Clinical Trial Protocol: RGN-NK-301/Ora Protocol # 15-110-0006

Protocol Title:	**A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy (SEER-1)**
Protocol Number:	RGN-NK-301/15-110-0006
Study Phase:	3
Product Name:	Thymosin β4 (RGN-259)
IND Number:	73446
Indication:	Neurotrophic Keratopathy
Investigators:	Multi-center clinical investigation
Sponsor:	ReGenTree, LLC 116 Village Boulevard, Suite 200 Princeton, NJ 08540, USA Phone number: (609)734-4328 Fax number: (609)228-5117
Contract Research Organization:	Ora, Inc. 300 Brickstone Square, 3rd Floor Andover, MA 01810, USA
IRB/IEC:	Alpha IRB 1001 Avenida Pico Suite C, #497 San Clemente, CA 92673, USA

	Date
Original Protocol:	17 August 2015
Amendment 1:	25 September 2015
Amendment 2:	26 February 2016
Amendment 3:	22 December 2016
Amendment 4:	04May 2017

SPONSOR PERSONNEL

Sponsor:	[redacted]
Medical Monitor	[redacted]

ORA PERSONNEL

Department Vice President	[redacted]
Department Senior Manager	[redacted]
Clinical Project Manager	[redacted]

SYNOPSIS

Protocol Title:	A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy (SEER-1)
Protocol Number:	RGN-NK-301
Investigational Product:	1) 0.1% RGN-259 Ophthalmic Solution 2) Placebo Ophthalmic Solution (Vehicle of RGN-259)
Study Phase:	3
Study Objective:	To compare the safety and efficacy of RGN-259 to placebo for the treatment of Neurotrophic Keratopathy (NK)
Overall Study Design:	
Structure:	Multi-center, double-masked, randomized, placebo-controlled study
Duration:	Approximately 6 weeks (43 days)
Controls:	Placebo Ophthalmic Solution (Vehicle of RGN-259)
Dosage/Dose Regimen/ Instillation/Application/Use:	Subjects eligible to be randomized will receive 1-2 drops of the following treatments to be administered in the affected eye(s) 5 times per day for 28 days (from Visit 1 to Visit 5). 1. 0.1% RGN-259 Ophthalmic Solution 2. Placebo Ophthalmic Solution Subjects will be randomized in [redacted] ratio [redacted]
Summary of Visit Schedule:	Seven visits over the course of approximately 6 weeks • Visit 1 = Day 1, Screening/Enrollment/Baseline • Visit 2 = Day 8 ± 2 day, 1-Week Follow Up • Visit 3 = Day 15 ± 2 day, 2-Week Follow Up • Visit 4 = Day 22 ± 2 day, 3-Week Follow Up • Visit 5 = Day 29 ± 2 day, 4-Week Follow-Up • Visit 6 = Day 36 ± 3 day, 1-Week Post-Treatment Follow-Up • Visit 7 = Day 43 ± 3 day, 2-Week Post-Treatment Follow-Up
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce the potential of bias during data collection and evaluation of clinical endpoints.
Study Population Characteristics:	
Number of Subjects:	Up to 100 subjects will be screened and approximately 46 subjects will be enrolled in this study [redacted] at approximately 20 clinical sites in the US.

Condition/Disease:	Neurotrophic Keratopathy
Inclusion Criteria:	**Subjects must:** a. Be male or female of any race, at least 18 years of age at Visit 1; b. Have provided verbal and written informed consent. c. Be able and willing to follow instructions, including participation in all study assessments and visits; d. Have a persistent epithelial defect (a defect that has not reduced in size) for at least [redacted] with failure of conventional, nonsurgical treatment using non-preserved ocular lubricants, non-preserved topical ophthalmic antibiotics, oral doxycycline, patching, serum tears and/or therapeutic contact lenses at the time of Visit 1; e. Have stage 2 or 3 neurotrophic keratopathy (Mackie Classification) in at least one eye [redacted] and which is confirmed not to be simply superficial punctate keratitis, at Visit 1; f. Have evidence of decreased corneal sensitivity [redacted] at Visit 1; g. Have at least one eye (the same eye) satisfy all criteria for d, e, f above h. If a female of childbearing potential, have a negative urine pregnancy test at Visit 1 and agree to use an adequate method of birth control throughout the study period. [Females are considered of childbearing potential unless they are surgically sterilized (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) or post-menopausal (at least 12 months since last menses). Adequate birth control is defined as use of hormonal contraceptives (oral, implantable, injectable or transdermal), spermicide in conjunction with a barrier such as condom or diaphragm, or an intrauterine device (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 patient becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study.]
Exclusion Criteria:	**Subjects must not:** a. Have any clinically significant slit lamp findings at Visit 1 that in the opinion of the investigator may interfere with the study parameters; b. Have significant blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergy that requires treatment at Visit 1; c. Have a lid function abnormality (ex. Lagophthalmos) which, in the opinion of the investigator, is the primary cause of the persistent epithelial defect;

	d. Be diagnosed with ongoing ocular infection (bacterial, viral or fungal) or active inflammation (e.g. follicular conjunctivitis) not related to NK in the affected eye at Visit 1; e. Have had any ocular surgical procedure that is not considered the primary cause of NK in the affected eye within 2 months prior to Visit 1, or have any scheduled ocular surgical procedure during the study period; f. Have had any ocular surgical procedure that is considered to be the cause of NK within 4 weeks prior to Visit 1; g. Have received Botox injection for blepharoptosis within the previous 90 days in the affected eye; h. Have started the use of topical steroids in the affected eye in the previous 2 weeks or systemic steroids in the previous 4 weeks; i. Have used contact lenses (excluding therapeutic contact lenses) within 14 days prior to Visit 1 or anticipates use of contact lenses during the study period; j. Have an uncontrolled systemic disease that in the opinion of the investigator may interfere with the study parameters; k. Anticipate a change in immunosuppressive therapy during the course of the study; l. Have a known allergy and/or sensitivity to the study drug or its components; m. Be a woman who is pregnant, nursing or planning a pregnancy; n. Be unwilling to submit a urine pregnancy test at Visit 1, Visit 5 and Visit 7 (or early termination visit) if of childbearing potential; o. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1; p. Have undergone surgical treatments for NK including tarsorrhaphy or amniotic membrane graft within the previous 6 weeks in the affected eye. q. Plan to use serum tears in the affected eye during the study period.
Study Formulations and Formulation Numbers:	Study Drug: RGN-259 Ophthalmic Solution (and Placebo) to be supplied by ReGenTree.
Evaluation Criteria:	
Efficacy Measures:	Primary Efficacy Measures: Percentage of subjects achieving complete healing of the persistent epithelial defect as determined by corneal fluorescein staining at 4 weeks (Visit 5). Secondary Efficacy Measures: • Percentage of subjects achieving complete healing of the persistent epithelial defect determined by corneal fluorescein staining at Visits 2, 3, 4, 6, and 7;

