AXEROVISION, INC.

Clinical Protocol AXR201901

CLINICAL PROTOCOL INCORPORATING AMENDMENT 02

NCT Number 04469998

Protocol Number:	AXR201901
Protocol Title:	A Phase I/II, Randomized, Double-Masked, Vehicle-Controlled Study of the Safety, Tolerability, and Efficacy of AXR-270 Topical Eyelid Cream in Treating Posterior Blepharitis Associated with Meibomian Gland Dysfunction.
Sponsor:	AxeroVision, Inc.
Medical Monitor:	Kenneth Sall, MD Lexitas Pharma Services, Inc. 313 Foster St. Durham, NC 27701
Issue Date:	Original: 16January2020 1st Amendment: 28April2020 2nd Amendment: 03Jun2020

Approved:

Houman David Hemmati (Jun 3, 2020 15:06 PDT)

Houman Hemmati, MD, PhD
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06032020
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Achim Krauss
Achim Krauss (Jun 3, 2020 15:23 PDT)

Achim Krauss, PhD
Chief Executive Officer

3 June 2020
Date

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Incorporating Amendment 02

Investigator Signature Page

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Contact for Serious Adverse Events:	Kenneth Sall, MD Lexitas Pharma Services, Inc. 313 Foster St. Durham, NC 27701 562-754-2947

Investigator Name (printed or typed):

_____

Investigator's Signature:

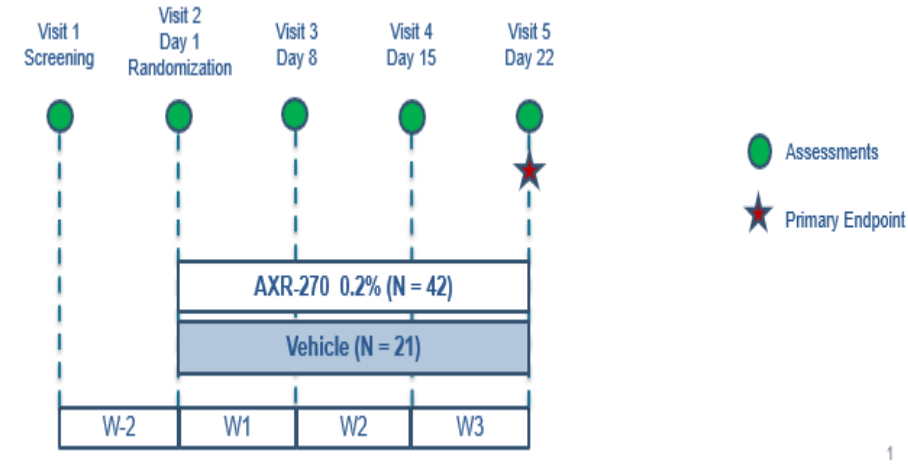
_____ _____

Date

SYNOPSIS

Study Title:	A Phase I/II, Randomized, Double-Masked, Vehicle-Controlled Study of the Safety, Tolerability, and Efficacy of AXR-270 Topical Eyelid Cream in Treating Posterior Blepharitis Associated with Meibomian Gland Dysfunction.
Study Objectives:	The primary objective of this study is to evaluate the safety and tolerability of two concentrations of AXR-270 Cream (0.2% AXR-270 Cream; 2.0% AXR-270 Cream) in treating posterior blepharitis associated with Meibomian Gland Disease (MGD). The secondary objective is to evaluate the efficacy of AXR-270 Cream in treating signs and symptoms of posterior blepharitis associated with MGD.
Study Population:	Subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD will be included in this trial.
Number of Subjects:	Approximately one hundred and twenty-six (126) subjects across 10-16 sites.
Investigational Products:	• 0.2% AXR-270 Topical eyelid Cream • 2.0% AXR-270 Topical eyelid Cream • AXR-270 Vehicle
Route and Duration of Administration:	AXR-270 Cream will be administered as a topical ophthalmic cream. Subjects will receive Investigational Product (IP) administered in the clinic at Day 1/Visit 2 and will self-administer either AXR-270 Cream or Vehicle once a day (QD) applied to upper and lower eyelid skin bilaterally for approximately 21 days.
Study Design:	This is a multi-center, double-masked, randomized, vehicle-controlled, two cohort study. Subjects will be randomized into either 0.2% AXR-270 Cream, 2.0% AXR-270 Cream or Vehicle administered in both eyes. **Cohort 1**: Approximately sixty-three (63) subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD meeting all inclusion/exclusion criteria at the Screening visit (Visit 1) will be asked to discontinue their eyelid hygiene regimen and use only Sponsor supplied commercial sterile eyelid wipes between Visit 1 and Visit 2 daily (Equalization Period). Subjects will then be evaluated at Baseline/Randomization (Visit 2; Week 0/Day 1) to confirm they continue to meet all inclusion/exclusion and are eligible for randomization. Note: The daily use of sponsor-supplied sterile eyelid wipes is to be discontinued after randomization at Visit 2. All subjects within this Cohort will be assessed for safety and exploratory efficacy. Both Investigator and subjects will be masked as to the IP. Subjects will be shown an instructional video on applying the investigational product to help ensure consistency in application across subjects. Further, the site should reinforce to the subject how to self-administer the IP to the eyelids and avoid ocular

	instillation. Subjects will self-administer a pre-specified volume (approximately 50 milligrams per eyelid) of 0.2% AXR-270 Cream or its Vehicle across the epidermis corresponding to the external surface overlying the tarsal plate of the upper and lower eyelids of both eyes. Refer to more detailed instructions in the Subject Dosing Instructions document. Blood draws for safety labs for all subjects will be performed prior to IP dosing in the clinic at Visit 2/Day 1. Following the in-clinic dose administration, subjects will be supplied with sufficient IP (2 tubes) to apply once daily at home in the evening during the treatment period. Subjects will self-administer IP QD in the evenings beginning on Day 2. On the following week (Visit 3; Week 1/Day 8), the Investigators will examine the subject and perform all safety and efficacy assessments (excluding safety labs and dilated Ophthalmoscopy). Subjects will return for a Week 2 (Visit 4; Day 15) visit, wherein the Investigators will examine the subject and perform all safety and efficacy assessments (excluding safety labs and dilated Ophthalmoscopy). Subjects will return the used IP and will be instructed to use the 2nd IP tube dispensed at Visit 2 to apply once daily at home in the evening for the remaining 1 week of treatment duration. Following the completion of the fifteenth (15th) subject from Visit 4 of Cohort 1, the Data Safety Review Committee (DSRC) will meet to review safety data and will make a recommendation about whether to allow escalation to the higher (2.0%) dose of AXR-270 Cream for Cohort 2, which if recommended, will begin immediately upon the completion of enrollment in Cohort 1 (See Appendix 2). Subjects will return for a Week 3 (Visit 5; Day 22) visit, wherein the Investigators will examine the subject and perform all safety and efficacy assessments (including safety labs). Subjects should not dose at Visit 5/Day 22 and following the visit, subjects will exit the study. Remaining IP will be collected from every subject. (See Appendix 1 for procedures planned for this study). **<u>Cohort 2</u>**: Following the completion of the fifteenth subject from Visit 4 of Cohort 1, the DSRC will meet to review safety data and will make a recommendation about whether to escalate to the higher (2.0%) dose of AXR-270 Cream for Cohort 2, which if recommended, will begin upon completion of enrollment in Cohort 1. The Screening and study visits will be conducted in the same fashion as described above for Cohort 1. Approximately sixty-three (63) subjects will be randomized to 2.0% AXR-270 Cream or its Vehicle.

	Study Schematic (Cohort 1):  Note: Cohort 2 (AXR-270 Cream 2.0% or vehicle) follows the same visit schedule as above and will start enrolling once enrollment of Cohort 1 is complete.
Safety Endpoints:	• Adverse event (AE) • Best corrected visual acuity (BCVA) • Slit-lamp biomicroscopy and external eye exam • Intraocular pressure (IOP) • Dilated ophthalmoscopy • Safety labs (Hematology, clinical chemistry, and urinalysis)
Efficacy Endpoints:	All efficacy endpoints are exploratory in nature. The following endpoints will be considered to assess the efficacy of AXR-270 Cream. 1. Change from baseline (Visit 2/Day 1) in the following individual subject-reported symptoms using Visual Analog Scale (VAS, 0-100 point scale) score in the AXR-270 Cream (0.2% or 2.0%) arms compared to Vehicle at Day 22: o Eye Discomfort o Eye Dryness 2. Change from baseline in Investigator-rated signs of MGD using individual severity scores in AXR-270 Cream arm compared to Vehicle at Day 22: o Total MGD Score: the sum of secretion in 5 central glands on each individual eyelid will be evaluated, each will be scored from 0-3; 0 = clear/slightly yellow, 1 = opaque/yellow, whitish, particulate, 2 = paste, 3 = none/occluded; total score will range from 0-15

	○ Vascularity of the eyelid margin (Grade 0-4; 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe vascular engorgement) 3. Change from baseline in Tear Break-up Time (TBUT) in AXR-270 Cream arm compared to Vehicle at Day 22. (Tear Break-up Time is the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film). 4. Change from baseline in Lissamine Green Staining (LGS) grade of the eyelid margin in AXR-270 Cream arm compared to Vehicle at Day 22. 5. Change from baseline in Total Fluorescein Corneal Staining (tFCS) score using the National Eye Institute (NEI) Industry Workshop (0-15 scale) in the AXR-270 Cream arm compared to Vehicle at Day 22. 6. Change from baseline in FCS by individual region in AXR-270 arm compared to Vehicle at Day 22 (0-3 scale). 7. Change from baseline in bulbar conjunctival hyperemia in AXR-270 Cream arm compared to Vehicle at Day 22. 8. Change from baseline in Ocular Surface Disease Index (OSDI) score (0-100) in AXR-270 Cream arm compared to Vehicle at Day 22. 9. Change from baseline in the modified BLepharItIS Symptom (BLISS) score in AXR-270 Cream arm compared to Vehicle at Day 22. 10. Change from baseline in the Schirmer in AXR-270 Cream arm compared to Vehicle at Day 22.
Inclusion Criteria:	At Visit 1 (and Visit 2 where applicable), individuals of any gender or any race will be eligible for study participation if they: 1. Have provided written informed consent prior to any study procedures. 2. Are 18 years of age or above. 3. Have a clinical diagnosis of moderate to severe MGD and who meet both of the following criteria, in at least one qualifying eyelid (upper and lower eyelid for each eye will be evaluated independently), at both Visit 1 (Screening) and again in the same eye/eyelid at Visit 2 (Randomization) examinations: a) Total MGD score ≥5 and ≤14 (the sum of secretion 5 central glands on the upper and lower eyelids will be evaluated, each will be scored from 0-3; 0 = clear/slightly yellow, 1 = opaque/yellow, whitish, particulate, 2 = paste, 3 = none/occluded; total score will range from 0-15). b) Clinical sign severity score of at least 2 (moderate) on vascularity of the eyelid margin 4. Have a score of ≥35 using on Eye Discomfort VAS (0-100 point scale) at both Visit 1 and Visit 2.

