Single-Arm, Single-Center, Randomized, Single-Masked Study to Evaluate Restylane-Defyne for Canalicular Occlusion in Participants with Mild to Moderate Dry Eye Disease

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PROTOCOL 0918 STUDY SYNOPSIS

Protocol Title	**Single-Arm, Single-Center, Randomized, Single-Masked Study to Evaluate Restylane-Defyne for Punctal Occlusion in Participants with Mild to Moderate Dry Eye Disease**
Study Period	Up to 3 months
Study Population	13 adult participants with mild to moderate dry eye disease
Primary Study Objectives	Safety and effectiveness assessments of Restylane-Defyne for punctal occlusion
Treatments	Participants will receive Restylane-Defyne in the inferior punctum of one eye and a sham injection in the inferior punctum of the fellow eye.
Study Design	Prospective, randomized, single-masked study with unilateral placement of Restylane-Defyne.
Sample Size	Up to 13 participants, with a goal of 10 participants finishing study.
Examination Schedule	Participants will have a Baseline Visit within 30 days prior to the initial device application. Device application will be initiated at Day 0 with follow-up visits at 3 days, 14 days and 42 days. Participants will exit the study after the 6-week visit exam.

Clinical Assessments

Assessments performed will include:

- Ocular Surface Disease Index questionnaire
- Slit-lamp biomicroscopy with grading of corneal staining
- Schirmer test with topical anesthetic
- Tear break-up time
- Tear meniscus height
- Corrected Distance Visual Acuity

Study Endpoints

- **Primary effectiveness endpoint**

Change in Schirmer score from baseline

- **Additional effectiveness endpoints**

Changes in OSDI score, corneal staining score, tear break-up time and tear meniscus height

- **Primary safety endpoint**

Proportion of participants that experience one or more device-related adverse events (e.g., irritation, conjunctival injection, epiphora, subconjunctival hemorrhage, canaliculitis, punctal stenosis, eyelid telangiectasia, eyelid edema, eyelid induration, eyelid erythema).

- **Additional safety assessments**

Corrected distance visual acuity, slit lamp biomicroscopy findings

Inclusion Criteria

To be eligible for the study, potential participants must meet all of the following inclusion criteria at the Screening Visit:

- Twenty-one (21) to 80 years of age
- Baseline Ocular Surface Disease Index score of at least 13 with no more than 3 responses of "not applicable" for each eye individually
- In the study eye, a baseline Schirmer test with anesthetic of ≤ 10 mm/5 minutes
- Literate, able to speak English and able to complete the questionnaire independently
- Willing to sign the informed consent and deemed capable of complying with the requirements of the study protocol.

Exclusion Criteria

- To be eligible for the study, potential participants must not meet any of the following exclusion criteria:
  - Use of ophthalmic cyclosporine or lifitegrast within 30 days prior to Day 0
  - History of surgical punctal occlusion (e.g., cautery), canalicular infection or canalicular surgery
  - Corneal transplant in either eye
  - Ocular surgery (such as cataract surgery or LASIK) in either eye within six months of the Baseline Visit
  - A systemic condition or disease not stabilized or judged by the investigator to be incompatible with participation in the study (e.g. current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease)
  - The history or presence of any ocular disorder or condition in either eye that, in the opinion of the investigator, would interfere with the interpretation of the study results (e.g., significant corneal or conjunctival scarring, pterygium or nodular pinguecula; current ocular infection (except mild blepharitis), conjunctivitis or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; history of ocular herpetic infection; evidence of keratoconus; lid or lacrimal cancer.

- Active severe systemic allergy, seasonal allergies, rhinitis or sinusitis requiring treatment (i.e. antihistamines, decongestants, oral or aerosol steroids)
- Use of steroids, including administration by systemic, inhaled or topical ocular routes (dermatologic steroids not applied to the eyelids are allowed)
- Participation in a clinical trial during the past 30 days
- Women who are pregnant, planning a pregnancy, or nursing at study entry.

