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Protocol AXR201901

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

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Phase:	1/2
Methodology:	Randomized, Double-Masked, Vehicle-Controlled
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SIGNATURE PAGE

Protocol Title: A Phase I/II, Randomized, Double-Masked, Vehicle-Controlled Study of the Safety, Tolerability, and Efficacy of AXR-207 Topical Eyelid Cream in Treating Posterior Blepharitis Associated with Meibomian Gland Dysfunction

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Sponsor Approval

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

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

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

Sponsor:	AxeroVision, Inc.		
Protocol:	AXR201901		
Document Version No.:	1.1	**Document Date:**	26-OCT-2020

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
API	Active Pharmaceutical Ingredient
AR(1)	Autoregressive (1)
ATC3	Anatomic Therapeutic Class 3
BCVA	Best Corrected Visual Acuity
BLISS	BLepharItIS Symptom
CROs	Contract Research Organizations
CS	Compound symmetry
CSR	Clinical study report
DED	Dry Eye Disease
EDE	Evaporative Dry Eye
FAS	Full Analysis Set
FCS	Fluorescein Corneal Staining
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
LGS	Lissamine Green Staining
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Dysfunction
OSDI	Ocular Surface Disease Index
PPS	Per Protocol Set
PT	Preferred Term
QD	Once daily
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SOC	System Organ Class
TBUT	Tear Break up Time

Abbreviation	**Definition**
UN	Unstructured
VAS	Visual Analog Scale
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This document presents the statistical analysis plan (SAP) for AxeroVision, Inc. protocol AXR201901: A Phase I/II, Randomized, Double-Masked, Vehicle-Controlled Study of the Safety, Tolerability, and Efficacy of AXR0270 Topical Eyelid Cream in Treating Posterior Blepharitis Associated with Meibomian Gland Dysfunction.

This SAP is based on Protocol Amendment 2, dated 03 June 2020. It contains the analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the clinical study report (CSR). This SAP also outlines any differences in the currently planned analytical objectives relative to those planned in the study protocol. Operational aspects related to collection and timing of planned clinical assessments are not repeated in the SAP unless relevant to the planned analyses.

Posterior blepharitis is a condition characterized by inflammation of the posterior lid margin. The condition may be inclusive of Meibomian Gland Dysfunction (MGD) in which there is an alteration in the quality and expression of gland secretions [1]. MGD is recognized as one of the most common pathologies seen by Ophthalmologist and is a significant contributor to Evaporative Dry Eye (EDE) which is further considered the leading cause of Dry Eye Disease (DED) [1, 2]. MGD is commonly treated on a chronic basis [2] via either mechanical therapy (lid hygiene, lid massage and lid compression/expression) alone or in combination with topical or systemic antibiotics or topical cyclosporine. DED is a widespread dysfunction of the tears and ocular surface and is characterized by ocular signs such as inflammation of the ocular surface [3] and tear film instability [4, 5, 6] resulting in corneal and conjunctival epithelial changes.

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 [2, 3, 7, 8]. Pflugfelder and colleagues [9] demonstrated that a topical corticosteroid may achieve the objective of a short-term treatment of acute exacerbations of DED signs or symptoms.

AxeroVision Inc. intends to develop AXR-270 Cream for the treatment of MGD secondary to posterior blepharitis. The AXR-270 Cream investigation product (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.

1.2. Objectives of Statistical Analysis

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.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is a multi-center, double-masked, randomized, vehicle-controlled, two cohort study. Approximately 126 subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD will be enrolled in the trial. Subjects will be randomized into one of the three treatments below.

- 0.2% AXR-270 Cream (approximately 42 subjects in Cohort 1)
- 2.0% AXR-270 Cream (approximately 42 subjects in Cohort 2)
- Vehicle (approximately 42 subjects, 21 in Cohort 1 and 21 in Cohort 2)