	5. Meet the following criteria, in both or the same qualifying eye as in Inclusion #3, at both Visit 1 (Screening) and Visit 2 (Randomization) examinations: a) tFCS score ≥3 and ≤14 in the NEI/Industry Workshop scale (0-15 scale) b) Schirmer score of >7 mm without topical anesthesia 6. OSDI score >30 at both Visit 1 and Visit 2. 7. Required use of non-prescription over the counter (OTC) artificial tear substitute for symptoms of dry eye more than 3 times per day for 3 consecutive days within 30 days prior to the Screening Visit (Visit 1) and willingness to suspend use of tear substitutes at Visit 1 and for the duration of study participation. 8. Are willing and able to follow instructions and willing to be present for the required study visits for the duration of the study. 9. Have a Logarithm of the Minimum Angle of Resolution (LogMAR) BCVA equal to or better than +0.7 using corrective lenses if necessary, in both eyes at both Visit 1 and Visit 2, by Early Treatment of Diabetic Retinopathy Study (ETDRS) or modified ETDRS. 10. If female, are non-pregnant, non-lactating and women of childbearing potential (WOCBP) must be using an acceptable method of birth control [e.g., an Intrauterine Contraceptive Device (IUCD) with a failure rate of <1%, hormonal contraceptives, or a barrier method] for the duration of the study. If a female subject is currently abstinent, they must agree to use one of the acceptable methods of birth control before they become sexually active. • Non-childbearing potential is defined as a woman who is postmenopausal for 12 consecutive months or a woman who is post hysterectomy, bilateral oophorectomy or 3 months status post bilateral tubal ligation.
Exclusion Criteria:	In order for subjects to be eligible at Visit 1 they may not: 1. Have presence or history of iritis/uveitis in either eye. 2. Have lid structural abnormalities including but not limited to entropion or ectropion that in the opinion of the Investigator may confound the study data. 3. In the study eyelid, have greater than 4 glands that are not expressible from the 5 upper and/or 5 lower eyelid meibomian glands at both Visit 1 and Visit 2. 4. Subjects with ocular inflammatory conditions (e.g., conjunctivitis, keratitis, severe anterior blepharitis, etc.) not related to MGD. 5. Subjects who in the study eye have tFCS score = 15 or a FCS score = 3 in either eye in the superior region NEI/Industry Workshop scale or

	subjects who have FCS with diffuse confluent staining, filaments or frank epithelial defects at either Visit 1 or Visit 2. 6. Have suspected ocular fungal, viral or bacterial infection. 7. Subjects who within the past 6 months have had cauterization of the punctum. Non-dissolvable plugs must not be inserted within 2 weeks of Screening (Visit 1) and current non-dissolvable plugs in position must be stable in the Investigator's opinion. 8. Use of any of the prohibited medications (see Table 2: List of Prohibited Medications and/or procedures) within a time period prior to or upon Screening (Visit 1). NOTE: These medications may not be used after Visit 1 through the end of the study. 9. Use short-term dissolvable plugs for 3 months prior to Screening (Visit 1) and long-term dissolvable plugs within 6 months prior to Screening (Visit 1). 10. Any prior use of isotretinoin. 11. Are unwilling to discontinue use of cosmetic makeup applied to the eyelids or eyelashes on the day of a study visit after Visit 1. 12. Have a known hypersensitivity to active ingredient or to any of the other ingredients in the IP. 13. Are unable or unwilling to withhold the use of eyelid scrubs or use of mechanical eyelid cleaning therapy during the study, other than the Sponsor supplied commercial sterile eyelid wipes from Visit 1 through Visit 2. After Visit 2, subjects are also permitted to follow their usual routine to remove eyelid or eyelash makeup (including eyelid wipes if applicable), ensuring that no new products/techniques are introduced during the study. 14. Have been diagnosed with glaucoma, are currently using any glaucoma medication or known to have elevated IOP related to steroid use. 15. Have a history of herpetic keratitis. 16. Have a concomitant ocular pathology other than condition under study assessed as potentially confounding by the Investigator. 17. Have a serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance. 18. Have been exposed to any investigational drug or investigational device within the preceding 30 days.

	19. Are an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same. 20. Have trigger factors that in the opinion of the Investigator may confound the data, including but not limited to conjunctivochalasis, allergic conjunctivitis, contact lens intolerance, trichiasis, epithelial basement membrane dystrophy, infectious keratitis or conjunctivitis. 21. Have a documented history of ocular allergies, which, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR	Adverse Reaction
API	Active Pharmaceutical Ingredient
BCVA	Best Corrected Visual Acuity
BLISS	BLepharITIS Symptom
CDC	Centers for Disease Control
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CS	Clinically Significant
CCLRU	Cornea and Contact Lens Research Unit
DED	Dry Eye Disease
DEWS	Dry Eye Workshop
DSRC	Data Safety Review Committee
eCRF	Electronic Case Report Form
EDE	Evaporative Dry Eye
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FCS	Fluorescein Corneal Staining
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ID	Identification
IMPD	Investigational Medicinal Product Dossier
IOP	Intraocular Pressure

IP	Investigational Product
IRB	Institutional Review Board
IUCD	Intrauterine Contraceptive Device
IWRS	Interactive Web Response System
LASIK	Laser-Assisted In Situ Keratomileusis
LGS	Lissamine Green Staining
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
mm	Millimeter
NCS	Non-Clinically Significant
NEI	National Eye Institute
NSAID	Non-steroidal anti-inflammatory drug
OSDI	Ocular Surface Disease Index
OTC	Over the Counter
OU	Oculus Uterque (both eyes)
PDF	Portable Document Format
PPS	Per Protocol Set
PK	Pharmacokinetics
QD	Once Daily
SAE	Serious Adverse Event
SAF	Safety Set
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
TBUT	Tear Break-Up Time
tFCS	Total Fluorescein Corneal Staining
UPT	Urine Pregnancy Test
VA	Visual Acuity
VAS	Visual Analog Scale
WOCBP	Women of Child Bearing Potential

1. INTRODUCTION

Posterior blepharitis is a condition characterized by inflammation of the posterior lid margin. The condition may be inclusive of MGD in which there is an alteration in the quality and expression of gland secretions (Nelson, 2011). Meibomian gland dysfunction is associated with posterior blepharitis, plays an essential role in the health and stability of the tear film and in maintaining optimal ocular surface condition. It is recognized as one of the most common pathologies seen by Ophthalmologist and is a significant contributor to Evaporative Dry Eye (EDE) is further considered the leading cause of Dry Eye Disease (DED) (Nelson, 2011; DEWS II Report 2017). Meibomian gland dysfunction is commonly treated on a chronic basis (DEWS II Report 2017) via either mechanical therapy (lid hygiene, lid massage and lid compression/expression) alone or in combination with topical or systemic antibiotics or topical cyclosporine.

Dry Eye Disease is a widespread dysfunction of the tears and ocular surface and is characterized by ocular signs such as inflammation of the ocular surface (Pflugfelder, 1999) and tear film instability (Holly, 1973; Bron, 2001; Goto, 2003) resulting in corneal and conjunctival epithelial changes. Dry Eye Disease is a dysfunction with etiologies inclusive of aqueous deficient and evaporative DED (DEWS II Report 2017). These changes are understood to be the underlying basis for EDE in human subjects (Foulks, 2003; DEWS II Report 2017).

A number of studies and reports support the short-term use of topical corticosteroids known to be potent anti-inflammatory agents in the treatment of patients with DED (Avunduk et al, 2003; DEWS II Report 2017; Pflugfelder et al, 1999; Yang et al, 2006). While topical ophthalmic corticosteroids are approved by the Food and Drug Administration (FDA) for corticosteroid-responsive inflammatory conditions of the conjunctiva, cornea, and anterior globe, they are generally only recommended for short-term use, as prolonged use may result in adverse ocular events, including elevated Intraocular Pressure (IOP), cataracts, and ocular infection (Becker, 1964; Bowling and Russell, 2011; Dinning, 1976). Short-term corticosteroid therapy can serve as both an important adjunct to existing chronic therapies (e.g., artificial tears) and can also be used to address environmental and iatrogenic induced breakthrough periods of increased ocular surface inflammation (Becker, 1964; Behrens et al, 2006).

Pflugfelder and colleagues (Pflugfelder, 2004) demonstrated that a topical corticosteroid may achieve the objective of a short-term treatment of acute exacerbations of DED signs or symptoms. They evaluated loteprednol etabonate ophthalmic suspension (0.5%) dosed 4 times daily versus placebo for the treatment of DED in patients with delayed tear clearance. In patients with at least moderate clinical inflammation, significant differences in clinical signs (nasal and tarsal hyperemia) between groups were observed as early as Week 2 and persisted

through Week 4 of the study. In addition, the improvement in the redness Visual Analog Scale (VAS) score was consistently 20% better in the loteprednol-treated patients compared with the Vehicle-treated patients.

AxeroVision, Inc. intends to develop AXR-270 Cream, for the treatment of MGD secondary to posterior blepharitis. Study AXR201901 will evaluate the safety and tolerability of AXR-270 Cream in subjects with lid margin inflammation (as characterized by eyelid margin hyperemia) due to Meibomian Gland Dysfunction. Additional information about AXR-270 Cream, including nonclinical pharmacology study results, and potential risks and benefits to human subjects, is found in the Investigator's Brochure.

AXR-270 was initially in clinical development for asthma, chronic obstructive pulmonary disease (COPD) and atopic dermatitis. Early testing was conducted in the European Union (EU), under an Investigational Medicinal Product Dossier (IMPD), and consisted of evaluation in 24 healthy male volunteers administered via topical administration with the goal of identifying any blanching response in the skin at doses up to 4000ng using a method described by McKenzie and Stoughton (McKenzie and Stoughton, 1962). It was later delivered via inhalation to 36 healthy male subjects in a dose escalation safety study with both single and repeat doses. Additionally, a repeat dose study in 24 male steroid naive asthmatics and 36 mild to moderate subjects with mild asthma for one (1) month. AXR-270 was then evaluated in 12 healthy adult male subjects for 14 days of oral inhalation and as a dermal cream for 42 days in 20 healthy volunteers and for 21 days in 25 patients with moderate or severe atopic dermatitis.

Based on the physicochemical characteristics of AxeroVision's topical cream formulation, reported anti-inflammatory properties of AXR-270 Cream and rationale described above, development of AXR-270 Cream is proposed for ophthalmic conditions, such as MGD, in which ocular inflammation is thought to be the source of pathology.

1.1. DESCRIPTION OF INVESTIGATIONAL PRODUCT

AXR-270 Cream (0.2% and 2.0%) contain AXR-270 as an active pharmaceutical ingredient (API).

The AXR-270 Vehicle control has the same composition as AXR-270 Cream except that it does not contain AXR-270.

1.2. JUSTIFICATION FOR ROUTE OF ADMINISTRATION AND DOSE SELECTION

AXR-270 will be administered as a topical ophthalmic cream. Subjects will receive IP administered in the clinic at Day 1/Visit 2 and will then self-administer either AXR-270 Cream or Vehicle once a day (QD) applied to upper and lower eyelid skin bilaterally for approximately 21 days. The concentrations of AXR-270 Cream and dosing schedule were chosen based on nonclinical pharmacokinetic and toxicology studies and data reflecting relative safety multiples. For details on the pharmacokinetic and toxicology studies and the respective safety multiples, see the Investigator's Brochure.

The purpose of using lid wipes during the Equalization Period (between Visit 1 and Visit 2) is to normalize baseline conditions between subjects as much as possible.