	• Epithelial Defect Measurement and Classification at Visits 2, 3, 4, 5, 6, and 7; • Tear Film Break-up Time at Visits 5, 6, and 7; • Ocular Discomfort using Ora Calibra™ Discomfort and 4-Symptom Questionnaire at Visits 2, 3, 4, 5, 6, and 7; • Visual Acuity at Visits 2, 3, 4, 5, 6, and 7.
Safety Measures:	• Visual Acuity (ETDRS); • Slit-Lamp Biomicroscopy; • Cochet-Bonnet; • Adverse Event Query; • Dilated Fundoscopy; • Intraocular Pressure.

General Statistical Methods and Types of Analyses

Analysis Populations:

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

Sample Size:

[redacted]

Primary Efficacy Analysis:

[redacted]

[redacted]

Secondary Efficacy Analyses:

[redacted]

Summary of Known and Potential Risks and Benefits to Human Subjects

There are no known risks associated with the ocular instillation of RGN-259 ophthalmic solution. Doses up to 0.1% produced no local or systemic toxicity and did not induce any signs of ocular disease in a 28-day repeated-dose study in rabbits. In two Phase 2 studies evaluating 0.1% Tβ4 Ophthalmic solution, there were no Tβ4-related adverse events reported.

Potential risks are minimal based on (1) the safety profile of Tβ4 in nonclinical toxicology and safety pharmacology studies where systemic doses [redacted] produced no observed adverse events. In a Phase 1 study in healthy volunteers, systemic doses of Tβ4 injectable solution up to [redacted] mg/kg bw/day yielded no dose limiting toxicities and no serious adverse events. Three unexpected and possibly related adverse events; dizziness (1 subject), headache (1 subject) and pyrexia (1 subject) were reported as the only adverse events reported.

Potential benefits of RGN-259 include improvements in various signs and symptoms associated with NK.

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of covariance
CI	Confidence interval
CL	Clearance
CRF	Case Report Form
CRO	Clinical (or Contract) Research Organization
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCPs	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional/Independent Review Board
ITT	Intent-to-Treat
i.v.	Intravenously; Intravenous
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NK	Neurotrophic Keratopathy
NGF	Nerve Growth Factor
PK	Pharmacokinetics
PP	Per Protocol
ROPI	Report of Prior Investigations
SAE	Serious Adverse Event
SD	Standard deviation
RGN-259	Thymosin Beta-4
TEAE	Treatment-Emergent Adverse Events
TFBUT	Tear-Film Break-Up Time
Vd	Volume of distribution
WHO Drug	World Health Organization Drug Dictionary

1 INTRODUCTION

Neurotrophic keratopathy (NK) is a degenerative corneal disease that occurs as a result of partial or total impairment of trigeminal innervation. The resulting loss of corneal sensitivity (anesthesia) leads to a reduction in lacrimation and a decline in status, metabolism, and mitosis of corneal epithelial cells. Ultimately NK results in a deficiency in epithelial repair, stromal edema, loss of microvilli, and abnormal basal lamina homeostasis. Patients with NK develop poorly-healing, recurrent corneal abrasions or defects that are slow to respond to current therapies. NK is most commonly associated with diabetes or herpes zoster-infected patients, but can also be the result of trauma to the eye or the trigeminal nerve. While the condition is rare, there is a significant need for improvement in therapeutic options, as the wounds associated with NK can be threatening to the eyesight.

1.1 The Pharmacology of Thymosin β4 (Tβ4)

Tβ4 is a synthetically produced copy of a naturally occurring 43-amino acid peptide. The natural peptide is found in high concentrations in the majority of tissue types, with the highest concentrations in blood platelets and white blood cells. It is also found extracellularly in blood plasma or in wound fluid (Huff, 2001). It is one of a family of at least 16 highly conserved peptides, collectively called the β-thymosins, which are present in high concentrations in almost every cell type.

Tβ4 has wound healing and anti-inflammatory properties. It is thought to exert its therapeutic effect through promotion of keratinocyte and endothelial cell migration, increased collagen deposition, and stimulation of angiogenesis (Huff, 2002). It is released from platelets and is selectively cross-linked by factor XIIIa, a tissue transglutaminase, to molecules including actin, collagen, fibrin, and fibrinogen (Malinda, 1999). Tβ4 also up-regulates expression of laminin-5, a protein involved in adhesion and migration of cells that function in the wound-healing process (Sosne 2004). It also inhibits the activation of the transcription factor (nuclear factor κB, NFκB), a key regulator of inflammatory responses (Sosne 2007).

1.2 Toxicology Overview

Tβ4 plays a role in vascular biology by acting as a chemo-attractant for endothelial cells, and stimulating angiogenesis, promoting cell migration, and attenuating apoptotic activities in some cells. These properties suggest a potential for Tβ4 to play a role in tumor metastasis, but the data supporting such potential is equivocal. While various reports have shown that Tβ4 is upregulated in a number of metastatic cells, a correlation between Tβ4 expression and malignancy has not been established (Yamamoto, 1993). Forced over-expression of Tβ4, either *in vitro* or *in vivo*, does not induce tumorogenesis (Cha, 2003; 2010).