TABLE OF ABBREVIATIONS

AE	Adverse event
ATD	Aqueous tear deficiency
CDVA	Corrected distance visual acuity
CE	*Conformité Européenne* (European Conformity)
CRF	Case report form
DED	Dry eye disease
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic Acid
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISO	International Standards Organization
logMAR	Logarithm of the minimum angle of resolution
NEI	National Eye Institute
OSDI	Ocular Surface Disease Index
PP	Per protocol
SAE	Serious adverse event
UADE	Unanticipated adverse device effect

1. INTRODUCTION

1.1. Background

The 1995 National Eye Institute (NEI)/Industry Dry Eye Workshop defined dry eye disease (DED) as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability with potential damage to the ocular surface. Dry eye disease has a complex pathophysiology and a multifactorial etiology related to an inadequacy of one or more layers of the tear film. It is accompanied by increased osmolarity of the tears and inflammation of the ocular surface.[1] An estimated 25 million Americans are reported to have DED,[2] one of the most common reasons patients seek care with their eye care professional.[3]

DED has multiple causes and consequences, ranging in severity from mild discomfort and pain to a decrement in visual acuity resulting from irregularities in the corneal surface. Signs of DED include reduced tear volume, delayed tear clearance, abnormal tear osmolarity, decreased tear breakup time, punctate keratitis and distorted mires on keratometry or corneal topography. Symptoms include dryness, grittiness, burning, stinging, discomfort, photophobia, redness, tearing, reduced ability for prolonged reading or computer work, and fluctuating vision. These symptoms are typically worse later in the day and can be triggered or exacerbated by environmental conditions such as low humidity.

The severity and prevalence of DED in the general population increases with age and is particularly common in post-menopausal women and in those age 65 and older. While patients with mild to moderate dry eye experience a range of complaints, as described above, patients with severe dry eye are at risk for more serious ocular findings, such as punctate keratopathy evidenced by significant fluorescein staining of the cornea. More severely affected patients can experience a quality of life deficiency comparable to that of moderate to severe angina.[4] Studies suggest that dry eye is associated with significant impact on visual function, including reading and driving[5] as well as daily activities, social and physical functioning, workplace productivity and quality of life.[6]

Treatment for DED is generally palliative in nature and intended to supplement the patient's natural tears or to improve the residence time of the limited volume of tears present. Depending on the severity of disease and the underlying etiology of DED, options include artificial tear substitutes (solutions, ointments, and gels), punctal plugs, warm compresses, environmental modification, omega-3 fatty acid supplements, and moisture chamber goggles.[7, 8] For patients with an inflammatory component to their DED, topical cyclosporine (Restasis; Allergan) and lifitegrast (Xiidra; Shire) are options, and an eyelid thermal pulsation system (Lipiflow Thermal Pulsation System; TearScience Inc.) can be used by patients with concomitant evaporative dry eye (i.e. lipid deficiency dry eye). Patients with aqueous tear deficiency can use a nasal neurostimulator to temporarily increase tear production (TrueTear; Allergan). Patients with more severe disease may be treated with punctal cautery, systemic cholinergic agonists, systemic anti-inflammatory agents, mucolytic agents, autologous serum tears, PROSE scleral contact lenses[9] and tarsorrhaphy.

The most commonly used palliative option for DED, artificial tear substitutes, have significant limitations as therapeutic modalities for this condition. Many artificial tear formulations contain preservatives such as benzalkonium chloride, which have been shown to be toxic to the corneal epithelium. Although commercially available, preservative-free artificial tear products include a risk of microbial contamination if improperly stored, a limited time after opening before disposal, and a significantly greater expense than the preserved option.

Punctal plugs are associated with poor retention and complications. A study focused on the time course of retention showed that 29% of plugs were lost within the first month of use[10] and another showed that only 56% of silicone plugs were retained after two years.[11] Complications include plug migration, biofilm formation and infection.[12] Punctal plugs that are displaced into the lacrimal system may pass through the system, but blockage and secondary infection have been reported.

Given the limitations of the most commonly available therapies for DED (artificial tears and punctal plugs), it is not surprising that DED continues to be considered one of the most poorly treated diseases in ophthalmology.