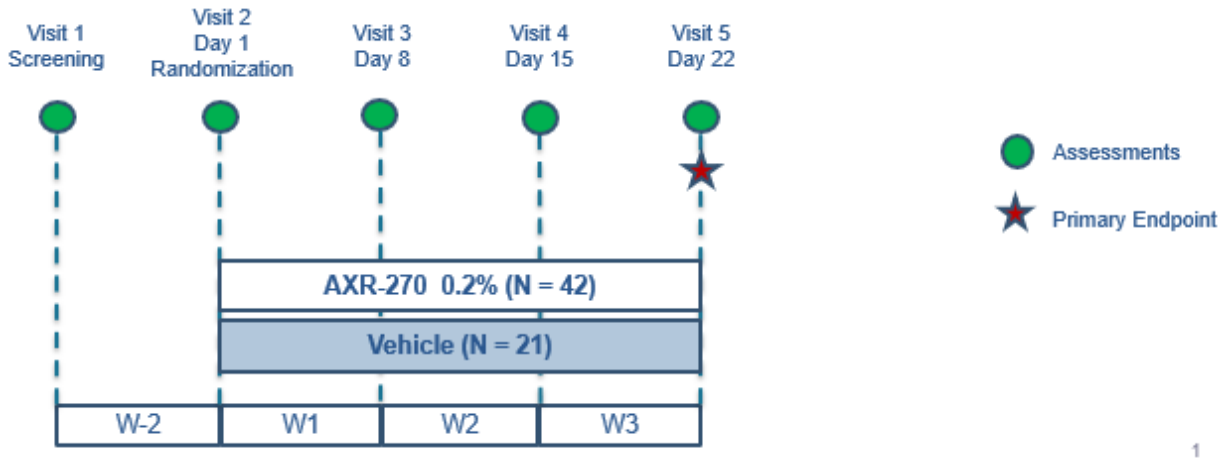
Randomly assigned treatments will be administered in both eyes.

In Cohort 1, approximately 63 subjects with a diagnosis of symptomatic posterior blepharitis associated with MGD meeting all inclusion/exclusion criteria at the Screen 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 (Visit 2; Week 0/Day 1) to confirm that they meet all inclusion/exclusion criteria and are eligible for 2:1 randomization to 0.2% AXR-270 Cream or its Vehicle. Subjects will receive in-clinic dose administration and then supplied with sufficient IP to apply once daily (QD) at home in the evening during the treatment period. Subjects will self-administer IP QD (approximately 50 mg per eyelid) in the evenings beginning on Day 2. Subjects will return for assessments on Visit 3 (Week 1/Day 8), Visit 4 (Week 2/Day 15), and Visit 5 (Week 3/Day 22).

Following the completion of the 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 on whether to escalate to a higher 2.0% dose of AXR-270 Cream for Cohort 2, which if recommended, will begin immediately upon completion of enrollment in Cohort 1.

In Cohort 2, approximately 63 subjects will be randomized 2:1 to 2.0% AXR-270 Cream or its Vehicle. Cohort 2 will follow the same visit schedule as Cohort 1.

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.

2.2. Randomization Methodology

At Visit 2, 14 (±2 days) after Visit 1 (Screening), subjects' eligibility for randomization will be determined.

Subjects will be randomized into one of the three treatments below.

- 0.2% AXR-270 Cream (approximately 42 subjects in Cohort 1)
- 2.0% AXR-270 Cream (approximately 42 subjects in Cohort 2)
- Vehicle (approximately 42 subjects, 21 in Cohort 1 and 21 in Cohort 2)

Randomly assigned treatments will be administered in both eyes.

2.3. Stopping Rules and Unmasking

2.3.1. Stopping Rules

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, Food and Drug Administration (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.

2.3.2. Unmasking

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.

2.4. Study Procedures

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

Table 1 Schedule of Assessments

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Day minus 14 (±2 days)	Day 1	Day 8 (±2 days)	Day 15 (±3 days)	Day 22 (±3 days)
	Screening	Randomization	Week 1	Week 2	Week 3
	Equalization Period	Treatment Period			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

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Procedures	**Day minus 14 (±2 days)**	**Day 1**	**Day 8 (±2 days)**	**Day 15 (±3 days)**	**Day 22 (±3 days)**
	Screening	**Randomization**	**Week 1**	**Week 2**	**Week 3**
	Equalization Period	**Treatment Period**			**Study Termination**
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

2.5. Efficacy, Pharmacokinetic, and Safety Variables

2.5.1. Efficacy Variables

The following efficacy variables will be used to evaluate the efficacy of AXR-270 Cream in treating signs and symptoms of posterior blepharitis associated with MGD.

The following parameters will be assessed by eyelid:

- Vascularity of eyelid margin
- Total MGD Score
- Lissamine Green Staining (LGS) grade of eyelid margin

All three variables will be analyzed as continuous variables.

The following parameters will be assessed by eye:

- Visual Analog Scale (VAS) for Eye Discomfort (one score for both eyes)
- VAS for Eye Dryness (one score for both eyes)
- Tear Break up Time (TBUT)
- Total and Individual Fluorescein Corneal Staining (FCS) score
- Ocular Surface Disease Index (OSDI) (subject level)
- Modified BLepharItIS Symptom (BLISS) (one score for both eyes)
- Bulbar Conjunctival Hyperemia
- Unanesthesized Schirmer score

All variables besides the Modified BLISS will be analyzed as continuous variables. The Modified BLISS will be analyzed as a categorical variable.