There is no structure-activity relationship suggesting carcinogenic risk, and no evidence of pre-neoplastic lesions in any repeat-dose toxicity study of Tβ4. In twenty-four nonclinical toxicology and safety pharmacology studies, ReGenTree has established the safety of Tβ4 for its current and planned uses in man. Because of its high concentration and ubiquitous distribution, it has been suggested that Tβ4 functions as both an intracellular structural element and as a regulatory molecule when released from cells either by secretion, cell death, or lysis (Goldstein et al., 2005). It is likely that its high endogenous concentration is, at least in part, the driving force behind the high safety factor and negligible toxicologic effects observed with pharmacological doses of Tβ4.

Developmental toxicology was examined in a series of studies using both rats and rabbits as test species (study numbers 20024503, 20024504, 20024505, and 20024506). For each species, a dose-finding screen was followed by a study with daily dosing of animals throughout pregnancy. There were no adverse effects observed to either maternal or embryonic/fetal animals in any of these studies. The no observable adverse effect level (NOAEL) for rats was [redacted]. These were the highest doses used in each species.

An ocular toxicity study (BGY00015) was also performed to assess the potential ocular and systemic toxicity of Tβ4 ophthalmic drops. Rabbits received 4 drops, 4 times daily for 28 consecutive days. None of the 3 doses used [redacted] caused any local or systemic toxicity, and none elicited any other adverse ocular effects.

A total of 108 patients have been enrolled in 4 clinical studies employing the 0.1% concentration of Tβ4 ophthalmic drops, and the drug has been shown to be safe and well-tolerated. The largest of these, a 72-patient trial of 0.1% Tβ4 ophthalmic drops for treatment of dry eye, reported no significant adverse effects and no clinically significant changes in any safety parameters.

1.3 Pharmacokinetics and Dose-Range Selection

The plasma pharmacokinetics (PK) of daily doses of [redacted] mg/kg/day Tβ4 for 28 days were characterized following single and repeat bolus intravenous (iv) injections to male and female Sprague-Dawley rats (Study 20018593). The T1/2 estimate ranged from [redacted] hours for males and from [redacted] hours for females. The volume of distribution (Vd) estimates for both males and females indicated distribution beyond the vasculature. The clearance (CL) ranged from [redacted] mL/h/kg and [redacted] mL/h/kg and [redacted] mL/h/kg for males and females, respectively. The increases in exposure between [redacted] mg/kg/day were approximately dose proportional on Days 1 and 28. Exposure to Tβ4 tended to be higher for males than for females. No notable accumulation of Tβ4 was observed following repeated administration for 28 days. In conclusion, administration of Tβ4 Injectable Solution by once daily iv injection was well

tolerated in rats at levels up to [redacted] mg/kg/day. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 300 mg/kg/day.

To further assess PK activity of Tβ4, radiolabled ^{14}C-Tβ4 was administered iv to male and female Sprague-Dawley rats (Study 2116-001). The peak of radioactivity (T_{max}) in plasma was observed at 5 minutes post-dose (first time point assessed) for both males and females. For both sexes, the C_{max} at 5 minutes post-dose was followed by a steep decline to 4 hours (distribution phase), with a much more gradual decline through 48 hours (elimination phase). There were no differences between the plasma PK curves for males and females. Whole blood was also measured for both sexes, and as with plasma, there were essentially no differences between the blood PK curves for males and females. No significant distribution to the erythrocytes was noted through 24 hours for either sex.

While there were no Phase 1 studies of ophthalmic formulations of Tβ4, a double-blind, randomized, placebo-controlled, dose response study was conducted using four cohorts with 10 healthy subjects each given a single intravenous dose of Tβ4 or placebo. Cohorts received ascending doses of either [redacted] mg of Tβ4 (Phase 1A). Following safety review of the Phase 1A data, subjects in Phase 1B received the same doses administered to those in Phase 1A but daily for 14 consecutive days. Safety evaluations, incidence of unexpected adverse events (AEs) and PK parameters were evaluated. AEs were infrequent and mild and moderate in intensity. There were no deaths, no dose limiting toxicities or SAEs. The PK profile showed a dose proportional response, increasing half-life with increasing dose and minimal drug accumulation.

For the previous dry eye clinical trial (RGN-DE-202), the 0.1% concentration of Tβ4 was chosen and was shown to be safe, well tolerated, and produced clinically significant effects in ocular discomfort and corneal staining. Following this, physician-sponsored studies used 0.1% Tβ4 under a compassionate IND to treat nine patients with NK, six of whom had discrete geographic, non-healing lesions, and three of whom had punctate lesions. The physicians reported that the six with discrete geographic lesions completely healed or almost completely healed during the treatment course or shortly thereafter using the 0.1% concentration four times daily (Dunn, 2010a). For these reasons, we propose to use this same concentration of 0.1% Tβ4 for the studies of NK.

1.4 Study Rationale

ReGenTree's plan is to develop 0.1% Tβ4, formulated as RGN-259 sterile, preservative-free eye drops, as an agent to treat ocular surface defects associated with dry eye, neurotrophic keratopathy, chemical injury, or other underlying pathologies or injuries to the eye. This course of development is suggested by the limited pharmacological interventions for enhancing corneal wound healing, repair and regeneration and by the known activities of RGN-259. The selection of

NK as a condition to assess treatment efficacy is based on the known spectrum of RGN-259 activity and the lack of available treatments for NK.

2 STUDY OBJECTIVES

The objective of this study is to assess the safety and efficacy of RGN-259 Ophthalmic Solution compared to placebo for the treatment of NK after a 4 week, 5 times per day, treatment period and a 2-week post-treatment follow up.

