10 ± 1, Screening

- Informed consent/Health Information Portability and Accountability Act (HIPAA) consent
- Demographic data, medical/medication, and ocular history
- Urine Pregnancy Test (if applicable)
- Ocular Surface Disease Index (OSDI)
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Visual Analog Scale (VAS)
- Best Corrected Visual Acuity (BCVA)
- Slit lamp biomicroscopy
- Ora Calibra® Conjunctival redness
- Corneal sensitivity Cochet-Bonnet
- Tear film break-up time (TFBUT)
- Fluorescein staining (Ora Calibra® scale); regions: central, superior, inferior, temporal, nasal, corneal sum, conjunctival sum, and total eye score
- Lissamine green staining (Ora Calibra® scale); regions: inferior, superior, central, temporal, nasal, corneal sum, conjunctival sum, and total eye score)
- Review inclusion and exclusion criteria
- Run-in (vehicle) dose
- Dispense vehicle to all qualifying patients for BID dosing until Visit 2
- Adverse Event Query
- Schedule Visit 2

Visit 2 = Day 1, Confirmation / Baseline

- Study Drug Collection
- Medical/medication update
- Adverse event query
- Ocular Surface Disease Index (OSDI)
- Ora Calibra® Ocular Discomfort Scale

- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- BCVA
- Slit lamp biomicroscopy
- Ora Calibra® Conjunctival redness
- Corneal Sensitivity (Cochet-Bonnet)
- Tear Osmolarity
- InflammaDry® (MMP-9) testing
- Tear film break-up time (TFBUT)
- Corneal and conjunctival fluorescein staining
- Corneal and conjunctival lissamine green staining
- Unanesthetized Schirmer's Test
- Intraocular Pressure (IOP)
- Dilated fundoscopy
- Review inclusion and exclusion criteria
- Randomize qualifying subjects
- Study treatment dose
- Dispense study drug/placebo "A" bottle for BID dosing
- Dispense dosing diary
- Adverse Event Query
- Schedule Visit 3

Visit 3 = Day 8 ± 1, One Week Follow-Up

- Study Drug/Diary Collection and Accountability
- Medical/medication update
- Adverse event query
- OSDI
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- BCVA
- Slit lamp biomicroscopy
- Ora Calibra® Conjunctival redness
- Corneal sensitivity (Cochet-Bonnet)
- TFBUT
- Corneal and conjunctival fluorescein staining
- Corneal and conjunctival lissamine green staining
- Unanesthetized Schirmer's Test

- Study Drug/Diary Dispensation
    - Re-dispense subject's "A" bottle
- Adverse Event Query
- Schedule Visit 4

Visit 4 = Day 15 ± 1, Two Week Follow-Up

- Study Drug/Diary Collection and Accountability
- Medical/medication update
- Adverse event query
- Urine Pregnancy Test (if applicable)
- OSDI
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- Best Corrected Visual Acuity
- Slit lamp biomicroscopy
- Ora Calibra® Conjunctival redness
- Corneal Sensitivity (Cochet-Bonnet)
- TFBUT
- Corneal and conjunctival fluorescein staining
- Corneal and conjunctival lissamine green staining
- Unanesthetized Schirmer's Test
- Study Drug/Diary Dispensation
    - Dispense subject's "B" bottle
- Schedule Visit 5

Visit 5 = Day 29 ± 2, Four Week Follow-Up and Study Exit

- Study Drug/Diary Collection and Accountability
- Medical/medication update
- Adverse event query
- Urine Pregnancy Test (if applicable)
- OSDI
- Ora Calibra® Ocular Discomfort Scale
- Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- VAS
- BCVA
- Slit lamp biomicroscopy
- Ora Calibra® Conjunctival redness

- Corneal sensitivity (Cochet-Bonnet)
- Tear Osmolarity
- InflammaDry® (MMP-9) testing
- TFBUT
- Corneal and conjunctival fluorescein staining
- Corneal and conjunctival lissamine green staining
- Unanesthetized Schirmer's Test
- Intraocular Pressure (IOP)
- Dilated fundoscopy
- Blood Draw (optional) for enkephalin testing
- Adverse Event Query
- Study exit

Adverse Events (AEs) (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate CRF.

If a female has a positive pregnancy test during the study, then the investigator will notify Ora immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Ora.

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

- Slit-lamp Biomicroscopy;
- Visual Acuity;
- Intranasal Examination;
- Urine Pregnancy Test (if applicable);
- Assessment of AEs;
- Assessment of concurrent medications and/or treatments; and
- 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 at Visits 1, 2, 3, and 4, and provided with written instructions. Subject diaries and study drug will be collected at each visit from Visit 1 up to and including Visit 5 to assess subject compliance with the protocol.