1.2. Cross-Linked Hyaluronic Acid as a Device for Punctal Occlusion

Hyaluronic acid (HA) is a colorless and odorless mucopolysaccharide gel that occurs naturally in the human body, including in the eye, and serves as a scaffolding for collagen.

Hyaluronic acid is a substance well known in medicine with several FDA approved applications. HA has been used for years by cataract surgeons, who inject it directly into the anterior chamber of the eye to maintain space during surgery. More recently HA has been utilized to fill wrinkles in the face. Approved for this indication (PMA P140029), Restylane Defyne is a sterile transparent gel composed of cross-linked sodium hyaluronate of bacterial origin. The product has a HA concentration of 20 mg/ml in phosphate buffered saline at pH 7 and contains 3 mg/ml lidocaine hydrochloride added to the gel to achieve a pain-relieving effect.

Adding HA to artificial tears has been reported to be beneficial in treatment of dry eyes.[13] Because HA is soft enough to conform to the delicate inner walls of the canaliculus and block tear outflow, a canalicular plug made of HA could be useful in blocking the outflow of tears and also potentially adding its own lubricating effects. The HA would be injected into the canaliculus below the lid margin and would not rub on the lid or irritate the eye.

A unique advantage of the HA plug is full reversibility. HA is degraded by the enzyme hyaluronidase, and this is routinely used in eye surgery and with facial fillers. The effect of removing the HA is almost instantaneous. If a patient no longer needed plugs, then the procedure to remove an HA plug is to irrigate the tear duct with hyaluronidase. Both hyaluronic acid and hyaluronidase are FDA approved compounds in eye and skin procedures, with a long safety record. The placement of these products does not require

injection with a needle, but rather a gentle, simple placement with a tapered cannula in an existing body cavity of the tear duct outflow system, the canaliculus.

1.3. Summary of Findings from Previous Studies

In a pilot clinical study, Restylane was used to bilaterally occlude the lower lacrimal canaliculi in 74 participants. A total of 148 plugs were inserted as all participants had both lower puncta treated. 58 patients completed the study; 46 patients were female and 12 were male. Of the patients that did not complete the study, most missed a critical follow up visit and were excluded from evaluation per the study protocol. No patient dropped out due to dissatisfaction or a complication. The average age in the study was

66.5 years. All but 3 participants were Caucasian (2 African Americans and 1 Asian). The investigator noted that the HA plug was easy to insert.

A statistically significant increase in Schirmer score was observed in each eye at the 1- and 3-month visits by two-tail t-test (Figure 1).

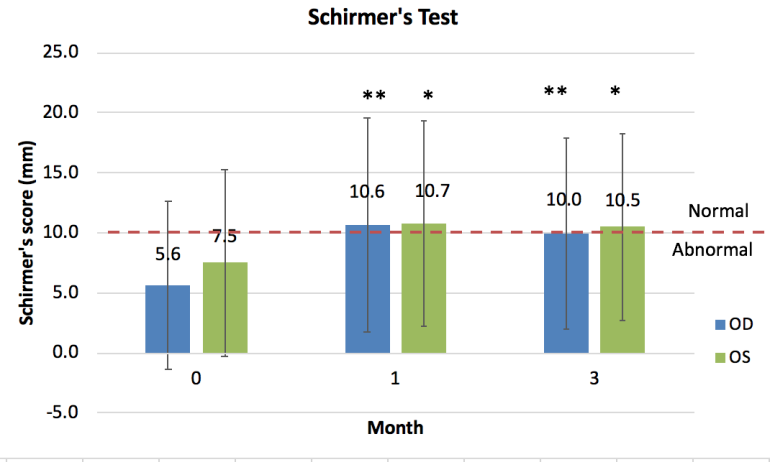


Figure 1. Schirmer scores. **p = 0.0006 and 0.0015 at 1 and 3 months, respectively; *p = 0.028 and 0.032 at 1 and 3 months, respectively.

In addition, significant improvements in tear break-up time (TBUT) and tear meniscus height were observed (Figures 2 and 3).