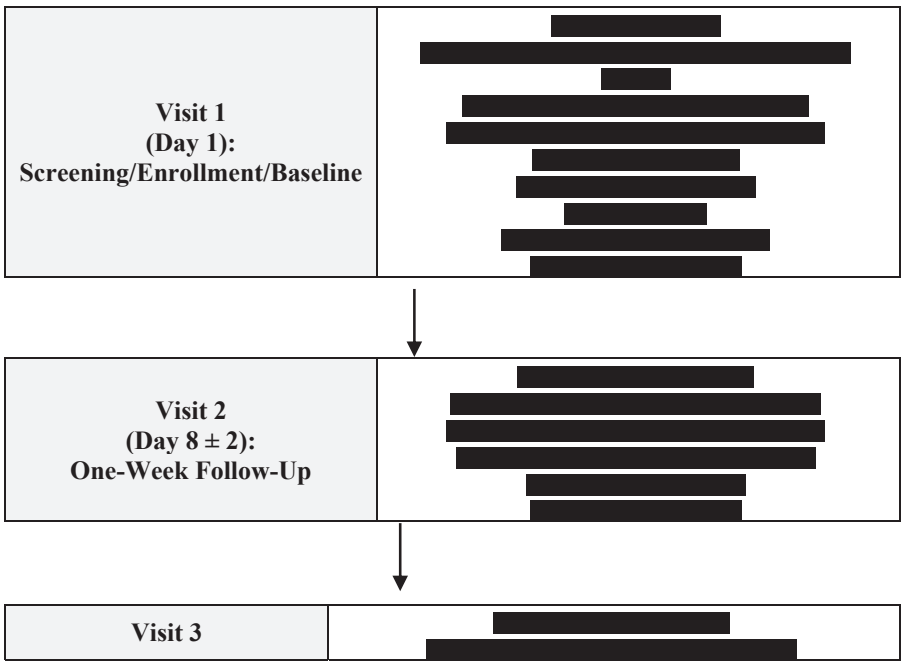
3 CLINICAL HYPOTHESIS

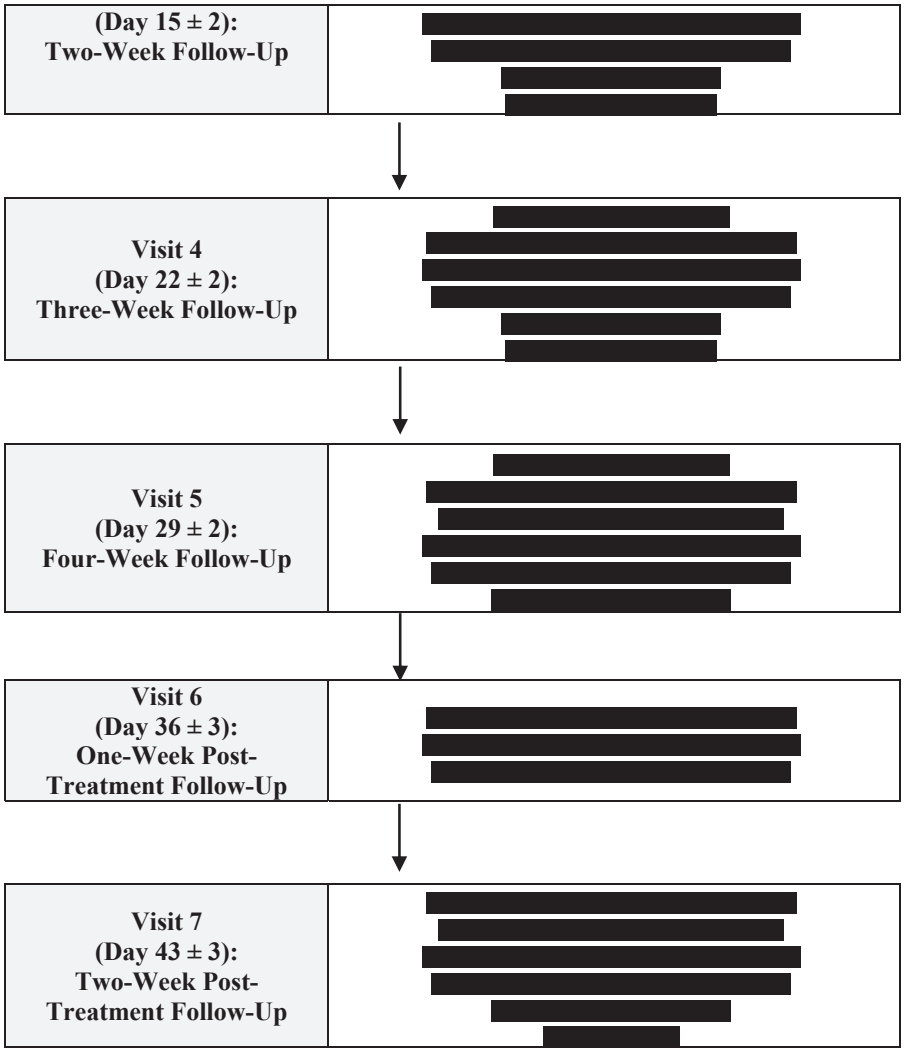
The clinical hypothesis for this study is the following:

- Significantly more subjects receiving RGN-259 ophthalmic solution will have a clearing of a persistent epithelial defect at Visit 5 (Day 29) when compared to subjects receiving placebo.

4 OVERALL STUDY DESIGN

This is a Phase 3, multicenter, randomized, double-masked study designed to evaluate the efficacy and safety of RGN-259 ophthalmic solution compared to placebo in patients with neurotrophic keratopathy. Approximately 46 male and female patients at least 18 years of age with stage 2 or stage 3 neurotrophic keratopathy (Mackie Classification) and meeting all other study eligibility criteria will be randomized to receive treatment with [redacted]. This study will consist of two periods: a 28-day treatment period and a 14-day post-treatment period. A study flow chart appears below:





Patients who terminate early during the treatment period or post-treatment period will be asked to complete safety assessments. Patients who are terminated early from the study will not be replaced.

In this study, the vehicle of RGN-259 ophthalmic solution has been selected as the placebo control to objectively evaluate the efficacy and safety of RGN-259 ophthalmic solution. In addition, randomized assignment and double-masked design features have been implemented to minimize any bias for patient selection and data evaluation.

5 STUDY POPULATION

5.1 Number of Subjects (approximate)

It is estimated that approximately 100 subjects will be screened to enroll approximately 46 subjects at approximately 20 clinical sites in the US.