Subject dosing compliance will be determined by the subject's response or lack thereof to the prompt "Was the dose taken?" in the subject diary. If more than 20% of the responses to the total expected dose-taken prompts are checked "no," left blank, or missing, then the subject will be deemed noncompliant for dosing and a deviation recorded. In addition, if more than 20% of all expected diary symptom assessments are missed, then the subject will be deemed noncompliant and a diary deviation recorded.

Subject's bottles may also be weighed at each visit to determine dosing accountability.

8.6 Subject Disposition

8.6.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

8.6.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- subject request/withdrawal
- AEs
- protocol violations
- administrative reasons (e.g., inability to continue, lost to follow up)
- sponsor termination of study
- other

Note: In addition, any subject may be discontinued for any sound medical reason.

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

8.7 Study Termination

The study may be stopped at any time by the investigator and/or Ora.

8.8 Study Duration

An individual subject's participation will involve 5 visits over approximately 38 days.

8.9 **Monitoring and Quality Assurance**

For the conduct of this trial, an assigned Ora, Inc. CRA will conduct an initial SIV, providing an in-depth review of the protocol with emphasis that the trial will be conducted according to the pertinent regulatory requirements. Interim monitoring visits (IMVs) are not planned, however to ensure patient safety and efficacy, weekly contact with PI or authorized delegate will occur in order to:

- Confirm eligible subjects are being properly consented
- Assess status and document any adverse events associated with the study procedures and IP. Should there be any unexpected adverse events, or an abnormally high number of adverse events occurring among enrolled subjects, the CRA will alert the Lead CRA and Project Manager in order to determine whether an on-site IMV is warranted
- Confirm administration and storage of IP is being conducted and monitored as per protocol design.

At the conclusion of the trial, after all eligible/enrolled subjects have had their last on-site visit, the CRA will conduct a Close-Out Visit (COV). During the COV the CRA will:

- Review all ICFs
- Assess data integrity by selecting a random sampling of 10% of total subjects enrolled and conduct a thorough review of source to verify adequacy of data collection (GDP), subject eligibility and safety (GCP).
- CRA will query any discrepant data. If any findings constitute Major protocol deviations, the Lead and PM will be notified to determine if additional data review is warranted.
- Reconcile and return IP
- Review and reconcile site's ISF to Ora's TMF.

Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies and Ora, Inc. Quality Assurance and/or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the CRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to IP, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician 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 subject. The assessment of severity is made irrespective of relationship to IP 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 Investigational Product

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- ***Suspected*:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:

- *Definite*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
- *Probable*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- *Possible*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.

- ***Not Suspected:*** A reasonable possibility does not exist that the IP caused the AE.
  - *Not Related:* Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. Types of evidence that would suggest a causal relationship between the IP and the AE event include: a single occurrence of an event that is uncommon and known to be strongly associated with IP exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with IP exposure, but is otherwise uncommon in the population exposed to the IP (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the IP-treatment group than in a concurrent or historical control group.

9.1.3 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the IP 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:*** An AE unrelated to the IP.

AE events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product 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 serious if, in the view of the investigator, 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 the investigator its occurrence places the 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.

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

Note: A serious adverse event (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.

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate CRF. AE's will be collected from first dose of study drug to 30 days after treatment discontinuation.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora 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 IP, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate CRFs. The investigator is obligated to pursue and obtain information requested by Ora 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 notify Ora immediately; 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 Ora 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 IP; and inform the IRB of the SAE within their guidelines for reporting SAEs.

Contact information for reporting SAEs and ADEs:

Clinical Project Manager:	**Phoebe Carter**
Company:	Ora, Inc.
Office Telephone:	(978) 685-8900 x9496
Alternative Telephone:	(978) 409-0955
Office Facsimile:	(978) 849-7371

9.4 Procedures for Unmasking (if applicable)

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment arm has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora should be notified before unmasking study drug. Ora must be informed immediately about any unmasking event.

If the investigator identifies a medical need for unmasking the treatment assignment of a subject, he should contact Ora prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will

determine if the unmasking request should be granted. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using the unmasking report. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File (TMF). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file. Unmasked subjects will be discontinued from the study.

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 subject is lost to follow-up, the investigator should make 3 reasonable attempts to contact the subject via telephone, post, or certified mail. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE CRF with the status noted.

If the investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Analysis Populations

Analysis Populations

- Modified Intent-to-Treat Population – The modified intent-to-treat (mITT) population includes all randomized subjects with at least one post visit 2 study assessment. Efficacy analysis will be performed on the mITT population. Subjects in the mITT population will be analyzed as randomized.

- Safety Population – The safety population includes all subjects who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

The statistical analysis of safety data will be performed for the safety population. The analysis of baseline and all efficacy data will be performed for the mITT population.

Sample Size:

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

Multiplicity Consideration:

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

Safety Variables:

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, corneal sensitivity, dilated fundoscopy, intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye may be summarized separately. Summaries of the comfort data from the Comfort Assessment of the study will be performed on the safety population from that Assessment. The statistical analysis of safety data will be performed for the safety population, separately for the Comfort Assessment and the Safety and Efficacy Assessment of the study. The analysis of baseline and all efficacy data in the Safety and Efficacy Assessment of the study will be performed for the mITT population. The efficacy analyses may also be performed on the PP population as sensitivity analyses.