For subjects wearing eyelid or eyelash makeup, remove makeup before IP application. (Use of eyelid or eyelash makeup may be resumed between clinic visits with the exception of the day of study visits). Subjects should be instructed to follow their usual routine to remove eyelid or eyelash makeup between Visits 2 and 5 (including eyelid wipes, if applicable), ensuring that no new products/techniques are introduced during the treatment period. Each dose of IP should be applied onto the upper and lower eyelids (refer to detailed instructions in the Subject Dosing Instructions document). Subjects will also view an instructional video at Visit 2 demonstrating the proper dosing technique.

Subjects should not wipe away excess cream unless there is a concern of the cream running onto the ocular surface. For subjects who wish to apply eyelid makeup, they should wait until the next morning before cleaning the eyelids and applying makeup.

1.3. GCP COMPLIANCE

This clinical trial will be conducted in compliance with the protocol, International Council on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements.

1.4. POPULATION TO BE STUDIED

Approximately one hundred and twenty-six (126) subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD will be enrolled in the trial.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. OBJECTIVE

The primary objective of this study is to evaluate the safety and tolerability of two concentrations (0.2% and 2.0%) of AXR-270 Cream in treating posterior blepharitis associated with MGD.

The secondary objective is to evaluate the efficacy of AXR-270 Cream in treating signs and symptoms of posterior blepharitis associated with MGD.

3. TRIAL DESIGN

3.1. STUDY ENDPOINTS

3.1.1. Safety Endpoints

- Adverse events (AE)
- Best corrected visual acuity (BCVA)
- Slit-lamp biomicroscopy and external eye exam
- Intraocular pressure (IOP)
- Dilated ophthalmoscopy
- Safety Labs (Hematology, clinical chemistry, and urinalysis)

3.1.2. Efficacy Endpoints

All efficacy endpoints are exploratory in nature. The following endpoints will be considered to assess the efficacy of AXR-270 Cream.

1. Change from baseline in the following individual subject-reported symptoms using VAS (0-100 point scale) in the AXR-270 Cream (0.2% or 2.0%) arms compared to Vehicle at Day 22:
    - Eye Discomfort
    - Eye Dryness
2. Change from baseline in Investigator-rated signs of MGD using individual severity scores in AXR-270 Cream arm compared to Vehicle at Day 22:
    - Total MGD Score: the sum of secretion in 5 central glands on each individual eyelid will be evaluated, each will be scored from 0-3; 0 = clear/slightly yellow, 1 = opaque/yellow, whitish, particulate, 2 = paste; 3 = none/occluded; total score will range from 0-15
    - Vascularity of the eyelid margin (Grade 0-4)
3. Change from baseline in TBUT in AXR-270 Cream arm compared to Vehicle at Day 22. (Tear Break-up Time is the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film).
4. Change from baseline in LGS grade of the eyelid margin in AXR-270 Cream arm compared to Vehicle at Day 22.
5. Change from baseline in tFCS score (NEI/Industry Workshop; 0-15 scale) in the AXR-270 Cream arm compared to Vehicle at Day 22.
6. Change from baseline in FCS by individual region in AXR-270 Cream arm compared to Vehicle at Day 22 (0-3 scale).

7. Change from baseline in bulbar conjunctival hyperemia in AXR-270 Cream arm compared to Vehicle at Day 22.
8. Change from baseline in OSDI score (0-100) in AXR-270 Cream arm compared to Vehicle at Day 22.
9. Change from baseline in the modified BLepharItIS Symptom (BLISS) score in AXR-270 Cream arm compared to Vehicle at Day 22.
10. Change from baseline in the Schirmer in AXR-270 Cream arm compared to Vehicle at Day 22.

3.2. DESCRIPTION OF TRIAL DESIGN

Design and Investigational Plan:

This is a multi-center, double-masked, randomized, vehicle-controlled, two cohort study. Subjects will be randomized into either 0.2% AXR-270 Cream (approximately 42 subjects in Cohort 1), 2.0% AXR-270 Cream (approximately 42 subjects in Cohort 2) or Vehicle (approximately 42 subjects) administered in both eyes.

Cohort 1:
Approximately sixty-three (63) subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD meeting all inclusion/exclusion criteria at the Screening visit (Visit 1) will be asked to discontinue their eyelid hygiene regimen and use only Sponsor supplied commercial sterile eyelid wipes between Visit 1 and Visit 2 daily (Equalization Period). Subjects will then be evaluated at Baseline/Randomization (Visit 2; Week 0/Day 1) to confirm they continue to meet all inclusion/exclusion and are eligible for randomization. Note: The use of sponsor-supplied sterile eyelid wipes is to be discontinued after randomization at Visit 2. All subjects within this Cohort will be assessed for safety and exploratory efficacy. Both Investigator and subjects will be masked as to the IP. Subjects will be shown an instructional video on applying the investigational product to help ensure consistency in application across subjects. Further, the site should reinforce to the subject how to self-administer the IP to the eyelids and avoid ocular instillation. Subjects will self-administer a pre-specified volume (approximately 50 milligrams per eyelid) of 0.2% AXR-270 Cream or its Vehicle across the epidermis corresponding to the external surface overlying the tarsal plate of the upper and lower eyelids of both eyes. Refer to more detailed instructions in the Subject Dosing Instructions document. Blood draws for safety labs for all subjects will be performed prior to IP dosing in the clinic at Visit 2/Day 1. Following the in-clinic dose administration, subjects will be supplied with sufficient IP (2 tubes) to apply once daily at home in the evening during the treatment period. Subjects will self-administer IP QD in the evenings beginning on Day 2.

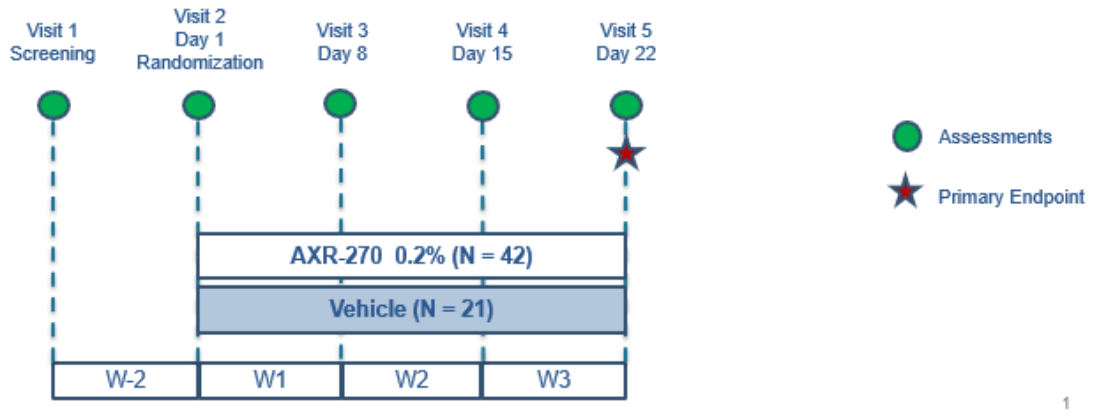
On the following week (Visit 3; Week 1/Day 8), the Investigators will examine the subject and perform all safety and efficacy assessments (excluding safety labs and dilated Ophthalmoscopy).

Subjects will return for a Week 2 (Visit 4; Day 15) visit, wherein the Investigators will examine the subject and perform all safety and efficacy assessments (excluding safety labs and dilated Ophthalmoscopy). Subjects will return the used IP and will be instructed to use the 2nd IP tube dispensed at Visit 2 to apply once daily at home in the evening for the remaining 1 week of treatment duration.

Following the completion of the fifteenth (15th) subject from Visit 4 of Cohort 1, the Data Safety Review Committee (DSRC) will meet to review safety data and will make a recommendation about whether to escalate to the higher (2.0%) dose of AXR-270 Cream for Cohort 2, which if recommended, will begin immediately upon completion of enrollment in Cohort 1.

Subjects will return for a Week 3 (Visit 5; Day 22) visit, wherein the Investigators will examine the subject and perform all safety and efficacy assessments (including safety labs). Subjects should not dose at Visit 5/Day 22 and following the visit, subjects and will exit the study. Remaining IP will be collected from every subject. (See Appendix 1 for procedures planned for this study).

FIGURE 1: STUDY SCHEMATIC (COHORT 1)



Note: Cohort 2 (AXR-270 2.0% Cream or vehicle) follows the same visit schedule as above and will start enrolling once enrollment of Cohort 1 is complete.

Cohort 2:
Following the completion of the fifteenth subject from Visit 4 of Cohort 1, the DSRC will meet to review safety data and will make a recommendation about whether to escalate to the

higher (2.0%) dose of AXR-270 Cream for Cohort 2, which if recommended, will begin immediately upon completion of enrollment in Cohort 1.

The Screening and study visits will be conducted in the same fashion as described above for Cohort 1. Approximately sixty-three (63) subjects will be randomized to 2.0% AXR-270 Cream or its Vehicle. A study schematic follows (Figure 1).

3.2.1. Investigational Product

The AXR-270 Cream IP is a sterile, water in oil, cream formulation in which micronized AXR-270 Active Pharmaceutical Ingredient (API) is suspended uniformly for topical application to the upper and lower eyelids at either 0.2% or 2.0% concentrations.

The IP is packaged in laminated polyfoil tubes. Each tube will contain 5g of sterile AXR-270 topical cream. Subjects randomized to the Vehicle control arm will receive the same containers containing all components at the concentrations used in the AXR-270 Cream except for the active component.

The product composition is presented in Table 1.

Table 1: Composition of AXR-270 Investigational Product (0.2% and 2.0% Concentrations, Vehicle)

Material	Grade	Function	Vehicle Formula (% w/w)	0.2% AXR-270 Cream Formula (% w/w)	2.0% AXR-270 Cream Formula (% w/w)
White Petrolatum	USP	Vehicle	47.89	47.69	45.89
Emulsifier 10	N/A	Emulsifier	3.30	3.30	3.30
ST- Elastomer 10	N/A	Emulsifier	2.00	2.00	2.00
Mineral Oil	USP	Vehicle	8.00	8.00	8.00
ST-Cyclomethicone 5-NF	NF	Emollient	6.60	6.60	6.60
Propylene Glycol	USP	Solvent	8.00	8.00	8.00
Methylparaben	NF	Preservative	0.08	0.08	0.08
Propylparaben	NF	Preservative	0.02	0.02	0.02

Sterile Water for Irrigation	USP	Vehicle	24.00	24.00	24.00
Anhydrous Citric Acid	USP	Buffer	0.05	0.05	0.05
Dibasic Sodium Phosphate	USP	Buffer	0.06	0.06	0.06

Each randomized, double-masked IP kit contains 3 tubes of IP, each tube sufficient for 2 weeks of dosing.

IP Dispensation Instructions

At Visit 2, randomized subjects will be assigned to an IP Kit which contains three tubes of Double-Masked IP (AXR-270 Cream or Vehicle). The first dose of Double-Masked IP (AXR-270 Cream or Vehicle) will be self-administered by the subject at Visit 2 under supervision of the site staff.

AXR-270 Cream should be stored at 2° to 8°C (36° to 46°F); excursions permitted between 0° and 15°C (32° and 59°F). Transient spikes up to 25°C (77°F) and not to exceed 24 hours are permitted. IP should be protected from light and moisture. The refrigerator will be temperature monitored. IP will be supplied to subjects in coolers with gel packs to maintain refrigerated temperature while in transit.