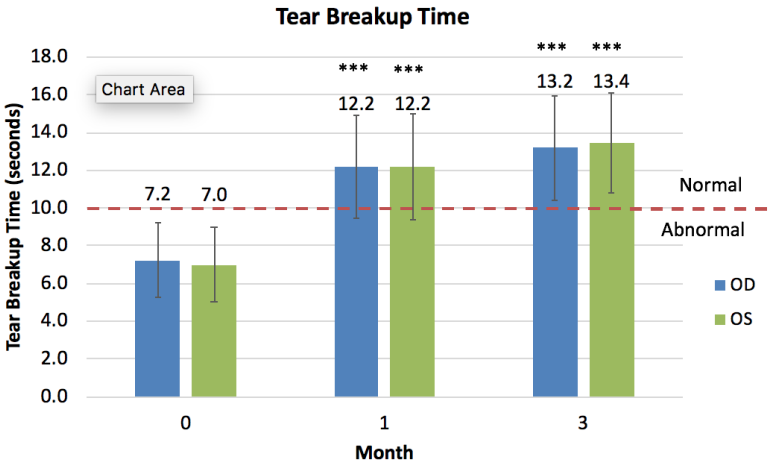


Figure 2. TBUT. ***p < 0.000 at 1 and 3 months.

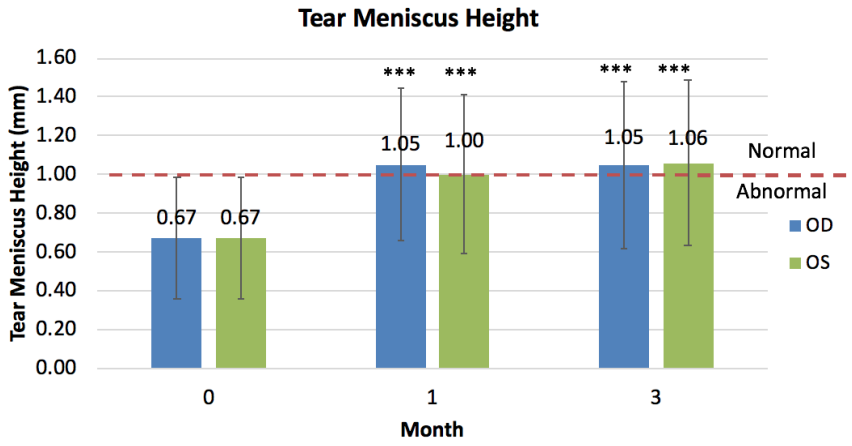


Figure 3. Tear meniscus height. ***p < 0.000 at 1 and 3 months.

When questioned at 6-moths, 83% of participants responded that they would have the treatment again. On a numerical scale, with "1" for agree to "5" for disagree, the average score was 2.4 when patients were asked if their eyes felt better after receiving the HA plug. Of note, these numerical values were reported at a 6- month phone interview, indicating that some patients were benefitting from the HA filler even after 6 months from injection.

There was one case of conjunctivitis that resolved and was believed to be an incidental viral infection. There were no other adverse events reported, including no canaliculitis, swelling, bruising or intraocular inflammation.

A complete study report is provided in Appendix D, Pilot Study Report.

1.4. Risks and Benefits.

The risks associated with the use of this non-significant risk device are low. Restylane-Defyne is an approved product, and HA has been used as both a topical and intracameral ocular agent. Punctal plugs in general are not considered significant risk devices, and the use of cross-linked HA for punctal occlusion has previously been recognized as a non-significant risk device by the Sarasota Memorial Hospital Institutional Review Board in Sarasota, FL. For further information see documentation provided in Appendix C, Correspondence with Sarasota Memorial Hospital Institutional Review Board.

Potential adverse events which may occur during the course of this study include irritation, conjunctival injection, epiphora, subconjunctival hemorrhage, canaliculitis, punctal stenosis, eyelid telangiectasia, eyelid edema, eyelid induration and eyelid erythema. Potential benefits include decreased signs and symptoms of dry eye disease.