5.2 Study Population Characteristics

Subjects diagnosed with neurotrophic keratopathy in at least one eye and who meet all inclusion and exclusion criteria.

5.3 Inclusion Criteria

Subjects must:

a. Be male or female of any race, at least 18 years of age at Visit 1.
b. Have provided verbal and written informed consent;
c. Be able and willing to follow instructions, including participation in all study assessments and visits;
d. Have a persistent epithelial defect (a defect that has not reduced in size) for at least [redacted] with failure of conventional, nonsurgical treatment using non-preserved ocular lubricants, non-preserved topical ophthalmic antibiotics, oral doxycycline, patching, serum tears and/or therapeutic contact lenses at the time of Visit 1;
e. Have stage 2 or 3 neurotrophic keratopathy (Mackie Classification) in at least one eye of which the longest dimension (length or width) of the defect [redacted] and which is confirmed not to be simply superficial punctate keratitis, at Visit 1;
f. Have evidence of decreased corneal sensitivity [redacted] at Visit 1;
g. Have at least one eye (the same eye) satisfy all criteria for d, e, f above
h. If a female of childbearing potential, have a negative urine pregnancy test at Visit 1 and agree to use an adequate method of birth control throughout the study period. [Females are considered of childbearing potential unless they are surgically sterilized (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) or post-menopausal (at least 12 months since last menses). Adequate birth control is defined as use of hormonal contraceptives (oral, implantable, injectable or transdermal), spermicide in conjunction with a barrier such as condom or diaphragm, or an intrauterine device (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 patient becomes sexually active during the study, she must agree to use adequate birth control as defined above for the remainder of the study.]

5.4 Exclusion Criteria

Subjects must not:

a. Have any clinically significant slit lamp findings at Visit 1 that in the opinion of the investigator may interfere with the study parameters;

b. Have significant blepharitis, meibomian gland dysfunction (MGD), lid margin inflammation or active ocular allergy that requires treatment at Visit1;
c. Have a lid function abnormality (ex. Lagophthalmos) which, in the opinion of the investigator, is the primary cause of the persistent epithelial defect;
d. Be diagnosed with ongoing ocular infection (bacterial, viral or fungal) or active inflammation (e.g. follicular conjunctivitis) not related to NK in the affected eye at Visit 1;
e. Have had any ocular surgical procedure that is not considered the primary cause of NK in the affected eye within 2 months prior to Visit 1, or have any scheduled ocular surgical procedure during the study period;
f. Have had any ocular surgical procedure that is considered to be the cause of NK within 4 weeks prior to Visit 1;
g. Have received Botox injection for blepharoptosis within the previous 90 days in the affected eye;
h. Have started the use of topical steroids in the affected eye in the previous 2 weeks or systemic steroids in the previous 4 weeks;
i. Have used contact lenses (excluding therapeutic contact lenses) within 14 days prior to Visit 1 or anticipates use of contact lenses during the study period;
j. Have an uncontrolled systemic disease that in the opinion of the investigator may interfere with the study parameters;
k. Anticipate a change in immunosuppressive therapy during the course of the study;
l. Have a known allergy and/or sensitivity to the study drug or its components;
m. Be a woman who is pregnant, nursing or planning a pregnancy;
n. Be unwilling to submit a urine pregnancy test at Visit 1, Visit 5 and Visit 7 (or early termination visit) if of childbearing potential;
o. Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days of Visit 1;
p. Have undergone surgical treatments for NK including tarsorrhaphy or amniotic membrane graft within the previous 6 weeks in the affected eye;
q. Plan to use serum tears in the affected eye during the study period.

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. Subjects may withdraw consent from the study at any time. ReGenTree and/or

the Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure(s)

- [redacted]

6.1.2 Secondary Efficacy Measure(s)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.2 Safety Measures

- Visual Acuity (Early Treatment of Diabetic Retinopathy Study, ETDRS);
- Slit-Lamp Biomicroscopy;
- Cochet-Bonnet;
- Adverse Event Query;
- Dilated Fundoscopy;
- Intraocular Pressure.

7 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatments/Formulations/Composition

1) 0.1% RGN-259 Ophthalmic Solution

2) Placebo Ophthalmic Solution (Vehicle for RGN-259 Ophthalmic Solution)

7.1.2 Instructions for Use and Administration

- At the end of Visit 1, qualified subjects will be randomized and the first dose of Study Drug will be administered in the Clinic. A 1-week supply of RGN-259 Ophthalmic Solution or Placebo Ophthalmic Solution will be dispensed to use 5 times per day;
- At Visits 2, 3 and 4, remaining/used study drug will be collected from subjects for drug accountability. Subjects will receive an additional 1 week supply of the same study drug they were previously randomized to (at Visit 1), to use 5 times per day for 1 week;
- At Visit 5, remaining/used study drug will be collected from subjects for drug accountability.
- Subjects will be instructed to use study drug on the day of applicable visits (Visits 2, 3, 4, and 5) prior to the visit.

7.2 Other Study Supplies

HCG urine pregnancy tests, Wratten #2 yellow filter, sodium fluorescein or BioGlo™ Fuorescein Strips, 1% Tropicamide, and Fluoress.

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., prior to 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 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.

8.1.3 Washout Intervals

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

8.1.4 Procedures for Final Study Entry

Meet all inclusion and exclusion criteria.

8.1.5 Methods for Assignment to Treatment Groups:

At Visit 1, subjects who provide written informed consent will be assigned a unique 5-digit screening number, which includes the 2-digit site number plus a unique 3-digit screening number beginning with 001 (e.g., 11001, 11002, 11003, etc.). Screening numbers must be assigned in ascending consecutive order.

If all inclusion and exclusion criteria are met at Visits 1, each qualifying subject will then be assigned a 4-digit randomization number at the end of Visit 1. All randomization numbers will be assigned in strict numerical sequence and no numbers will be skipped or omitted. Assignment of qualified subjects to a treatment group will be accomplished by using a randomization code generated by an independent biostatistician. Investigators and study staff who will conduct the assignment procedure will be masked to the randomization code.