Timing of Self-Administration

At Visit 2, sufficient training will be provided to the subjects to self-administer their once-daily dose of double-masked IP. Subjects will then self-administer additional doses of IP at home for the remainder of the study. Two tubes of randomized double-masked IP will be dispensed to each subject at Visit 2 for self-administration. The first tube will be used from the time of Visit 2 to the time of Visit 4. The second IP tube will be used from Visit 4 to Visit 5 (note: if a subject is unable to come in to the clinic for Visit 4, they should begin dosing with the second tube on Day 15). One tube from the kit will be kept in reserve at the clinic. Refer to more detailed instructions in the Subject Dosing Instructions document.

3.2.2. Methods to Minimize Bias

To minimize bias, the following measures will be taken:

- IP allocation (AXR-270 Cream versus Vehicle) will be randomized and masked to the Sponsor, subjects, and investigative staff.
- The randomization schedule will be generated by an independent unmasked statistician (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study Investigator and members of the project team.

4. SELECTION OF SUBJECTS

4.1. SUBJECT INCLUSION CRITERIA

At Visit 1 (and Visit 2 where applicable), individuals of any gender or any race will be eligible for study participation if they:

1. Have provided written informed consent prior to any study procedures.
2. Are 18 years of age or above.
3. Have a clinical diagnosis of moderate to severe MGD and who meet both of the following criteria, in at least one qualifying eyelid (upper and lower eyelid for each eye that will be evaluated independently), at both Visit 1 (Screening) and again in the same eye/eyelid Visit 2 (Randomization) examinations:
    a) Total MGD score ≥5 and ≤14 (the sum of secretion 5 central glands on the upper and lower eyelids will be evaluated, each will be scored from 0-3; 0 = clear/slightly yellow, 1 = opaque/yellow, whitish, particulate, 2 = paste, 3 = none/occluded; total score will range from 0-15) and
    b) Clinical sign severity score of at least 2 (moderate) on vascularity of the eyelid margin
4. Have a score of ≥35 in Eye Discomfort VAS (0-100 point scale) at both Visit 1 and Visit 2.
5. Meet the following criteria, in both or the same qualifying eye as in Inclusion #3, at both Visit 1 (Screening) and Visit 2 (Randomization) examinations:
    1. tFCS score ≥3 and ≤14 (NEI/Industry Workshop scale; 0-15 scale)
    2. Schirmer score of >7 mm without topical anesthesia
6. OSDI score >30 at both Visit 1 and Visit 2.
7. Required use of non-prescription (OTC) artificial tear substitute for symptoms of dry eye more than 3 times per day for 3 consecutive days within 30 days prior to the Screening Visit (Visit 1) and willingness to suspend use of tear substitutes at Visit 1 and for the duration of study participation.
8. Are willing and able to follow instructions and willing to be present for the required study visits for the duration of the study.
9. Have a LogMAR BCVA equal to or better than +0.7 using corrective lenses if necessary, in both eyes at both Visit 1 and Visit 2, by Early Treatment of Diabetic Retinopathy Study (ETDRS) or modified ETDRS.
10. If female, are non-pregnant, non-lactating and women of childbearing potential (WOCBP) must be using an acceptable method of birth control [e.g., an Intrauterine Contraceptive Device (IUCD) with a failure rate of <1%, hormonal contraceptives, or a barrier method] for the duration of the study. If a female subject is currently abstinent, they must agree to use one of the acceptable methods of birth control before they become sexually active.

- A non-childbearing potential is defined as a woman who is postmenopausal for 12 consecutive months or a woman who is post hysterectomy, bilateral oophorectomy or 3 months status post bilateral tubal ligation.

4.2. SUBJECT EXCLUSION CRITERIA

In order for subjects to be eligible at Visit 1 they may not:

1. Have presence or history of iritis/uveitis in either eye.
2. Have lid structural abnormalities including but not limited to entropion or ectropion that in the opinion of the Investigator may confound the study data.
3. In the study eyelid, have greater than 4 glands that are not expressible from the 5 upper and/or 5 lower eyelid meibomian glands at both Visit 1 and Visit 2.
4. Subjects with ocular inflammatory conditions (e.g., conjunctivitis, keratitis, severe anterior blepharitis, etc.) not related to MGD.
5. Subjects who in the study eye have tFCS total score = 15 or a FCS score = 3 in either eye in the superior region NEI/Industry Workshop scale or subjects who have FCS with diffuse confluent staining, filaments or frank epithelial defects at either Visit 1 or Visit 2.
6. Have suspected ocular fungal, viral or bacterial infection.
7. Subjects who within the past 6 months have had cauterization of the punctum. Non-dissolvable plugs must not be inserted within 2 weeks of Screening (Visit 1) and current non-dissolvable plugs in position must be stable in the Investigator's opinion.
8. Use of any of the prohibited medications (see Table 2: List of Prohibited Medications and/or procedures) within a time period prior to or upon Screening (Visit 1). NOTE: These medications may not be used after Visit 1 through the end of the study.

Table 2: List of Prohibited Medications and/or Procedures

Medication	Minimum Washout Period Prior to Screening (Visit 1)
Have had incisional ocular surface surgery (e.g., LASIK, refractive, pterygium removal)	12 months
Penetrating intraocular surgery	90 days
Topical ocular or systemic antibiotics for the treatment of an ocular condition	30 days

Topical cyclosporine	30 days
Lifitegrast	30 days
Systemic corticosteroids (oral, injectable, inhaled, and nasal)	30 days
Topical ocular corticosteroids, ocular non-steroidal anti-inflammatory drugs (NSAIDs), and topical dermatologic corticosteroids on the face within 30 days prior to Visit 1 and during study participation. Topical dermatologic corticosteroids not used on the face are allowed if applied to less than 3 areas for less than 3 consecutive days	30 days
Topical ocular antihistamine and/or mast cell stabilizers within 30 days prior to Visit 1 or during study participation. Have used topical ocular vasoconstrictors for the purpose of eye whitening within 30 days prior to Visit 1 (phenylephrine used to dilate the eyes is allowed)	30 days
Treatments for MGD including but not limited to thermal pulsation (Lipiflow), debridement of lid margin (BlephEx), thermal application (MeiBoFlo, Tear Care), or meibomian gland probing	30 days
All topical ophthalmic gels, ointments or drops (including artificial tears) and the TrueTear® Stimulator	2 days
Contact Lenses	At Screening

9. Use short-term dissolvable plugs for 3 months prior to Screening (Visit 1) and long-term dissolvable plugs within 6 months prior to Screening (Visit 1).
10. Any prior use of isotretinoin.
11. Are unwilling to discontinue use of cosmetic makeup applied to the eyelids or eyelashes on the day of a study visit after Visit 1.
12. Have a known hypersensitivity to active ingredient or to any of the other ingredients in the IP.
13. Are unable or unwilling to withhold the use of eyelid scrubs or use of mechanical eyelid cleaning therapy during the study, other than the Sponsor supplied commercial sterile eyelid wipes from Visit 1 through Visit 2. After Visit 2, subjects are also permitted to follow their usual routine to remove eyelid or eyelash makeup (including eyelid wipes), ensuring that no new products/techniques are introduced during the study.
14. Have been diagnosed with glaucoma, are currently using any glaucoma medication or known to have elevated IOP related to steroid use.

15. Have a history of herpetic keratitis.
16. Have a concomitant ocular pathology other than condition under study assessed as potentially confounding by the Investigator.
17. Have a serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance.
18. Have been exposed to any investigational drug or investigational device within the preceding 30 days.
19. Are an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.
20. Have trigger factors that in the opinion of the Investigator may confound the data, including but not limited to conjunctivochalasis, allergic conjunctivitis, contact lens intolerance, trichiasis, epithelial basement membrane dystrophy, infectious keratitis or conjunctivitis.
21. Have a documented history of ocular allergies, which, in the judgment of the Investigator, are likely to have an acute increase in severity due to the expected timing of the exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.

4.3. STUDY EYE/EYELID

The study eye/eyelid is the eye with the eyelid having the worst (higher) score defined as the sum of the following two severity scores for the clinical signs of MGD:

1. Vascularity of eyelid margin
2. Total MGD Score

If both eyes, and eyelids, have the same score, then select the right eye and upper eyelid.

4.4. RANDOMIZATION

At the Randomization Visit (Visit 2), an eligible subject must continue to meet all clinical inclusion/exclusion criteria as defined in Sections 4.1 and 4.2. Note: Subjects must meet all criteria from Visit 2 eye/eyelid specific criteria in the same qualifying eye and/or qualifying eyelid as in Visit 1.

5. PROCEDURES

Written Informed Consent and Health Insurance Portability and Accountability Act (HIPAA) authorization will be obtained from all subjects prior to any study procedures being performed. Visit assessments will be performed in the order suggested **in both eyes**.

5.1. VISIT DESCRIPTIONS

NOTE: In light of the Coronavirus Disease 2019 (COVID-19) pandemic, the site should utilize risk mitigation techniques for all in-clinic visits as described by the American Academy of Ophthalmology (Appendix 17).

5.1.1. Visit 1 (Screening): Day minus 14 (±2 days) prior to Visit 2

The following will be performed/assessed in the order suggested below and in both eyes:

- Explain the purpose and conduct of the study to the subject, answer the subject's questions, and obtain written informed consent.
- Obtain information including demographics, concomitant medications, ocular and systemic medical and medication history and surgical history.*
- Evaluate eligibility
- A Screening Identification (ID) should be assigned to the Subject once any Visit 1 procedures (other than ICF) are performed. The Subject ID format will be XXX-001 where XXX represents the site number and the last three digits represent the unique subject number.
- Subject-rated symptom assessments (in this order):
    - Individual Symptom Assessment via VAS
    - OSDI
    - Modified BLISS
- Urine Pregnancy Test (UPT) for all eligible women of childbearing potential. *
- For subjects presenting at Visit 1 or Visit 2 with makeup applied to the eyelids or eyelashes, subjects should use a Sponsor provided lid scrub to remove the makeup. (Subjects may resume using makeup between study visits but not on the day of a study visit). Study specific testing related to the evaluation of the eye and eyelids should start 15 minutes after makeup removal.
- For subjects presenting at any post-randomization visit with makeup applied to the eyelids or eyelashes, the site staff should use the Sponsor provided lid scrub to remove the eyelid makeup. Care should be taken not to aggressively clean the lid

margin with the lid scrub and only to gently remove any remaining makeup from the skin surface.

- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of MGD (in both eyes for upper and lower lids)
    - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)
- Wait 15-20 minutes after LGS before proceeding
- Unanesthetized Schirmer test
- IOP
- Dilated Ophthalmoscopy
- Determine if the subject is eligible to continue in the study. Do not continue screening any subject who does not meet eligibility requirements. Any subject who does not meet eligibility requirements will be designated as a Screen Failure.
- Instruct the subject to discontinue using all prohibited medications for the remainder of the study.
- If the subject is qualified, a four-week supply of commercial lid wipes will be provided.
- Schedule the subject to return for Visit 2 (Day 1) and remind subjects to bring the remaining lid wipes to Visit 2.

* May be performed at any time during the visit in order to facilitate subject and site schedules.