2. STUDY OBJECTIVES

The objective of this pilot study is to investigate the safety and effectiveness of HA lacrimal occlusion in patients with mild to moderate dry eye disease.

3. STUDY DESIGN

3.1. Description of Study Design

The study is a single-arm, single-center, randomized, single-masked prospective study to evaluate Restylane-Defyne for canalicular occlusion in participants with mild to moderate dry eye disease.

Each participant will have a Screening Visit to determine eligibility. Prior to performing any testing specifically for the Screening Visit, participants will be provided with an IRB approved informed consent form and be given the chance to review and ask questions before written informed consent is obtained. The Screening Visit should occur within 30 days prior to application of the HA gel on Study Day 0 and may occur on Day 0. Participants that meet all eligibility criteria will be invited to participate in the study.

Participants that return or are present for Study Day 0 will be enrolled in the study and will receive the device. Participants will be followed for 42 days and will be seen for follow-up exams at 3, 14 and 42 days.

Participants may continue to use their artificial tears. The use of artificial tears will be recorded.

3.2. Study Endpoints

3.2.1. Effectiveness Endpoints

The primary effectiveness endpoint will be change in Schirmer score from baseline. Secondary effectiveness endpoints include changes in Ocular Surface Disease Index (OSDI) score, corneal staining score, tear break-up time and tear meniscus height

3.2.2. Safety Endpoints

The primary safety endpoint will be the proportion of participants that experience one or more device-related adverse events (e.g., irritation, conjunctival injection, epiphora, subconjunctival hemorrhage, canaliculitis, punctal stenosis, eyelid telangiectasia, eyelid edema, eyelid induration, eyelid erythema).

3.3. Study Population

The study will enroll up to 13 participants at one site that provide informed consent and meet the eligibility criteria below.

3.3.1. Inclusion Criteria

To be eligible for the study, potential participants must meet all of the following inclusion criteria at the Screening Visit:

- Twenty-one (21) to 80 years of age
- Baseline OSDI score of at least 13 with no more than 3 responses of "not applicable"
- In both eyes, a baseline Schirmer test with anesthetic of ≤ 10 mm/5 minutes
- Literate, able to speak English and able to complete the questionnaire independently
- Willing to sign the informed consent and deemed capable of complying with the requirements of the study protocol.

3.3.2. Exclusion Criteria

To be eligible for the study, potential participants must not meet any of the following exclusion criteria:

- Use of ophthalmic cyclosporine or lifitegrast within 30 days prior to Day 0
- History of surgical punctal occlusion (e.g., cautery), canalicular infection or canalicular surgery
- Corneal transplant in either eye
- Ocular surgery (such as cataract surgery or LASIK) in either eye within six months of the Baseline Visit
- A systemic condition or disease not stabilized or judged by the investigator to be incompatible with participation in the study (e.g. current systemic infection, uncontrolled autoimmune disease, uncontrolled immunodeficiency disease)
- The history or presence of any ocular disorder or condition in either eye that, in the opinion of the investigator, would interfere with the interpretation of the study results (e.g., significant corneal or conjunctival scarring, pterygium or nodular pinguecula; current ocular infection (except mild blepharitis), conjunctivitis or inflammation not associated with dry eye; anterior (epithelial) basement membrane corneal dystrophy or other clinically significant corneal dystrophy or degeneration; history of ocular herpetic infection; evidence of keratoconus; lid or lacrimal cancer.
- Active severe systemic allergy, seasonal allergies, rhinitis or sinusitis requiring treatment (i.e. antihistamines, decongestants, oral or aerosol steroids)
- Use of steroids, including administration by systemic, inhaled or topical ocular routes (dermatologic steroids not applied to the eyelids are allowed)
- Participation in a clinical trial during the past 30 days
- Women who are pregnant, planning a pregnancy, or nursing at study entry.

3.3.3. Inclusion/Exclusion Exceptions

The investigator has the right to exclude a potential participant's enrollment in the study if s/he deems it in the best interest of the participant. Reasons for exclusion on this basis will be recorded.