2.5.2. Pharmacokinetic Variables

Pharmacokinetic variables are not applicable to this study.

2.5.3. Safety Variables

Safety variables include:

- Adverse Events (AEs)
- 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. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- 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 (see Section 3.2) 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.

3.2. Protocol Deviations

At the discretion of the sponsor, significant protocol deviations as determined by a review of the data prior to unmasking of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the PPS. The sponsor, or designee, will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of the protocol deviation, and clearly identify whether or not this deviation warrants exclusion from the PPS. This file will be finalized prior to hard database lock.

All protocol deviations will be presented in the data listings and significant protocol deviations will be flagged.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

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

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. Baseline is considered to be the last assessment prior to first dose. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the VAS scores, Total MGD score, eyelid margin vascularity, LGS grade, conjunctival hyperemia, Schirmer score, TBUT, FCS, and OSDI with all tests conducted at the 2-sided, 0.05 level of significance. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coding using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 – updated Apr2020. Concomitant medications will be coded using B3 World Health Organization (WHO) Drug Global – March 2020.

4.2.3. Methods of Pooling Data

Vehicle from Cohort 1 and Cohort 2 will be pooled for analysis.

4.2.4. Adjustments for Covariates

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.2.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study.

4.2.6. Subpopulations

No analyses of subgroups of subjects are planned.

4.2.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdraw from the study will not be replaced.

4.2.8. Missing, Unused, and Spurious Data

Any missing, unused, or spurious data will be noted in the final CSR. The data will be analyzed as recorded on the CRF. The last observation carried forward (LOCF) approach will be used to analyze incomplete datasets.

All data recorded on the CRF will be included in data listings that will accompany the clinical study report.

4.2.9. Visit Windows

Table 2 Evaluation Intervals for Efficacy Analysis

Evaluation	Protocol-Specified Interval	Interval for Analysis
Visit 1 (Day minus 14)	Day -16 to Day -12	Day -16 to Day -12
Visit 2 (Day 1)	Day 1	Day 1
Visit 3 (Day 8)	Day 6 to Day 10	Day 5 to Day 11
Visit 4 (Day 15)	Day 12 to Day 18	Day 12 to Day 18
Visit 5 (Day 22)	Day 19 to Day 25	Day 19 to Day 28

4.3. Interim Analyses

An interim analysis is not planned for this study.

4.4. Subject Disposition

Subject disposition will be tabulated by treatment group, including the number screened overall, the number and percent randomized, the number and percent dosed with 0.2% AXR-270 Cream, the number and percent dosed with 2.0% AXR-270 Cream, the number and percent dosed with Vehicle, the

number and percent that completed the treatment, the number and percent that discontinued treatment and the reasons for discontinuation, the number and percent that completed the study, the number and percent that discontinued prior to completing the study and the reasons for discontinuation, and the number in each subject population for analysis.

A summary will be provided for investigator enrollment by country, study center, and investigator name(s) by treatment dose and overall.

A by-subject listing of study completion information, including the reason for premature treatment and/or study discontinuation, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Baseline and demographic information will be summarized for the FAS, PPS, and SAF using descriptive statistics by treatment group. Medical history will be summarized for the FAS by treatment group, where medical history includes systemic surgical, ocular surgical, systemic non-surgical, and ocular non-surgical history summarized separately by treatment group. No formal statistical comparisons will be performed.

Baseline, demographic, and medical history data will be provided in data listings.

4.6. Efficacy Evaluation

Efficacy analysis will be conducted using the FAS and PPS as outlined below.

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

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-related signs of MGD using individual severity scores in AXR-270 Cream arms 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 eyelid margin (Grade 0-4)
3. Change from baseline in average TBUT in AXR-270 Cream arms compared to Vehicle at Day 22. (TBUT 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 upper lid horizontal length staining, longest sagittal width of staining, and LGS score of the eyelid margin in AXR-270 Cream arms compared to Vehicle at Day 22
5. Change from baseline in tFCS score (NEI/Industry Workshop; 0-15 scale) in the AXR-270 Cream arms compared to Vehicle at Day 22
6. Change from baseline in FCS (0-3 scale) by individual region (5 zones) in AXR-270 Cream arms compared to Vehicle at Day 22
7. Change from baseline in bulbar conjunctival hyperemia (0-4 scale) in AXR-270 Cream arms compared to Vehicle at Day 22
8. Change from baseline in OSDI score (0-100) in AXR-270 Cream arms compared to Vehicle at Day 22
9. Change from baseline in the modified BLISS score in AXR-270 Cream arms compared to Vehicle at Day 22
10. Change from baseline in the Schirmer score in AXR-270 Cream arm compared to Vehicle at Day 22