10.2 **Statistical Hypotheses**

For each efficacy endpoint and time point, the statistical hypotheses are as follows:

H_0: There is no difference between the Naltrexone Ophthalmic Solution treatment group and placebo for the respective endpoint.

H_1: There is a difference between the Naltrexone Ophthalmic Solution treatment group and placebo for the respective endpoint. A difference in favor of Naltrexone Ophthalmic Solutions will be considered a success for that endpoint.

10.3 **Sample Size**

The study is not powered to show statistical differences for any of the efficacy endpoints. The sample size was determined based on prior clinical trial experience with in subjects with dry eye syndrome and is deemed to be robust sufficient to

evaluate the safety and tolerability of Naltrexone Ophthalmic Solution in this population and to gather efficacy data that will aid in powering future clinical trials.

With a sample size of 60 subjects in the Safety and Efficacy Assessment, the study will have 79% probability of detecting AEs occurring at a rate of 5% or more in either treatment arm.

10.4 Statistical Analysis

10.4.1 General Considerations

The quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative variables will be summarized using counts and percentages.

All summaries will be presented by treatment group.. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

Baseline measures are defined as the last measure prior to the initiation of study treatment, usually at Visit 2.

10.4.2 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the worst eye.

10.4.3 Missing Data

The efficacy analyses will be performed using observed data.

10.4.4 Multiplicity Consideration

There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early phase, exploratory study.

10.4.5 Safety Variables

Frequencies and percentages of subjects with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs causing premature discontinuation will be provided by treatment group. An AE is treatment emergent if it occurs or worsens after the first dose of study treatment. Separate summaries will be provided for ocular specific and all AEs (including systemic).

Other safety endpoints including visual acuity, slit-lamp biomicroscopy, corneal sensitivity, dilated fundoscopy, intraocular pressure will be summarized by treatment group and visit using descriptive statistics. Changes or shifts from baseline will also be summarized where appropriate. For assessments performed by eye, study eye and fellow eye

may be summarized separately. Summaries of the comfort data from the Comfort Assessment of the study will be performed on the safety population from that Assessment. The statistical analysis of safety data will be performed for the safety population, separately for the Comfort Assessment and the Safety and Efficacy Assessment of the study. The analysis of baseline and all efficacy data in the Safety and Efficacy Assessment of the study will be performed for the mITT population. The efficacy analyses may also be performed on the PP population as sensitivity analyses.

10.4.6 Efficacy Analyses

The continuous and ordinal secondary efficacy variables collected at each visit will be summarized descriptively (n, mean, standard deviation, median, min and max), and analyzed with two-sample t-tests comparing each of the active treatment groups to placebo. All visit-based data will be analyzed at each visit and change from baseline. A Wilcoxon rank sum test and an ANCOVA model adjusting for baseline may be assessed where appropriate.

A full statistical analysis plan (SAP) will be finalized before database lock and unmasking.

10.4.7 Interim Analyses

No interim analyses are planned.

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

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonisation (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 IP 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 Ora and receive approval/favorable opinion from an IRB/IEC 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 Ora prior to submission to the governing IRB/IEC 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 Ora and provided in writing by Ora prior to the consent process.

11.1.2 Institutional Review Board (IRB) Approval

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

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

11.2 Ethical Conduct of the 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 as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora and the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the 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 aforementioned 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 IP 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 X-rays, laboratory tests, and EKGs. 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 IP, 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 IP. These documents will be retained for a longer period if required by the applicable regulatory requirements.

If the 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.

11.5 **Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product**

11.5.1 Labeling/Packaging

For the run-in period, 1 bottle of will be dispensed for two weeks of BID dosing.

Investigational drug will be packaged and labeled into clinical kits. Study drug will be provided as subjects' kits containing 1 bottle of Naltrexone Ophthalmic Solution or Vehicle Ophthalmic Solution. The required medication until the next visit will be dispensed to the subject (see Section 7.1.2 for details). The kit with remaining medication will be kept at the site.

11.5.2 Storage of Investigational Product

The IP must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

Study drug must be refrigerated, protected from light, and secured at the investigational site in a locked container. Subjects should be instructed to store study drug in the same manner, but at room temperature, at home.

11.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the principal investigator or his/her named sub-investigator(s), and is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

The investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP dispensed to subjects, amount of IP returned to the investigator by the subjects, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the IP.

11.5.4 Return or Disposal of Investigational Product

All IP will be returned to the sponsor or their designee or destroyed at the study site. The return or disposal of IP will be specified in writing.

11.6 **Recording of Data on Source Documents and Case Reports Forms (CRFs)**

The investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's CRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. 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.