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 electronic case report form (eCRF) 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/ treatments during the study are outlined in the Exclusion Criteria (Section 5.4).

8.2.2 Allowed Concomitant Medications/ Treatments/ Procedures

Subjects who are taking antibiotic eye drops or ointments or non-preserved artificial tears for at least two weeks at the time of screening may continue to use them throughout the study at the discretion of the Investigator. However, these medications should not be started after the subject begins the study.

If a subject is taking one of the above listed allowed concomitant eye drops or ointments during the study the subject should be instructed to dose with the study eye drops first and wait at least 5 minutes before dosing with the other medication.

The use of these medications will be collected and recorded in the concomitant medications page of the eCRF.

8.2.3 Escape Medications

At the discretion of the investigator, subjects may use topical steroid as an escape medication. Subjects receiving the escape medications will be exited, and will be counted as subjects who did not have complete healing of the epithelial defect in the primary efficacy analysis.

8.2.4 Escape Surgical Intervention

At the discretion of the investigator, subjects may undergo surgical intervention (ex. tarsorraphy, amniotic membrane graft) to address their persistent epithelial defect. Subjects receiving surgical intervention will be exited, and will be counted as subjects who did not have complete healing of the epithelial defect in the primary efficacy analysis.

8.2.5 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)

Visit 1 (Day 1): Screening/Enrollment/Baseline

The following procedures will be performed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Visit 2 (Day 8 ± 2): One-Week Follow-Up

The following procedures will be performed:

[redacted]

[redacted]

Visit 3 (Day 15 ± 2): Two-Week Follow-Up

The following procedures will be performed:

[redacted]

[redacted]

Visit 4 (Day 22 ± 2): Three-Week Follow-Up

The following procedures will be performed:

[redacted]

Visit 5 (Day 29 ± 2): Four-Week Follow-Up

The following procedures will be performed:

[redacted]

[redacted]

Visit 6 (Day 36 ± 3): One-Week Post-Treatment Follow-Up

The following procedures will be performed:

[redacted]

Visit 7 (Day 43 ± 3): Two-Week Post-Treatment Follow-Up

The following procedures will be performed:

[redacted]

[redacted]

Adverse Events (both elicited and observed) will be monitored throughout the study. All adverse events (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness. All adverse events will be documented on the appropriate Source Document and electronic case report form (eCRF).

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

[redacted]

8.4.2 Unscheduled Visits

[redacted]

[redacted]

8.4.3 Early Termination Visits

These visits will be performed for any subject that is discontinued from the study prior to completion (for reasons listed in Section 8.6.2). All procedures performed at an early termination visit will be recorded in the source documents and on the appropriate eCRF pages. Any procedure indicated in the eCRF that is not performed should be indicated as "Not done."

Evaluations that may be conducted at an Early Termination Visit include:

[redacted]

8.5 Compliance with Protocol

Subjects will be instructed on proper instillation and storage of study drug at the end of Visits 1, 2, 3, and 4 and given written instructions. Study

drug will be collected at each visit up to and including Visit 5 to assess dosing compliance. Dosing compliance will be based on the used vial count. If the subject uses [redacted] study drug during a dosing period, a subject will be deemed non-compliant and a dosing deviation will be recorded. These guidelines will be used by the Investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

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 no longer willing to comply with study protocol;
- adverse events;
- protocol violations;
- lack of efficacy;
- administrative reasons (e.g. inability to continue, lost to follow-up);
- Sponsor termination of study;
- any sound medical reason in the Investigator's opinion.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora, Inc. and/or ReGenTree and will be clearly documented on the eCRF.

8.7 Study Termination

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

8.8 Study Duration

An individual subject's participation will involve 7 visits over approximately a 6-week period.

8.9 Monitoring and Quality Assurance

During the course of the study an Ora, Inc. will make routine site visits to review protocol compliance, ensure subject safety, assess study drug accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, Ora, Inc. Quality Assurance, ReGenTree, 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 adverse event (AE) is defined as any untoward medical occurrence associated with the use of an investigational medicinal product (IMP) in humans, whether or not considered IMP-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 investigational product, without any judgment about causality. An AE can arise from any use of the investigational product (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.

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 sections of the eCRF. 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 investigational product, action(s)

taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient/subject. The assessment of severity is made irrespective of relationship to investigational product 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 investigational product should be determined by the investigator using these explanations:

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

9.1.3 Expectedness

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

- *Unexpected*: an AE that is not listed in the Investigator's Brochure (IB) or Report of Prior Investigations (ROPI) or is not listed at the specificity or severity that has been observed.
- *Expected*: an AE that is listed in the IB or ROPI at the specificity and severity that has been observed.
- *Not applicable:* an AE unrelated to the investigational product.

Adverse 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, ReGenTree's, and Ora's determination.

9.2 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;
  - Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;
  - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.
  - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - Note: A serious AE (SAE) specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (eg, 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 patient or 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, ReGenTree, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to Ora, ReGenTree, 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 investigational product, must be immediately reported. All information relevant to the SAE must be recorded on the appropriate case report forms. The Investigator is obligated to pursue and obtain information requested by Ora and/or ReGenTree in addition to that information reported on the case report form. All subjects experiencing an SAE must be followed up and the outcome reported.

In the event of an SAE, the Investigator must notify Ora and ReGenTree 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 and ReGenTree 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 investigational product; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting SAEs:

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 has been assigned to a patient. When possible (i.e., in non-emergent situations), Ora and/or ReGenTree should be notified before unmasking study drug.

Serious unexpected suspected adverse reactions, which are subject to expedited reporting, will be unmasked before submission to the Regulatory Authorities. The procedure for unmasking will be described in a separate Safety Plan for this 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 patient is lost to follow-up or until the AE is otherwise re-classified. Resolution means the patient has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-ups will be documented in the patient's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to Ora and ReGenTree within 24 hours of the site's awareness of the event. 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. STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

9.6 Study Populations

The following analysis populations are considered:

- [redacted]
- [redacted]
- [redacted]

9.7 Efficacy measures:

Primary Efficacy Measures:

- [redacted]

Secondary Efficacy Measure(s)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

9.8 Safety measures:

- Visual Acuity (ETDRS);
- Slit-Lamp Biomicroscopy;

- Cochet-Bonnet;
- Adverse Event Query;
- Dilated Fundoscopy;
- Intraocular Pressure.