VAS scores, Total MGD score, eyelid margin vascularity, LGS grade, conjunctival hyperemia, Schirmer score, TBUT, FCS, and OSDI of the study eye/eyelid will be analyzed as continuous data. Analysis will be performed at each timepoint for the value at that timepoint and change from baseline using summary statistics. Change from baseline will also be analyzed with a longitudinal model with terms for baseline value and treatment.

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

1. Vascularity of eyelid margin
2. Total MGD Score

If both eyes, and eyelids, are eligible and have the same score, then select the right eye and upper eyelid. The non-study eyelid will only be the other eyelid(s) that meet all the eligibility rules that the study eyelid met as defined below.

A study eye/eyelid is eligible if Inclusion Criteria #3, Inclusion Criteria #5, and Exclusion Criteria #3 are met for the same eyelid at Visit 1 and Visit 2.

Inclusion Criteria #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 the individual score of 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

Inclusion Criteria #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)

b) Schirmer score of >7 mm without topical anesthesia

Exclusion Criteria #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.

Least squares means for each treatment group and for the differences between 0.2% AXR-270 Cream and Vehicle, 2.0% AXR-270 Cream and Vehicle, and 0.2% AXR-270 Cream and 2.0% AXR-270 Cream will be presented from each model together with two-sided p-values and 95% confidence intervals at each post-baseline visit. The differences between Day 8 and baseline, Day 15 and baseline, and Day 22 and baseline for each treatment individually will also be presented from the model with two-sided p-values and 95% confidence intervals at each post-baseline visit.

Sample SAS longitudinal model code:

```
PROC MIXED DATA=INDATA;
  BY <EYE> <PARAMETER>; ** include <EYE> as applicable;
  CLASS <TREATMENT> <SUBJECT> <VISIT>;
  MODEL <ENDPOINT>=<TREATMENT> <VISIT> <TREATMENT>*<VISIT> <BASELINE>;
  REPEATED <VISIT> / SUBJECT=<SUBJECT> TYPE=UN;
  RANDOM Intercept;
  LSMEANS <TREATMENT>*<VISIT> / CL ALPHA=0.05;
  ESTIMATE '2.0 - Vehicle @ Day 8' <TREATMENT> -1 0 1
                                   <TREATMENT>*<VISIT> -1 0 0 0 0 0 1 0 0 /
                              CL ALPHA=0.05;
  ESTIMATE '0.2 - Vehicle @ Day 8' <TREATMENT> -1 1 0
                                   <TREATMENT>*<VISIT> -1 0 0 1 0 0 0 0 0 /
                              CL ALPHA=0.05;
  ESTIMATE '2.0 - 0.2 @ Day 8' <TREATMENT> 0 -1 1
                                <TREATMENT>*<VISIT> 0 0 0 -1 0 0 1 0 0 / CL
                              ALPHA=0.05;
  ESTIMATE 'Day 8 - Baseline for 2.0' <TIME> -1 0 1
                                      <TREATMENT>*<TIME> -1 0 1 0 0 0 0 0 0 /
                              CL ALPHA=0.05;
RUN;
```

Where <TREATMENT> is sorted in ascending order of 0.2% AXR-270, 2.0% AXR-270, then Vehicle and <VISIT> is sorted in ascending order of Day 8, Day 15, and Day 22.
The variance-covariance structure (TYPE=) will unstructured (UN). In the event that UN does not converge, then autoregressive (AR(1)) and compound symmetry (CS) will be used in that order until the model converges. A random subject intercept will also be included in the model (using Random INT statement in Proc mixed). An additional BY statement for eye will be added for endpoints that are evaluated by study/non-study eye.

Analysis of the non-study eye/eyelids will also be conducted on each of the above endpoints as supportive analysis.

If any values are missing for the study eye/eyelid, a sensitivity analysis will be conducted where missing values are imputed with the LOCF method.