11.7 **Handling of Biological Specimens**

Not Applicable.

11.8 **Publications**

Authorship and manuscript composition will reflect cooperation among all parties involved in the study.

REFERENCES

Liang D, Sassani JW, McLaughlin PJ, Zagon IS. Topical Application of Naltrexone to the Ocular Surface of Healthy Volunteers: A Tolerability Study. J Ocul Pharmacol Ther. 2016 Mar;32(2):127-32. doi: 10.1089/jop.2015.0070. Epub 2016 Jan 7.

Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology. 2003 Jun;110(6):1096-101.

McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. Ophthalmology. 1998 Jun;105(6):1114-9.

Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003 Aug;136(2):318-26.

Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol. 2009 Jun;127(6):763-8. doi: 10.1001/archophthalmol.2009.103.

13 APPENDICES

APPENDIX 1: SCHEDULE OF VISITS AND MEASUREMENTS

Procedure	Visit 1 Day-10 ±1	Visit 2 Day 1	Visit 3 Day 8 ± 1	Visit 4 Day 15 ± 1	Visit 5 Day 29 ±2
Informed Consent	X				
Demographic Data	X				
Medical/Medication History	X				
Medical/Medication History Update		X	X	X	X
Randomization		X			
Urine pregnancy test	X				X
OSDI© questionnaire	X	X	X	X	X
Ora Calibra® Ocular Discomfort Scale	X	X	X	X	X
Ora Calibra® Ocular Discomfort & 4 Symptom Questionnaire	X	X	X	X	X
Visual Acuity Scale (VAS)	X	X	X	X	X
BCVA	X	X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X
Ora Calibra® Conjunctival redness	X	X	X	X	X
Corneal Sensitivity (Cochet-Bonnet)	X	X	X	X	X
Tear Osmolarity		X			X
InflammaDry® (MMP-9) testing		X			X
TFBUT	X	X	X	X	X

Corneal and conjunctival fluorescein staining	X	X	X	X	X
Corneal and conjunctival lissamine green staining	X	X	X	X	X
Schirmer's Test		X	X	X	X
IOP		X			X
Dilated Fundoscopy		X			X
ENK blood draw (optional)					X
Review Eligibility Criteria	X	X	X	X	X
Run-in (vehicle) instillation at study site	X				
Study drug/placebo instillation at study site		X	X	X	X
Run-in (vehicle) Dispensed	X				
Run-in (vehicle) Returned		X			
Adverse Event Query	X	X	X	X	X
Investigational Product Dispensed		X	X	X	
Investigational Product Returned			X	X	X
Dosing Diary Dispensed	X	X	X	X	
Exit from Study					X

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

Visual Acuity Procedures (ETDRS Chart)

LogMAR visual acuity (VA) must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. VA should be evaluated at the beginning of each visit in the study (i.e., prior to slit-lamp examination). VA testing should be done with most recent correction.

Equipment

The VA chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only the 'R' charts, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (e.g., that was a "C" not an "O") before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. 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 1 of 2 letters, he or she should be asked to choose 1 letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR VA for that eye.

For example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	= 0.18

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of VA during the study, all VA 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 forgets his glasses), the reason for the change in correction should be documented.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score) from baseline (Visit 1) will be considered an Adverse Event.

Slit Lamp Biomicroscopy Procedures

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) or not clinically significant (NCS). The following will be examined:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens

- Eyelid

External magnification and biomicroscopy will be performed using a slit-lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

Dilated Fundoscopy

Dilated fundus exams will be performed using indirect ophthalmoscopy. The investigator will make observations of the vitreous, retina, macula, choroid and optic nerve.

Observations will be graded as Normal or Abnormal. Abnormal findings that are clinically significant (as determined by the investigator that may interfere with study parameters or otherwise confound the data) and those that are not clinically significant will be described. An indirect Fundoscopy examination should be performed if retinal disease is detected. A 78 or 90 diopter lens should also be used as needed.

- Vitreous: Examination should emphasize the visual axis.
- Retina, Macula, Choroid: Include an observation of the retina and its blood vessels. Eyes should be excluded from the study if active inflammation is present.
- Optic Nerve: Significant damage or cupping to the optic nerve should be noted.

It is recommended that tropicamide 1% ophthalmic solution be used to dilate subjects. The use of cyclopentolate 1% ophthalmic solution is recommended as secondary dilating medication, should the need arise.

Intraocular Pressure

Intraocular pressure (IOP) will be measured in each eye by contact tonometry by the examiner and the results will be recorded in mmHg. A single measurement is made to obtain a determination of IOP. The same tonometer employing the investigator's standard technique will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject.

InflammaDry®

Levels of MMP-9 will be measured in each eye using InflammaDry at Visit 1, Visit 3 and Visit 5. The test will be recorded as either positive or negative. Sample should not be taken within two hours of any medication being instilled in either eye.