3.3.4. Discontinuation

A participant may voluntarily discontinue participation in the study at any time without prejudice. The investigator may elect to discontinue a participant for reasons unrelated to the study device (e.g. failure to comply with the study protocol, missed visits, etc.) or for reasons related to the study device (e.g. adverse event). In any event, the reason(s) for discontinuation should be recorded on the CRF. Possible reasons for study discontinuation can include the following:

- AEs necessitating discontinuation from the study
- The participant fails to comply with the study protocol or misses visits
- Participant decision unrelated to AEs
- Investigator decision (specify on CRF)
- Other reason (specify on CRF)

If a participant chooses to discontinue his/her participation or is discontinued by the investigator, the exit CRF should be completed. In case of premature discontinuation from the study, the examiner should perform any testing required to ensure that the participant's ocular health is within normal limits, if the participant agrees.

Participants to be discontinued for AE(s) will be followed until the event is resolved or considered medically stable by the investigator if the participant agrees. If a participant is lost-to-follow-up, the investigator should do his/her best to contact the participant initially by phone, then by letter, and finally by certified mail. Evidence of these contacts should be recorded in the participant's medical chart.

Participants discontinued prior to the initial device application (Day 0) may be replaced and new participants will be assigned new study ID numbers.

3.3.5. Pregnancy

Women of childbearing potential (WOCBP) includes any females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or are not postmenopausal with at least 12 months since last menses. WOCBP will be required to use designated methods of birth control during the course of the study. All women who are pregnant, nursing an infant, or planning a pregnancy will be excluded from participation.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). A pregnancy test should be performed and, if the results are positive, the participant should discontinue use of the device and exit from the study. The Exit CRF should be completed and the reason for discontinuing the study should be recorded as pregnancy.

If a participant or investigator suspects that the participant may be pregnant prior to study device application, the study device must be withheld until the results of pregnancy testing are available. If pregnancy is confirmed, the participant must not administer the study device and must not be enrolled in the study or will be withdrawn from the study.

3.4. Expected Duration of Follow-up and of Study

Participants will have the investigational device for up to 42 days. Total elapsed time for study participation will be up to 72 days. The expected duration for the entire study will be up to approximately 3 months.

3.5. Enrollment

Prior to the Screening Visit, potential participants will be provided with an IRB approved informed consent document and have the opportunity to review and ask questions before giving written informed consent. If required, the participant will sign and date the informed consent document in the presence of a witness. The investigator or appropriate staff member will also sign and date the consent form as required. The original will be retained with the participant records and a copy will be provided to the participant.

Once informed consent has been provided, the participant can undergo screening procedures. During the screening examination, participants should be identified only by their initials in the screening and enrollment log. For participants who have no middle name, a dash (-) should be used in place of the middle initial. After the participant has completed the required testing and met eligibility, the participant is considered eligible to participate and will be scheduled to return for Day 0. Once the participant returns for Day 0 and uses the device, they will be considered enrolled in the study and receive a unique identification number.

3.6. Randomization

This is a single-arm, randomized, single-masked study in which one eye will receive the device in the lower canaliculus and the fellow eye will receive a sham injection of saline in the lower canaliculus. The eye which receives the device will be determined by a randomization sequence. The participant will remain masked as to which eye received the device and which eye received the sham.

3.7. Clinical Assessments

The following clinical assessments will be performed for this study:

- Ocular Surface Disease Index (OSDI) questionnaire for each eye individually
- Corrected Distance Visual Acuity
- Tear break-up time
- Tear meniscus height
- Slit-lamp biomicroscopy
- Corneal staining scored using the NEI grid and grading system
- Schirmer test with topical anesthetic

A detailed description of the procedure for each assessment can be found in Appendix B.

3.8. Visit Schedule

This study consists of five visits: Screening, Day 0, Day 3, Day 14 and Day 30. A Schedule of Assessment with a summary of the testing required at each visit can be found in Appendix A.

3.8.1. Screening (Day -30 to 0)

Any tests or procedures that are performed to confirm eligibility and are not standard of care must be performed AFTER the potential participant has signed the Informed Consent Form.