In addition, time to resolution and responder analysis will be performed for the following efficacy variables:

- Eye Discomfort VAS (6 responder levels)
  - 20%, 30%, 50%, and 100% improvement
  - 10+ points and 15+ points improvement
- Eye Dryness VAS (6 responder levels)
  - 20%, 30%, 50%, and 100% improvement
  - 10+ points and 15+ points improvement
- Study Eyelid Total MGD (2 responder levels)
  - 0 Score
  - 3+ points improvement
- Study Eyelid Margin Vascularity (1 responder level)
  - 1+ step improvement
  - 2+ step improvement
- Study Eye TBUT (2 responder levels)
  - ≥7 seconds
  - ≥10 seconds
- Study Eye LGS Score (2 responder levels)
  - 0 Score
  - 3+ step improvement
- Study Eye tFCS (2 responder levels)
  - 0 Score
  - 3+ step improvement
- Study Eye FCS Central Zone (2 responder levels)
  - 0 Score
  - 1+ step improvement
- Study Eye FCS Inferior Zone (2 responder levels)
  - 0 Score

  - 1+ step improvement
- Study Eye FCS Nasal Zone (2 responder levels)
  - 0 Score
  - 1+ step improvement
- Study Eye FCS Superior Zone (2 responder levels)
  - 0 Score
  - 1+ step improvement
- Study Eye FCS Temporal Zone (2 responder levels)
  - 0 Score
  - 1+ step improvement
- Study Eye Bulbar Conjunctival Hyperemia (2 responder levels)
  - 0 Score
  - 1+ step improvement
- OSDI (1 responder level)
  - <13 Score
- Study Eye Unanesthetized Schirmer Test (1 responder level)
  - >14 mm

Improvement as mentioned above means reduction in score.

Time to resolution will be defined as the duration between the date that a subject's study eye/eyelid or subject, as appropriate per the endpoint (see Section 2.5.1), reaches a predefined "resolution" value post-baseline and the date of the first dose of study drug, i.e., (date of response – date of first dose) + 1. Time to resolution will be summarized by treatment. The differences, 95% CIs, and p-values, assuming equal variance (pooled), from a two-sample t-test will be provided for 0.2% AXR-270 vs Vehicle, 2.0% AXR-270 vs Vehicle, and 2.0% AXR-270 vs 0.2% AXR-270.

Counts and percentages of subjects/eyes that respond will be presented by treatment. P-values from a chi-squared test will be provided for 0.2% AXR-270 vs Vehicle, 2.0% AXR-270 vs Vehicle, and 2.0% AXR-270 vs 0.2% AXR-270.

By subject listings will be provided for each of the efficacy variables.

Change from baseline figures will be presented for the following:

- Eye discomfort VAS
- Eye dryness VAS
- Total MGD Score
- Vascularity of the eyelid margin
- Upper lid LGS
- tFCS
- Bulbar conjunctiva Hyperemia
- OSDI
- Modified BLISS
- Unanesthesized Schirmer Test

- IOP

The mean change from baseline by treatment will be plotted along the y-axis and visit along the x-axis. Standard deviation bars will be presented along with an asterisk (*) above or below the bars to indicate whether there is significance at an α=0.05 level for the treatment compared to vehicle.

4.7. Pharmacokinetic Evaluations

Pharmacokinetic analyses are not applicable to this study.

4.8. Safety Analyses

Safety analyses will be conducted using the SAF.

4.8.1. Adverse Events

Adverse events will be coded using MedDRA and displayed in tables and listings using System Organ Class (SOC) and Preferred Term (PT) separately for ocular and non-ocular events.

Analyses of AEs will be performed separately for those events that are considered pre-treatment and treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication through the end of the study or any event that was present at baseline but worsened in intensity.

AEs are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or PT).

AEs will be tabulated by treatment group with respect to their severity (mild, moderate, severe) and relationship (unrelated, unlikely, possible, probable, definite) to the IP. The number and percentage of subjects with any treatment-emergent adverse event will be tabulated by treatment group and overall with respect to their severity and relationship to the IP. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

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

All missing dates of events that occur will be queried for a date. If no date is obtained, the following imputation rules will apply:

- For start dates, missing months and days will be imputed as ‘01’, provided this occurs on or after the date of first study drug administration. Otherwise, the day or month (as appropriate) of the first administration of study drug will be used.
- For stop dates, missing months will be imputed as ‘12’ and missing days will be imputed as the last day of the month. If this creates a date after discontinuation/completion, the date of discontinuation/completion will be used.

Where an AE is associated with a partially or fully missing start date or time, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is treatment emergent.

The imputed dates will only be used to classify events as pre-treatment or treatment emergent. Imputed dates will only be used in the table analyses. Listings will display the available date data.