1. Open the Sterile Sample Collector (Package I)

2. Use the sampling fleece, gently dab along the palpebral conjunctiva until saturated

3. Open the Test Cassette (Package II), remove the protective cap, and insert the sampling fleece where indicated, ensuring to press down to hear the double click.

4. Place the absorbent tip in the buffer solution for at least 20 seconds.

5. Put the protective cover back over the Test Cassette and lay flat for at least 10 minutes before interpreting results.

6. Repeat test in other eye.

Tear Osmolarity

Tear osmolarity will be measured in each eye using the TearLab© osmolarity system. Tear osmolarity will be taken once from the temporal canthus of each eye and the measurement will be recorded. A second reading may be taken if first reading is out of range. A maximum of 2 attempts will be made per eye. Tear osmolarity will be measured in mOsm/L.

1. Turn the Reader on.

2. Remove a Test Card from its package.

3. Attach a Test Card by sliding the wings of the Test Card onto the TearLab Pen. The Pen will light up and beep when the card is attached properly. The green light will stay on until you collect tears or the Pen times out (after two minutes).

4. While holding the Test Card wings, remove the protective cover from the Test Card just before tear collection.

5. Collect a tear fluid sample as described in the TearLab Osmolarity System User Manual or Quick Reference Guide. IMPORTANT: Any Test Card that does not contain a protective cover should not be used for subject testing.

6. Dock the Pen into the Reader within 40 seconds. Do NOT remove the Test Card from the Pen before docking or all data will be lost.

7. Locate the code on the top of the Test Card. Press the RECALL key below the up or down arrows on the Reader keypad to match the Test Card code. Press OK or wait eight seconds for the Reader to accept the code.

8. The Reader will display the Test Result in a few seconds. Record the Test Result in the source document.

9. Remove the Test Card by pressing your thumb forward on top of the Test Card. Do not pull from the wings. Dispose in an appropriate container.

10. Repeat in the other eye for a total of 2 measurements.

Ora Calibra® Ocular Discomfort Scale for Dry Eye

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

Ocular discomfort scores will be subjectively graded by the subjects according to the following scale, rating each eye separately.

0	**No discomfort**
1	**Intermittent awareness**
2	**Constant awareness**
3	**Intermittent discomfort**
4	**Constant discomfort**

Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire for Dry Eye

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

Subjects will rate the severity of each of the following symptoms, with regard to how both their eyes feel, in general – overall ocular discomfort, burning, dryness, grittiness and stinging according to the following 6-point (0 to 5) scale where 0 = none and 5 = worst.

0 1 2 3 4 5

(None) (Worst)

Visual Analogue Scale (VAS)

Subjects will be asked the following questions regarding ocular discomfort (unrelated to study drug instillation) at all visits.

The subject will be asked to rate each ocular symptom due to ocular dryness by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to "no discomfort" and 100% corresponds to "maximal discomfort"

Burning/ Stinging	0%	100%
Itching	0%	100%
Foreign Body Sensation	0%	100%
Blurred Vision	0%	100%
Eye Dryness	0%	100%
Photophobia	0%	100%
Pain	0%	100%

Ocular Surface and Disease Index (OSDI) © for Dry Eye

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

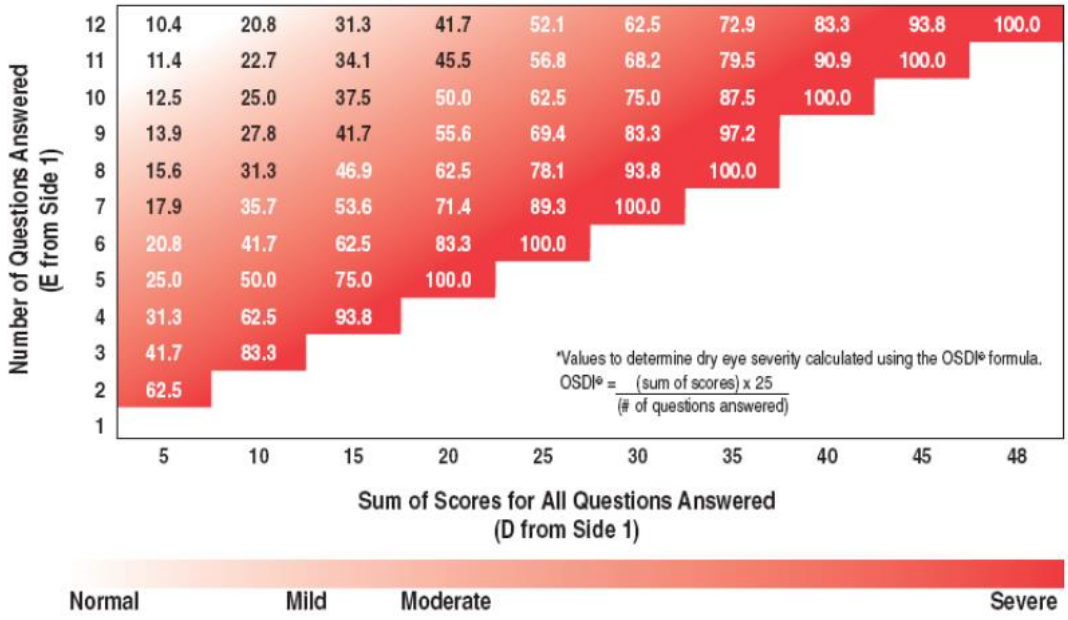
Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Ora proprietary scales – Not for distribution without permission