The following procedures are performed at the Screening visit:

- Obtain medical history and confirm potential participant's age
- Obtain written informed consent
- Perform urine pregnancy test for women of childbearing age
- Have potential participant complete the Ocular Surface Disease Index OSDI) for each eye individually
- Perform Corrected Distance Visual Acuity
- Perform baseline TBUT test
- Perform baseline tear meniscus height test
- Administer fluorescein stain
- Perform slit-lamp biomicroscopy and assess corneal staining using the NEI grid and scoring system
- Perform baseline Schirmer test with topical anesthetic

If at any point in this process, the potential participant fails to meet eligibility, the process should be discontinued, and the potential participant should be recorded as a screen failure along with the reason.

3.8.2. Day 0

The following procedures are performed at the Day 0 visit:

- Have participant complete the OSDI for each eye individually
- Perform Corrected Distance Visual Acuity
- Instill HA device in inferior canaliculus of eye randomized to the device
- Instill saline in inferior canaliculus of fellow eye

3.8.3. Day 3 and 14

The following procedures are performed at the intermediate follow-up visits, Days 3 and 14:

- Have participant complete the OSDI for each eye individually
- Perform corrected distance visual acuity
- Perform slit-lamp biomicroscopy

3.8.4. Day 42

The following procedures are performed at the Day 30 visit:

- Have participant complete the Ocular Surface Disease Index OSDI) for each eye individually
- Perform Corrected Distance Visual Acuity
- Perform TBUT test
- Perform tear meniscus height test
- Administer fluorescein stain
- Perform slit-lamp biomicroscopy and assess corneal staining using the NEI grid and scoring system
- Perform Schirmer test with topical anesthetic
- Remove device from inferior canaliculus by irrigation (if necessary for complete removal, hyaluronidase may be used)

3.9. Concomitant Medications and Therapies

All concomitant medications used within the 30 days prior to the screening visit, including medications used for relief of dry eye symptoms, will be documented on the case report form. Any initiation of new medications or changes to current medications during the course of the study should be recorded on the appropriate case report form. No other experimental drug or device should be used within 30 days prior to the Screening Visit or during the course of the clinical trial.

At the end of the Screening Visit, participants should be instructed not to use perfume or make-up on study days. Participants should also be instructed to refrain from administration of any chronic ophthalmic medication for two hours before their visit.

3.10. Participant Completion Procedures

A participant's participation in the study will be considered to have been completed when all assessments have been performed in accordance with the study protocol. At the end of the study, participants will be exited. If a participant chooses to discontinue the study before completion, the participant will be exited from the study.

3.11. Study Termination

The investigator reserves the right to discontinue the study for any safety or ethical reason at any time.

4. STATISTICS

4.1. Sample Size

This is a pilot, feasibility study. No sample size calculation has been performed.

4.2. Clinical Hypothesis

As a pilot, feasibility study, there is no clinical hypothesis.

4.3. Randomization

This is a single-arm, randomized, single-masked study in which one eye will receive the device in the lower canaliculus and the fellow eye will receive a sham injection of saline in the lower canaliculus. The eye which receives the device will be determined by a randomization sequence.

4.4. General Statistical Considerations

4.4.1. Participant Accountability and Missing Data

Participants who withdraw from the study will be tabulated with the reasons for the withdrawal.

4.5. Participant Demographic and Baseline Characteristics

The demographic and baseline characteristics of the study population observed will be presented descriptively. For continuous variables such as participant age, the mean, standard deviation (SD), median and range will be presented. For categorical variables such as gender, the number with or experiencing the condition, the total number evaluated, the percentage, and the exact 95% confidence interval on the percentage will be presented.

4.6. Effectiveness Analyses

The assessment of effectiveness will be based on the changes in the primary and secondary effectiveness endpoints from baseline to 6 weeks in the eye which receives the device as compared with the eye which receives the sham injection.