All AEs occurring on study will be listed in separate subject data listings for ocular or non-ocular events with a flag for those that are treatment emergent.

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

4.8.2. Laboratory Data

Clinical laboratory values will be expressed using conventional units.

The actual value and change from baseline to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used.

Shift from baseline tables to each on study evaluation will be provided by treatment group. The categories will include low, normal, high, and missing.

Values below the Lower Level of Quantification (LLQ) or above the Upper Level of Quantification (ULQ) will be imputed as one unit less or more respectively than the precision of measurement. <xxx will be computed to xxx-1, <xxx.x to xxx.x-0.1, etc. >xxx will be computed to xxx+1, >xxx.x to xxx.x+0.1, etc.

All laboratory data will be provided in data listings.

4.8.3. Dilated Ophthalmoscopy

Dilated ophthalmoscopy findings will be summarized descriptively, including the number and percent of subjects with normal and abnormal results for the retina and optic nerve results at Baseline and each study visit by treatment group and study or non-study eye. Summary statistics will be provided for the cup-to-disc ratio at each study visit by treatment group and study or non-study eye.

All dilated ophthalmoscopy findings will be provided in a data listing.

4.8.4. Intraocular Pressure

The actual value and change from baseline to each on study evaluation will be summarized for intraocular pressure (mmHg) for the study eye and non-study eye by treatment group. Counts and percentages of subjects by study eye and non-study eye with elevations in IOP at any point in the study will also be provided for the following elevation categories:

- IOP increase from baseline ≥10 mmHg

- Absolute IOP value >25 mmHg
- Absolute IOP value >30 mmHg

If a subject has an absolute IOP value >30 mmHg, they will be counted in both categories of 'Absolute IOP value >25 mmHg as well as in 'Absolute IOP value >30 mmHg'. All intraocular pressure data will be provided in data listing with elevation categories flagged.

4.8.5. Best Corrected Visual Acuity

The actual value and change from baseline to each on study evaluation will be summarized for the calculated logMAR score for the study eye and non-study eye by treatment group.

All BCVA data will be provided in data listings.

4.8.6. Slit-lamp Biomicroscopy and External Eye Exam

Slit-lamp biomicroscopy and external eye exam findings will be summarized descriptively, including the number and percent of subjects with normal/not present and abnormal/present results for lashes, eyelid edema, eyelid skin, conjunctival edema, palpebral conjunctival erythema, corneal infiltrates, corneal endothelial changes, and corneal edema results at baseline and each study visit by treatment group and study or non-study eye.

All slit-lamp biomicroscopy and external eye exam data will be provided in data listings.

4.8.7. Urine Pregnancy Test and Concomitant Medications

All urine pregnancy and concomitant medication data will be provided in data listings.

4.8.8. IP Comfort Assessment

The actual value and change from baseline to each on study evaluation will be summarized for the IP Comfort Assessment by treatment group.

All IP Comfort Assessment data will be provided in data listings.

5. CHANGES TO PLANNED ANALYSES

The following analyses are provided in the SAP but not planned in the protocol:

- Responder analysis in Section 4.6
- Time to resolution analysis in Section 4.6
- Additional evaluation of the difference between 2.0% AXR-270 Cream and 0.2% AXR-270 Cream at each post-baseline visit
- Additional evaluation of the within treatment change-from-baseline difference at each post-baseline visit

6. REFERENCES

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7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be Generated