5.1.2. Visit 2 (Randomization): Day 1

Visit 2 will occur 14 (±2 days) after Visit 1 (Screening). The following will be performed/assessed in both eyes:

- Evaluate continued eligibility
- Subject-rated symptom assessments (in this order):
    - Individual symptom assessment via VAS
    - OSDI
    - Modified BLISS
- Use of any concomitant medications since the last visit

- Occurrence of any AEs since the last visit
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of signs of MGD
    - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)
- Wait 15-20 minutes after LGS before proceeding
- Unanesthetized Schirmer test
- IOP
- Safety laboratory blood draw
- Determine if subject is eligible for randomization

For eligible subjects, the following is the process regarding administration of Double-Masked IP whereby the trained site staff will conduct the following procedures:

- Enter subject information into IWRS to determine randomization code and Kit Number. Cohort 1 versus Cohort 2 will be part of the Interactive Web Response System (IWRS) input
- Show the subjects an instructional video on applying the investigational product. Review Subject Dosing Instructions document, reiterating that the subject should administer IP across the entire surface (corresponding to the tarsal plate) of the upper and lower eyelids of both eyes
- Subject will self-administer first dose of double-masked IP in clinic under the supervision of site staff. The site staff will record the Day 1 dosing time in the source document.
- Assess for occurrence of any IP related AEs
- The subject will complete the IP Comfort Assessment in the clinic approximately 2 minutes following administration. Site will document in the source document.
- Dispense three Daily Dosing Diaries (including IP Comfort Assessment) to the subject. *Note: each diary will contain sufficient entries for approximately one week of dosing*
- Instruct subject to bring completed diaries, cooler/gel packs and used/unused IP to each subsequent clinic visit

- Dispense two tubes of IP to the subject and instruct the subject to open only one tube initially and apply once daily at home in the evening beginning on Day 2
- Dispense a cooler and gel packs to the subject for the purpose of transporting IP. Remind the subject to store the IP and the gel packs in the refrigerator at home and to use the cooler/refrigerated gel packs any time IP is transported including to/from study visits
- Reinforce the subject instructions to administer IP across the entire surface of the upper and lower eyelids of both eyes QD and to record each administration and IP Comfort Assessment on the daily dosing diary
- **Remind subjects to discontinue the use of eyelid wipes for the remainder of the study except if used for routine makeup removal.** Collect Sponsor-provided eyelid wipes from the subject
- Schedule the subject to return for Visit 3 (Day 8 ±2 days)

5.1.3. Visit 3: Day 8 (±2 days)

This visit will occur on Day 8 as calculated from Visit 2: Day 1, and the following will be performed in both eyes:

- Subject-rated symptom assessments (in this order):
    - Individual Symptom Assessment via VAS
    - OSDI
    - Modified BLISS
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Review/collect Daily Dosing Diary #1 (including IP Comfort assessment) to assess compliance
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of signs of MGD
    - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)
- Wait 15-20 minutes after LGS before proceeding

- Unanesthetized Schirmer test
- IOP
- Reinforce the subject instructions to administer IP across the entire surface of the upper and lower eyelids of both eyes QD and to record each administration and IP comfort assessment on the daily dosing diary.
- Schedule the subject to return for Visit 4 (Day 15 ±3 days).

5.1.4. Visit 4: Day 15 (±3 days)

This visit will occur on Day 15 as calculated from Visit 2: Day 1, and the following will be performed in both eyes:

- Subject-rated symptom assessments (in this order):
  - Individual Symptom Assessment via VAS
  - OSDI
  - Modified BLISS
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Review/collect Daily Dosing Diary #2 (including IP Comfort assessment) to assess compliance
- Collect used tube of double-masked IP and remind subject to begin dosing with second tube
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of signs of MGD
  - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)
- Wait 15-20 minutes after LGS before proceeding
- Unanesthetized Schirmer test
- IOP

- Reinforce the subject instructions to administer IP across the entire surface of the upper and lower eyelids of both eyes QD and to record each administration and IP comfort assessment on the daily dosing diary.
- Schedule the subject to return for Visit 5 (Day 22 ±3 days).
- **NOTE: For Cohort 1, when the first 15 subjects across all study sites have completed Visit 4, the DSRC will convene to review data and make recommendation regarding escalation to Cohort 2.**

5.1.5. Visit 5: Day 22 (±3 days)

This visit will occur on Day 22 as calculated from Visit 2: Day 1, and the following will be performed in both eyes:

- Subject-rated symptom assessments (in this order):
  - Individual Symptom Assessment via VAS
  - OSDI
  - Modified BLISS
- UPT (women of childbearing potential)
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Review/collect Daily Dosing Diary #3 (including IP Comfort assessment) to assess compliance
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of signs of MGD
  - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)
- Wait 15-20 minutes after LGS before proceeding
- Unanesthetized Schirmer test
- IOP
- Dilated Ophthalmoscopy
- Safety Laboratory blood draw

- Collect tube of double-masked IP and coolers/gel packs from the subject
- All subjects will be discharged from the study at this visit

5.1.6. Unscheduled Visit

Any visits or procedures performed beyond those specified within the protocol must be documented in the Unscheduled Visit pages of the electronic case report form (eCRF). Unscheduled visits may include but are not limited to reporting AEs, changes in concomitant medications, or ophthalmic assessments as deemed appropriate by an appropriately qualified physician.

5.1.7. Early Termination Visit

In the event of termination prior to Visit 5, every attempt will be made to ensure that all the following Visit 5 assessments are performed in both eyes at the Early Termination Visit prior to discharge from the study:

- Subject-rated symptom assessments (in this order):
    - Individual symptom assessments via VAS
    - OSDI
    - Modified BLISS
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Collect all used/unused IP and review/collect Daily Dosing Diaries (including IP Comfort assessment) to assess compliance
- UPT
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- TBUT
- FCS
- Investigator-rated assessment of MGD
    - See Appendix 3. Assessment of Efficacy for full description of Investigator-rated assessments for objective signs of change from baseline
- LGS (at a subset of sites)

- Wait 15-20 minutes after LGS before proceeding
- Unanesthetized Schirmer test
- IOP measurement
- Dilated Ophthalmoscopy
- Safety Laboratory blood draw

Include subject withdrawal criteria (i.e., terminating IP treatment/trial treatment).

5.2. SUBJECT WITHDRAWAL AND/OR DISCONTINUATION

Any subject who wishes to discontinue IP use or withdraw from participation in the study for any reason is entitled to do so without obligation. The Investigator may also discontinue any subject from IP use or from study participation, if deemed necessary.

Investigational product use may be discontinued, and any subject may be discontinued from study participation at any time during the study at the discretion of the Investigator or the Sponsor for any reason including but not limited to:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
2. Any Serious Adverse Event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
3. Subject's decision to withdraw.
4. Any woman who becomes pregnant while participating in the study. Information on the pregnancy and outcome will be requested.
5. Subject’s failure to comply with protocol requirements or study related procedures.
6. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

In the event study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have the subject complete Visit 5 assessments. If a non-serious AE is unresolved at the time of the subject’s final study visit, an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow all SAEs to resolution. The reason for premature discontinuation should be entered into the eCRF and recorded in the subject chart.

Subjects who withdraw from the study will not be replaced.

Additionally, the trial or parts of the trial may be discontinued by the Sponsor or at the recommendation of the Investigator after consultation with AxeroVision, Inc. This may be based on a significant number of AEs of a similar nature that warrant such action.

5.3. COLLECTION OF DATA

Source documentation for data collected in this study will be maintained at the investigative site. In cases where no source will be used (e.g., dosing diary), it will be noted in the Investigator files. The CRF will be electronic (eCRF) and data will be entered from source documentation into the eCRF. After study completion, an archival copy [e.g., Portable Document Format (PDF)] of the eCRF data will be retained by the site.

6. TREATMENT OF SUBJECTS

6.1. INVESTIGATIONAL PRODUCTS TO BE ADMINISTERED

All subjects meeting Randomization criteria at Visit 2 will be randomized to either AXR-270 Cream (0.2% or 2.0%) or Vehicle. Two tubes of randomized double-masked IP will be dispensed to each subject at Visit 2 for self-administration (with one tube from each kit remaining at the site to serve as a back-up). The first tube will be used from the time of Visit 2 to the time of Visit 4. The second IP tube will be used from Visit 4 to Visit 5 (note: if a subject is unable to come to the clinic for Visit 4, they should begin dosing with the second tube on Day 15). The first used tube of IP will be returned to the site at Visit 4. The second used tube of IP will be returned at Visit 5. The IP will be stored at the site in a secure area with limited access at controlled refrigerated temperature 2° to 8°C [36° to 46°F] with excursions permitted between 0° and 15°C [32° and 59°F]. Transient spikes up to 25°C (77 °F) and not to exceed 24 hours are permitted. The refrigerator will be temperature monitored. IP will be supplied to subjects in coolers with gel packs to maintain refrigerated temperature while in transit.

Subjects will be asked to administer IP QD in the evening (except on Day 1 when IP will be administered during the office visit). It is important that IP is applied to the full eyelid as per detailed instructions in the Subject Dosing Instructions document. Subjects should be instructed to wash hands thoroughly prior to and after administration of IP.

The subjects will record the date and time of administration of each dose of IP at the time of instillation in a dosing diary. Compliance with application of IP will be reviewed and assessed at Visit 3 through Visit 5.

6.2. CONCOMITANT MEDICATIONS

All medications that the subject has taken 1 month prior to Visit 1 and through Visit 5 or discontinuation from the study will be recorded in the eCRF and the subject chart. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an AE will be recorded for each medication.

6.2.1. Permitted Medications and Therapies

Medications and therapies not specifically excluded in Section 6.2.2 may be taken as necessary.

Omega-3 supplements are permitted if the dose is stable within 3 months of Visit 1 and expected to remain stable for the duration of the study.

6.2.2. Medications and Procedures Not Permitted

Medication	Minimum Washout Period Prior to Screening (Visit 1)
Have had incisional ocular surface surgery (e.g., LASIK, refractive, pterygium removal)	12 months
Penetrating intraocular surgery	90 days
Topical ocular or systemic antibiotics for the treatment of an ocular condition	30 days
Topical cyclosporine	30 days
Lifitegrast	30 days
Systemic corticosteroids (oral, injectable, inhaled, and nasal)	30 days
Topical ocular corticosteroids, ocular non-steroidal anti-inflammatory drugs (NSAIDs), and topical dermatologic corticosteroids on the face within 30 days prior to Visit 1 and during study participation. Topical dermatologic corticosteroids not used on the face are allowed if applied to less than 3 areas for less than 3 consecutive days	30 days
Topical ocular antihistamine and/or mast cell stabilizers within 30 days prior to Visit 1 or during study participation. Have used topical ocular vasoconstrictors for the purpose of eye whitening within 30 days prior to Visit 1 (phenylephrine used to dilate the eyes is allowed)	30 days
Treatments for MGD including but not limited to thermal pulsation (Lipiflow), debridement of lid margin (BlephEx), thermal application (MeiBoFlo, Tear Care), or meibomian gland probing	30 days
All topical ophthalmic gels, ointments or drops (including artificial tears) and the TrueTear® Stimulator	2 days
Contact Lenses	At Screening

From Visit 2:

- Eyelid scrubs (unless used as part of subject's routine eye make-up removal practice) or use of mechanical therapy.

6.3. INVESTIGATIONAL PRODUCT USE COMPLIANCE

Compliance will be assessed by comparing IP accountability records with the dosing information recorded daily in the daily dosing diary by the subject. Trained Site Coordinator will document this comparison along with verification of returned used and unused IP tubes. The number of missed doses as assessed at each clinic visit should be documented in the eCRF.