Ora Calibra® Conjunctival Redness Scale for Dry Eye

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

None	0 = Normal, without vasodilation
Trace	1 = Trace ciliary or conjunctival vasodilation
Mild	2 = Broad ciliary vasodilation;
Moderate	3 = Broad ciliary and slight, horizontal conjunctival vasodilation
Severe	4 = Broad ciliary and prominent, horizontal conjunctival vasodilation
Half (0.5) unit increments are allowed.	

Ora proprietary scale – Not for distribution without permission

Tear Film Break-Up Time (TFBUT)

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. To thoroughly mix the fluorescein with the tear film, the subject will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT.

With the aid of a slit-lamp, the examiner will monitor the integrity of the tear film, noting the time it takes to form micelles from the time that the eye is opened. TFBUT will be measured in seconds using a stopwatch and a digital image recording system for the right eye followed by the left eye. A Wratten #12 yellow filter will be used to enhance the ability to grade TFBUT.

For each eye, 2 measurements will be taken and averaged unless the 2 measurements are > 2 seconds apart and are each < 10 seconds, in which case, a third measurement would be taken and the 2 closest of the 3 would be averaged.

Fluorescein Staining

The examiner will instill 5 µL of 2% preservative-free sodium fluorescein solution into the inferior conjunctival cul-de-sac of each eye. In order to achieve maximum fluorescence, the examiner should wait approximately 3-5 minutes after instillation before evaluating 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 Ora Calibra® Corneal and Conjunctival Staining Scale and NEI scale. Digital images of fluorescein staining may be taken for digital analysis.

<u>Ora proprietary scale – Not for distribution without permission</u>

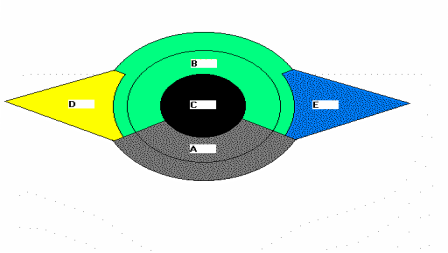
Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Fluorescein Staining

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

The following scale will be used to grade staining of the ocular surface (areas A, B, C, D, and E). Half (0.5) grade increments may be used.

None	0 = no staining
Trace	1 = occasional
Mild	2 = countable
Moderate	3 = uncountable, but not confluent
Severe	4 = confluent

Staining areas:



Staining Areas	Ocular Structure	Position
A – Inferior	Cornea	4-8 o'clock, extending 2 mm onto the conjunctiva
	Limbus/Conjunctiva	4-8 o'clock, extending 2 mm towards the center
B – Superior	Cornea	8-4 o'clock, extending 3 mm onto the conjunctiva
	Limbus/Conjunctiva	8-10 o'clock and 2-4 o'clock, extending 1 mm onto the conjunctiva; 10-2 o'clock, extending 2 mm onto the conjunctiva
C – Central	Cornea	Central cornea
D – Temporal	Conjunctiva	Triangular wedge of temporal conjunctiva
E – Nasal	Conjunctiva	Triangular wedge of nasal conjunctiva

NEI/Industry Workshop Scale for Grading of Fluorescein Staining

Score each of 5 areas on the cornea of each eye.

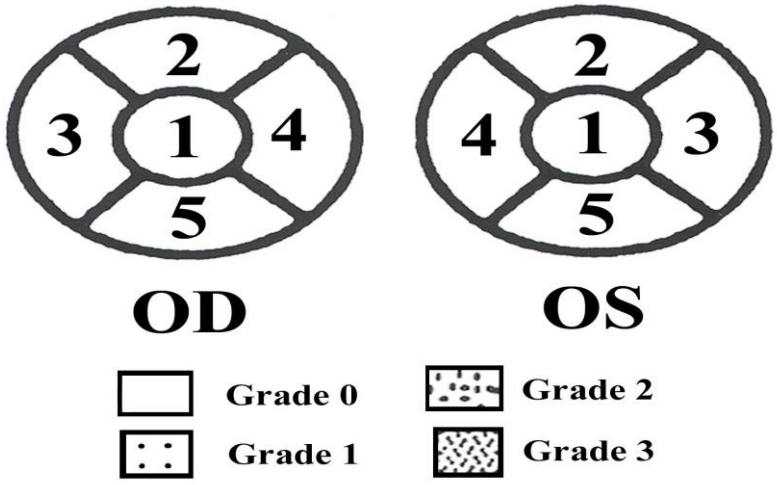


Diagram of the division of the corneal surface for measuring fluorescein uptake. A standardized grading system of 0-3 is used for each of the 5 areas on each cornea. Grade 0 will be specified when no staining is present. The maximum score is 15.