14.1.1	Investigator Enrollment Summary – Enrolled Subjects
14.1.2.1*	Overall Disposition and Subject Accountability – Full Analysis Set
14.1.2.2	Overall Disposition and Subject Accountability – Per Protocol Set
14.1.2.3	Overall Disposition and Subject Accountability – Safety Set
14.1.3.1	Demographic and Baseline Characteristics – Full Analysis Set
14.1.3.2	Demographic and Baseline Characteristics – Per Protocol Set
14.1.3.3	Demographic and Baseline Characteristics – Safety Set
14.1.4.1	Systemic Surgical History – Full Analysis Set
14.1.4.2	Ocular Surgical History by Eye – Full Analysis Set
14.1.5.1	Systemic Medical History – Full Analysis Set
14.1.5.2	Ocular Medical History by Eye – Full Analysis Set
14.2.1.1*	Eye Discomfort VAS Actual Values and Changes Over Time – Full Analysis Set
14.2.1.2	Eye Discomfort VAS Actual Values and Changes Over Time – Per Protocol Set
14.2.1.3	Sensitivity Analysis of Eye Discomfort VAS Actual Values and Changes Over Time – Full Analysis Set
14.2.2.1*	Eye Dryness VAS Actual Values and Changes Over Time – Full Analysis Set
14.2.2.2	Eye Dryness VAS Actual Values and Changes Over time – Per Protocol Set
14.2.2.3	Sensitivity Analysis of Eye Dryness VAS Actual Values and Changes Over Time – Full Analysis Set
14.2.3.1*	Total MGD Score Actual Values and Changes Over Time by Study/Non-study Eyelid – Full Analysis Set
14.2.3.2	Total MGD Score Actual Values and Changes Over Time by Study/Non-study Eyelid – Per Protocol Set
14.2.3.3	Sensitivity Analysis of Total MGD Score Actual Values and Changes Over Time by Study/Non-study Eyelid – Full Analysis Set
14.2.4.1*	Vascularity of the Eyelid Margin Actual Values and Changes Over Time by Study/Non-study Eyelid – Full Analysis Set
14.2.4.2	Vascularity of the Eyelid Margin Actual Values and Changes Over Time by Study/Non-study Eyelid – Per Protocol Set
14.2.4.3	Sensitivity Analysis of Vascularity of the Eyelid Margin Actual Values and Changes Over Time by Study/Non-study Eyelid – Full Analysis Set
14.2.5.1	Tear Break-Up Time (sec) Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.5.2	Tear Break-Up Time (sec) Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set

14.2.5.3	Sensitivity Analysis of Tear Break-Up Time (sec) Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.6.1*	Upper Lid LGS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.6.2	Upper Lid LGS Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set
14.2.6.3	Sensitivity Analysis of Upper Lid LGS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.7.1*	tFCS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.7.2	tFCS Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set
14.2.7.3	Sensitivity Analysis of tFCS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.8.1	Individual Region FCS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.8.2	Individual Region FCS Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set
14.2.8.3	Sensitivity Analysis of Individual Region FCS Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.9.1*	Bulbar Conjunctival Hyperemia Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.9.2	Bulbar Conjunctival Hyperemia Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set
14.2.9.3	Sensitivity Analysis of Bulbar Conjunctival Hyperemia Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.10.1*	OSDI Score Actual Values and Changes Over Time – Full Analysis Set
14.2.10.2	OSDI Score Actual Values and Changes Over Time – Per Protocol Set
14.2.10.3	Sensitivity Analysis of OSDI Score Actual Values and Changes Over Time – Full Analysis Set
14.2.11.1*	Modified BLISS at each Visit – Full Analysis Set
14.2.11.2	Modified BLISS at each Visit – Per Protocol Set
14.2.11.3	Modified BLISS Shifts from Baseline Over Time – Full Analysis Set
14.2.11.4	Modified BLISS Shifts from Baseline Over Time – Per Protocol Set
14.2.12.1*	Unanesthesized Schirmer Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.12.2	Unanesthesized Schirmer Actual Values and Changes Over Time by Study/Non-study Eye – Per Protocol Set
14.2.12.3	Sensitivity Analysis of Unanesthesized Schirmer Actual Values and Changes Over Time by Study/Non-study Eye – Full Analysis Set
14.2.13	Time to Resolution – Full Analysis Set
14.2.14	Responder Analysis – Full Analysis Set

14.3.1.1.1	Overview of Pre-treatment Non-ocular Adverse Events – Safety Set
14.3.1.1.2*	Overview of Treatment Emergent Non-ocular Adverse Events – Safety Set
14.3.1.2.1	Overview of Pre-Treatment Ocular Adverse Events – Safety Set
14.3.1.2.2*	Overview of Treatment Emergent Ocular Adverse Events – Safety Set
14.3.1.3.1	Non-ocular Pre-Treatment Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.3.2	Non-ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.4.1	Ocular Pre-Treatment Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.4.2	Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.5.1	Severity of Non-ocular Pre-Treatment Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.5.2	Severity of Non-ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.6.1	Severity of Ocular Pre-Treatment Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.6.2	Severity of Ocular Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Safety Set
14.3.1.7.1	Relationship of Non-ocular Pre-Treatment Adverse Events to IP by System Organ Class and Preferred Term – Safety Set
14.3.1.7.2	Relationship of Non-ocular Treatment Emergent Adverse Events to IP by System Organ Class and Preferred Term – Safety Set
14.3.1.8.1	Relationship of Ocular Pre-Treatment Adverse Events to IP by System Organ Class and Preferred Term – Safety Set
14.3.1.8.2	Relationship of Ocular Treatment Emergent Adverse Events to IP by System Organ Class and Preferred Term – Safety Set
14.4.1.1	Serum Chemistry Actual Values and Changes Over Time – Safety Set
14.4.1.2	Hematology Actual Values and Changes Over Time – Safety Set
14.4.1.3	Serum Chemistry Shift Over Time – Safety Set
14.4.1.4	Hematology Shift Over Time – Safety Set
14.4.2.1	Dilated Ophthalmoscopy by Study/Non-study Eye – Safety Set
14.4.2.2*	Intraocular Pressure Actual Values and Changes Over Time by Study/Non-study Eye – Safety Set
14.4.2.3	Elevations of Intraocular Pressure by Study/Non-study Eye – Safety Set
14.4.2.4	BCVA Actual Values and Changes Over Time by Study/Non-study Eye – Safety Set
14.4.2.5	Slit-lamp Biomicroscopy and External Eye Exam by Study/Non-study Eye – Safety Set
14.4.2.6	IP Comfort Assessment – Safety Set