9.9 Statistical Hypothesis and Sample Size

H_0: There is no difference between study eyes treated with RGN-259 and study eyes treated with placebo, RGN-259 – placebo, in the percentage of study eyes achieving complete healing of epithelial defect at Day 29 (Visit 5).

H_A: There is a difference between study eyes treated with RGN-259 and study eyes treated with placebo, RGN-259 – placebo, in the percentage of study eyes achieving complete healing of epithelial defect at Day 29 (Visit 5).

The study will be considered a success if H_0 is rejected in favor of H_A [redacted]

[redacted]

9.10 Statistical Analysis

9.10.1 General Considerations

[redacted]

[redacted]

9.10.2 Unit of Analysis

[redacted]

9.10.3 Missing Data

[redacted]

9.10.4 Primary Efficacy Analyses

[redacted]

9.10.5 Secondary Efficacy Analyses

[redacted]

9.10.6 Adverse Events

Adverse events will be coded using the MedDRA dictionary. 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. Furthermore, frequencies will be given of subjects with TEAEs by

- System organ class and preferred term,
- System organ class, preferred term and maximal severity,
- System organ class and preferred term for related TEAEs (at least possibly related or unknown relationship), and
- System organ class, preferred term and maximal severity for related TEAEs.

Separate summaries will be provided for ocular (study eye and any treated eye) and non-ocular TEAEs.

9.10.7 Laboratory Data

N/A

9.10.8 Interim Analyses

No interim analyses are planned for this study.

9.10.9 Quality Assurance of Data Processing

To ensure accurate, complete, and reliable data, ReGenTree or its representatives will provide instructional material to the study sites, as appropriate; instruct the investigators and study personnel on the protocol, the completion of the eCRFs, and study procedures; communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic visits to the study site. During those visits, ReGenTree or its representatives will monitor the subject data recorded in the eCRF against source documents at the study site. ReGenTree or its representatives will review and evaluate eCRF data and use standard computer edits to detect errors in data collection. When the database has been declared to be complete and accurate, the database will be locked and the treatment codes will be unmasked. Any changes to the database after that time can only be made by joint written agreement between ReGenTree, Ora, Inc. and the Study Biostatistician.

AEs and medical history will be coded using MedDRA version 17.0 or higher, and concomitant medications will be coded using WHO Drug, Enhanced B2, September 2015 version or higher.

10 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 Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of investigational products in the countries involved will be adhered to.

10.1 Protection of Human Subjects

10.1.1 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.

All informed consent/assent forms must be approved for use by ReGenTree and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (eg, 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.

10.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board 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/ERC approved version of the informed consent form will be used.

10.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki (Appendix 3).

10.3 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 in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of Ora, ReGenTree, 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 study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the 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 investigational product may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

10.4 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 ECGs. The Investigator's copy of the Case Report Forms serves as the Investigator's record of a subject's study-related data.

10.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all investigational products and copies of case report forms 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 investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with ReGenTree. It is the responsibility of the ReGenTree or it's representative to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody

must be transferred to a person who will accept the responsibility. ReGenTree must be notified in writing of the name and address of the new custodian.

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

10.5.1 Labeling/Packaging

This is a masked study and the subject numbers are assigned as described in Section 8.1.5. Pouches of five monodoses will be packed in clinical kits. Pouches and clinical kits will be labeled according to the applicable regulatory requirements. The labels will include instructions for use and storage.

10.5.2 Storage of Investigational Product

The investigational product must be stored in a secure area, accessible only to the Investigator and his/her designees, refrigerated at 2-8º C, and protected from freezing and strong light. The investigational product will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. Subjects will be provided with detailed instructions on drug storage and accountability.

10.5.3 Accountability of Investigational Product

The investigational product 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 investigational product must only be distributed to subjects properly qualified under this protocol to receive investigational product.

The Investigator must keep an accurate accounting of the investigational product received from the supplier. This includes the amount of investigational product dispensed to subjects, amount of investigational product 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 investigational product.

10.5.4 Return or Disposal of Investigational Product

All investigational products will be returned to ReGenTree or their designee or destroyed at the study site. The return or disposal of investigational product will be specified in writing.

10.6 Recording of Data on Source Documents and Electronic Case Reports Forms (eCRFs)

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject's eCRF, 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 (i.e., 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.

10.7 Handling of Biological Specimens

Not applicable

10.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. The study Sponsor will have the final decision regarding the manuscript and publication.

11 REFERENCES

Dunn SP, Heidemann DG, Chow CYC, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Treatment of Chronic Nonhealing Neurotrophic Corneal Epithelial defects with Thymosin β4. *Ann. N.Y. Acad. Sci.* 2010a, 1194:199-206.

Dunn SP, Heidemann DG, Chow CYC, Crockford D, Turjman N, Angel J, Allan CB, Sosne G. Treatment of Chronic Nonhealing Neurotrophic Corneal Epithelial defects with Thymosin β4. Archives of Ophthalmology 2010b, 128:636-638.

Huff T, Müller CS, Otto AM, Netzker R, Hannappel E. Beta-Thymosins, small acidic peptides with multiple functions. Int Journal Biochem Cell Biol, 2001; 33(3):205-20.

Huff T, Otto AM, Müller CS, Meier M, Hannappel E. Thymosin beta4 is released from human blood platelets and attached by factor XIIIa (transglutaminase) to fibrin and collagen. FASEB J, 2002; 16:691-6.Mackie IA: Neuroparalytic keratitis; in Roy FH, Meyer SM, Fraunfelder F (eds): Current Ocular Therapy. Philadelphia, WB Saunders, 1995, pp 452-454.