Ora proprietary scale – Not for distribution without permission

Lissamine Green Staining

The Investigator will instill 10 µL of lissamine green solution into the inferior conjunctival cul-de-sac and wait approximately 30 seconds before evaluating staining. The subject will be instructed to blink several times to distribute the lissamine green. The staining will be graded with the Ora Calibra® Corneal and Conjunctival Staining Scale as well as the NEI scale. Digital images of lissamine green staining may be taken for digital analysis.

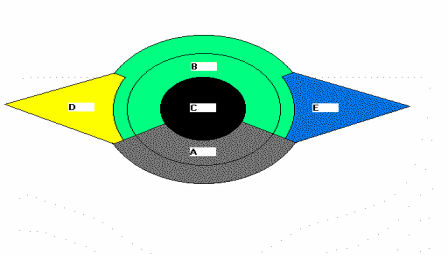
Ora Calibra® Corneal and Conjunctival Staining Scale for Grading of Lissamine Green Staining

This procedure will be performed according to Ora, Inc. SOPs and/or guidance documents.

The following scale will be used to grade staining of the ocular surface (areas A, B, C, D, and E). Half (0.5) grade increments may be used.

None	0 = no staining
Trace	1 = occasional
Mild	2 = countable
Moderate	3 = uncountable, but not confluent
Severe	4 = confluent

Staining areas:



Staining Areas	Ocular Structure	Position
A – Inferior	Cornea	4-8 o'clock, extending 2 mm onto the conjunctiva
	Limbus/Conjunctiva	4-8 o'clock, extending 2 mm towards the center
B – Superior	Cornea	8-4 o'clock, extending 3 mm onto the conjunctiva
	Limbus/Conjunctiva	8-10 o'clock and 2-4 o'clock, extending 1 mm onto the conjunctiva; 10-2 o'clock, extending 2 mm onto the conjunctiva
C – Central	Cornea	Central cornea
D – Temporal	Conjunctiva	Triangular wedge of temporal conjunctiva
E – Nasal	Conjunctiva	Triangular wedge of nasal conjunctiva

NEI/Industry Workshop Scale for Grading of Lissamine Green Staining

The nasal and temporal conjunctivae are divided into 3 segments as diagrammed. Score each of the 6 areas of the conjunctiva of each eye.

1 – Temporal

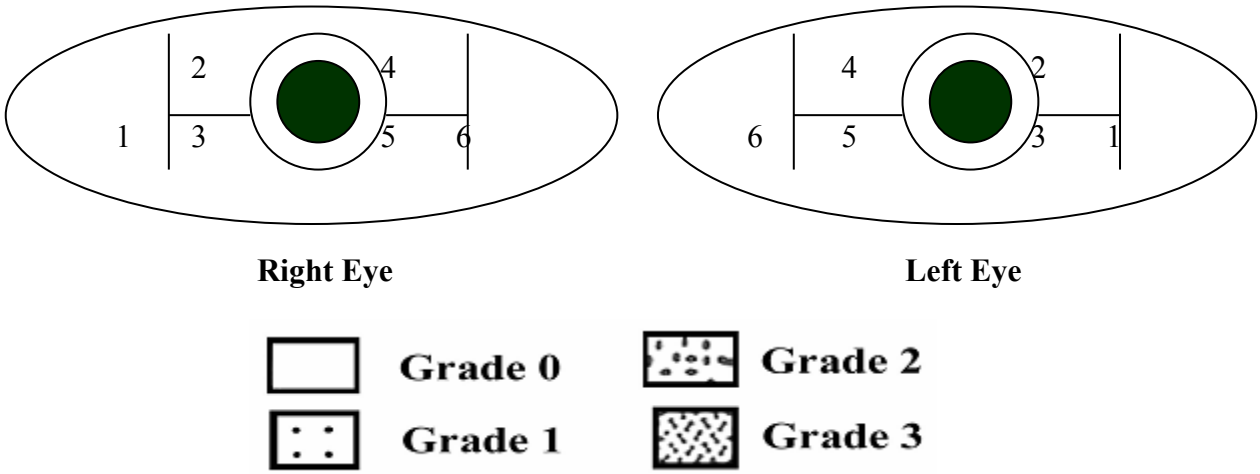
2 – Superior Temporal

3 – Inferior Temporal

4 – Superior Nasal

5 – Inferior Nasal

6 – Nasal



A standardized grading system of 0 - 3 is used for each of the 6 areas on each conjunctiva. Grade 0 will be specified when no staining is present. The maximum score is 18.