6.4. DRUG ACCOUNTABILITY

Sponsor study monitors or designees will conduct accountability of IP (AXR-270 Cream or Vehicle). Accountability will be ascertained by performing reconciliation between the number of kits/tubes sent to the site, accounted for at the time of reconciliation during routine monitoring and at the end of the study.

Clinical trial materials will be shipped to the investigational sites under sealed conditions. Shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of drug received at the site. Accurate records of receipt and disposition of the IP (e.g., dates, quantity, subject number, dose dispensed, returned) must be maintained by the Investigator or his/her designee. The Subject ID format will be XXX-001, where XXX represents the site number and the last three digits represent the unique subject number.

At the end of the study, all study materials, including any used and unused IP (AXR-270 Cream or Vehicle kits), as well as original tube containers (even if empty), will be destroyed or returned to the Sponsor (or designee) in accordance with Sponsor or designee's Standard Operating Procedures (SOPs), following approval by the Sponsor. All returns of IP will be documented. The study monitor or designee will verify drug accountability. All drug accounting procedures must be completed before the study is considered complete.

6.5. MAINTENANCE OF RANDOMIZATION AND PROCEDURE FOR BREAKING THE CODE

The Sponsor, the project teams at the designated Contract Research Organizations (CROs), and investigative staff responsible for assessments of study endpoints will be masked to IP assignments. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject as needed. Since there is no specific antidote to AXR-270 Cream, immediate emergency unmasking is not necessary. If the Investigator feels it is necessary to unmask a subject's assignment after an emergency situation, the Investigator may call the Medical Monitor and notify the Sponsor. The IP assignment will be revealed on a subject-by-subject basis with the approval of the Medical Monitor and Sponsor, thus leaving the masking of the remaining subjects intact.

A randomization code will be computer-generated by AxeroVision, Inc. or designee. Randomization team members will work independently of other team members at the CRO. Study personnel, study subjects, the Sponsor, and project teams at the CROs involved in the study will be masked to IP assignments.

7. ASSESSMENT OF EFFICACY

Efficacy assessments include the following:

- OSDI
- Modified BLISS
- Individual Symptom Assessments via VAS:
    - Eye Discomfort
    - Eye Dryness
- LGS (at a subset of sites)
- FCS
- Unanesthetized Schirmer Test
- TBUT
- Bulbar conjunctiva hyperemia grading
- Investigator-rated assessment of objective signs including change from baseline (Visit 2/Day 1) for:
    1. Total MGD Score
    2. Vascularity of the eyelid margin

8. ASSESSMENT OF SAFETY

8.1. SAFETY PARAMETERS

Safety parameters include:

- AE Monitoring
- BCVA
- Slit-lamp biomicroscopy and external eye exam
- IOP
- Dilated Ophthalmoscopy
- Safety lab draw

8.2. ADVERSE EVENT DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence associated with the use of an IP in humans, whether or not considered drug related.

Adverse Reaction (AR): Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected Adverse Reaction (SAR): Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected: An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

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

A **SERIOUS ADVERSE EVENT (SAE)** is any AE or suspected adverse reaction occurring at any dose that:

- Results in death.
- Is life-threatening.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization.
- Prolongs inpatient hospitalization.
- Is a congenital anomaly/birth defect.
- Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).

A **NON-SERIOUS ADVERSE EVENT** is any AE that does not meet the definitions for SAEs as described above.

Each **AE** will be classified as **SERIOUS** or **NON-SERIOUS** using the definitions provided above.

The SEVERITY of each AE will be classified as MILD, MODERATE, or SEVERE.
The Investigator will review each event and assess its RELATIONSHIP to use of IP (unrelated, unlikely, possibly, probably, definitely). The AE will be assessed using the following definitions:

Unrelated:

- Event occurring before dosing.
- Event or intercurrent illness due wholly to factors other than IP use.

Unlikely:

- Poor temporal relationship with IP use.
- Event easily explained by subject's clinical state or other factors.

Possible:

- Reasonable temporal relationship with IP use.
- Event could be explained by subject's clinical state or other factors.

Probable:

- Reasonable temporal relationship with IP use.

- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by subject's clinical state or other factors.

Definite:

- Distinct temporal relationship with IP use.
- Known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot be explained by subject's clinical state or other factors.

8.3. PROCEDURES FOR AE REPORTING BY THE INVESTIGATOR

AEs will be monitored throughout the study and will be recorded on the eCRF with the date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to use of IP), treatment required, and the outcome.

To elicit AEs, simple questions with minimal suggestions or implications should be used as the initial questions at all evaluation points during the trial. For example:

- How have you felt since your last assessment?
- Have you had any health problems since your last assessment?

The severity of each AE should be categorized as mild, moderate, or severe.

The causality of use of IP in relation to the AE will be assessed by the Principal Investigator after careful medical consideration and categorized as unrelated, unlikely, possible, probable, or definite.

If an AE occurs, the Investigator will institute support and/or treat as deemed appropriate. If a non-SAE is unresolved at the time of the last day of the study, an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow SAEs to resolution.

8.4. SERIOUS ADVERSE EVENT REPORTING BY THE INVESTIGATOR

Serious Adverse Event Reporting

It is the responsibility of the Investigators or their designees to report any event of this nature to the Sponsor or a designee within 24 hours of the event being brought to the Investigators' or their staffs' attention. It is also the responsibility of the Investigator to report all SAEs

reported at their site to their Institutional Review Board (IRB), as required. The Investigator should make every attempt to follow all SAEs to resolution.

The following information should be provided when an SAE is reported to the Sponsor or designee:

1. Protocol Number
2. Site Number
3. Subject Number
4. Subject Demographic information, including:
   - Date of Birth
   - Sex
   - Race
5. IP start date
6. Date of last dose of IP
7. Date investigational product reinitiated (if investigational product interrupted)
8. SAE information, including:
   - SAE term (diagnosis only; if known or serious signs/symptoms)
   - Description of SAE/narrative
   - Date/time of onset
   - Severity
   - Outcome
   - Date/time of resolution or death (if duration < 24 hours)
   - Relationship to IP
   - Action taken with IP
9. Criteria for classifying the event as serious, including whether the SAE:
   - Resulted in death
   - Was life-threatening
   - Required inpatient hospitalization
   - Prolonged inpatient hospitalization
   - Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
   - Was a congenital anomaly/birth defect
   - Important medical events that may not result in death, were not life-threatening, or did not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

10. Concomitant medications
11. Relevant history
12. Possible causes of SAE other than IP
13. Copy of AE page from the eCRF

NOTE: If a SAE occurs in any study involving AXR-270 Cream or Vehicle that is unexpected and is determined to be definitely related, probably related or possibly related to IP, all sites will be notified by the Sponsor and each site should report it to its IRB.

9. STATISTICS

9.1. STATISTICAL METHODS

Continuous measures (e.g., age) will be summarized descriptively by the mean, standard deviation, median, minimum and maximum values. Categorical measures will be summarized by the number and percent of subjects. The statistical analyses will be performed in accordance with a formal Statistical Analysis Plan (provided as a separate document). All study data will be listed by treatment, subject and visit (as applicable).

9.2. ANALYSIS POPULATIONS

The following analysis populations will be considered:

Full Analysis Set (FAS) – The FAS includes all randomized subjects. The efficacy analysis will be performed on the FAS. Subjects in the FAS will be analyzed as randomized.

Per Protocol Set (PPS) – The PPS includes subjects in the FAS who do not have significant protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PPS will be analyzed using observed data only for efficacy variables. Subjects in the PPS will be analyzed as treated.

Safety Set (SAF) – The SAF includes all randomized subjects who have received at least one dose of the IP. The SAF will be analyzed for all safety assessments. Subjects in the SAF will be analyzed as treated.

The statistical analysis of safety data will be performed for the SAF. The analysis of baseline and efficacy data will be performed for the FAS. Sensitivity analyses may be performed on the PPS.

9.3. SUBJECT DISPOSITION, DEMOGRAPHIC AND BACKGROUND CHARACTERISTICS

Subject disposition, demographic characteristics, and background variables will be summarized by treatment group.

9.4. ANALYSIS OF EFFICACY

To assess whether AXR-270 Cream is more effective than Vehicle, exploratory efficacy will be performed. The unit of analysis for ophthalmic efficacy measures depends on the measure itself. Some endpoints will be analyzed by eye whereas others will be analyzed by study eyelid, where study eye/eyelid are defined in Section 4.3.

The following parameters will be assessed by eyelid:

- Vascularity of eyelid margin
- Total MGD Score
- LGS grade

The following parameters will be assessed by eye:

- VAS for Eye Discomfort (one score for both eyes)
- VAS for Eye Dryness (one score for both eyes)
- TBUT
- Total and Individual FCS score
- OSDI (subject level)
- Modified BLISS (one score for both eyes)
- Bulbar Conjunctival Hyperemia
- Unanesthetized Schirmer score

VAS scores, Total MGD score, eyelid margin vascularity, LGS grade, conjunctival hyperemia, Schirmer score, TBUT, FCS, and OSDI will be analyzed as continuous data. Analysis will be performed at each timepoint using summary statistics as well as a longitudinal model.

All other parameters will be analyzed as categorical or discrete measures. Frequencies and percentages of each category as well as a shift from baseline (Visit 2/Day 1) to each timepoint will be summarized.

Analyses of all efficacy endpoints will be done using the FAS. Analyses on the study eye/eyelid will be repeated for all non-study eye/eyelids as supportive analyses. Analyses may also be repeated on the PPS.

9.5. ANALYSIS OF SAFETY

Analysis of safety data will be presented for all subjects in the Safety Population. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, most current version) and categorized by system organ class using preferred terms. AEs will be tabulated by treatment group with respect to their Severity and relationship to the IP. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, BCVA, dilated ophthalmoscopy, and slit-lamp biomicroscopy (including external eye exam) will be summarized as safety outcomes.

9.6. SAMPLE SIZE ESTIMATION

As this study is exploratory in nature, no formal sample size calculation was performed.

9.7. LEVEL OF SIGNIFICANCE

P-values will be descriptive in nature.

9.8. PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, OR SPURIOUS DATA

Any missing, unused, or spurious data will be noted in the final clinical study report. The data will be analyzed as reported. The last observation carried forward approach will be used to analyze incomplete datasets.

9.9. PROCEDURE FOR REPORTING DEVIATIONS FROM THE STATISTICAL PLAN

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the eCRF such as medical history) to the monitor or appropriate designee.

11. QUALITY CONTROL

The progress of the study will be monitored by on-site, written, e-mail, and telephone communications between personnel at the study center and the Sponsor (or designated monitor). The Investigator will allow AxeroVision, Inc. monitors or designees to inspect all eCRFs; subject records (source documents); signed informed consent forms; HIPAA authorizations; records of IP receipt, storage, and disposition; and regulatory files related to the study.

12. ETHICS

12.1. Institutional Review Board

This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the Sponsor or designee prior to the start of enrollment into the study. Materials used to recruit subjects will be approved by the appropriate IRB and the approvals made available to the Sponsor or designee prior to their use. In addition, the Investigator's Brochure should be submitted to the IRB. Written IRB approval must adequately identify the protocol and ICF. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to the Sponsor (or designated monitor).

Any modification of study procedures or amendments to the protocol must be approved by the IRB prior to implementation. In the event that a modification or amendment is considered by the Investigator to be immediately necessary to ensure subject safety, the Investigator will promptly notify his or her IRB and the Sponsor.