* Topline table

7.2. Data Listings to be Generated

16.2.1	Subject Disposition and Study Termination Information – All Subjects
16.2.2.1	Inclusion Criteria – All Subjects
16.2.2.2	Exclusion Criteria – All Subjects
16.2.2.3	Protocol Deviations – All Subjects
16.2.3.1	Subjects Excluded from Per Protocol Set – All Subjects
16.2.4.1	Demographic and Baseline Information – All Subjects
16.2.4.2	Systemic Surgical History – All Subjects
16.2.4.3	Ocular Surgical History – All Subjects
16.2.4.4	Systemic Medical History – All Subjects
16.2.4.5	Ocular Medical History – All Subjects
16.2.5.1	Product Dispense – All Subjects
16.2.5.2	Daily Dosing Diary – All Subjects
16.2.6.1	Eye Discomfort and Eye Dryness VAS – All Subjects
16.2.6.2	Meibomian Gland Dysfunction Scores – All Subjects
16.2.6.3	Vascularity of the Eyelid Margin – All Subjects
16.2.6.4	Tear Break-Up Time – All Subjects
16.2.6.5	Upper Lid Lissamine Green Staining – All Subjects
16.2.6.6	Individual Region and Total Fluorescein Corneal Staining – All Subjects
16.2.6.7	Bulbar Conjunctival Hyperemia – All Subjects
16.2.6.8	OSDI – All Subjects
16.2.6.9	Modified BLISS – All Subjects
16.2.6.10	Unanesthesized Schirmer Test – All Subjects
16.2.6.11	Responder Status and Time to Resolution – All Subjects
16.2.7.1	All Adverse Events – All Subjects
16.2.7.2	Subject Deaths – All Subjects
16.2.7.3	Serious Adverse Events – All Subjects
16.2.7.4	Adverse Events Leading to Withdrawal – All Subjects
16.2.8.1	Laboratory Results: Hematology – All Subjects
16.2.8.2	Laboratory Results: Chemistry – All Subjects
16.2.8.3	Laboratory Results: Urine Pregnancy Test – All Subjects
16.2.9.1	Dilated Ophthalmoscopy – All Subjects
16.2.9.2	Intraocular Pressure – All Subjects
16.2.9.3	BCVA – All Subjects
16.2.9.4	Slit-lamp Biomicroscopy and External Eye Exam – All Subjects
16.2.9.5	Concomitant Medications – All Subjects

7.3. Figures to be Generated

14.1.1	Change (Mean +/- SD) from Baseline of Eye Discomfort VAS – Full Analysis Set
14.1.2	Change (Mean +/- SD) from Baseline of Eye Dryness VAS – Full Analysis Set
14.1.3	Change (Mean +/- SD) from Baseline of Study Eye Upper Eyelid Total MGD Score – Full Analysis Set
14.1.4	Change (Mean +/- SD) from Baseline of Vascularity of the Study Eye Eyelid Margin – Full Analysis Set
14.1.5	Change (Mean +/- SD) from Baseline of Study Eye Upper Lid LGS – Full Analysis Set
14.1.6	Change (Mean +/- SD) from Baseline of Study Eye tFCS – Full Analysis Set
14.1.7	Change (Mean +/- SD) from Baseline of Study Eye Bulbar Conjunctiva Hyperemia – Full Analysis Set
14.1.8	Change (Mean +/- SD) from Baseline of Study Eye OSDI Score – Full Analysis Set
14.1.9	Change (Mean +/- SD) from Baseline of Study Eye Unanesthesized Schirmer Test – Full Analysis Set
14.1.10	Change (Mean +/- SD) from Baseline of Study Eye Intraocular Pressure – Full Analysis Set