Unanesthetized Schirmer's Test

Schirmer Tear Test will be performed according to the following procedure:

- Using a sterile Tear Flo Schirmer test strip (Rose Enterprises), a bend in the strip will be made in line with the notch in the strip.
- The subject will be instructed to gaze up and in.
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes.
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye.

Corneal Sensitivity

The aesthesiometer (Cochet–Bonnet) is a nylon thread contained in a pen–like case that can be extended specific distances from the tip of the case. The following steps will be followed by the examiner for evaluating corneal sensitivity:

1. Remove Cochet–Bonnet from box.

2. Extend the filament to 60 mm (the filament should not have bends in it – if it does, the readings will be incorrect and the filament should not be used).

3. The examiner will inform the subject that a thin delicate plastic filament will be used to test their corneal sensitivity and that they will feel the sensation similar to a strand of hair on their eye. (If the subject is hesitant, a spot on the subject's hand will be cleaned with an alcohol pad and the filament touched to the hand to demonstrate the painless contact).

4. The examiner will instruct the subject to say "Yes" when they feel sensation on their eyeball.

5. The examiner will place their free hand on the cheek below the eye being measured to stabilize subject's head position.

6. The examiner will position their hand with the device such that the filament is normal (90 degree angle with corneal surface). The device should be between the examiner's index, middle finger, and thumb.

7. The examiner will extend fingers such that the filament applies gentle pressure on the central corneal surface. The examiner will then ask subject if they can perceive the filament touching the central corneal surface.

   If the subject responds "Yes", the examiner will ensure the response is valid by performing a sham (not touching the cornea) application and also confirm that response was not due to eyelids touching the filament.

   If the subject responds "No", then the filament is shortened the length by 5mm and reapplied to the cornea.

   If the subject responds "Yes", record length; if the subject responds "No", go to step b.

Step 7 is repeated 3 times.

The filament is retracted such that only 10 mm are exposed.

The tip is wiped with an alcohol pad gently ENSURING that it does NOT bend the filament.

The alcohol is allowed to dry before reusing device (alcohol can cause corneal abrasions).

Enkephalin Blood Draw (optional)

Subjects may have their blood drawn at Visit 5 for testing of enkephalin levels. It is estimated that 1-2 mLs will be drawn for analysis. Further details on sample processing will be provided in a separate manual as applicable.

APPENDIX 3: SUBJECT DIARY

Visit 1 – Visit 2

Protocol: DDES001 / 18-110-0002 Subject ID: ___ ___ - ___ ___ ___ Subject Initials ___ ___ ___

Indicate if you took a dose by checking Yes or No for both morning and evening doses.

Date: ______________________________

Was the **MORNING** dose taken?	☐ Yes	☐ No	☐ N/A
Was the **EVENING** dose taken?	☐ Yes	☐ No	☐ N/A

Date: ______________________________

Was the **MORNING** dose taken?	☐ Yes	☐ No	☐ N/A
Was the **EVENING** dose taken?	☐ Yes	☐ No	☐ N/A

Date: ______________________________

Was the **MORNING** dose taken?	☐ Yes	☐ No	☐ N/A
Was the **EVENING** dose taken?	☐ Yes	☐ No	☐ N/A

Date: ______________________________

Was the **MORNING** dose taken?	☐ Yes	☐ No	☐ N/A
Was the **EVENING** dose taken?	☐ Yes	☐ No	☐ N/A

DO NOT DOSE ON THE MORNING OF YOUR NEXT VISIT

Version 0.1 | DRAFT | 12 Jun 2018 CONFIDENTIAL

APPENDIX 4: AMENDMENT SUMMARY

APPENDIX 5: APPROVALS

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of Topical Naltrexone Ophthalmic Solution on the Signs and Symptoms of Dry Eye in Diabetic Subjects
Protocol Number:	DDES001
Final Date:	21 June 2018

This clinical study protocol was subject to critical review and has been approved by the investigator. The following personnel contributed to writing and/or approving this protocol.

Signed:_____ Date:_____
Mike Shine
CEO, Ocunova

Signed:_____ Date:_____
George W. Ousler, III
VP, Dry Eye, Ora, Inc.

Signed:_____ Date:_____
Michael Watson
Director, Dry Eye, Ora, Inc.

Signed:_____ Date:_____
Phoebe Carter
Clinical Project Manager, Dry Eye, Ora, Inc.

Signed:_____ Date:_____
Eugene McLaurin, MD
Total Eye Care, PA

APPENDIX 6: INVESTIGATOR'S SIGNATURE

Protocol Title:	A Single-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of Topical Naltrexone Ophthalmic Solution on the Signs and Symptoms of Dry Eye in Diabetic Subjects
Protocol Number:	DDES001
Final Date:	21 June 2018

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 Ora and the sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) 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:_____

Dr. Eugene McLaurin
Principal Investigator
Total Eye Care, PA
6060 Primacy Pkwy, Memphis, TN 38119
(901) 761-4620