Investigators will report all SAEs reported at their site to their IRB, as appropriate.

12.2. Informed Consent Requirements

Written informed consent will be obtained from each participant prior to any study-related procedures being performed (prior to or upon Visit 1/Screening). A copy of the signed and dated informed consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigative site and be available for Sponsor or designee review.

Each informed consent will contain Investigator contact information with a telephone number the subject or the subject's authorized representative can call 24 hours a day if they have medical concerns.

13. DATA HANDLING AND RECORDKEEPING

All procedures for the handling and analysis of data will be conducted using GCP and will meet ICH guidelines and FDA regulations for the handling and analysis of data for clinical trials.

13.1. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and monitor(s) for resolution. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

13.2. Records Retention

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines.

14. PUBLICATION POLICY

The institution and Investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.

15. REFERENCES

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16. APPENDICES

APPENDIX 1: SCHEDULE OF EVENTS

Procedures	Visit 1 Day minus 14 (±2 days) Screening Equalization Period	Visit 2 Day 1 Randomization Treatment Period	Visit 3 Day 8 (±2 days) Week 1 Treatment Period	Visit 4 Day 15 (±3 days) Week 2 Treatment Period	Visit 5 Day 22 (±3 days) Week 3 Study Termination
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Randomization Criteria		X			
Demographics, Systemic and Ocular Medical History	X				
Subject-rated Symptom Assessments VAS (Eye Discomfort and Eye Dryness)	X	X	X	X	X
OSDI	X	X	X	X	X
Modified BLISS	X	X	X	X	X
Concomitant Medication Query	X	X	X	X	X
Adverse Event Query		X	X	X	X
UPT	X				X
BCVA	X	X	X	X	X
Slit-lamp Biomicroscopy (including External Eye Exam)	X	X	X	X	X
TBUT	X	X	X	X	X
FCS	X	X	X	X	X
Investigator-rated assessment of signs of MGD: Total MGD Score Eyelid margin vascularity Bulbar conjunctival hyperemia	X	X	X	X	X
LGS[a]	X	X	X	X	X
Unanesthetized Schirmer Test	X	X	X	X	X
IOP	X	X	X	X	X
Dilated Ophthalmoscopy	X				X
Safety Lab Draw		X			X
Dispense Investigational Product for Home Administration		X			
Dispense Daily Dosing Diaries / IP Comfort Assessment Questionnaire		X			
In Clinic Administration of Investigational Product, IP Comfort Assessment Questionnaire and Instruction on Proper Administration[b]		X			
Collect/Review Daily Dosing Diary, IP Comfort Assessment Questionnaire and Investigational Product			X[c]	X	X
Study Termination					X

Key: OSDI=Ocular Surface Disease Index; TBUT=Tear Break up Time; BLISS= BLepharItIS Symptom; AE=Adverse Event; UPT=Urine Pregnancy Test; IOP=Intraocular Pressure; VAS=Visual Analog Scale; BCVA=Best Corrected Visual Acuity; FCS=Fluorescein Corneal Staining; LGS=Lissamine Green Staining; IP=Investigational Product.

[a]Only to be performed at a subset of sites
[b]Includes dosing video on proper administration of IP
[c]IP will not be collected at Visit 3

APPENDIX 2: DATA SAFETY REVIEW COMMITTEE (DSRC)

A description of the function and membership of the masked DSRC will be detailed in a separate charter describing the agreed upon standard operating procedures. The general plan for the review and description of the committee is outlined here:

- A review of safety will be conducted by the DSRC after the last of those 15 subjects has completed Visit 4.
- The DSRC will be minimally comprised of an independent Ophthalmologist and a Statistician who are otherwise not involved in the conduct of the study.
- The DSRC may request the participation of an independent Statistician to assist in the assessment of the safety of the IP and the decision to continue enrolling subjects after the first 15 have been treated and have completed study procedures through Visit 4.
- In order to maintain the integrity of the trial, unless it is absolutely necessary, the safety evaluation should be conducted using masked subject-specific information.
- Upon review of the safety data obtained in the first 15 subjects in Cohort 1, the DSRC will issue a memorandum to AxeroVision, Inc. recommending one of the following:
    1. Continue with the low-dose Cohort 1 and expand study to high-dose Cohort 2 upon completion of enrollment in Cohort 1.
    2. Continue with enrollment in the low-dose Cohort 1 but conduct an additional review of safety information from the next 15 subjects reaching the 2-week mid-point of the study before deciding to recommend escalation to Cohort 2.
    3. Stop study due to safety concerns.
- If, upon the review of the masked safety information, the DSRC requires unmasked information in order to ensure the safeguard of the interests of the study subjects, the unmasked information will be provided per the details outlined in the charter.
- The DSRC will make every effort to arrive to a decision by consensus.

APPENDIX 3: INVESTIGATOR-RATED ASSESSMENT OF SIGNS OF MEIBOMIAN GLAND DYSFUNCTION

The investigator will rate the bilateral severity of the subject's MGD signs according to the following classification and for each eyelid:

1. Total MGD Score

A digital expression by applying pressure with thumb or forefinger will be used to express the meibomian gland of the UPPER eyelids. A cotton tip applicator is preferred but not required to evaluate the LOWER eyelids meibomian glands.

The character of the secretion of 5 central glands on both the upper and lower eyelids will be evaluated for each eye. Each of the glands will be scored from 0-3:

0 = clear/slightly yellow

1 = opaque/yellow, whitish, particulate

2 = paste

3 = none/occluded.

The total score will thus range from 0-15 for each eyelid.

2. Eyelid Margin Vascularity

0 = Normal – Typical vascularity for subject age

1 = Mild vascular engorgement – Slightly dilated and pink blood vessels

2 = Moderate vascular engorgement – Slightly more dilated pink/red blood vessels

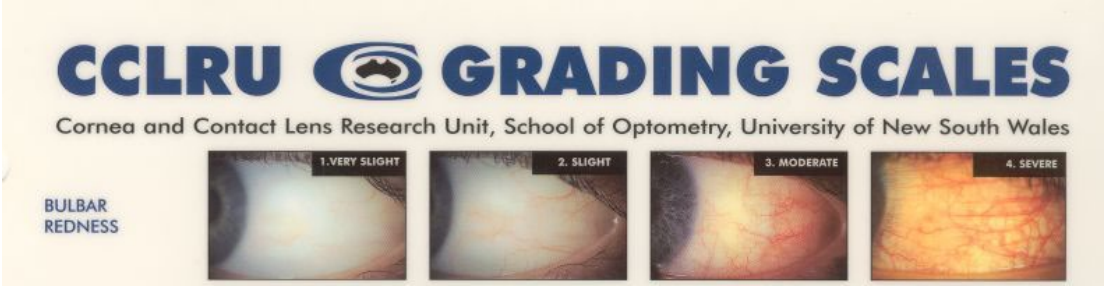
3 = Severe vascular engorgement – Multiple significantly dilated red blood vessels

4 = Very Severe vascular engorgement – Multiple significantly dilated deep red blood vessels

3. Bulbar Conjunctival Hyperemia

Investigator-Rated Assessment of Bulbar conjunctival hyperemia

Investigators will rate overall bulbar conjunctival hyperemia using the Cornea and Contact Lens Research Unit (CCLRU) Grading Scale.



0 = None

1 = Very Slight

2 = Slight

3 = Moderate

4 = Severe

APPENDIX 4: ETDRS BEST CORRECTED VISUAL ACUITY

Visual acuity testing should precede any examination requiring contact with the eye or instillation of study dyes, as is detailed in the order of assessments for each Visit in Section 5.1. Logarithm of the Minimal Angle of Resolution (LogMAR) visual acuity must be assessed using an ETDRS or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

An ETDRS or modified ETDRS chart may be used. If a Lighthouse chart is used (24.5" by 25"; either reflectance or retro-illuminated), the subject must view the chart from a distance of exactly 4 meters (13.1 feet). If smaller reproductions (18" by 18", e.g., Prevent Blindness) are used, the subject viewing distance should be exactly 10 feet. Reflectance wall charts should be frontally illuminated (60 watt bulb or a well-lit room).

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is 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 instead of the number. The subject should be asked to read slowly, about 1 letter per second, 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 before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart; the subject should be encouraged to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessments of visual acuity during the study, the same lighting conditions must be used consistently throughout the study.

Calculations: LogMAR VA = Baseline value + (n X 0.02)

where:

the baseline value is the LogMAR number of the last line read (at least 1 letter read correctly in this line), and "n" is the total number of letters missed up to and including the last line read, and "0.02" is the value for each letter.

APPENDIX 5: SLIT LAMP BIOMICROSCOPY

The biomicroscopy exam should be performed with the slit-lamp using a beam width and intensity that provide optimal evaluation of the anterior segment.

This procedure will be the performed in the same manner for all subjects observed at the Investigator's site. The site will record all ABNORMAL findings in the source document and the investigator will evaluate the ABNORMAL findings as Non-Clinically Significant (NCS) or Clinically Significant (CS). CS and NCS ABNORMAL findings will be recorded in the source documentation. However, only ABNORMAL CS descriptions will be captured in the eCRF.

Lashes

0 = Normal
1 = Abnormal

Eyelid

Edema

0 = Normal, no swelling of the lid tissue
1 = Abnormal

Skin

0 = Normal, including but not limited to thinning, pigment changes, dermatitis
1 = Abnormal

Conjunctiva

Edema

0 = Normal, no swelling of the conjunctiva
1 = Abnormal

Palpebral Conjunctival Erythema

0 = Normal, no redness of the conjunctiva
1 = Abnormal

Cornea

Infiltrates

0 = Absent
1 = Present

Endothelial Changes

0 = Normal, None
1 = Abnormal, pigment, keratoprecipitates, guttata

Edema

0 = Normal, None, transparent and clear

1 = Abnormal

Anterior Chamber

Cells

0 = Normal, No cells seen

1 = Abnormal (+ to +++ cells)

Flare

0 = Normal, No Tyndall effect

1 = Abnormal, Tyndall beam in the anterior chamber

Lens Pathology

0 = Normal, no opacity in the lens

1 = Abnormal, existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings

Sclera

0 = Normal

1 = Abnormal

APPENDIX 6: IOP MEASUREMENT

IOP measurements will be performed utilizing Goldmann applanation tonometry according to the Investigator's standard procedure. All pressures will be recorded in mmHg.

APPENDIX 7: DILATED OPHTHALMOSCOPY

Dilated Ophthalmoscopy will include assessment of the retina for any abnormal findings, optic nerve head for pallor and cupping (cup to disc ratio). After the Ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Visit 1, the Investigator will determine whether or not the abnormality would exclude subject from study participation.

APPENDIX 8: EYE DISCOMFORT, EYE DRYNESS SYMPTOM ASSESSMENT

Symptom Assessment Visual Analog Scale (VAS)

Subjects will be asked the following questions regarding their current symptoms (unrelated to Investigational Product instillation) at each visit.

The subject will be asked to subjectively rate each ocular symptom (OU) by placing a vertical mark on the horizontal line to indicate the level of eye discomfort and dryness. 0 corresponds to "No Symptoms" and 100 corresponds to "Severe Symptoms"

Subject Instructions: Please review the symptoms below. After your review, please rate how your eyes feel for each of the following symptoms by placing a single vertical mark that represents how your symptom feels at this moment.