Malinda KM, Sidhu GS, Mani H, Banaudha K, Maheshwari RK, Goldstein AL, Kleinman HK.
Thymosin beta4 accelerates wound healing. J Invest Dermatol, 1999; 113:364-8.

Sosne G, Lihua Xu, Prach Lisa, et al. Thymosin beta 4 stimulates laminin-5 production independent of TGF-beta. Experimental Cell Research, 2004; 293:175-183.

Sosne G, Qiu P, Christopherson PL, Kurpakus Wheater M. Thymosin beta 4 suppression of corneal NFkB: A potential anti-inflammatory pathway. Exp Eye Res, 2007, 84:663-669.

Appendix 1: Schedule of Visits and Measurements

Appendix 2: Examination Procedures, Tests, Equipment and Techniques

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 3: World Medical Association Declaration of Helsinki (2000)

Ethical principles for medical research involving human subjects.

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975.

35th WMA General Assembly, Venice, Italy, October 1983.

41st WMA General Assembly, Hong Kong, September, 1989.

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, ‘The health of my patient will be my first consideration’, and the International Code of Medical Ethics declares that ‘A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient’.
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are

vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research, and for those for whom the research is combined with care.

9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this document.

B. Basic principles for all medical research

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the

participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the nonwritten consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

To clarify further the WMA position on the use of placebo-controlled trials, the WMA Council issued, during October 2001, a note of clarification on article 29.

1. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
2. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient–physician relationship.
3. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

D. Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

1. Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

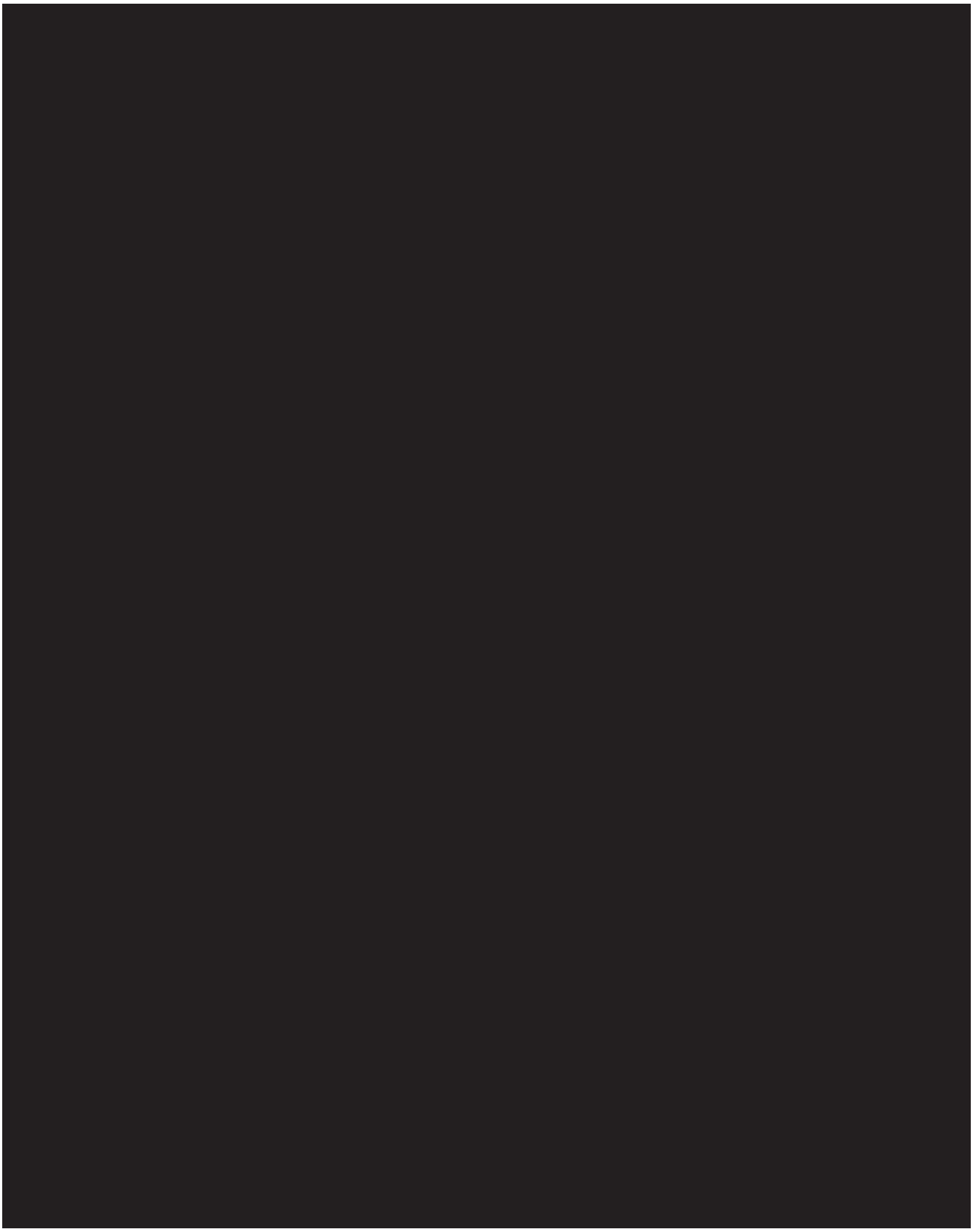
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[1]Note of clarification on paragraph 29 of the WMA Declaration of Helsinki. The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

1. Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Appendix 4: Amendment Summary of Changes



Appendix 5: Sponsor and Ora Approvals

Protocol Title: **A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy**

Protocol Number: RGN-NK-301/15-110-0006

Ora Protocol Signatory Page

Protocol Title: **A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy**

Protocol Number: RGN-NK-301/15-110-0006

Appendix 6: Investigator's Signature

Protocol Title:	**A Phase 3, Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of 0.1% RGN-259 Ophthalmic Solution for the Treatment of Neurotrophic Keratopathy**
Protocol Number:	RGN-NK-301/15-110-0006
Amendment 4 Date:	**04 May 2017**

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 ReGenTree, LLC. 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:_____