0 = No Symptoms and 100 = Severe Symptoms

Eye Discomfort	**0**	**100**
	|_____|	
Eye Dryness	**0**	**100**
	|_____|	

APPENDIX 9: MODIFIED BLISS

Check each box which most reflects the frequency of each symptom.

Symptoms	None of the time	Occasionally	Frequently	All of the time
Eyes that itch				
Eyes that burn				
Eyelids feel heavy or puffy				
Feel like something in your eye				
Dry eyes				
Gritty eyes				
Irritated eyes				
Eyes that tear or water				
Crusty eyes				
Eyelids that are stuck together				
Red eyes or eyelids				

https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/blepharitis

APPENDIX 10: TEAR BREAK-UP TIME (TBUT)

TBUT will be measured at each visit. To measure TBUT, fluorescein is instilled into the subject's tear film, the subject is allowed to blink once or twice to disperse the fluorescein, after approximately 30 seconds the subject is then asked not to blink while the tear film is observed under a broad beam of cobalt blue illumination using a slit-lamp.

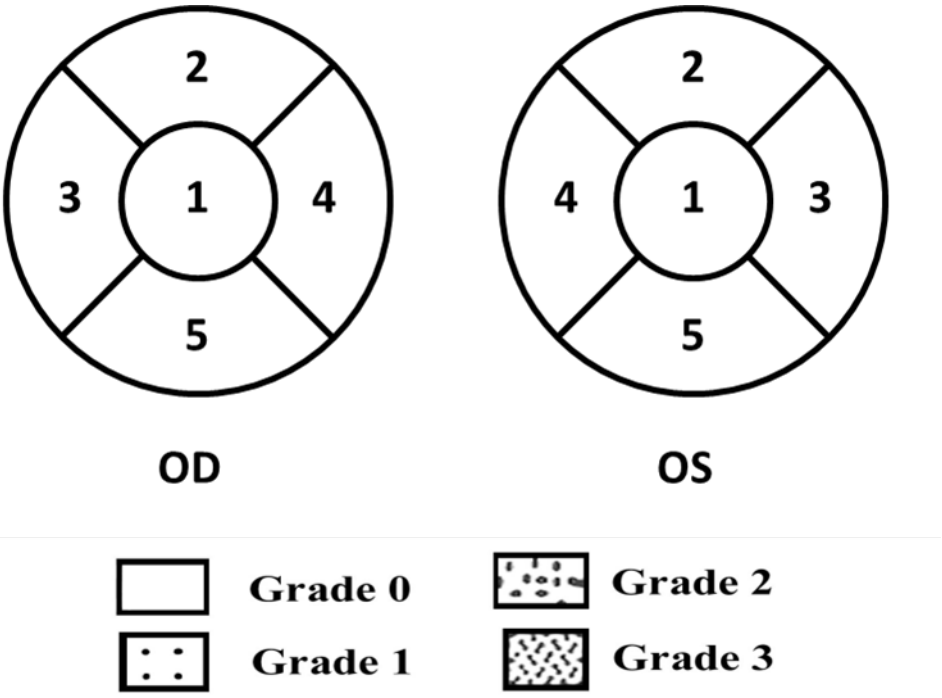
Using a stopwatch the TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. The time is measured to hundredth and using normal rounding rules, rounded to tenths. A TBUT under 10 seconds is considered abnormal.

A total of 2 measurements are obtained and entered into the record. If the 2 measurements are > 2 seconds apart then a third measurement is obtained and the closest 2 measurements are recorded.

NOTE: The TBUT and the FCS may be performed right eye then left eye or staggered with the TBUT for the left eye being done during the waiting period before completing the FCS for the right eye.

APPENDIX 11: FLUORESCEIN CORNEAL STAINING (FCS) / NATIONAL EYE INSTITUTE / INDUSTRY WORKSHOP SCALE

The 5 areas of the cornea will be scored by the investigator according to the following scoring system and the total score will also be calculated. NOTE: The TBUT and the FCS may be performed right eye then left eye or staggered with the TBUT for the left eye being done during the waiting period before completing the FCS for the right eye.



APPENDIX 12: UNANESTHETIZED SCHIRMER TEST

The Schirmer test will be conducted on unanesthetized eyes. A 35 mm x 5 mm filter paper strip is used to measure the amount of tears that are produced over 5 minutes. The strip is placed in the lower eyelid margin without the use of a preplaced ophthalmic anesthetic drop. After 5 minutes, the strip is removed and the amount of wetting is measured in millimeters. The wetting margin on the Schirmer strip is marked with a pen and the strip is placed in the subject's source document.

APPENDIX 13: OCULAR SURFACE DISEASE INDEX (OSDI)

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)

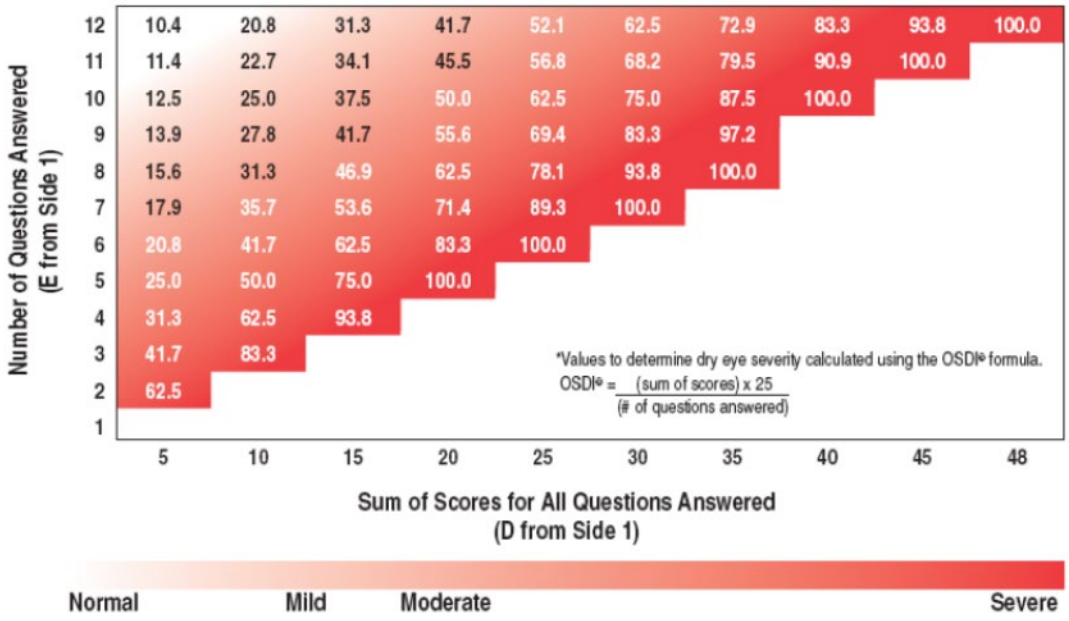
Please turn over the questionnaire to calculate the patient's final OSDI® score.

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

APPENDIX 14: DAILY DOSING DIARY

Subjects will be asked to record each day the following information related to administration of IP:

- Date
- Time of Administration
- IP Comfort Assessment (Below)

Each evening, the subject will be asked to respond to the following questions:

Investigational Product Comfort Assessment	
Overall tolerance of Investigational Product	1-Exellent 2-Good 3-Fair 4-Poor
Concern about the following immediately after application:	
Eyelid Redness	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned
Eyelid Stinging	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned
Eyelid Burning	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned
Heavy Eyelid Sensation	1-No Concern 2-Slightly Concerned

	3-Moderately Concerned 4-Very Concerned
Sticky Feeling in Eye	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned
Spreading into Eye	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned
Oily Feeling in Eye	1-No Concern 2-Slightly Concerned 3-Moderately Concerned 4-Very Concerned

APPENDIX 15: EYELID WIPE INSTRUCTIONS

Use 1 wipe to clean the eyelids of both eyes.

The desired area to clean is the skin of the eyelids at the area of the eyelashes.

Wash hands with soap and water, then dry hands.

Open the packet containing the moistened wipe and place over the index finger of either hand.

Gently close your eyelids. Forced, hard closure of the eyelids will prevent the wipe from cleaning the eyelash area of your eyelid.

Using a back and forth motion gently wipe the skin of the eyelid and eyelash area for approximately 30 seconds.

Use the underside of the wipe (portion of the wipe that was against the index finger) to clean the other eye.

You may use the same hand or other hand to clean the other eye.

APPENDIX 16: LID MARGIN LISSAMINE GREEN STAINING

Note: This procedure will only be performed at a subset of sites.

Set the slit-lamp to moderate illumination and low magnification.

- Apply Lissamine green dye to the inferior cul-de-sac of the right eye and wait at least 1 minute.
- With the subject's chin in the chinrest and the forehead against the forehead strap and evert the upper lid.
- Evaluate the lid margin anatomy starting with the Line of Marx. This should appear as a thin green line.
- The width of Lid Wiper area does not have exact landmarks to identify its width on the palpebral conjunctival surface and the Investigator judgment is required to approximate the width.
- The distal lid has rigidity due to the tarsal plate.
- The Lid Wiper area extends proximally from the Line of Marx to the first curve in the conjunctival surface.

LID WIPER GRADING

HORIZONTAL LENGTH STAINING	GRADE 0 < 2 mm	GRADE 1 2 mm to 4 mm	GRADE 2 5 mm to 9 mm	GRADE 3 >9 mm
LONGEST SAGITTAL WIDTH OF STAINING	GRADE 0 < 25 %	GRADE 1 25% to 50%	GRADE 2 51% to 75%	GRADE 3 >75%

Grade the length and sagittal width of the Lissamine staining and record the Grade score for the length and sagittal width.

Repeat the same procedure for the left eye.

APPENDIX 17:

American Academy of Ophthalmology Recommended protocols when scheduling or seeing patients

- If the office setup permits, patients who come to an appointment should be asked *prior to* entering the waiting room about fever and respiratory illness and whether they or a family member have had contact with another person with confirmed COVID-19 in the past 2 to 14 days. If they answer yes to either question, they should be sent home and told to speak to their primary care physician.
- Keep the waiting room as empty as possible, advise seated patients to remain at least 6 feet from one another. As much as prudent, reduce the visits of the most vulnerable patients.
- The use of commercially available slit-lamp barriers or breath shields is encouraged, as they may provide a measure of added protection against the virus. These barriers do not, however, prevent contamination of equipment and surfaces on the patient's side of the barrier, which may then be touched by staff and other patients and lead to transmission. Homemade barriers may be more difficult to sterilize and could be a source of contamination. In general, barriers are not a substitute for careful cleaning of equipment between patients and asking those patients who cough, sneeze, or have flu-like symptoms to wear masks during examination.
- To further decrease the risk of any virus transmission, ophthalmologists should inform their patients that they will speak as little as possible during the slit-lamp examination, and request that the patient also refrain from talking.
- For in-office procedures that require close physical proximity to the patient (e.g., intravitreal injection, lateral tarsorrhaphy), we recommend the patient wear a surgical mask or a cloth face covering if surgical masks are in short supply, and that the surgeon wear a surgical mask and eye protection. In regions with high prevalence of COVID-19, an N95 mask for the surgeon can be considered when available. The CDC's recommendations on N95 extended use and/or reuse should be followed.
- The CMS and HHS have allowed for the expanded use of telehealth services during the COVID-19 public health crisis. For more information on telephone services, internet-based consultation or telemedicine exam, visit the Academy's Coding for Phone Calls, Internet and Telehealth Consultations.