4.7. Safety Analyses

The primary safety endpoint will be the proportion of participants that experience one or more device-related adverse events. For corrected distance visual acuity, the proportion of participants s with an improvement of more than two lines (11 or more letters), a worsening of more than two lines and a change of two lines or less will be summarized along with the exact 95% confidence interval at each visit. Biomicroscopy

results will also be presented as the proportion of participants with a clinically significant change from Baseline at each visit. Particular attention will be paid to any changes to the corneal surface. Summaries will be provided of the proportion of participants that experienced an unexpected device-related serious adverse event, the proportion of participants that experienced any adverse event and the proportion of participants that experienced each unique adverse event.

4.8. Final Clinical Report

A final clinical study report will be prepared after completion of the study.

5. DATA MANAGEMENT

Standardized CRFs will be used for reporting the results of the study. All data from the study will be entered from the CRFs into a central database. Study participants will be identified on the CRFs and in the database using the participant ID to maintain confidentiality. Incoming data will be reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed by the investigator.

6. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1. Definitions

Adverse Event (AE): An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or any procedures involved (any procedure in the study protocol). For users or other persons this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): An AE should be classified as an SAE and reported as such if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death);
- It is life threatening (i.e., the AE places the participant at immediate risk of death);
- It requires or prolongs inpatient hospitalization. If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a participant is hospitalized to undergo coronary bypass surgery, the heart condition that necessitated the bypass should be recorded. Hospitalizations for diagnostic or elective surgical procedures or hospitalizations required to allow outcome measurement for the study should not be recorded as SAEs:

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions);
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational device;
- It is considered a significant medical event by the investigator based on medical judgment (e.g. may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above);
- It is considered sight-threatening by the investigator.

Unanticipated Adverse Device Effect (UADE): An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the informed consent form. UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants.

6.2. Adverse Event Assessment and Documentation

All participants who have been exposed to application of the study device should be evaluated for adverse events. All adverse events, regardless of severity and whether or not they are ascribed to the study device, should be recorded in the source documents and CRFs using standard medical terminology.

All adverse events should be evaluated beginning with onset and evaluation should continue until resolution is noted or until the investigator determines that the participant's condition is stable. The investigator should take appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication CRF.

Pre-existing conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF but should be recorded in the medical history. Changes in a chronic condition or disease that are consistent with natural disease progression do not need to be recorded as adverse events and should not be recorded on the AE pages of the CRF. Clinical study staff should start assessing participants for AEs from the time of the first device application.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event. If more than one distinct adverse event occurs, each event should be recorded separately. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should

be recorded as individual AEs (e.g. if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

Adverse events occurring secondary to other events (e.g. sequelae) should be identified by the primary cause. A "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example: Orthostatic hypotension $\Rightarrow$ fainting and fall to floor $\Rightarrow$ head trauma $\Rightarrow$ neck pain. The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

6.3. Classification

6.3.1. Intensity / Severity

All adverse events should be graded on a 4 point scale (mild, moderate, marked, severe) for intensity / severity. These definitions are as follows:

- Mild: Transient discomfort; no medical intervention / therapy required and does not interfere with daily activities.
- Moderate: Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.
- Marked: Considerable discomfort with limitation in daily activities; some assistance usually required; medical intervention/therapy usually required.
- Severe: Extreme discomfort and limitation in daily activities; significant assistance required; ***significant*** medical intervention/therapy required.

Note: There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events.

6.3.2. Expectedness

All AEs should be evaluated as to whether they are expected or unexpected.

- Expected (anticipated): An adverse event is expected when the nature, severity or degree of incidence was previously described.
- Unexpected (unanticipated): An adverse event is unexpected when the nature, severity or degree of incidence was not previously described.

6.3.3. Relatedness

The study investigator should evaluate if the AE is related to the use of the study device. Relationship is defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study device such that:

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and device application, and/or
- A causal relationship is considered biologically implausible, and/or
- The AE can be attributed to concurrent/underlying illness, other drugs or procedures.

Possibly related: Evidence indicates a possible relationship to the study device such that:

- The event occurs within a reasonable period of time relative to the application that makes a causal relationship possible, but plausible explanations may also be provided by other causes such as other drugs, products, chemicals, underlying disease, environment, etc., and/or
- The event is possibly related to the study application.

Related: Evidence indicates a reasonable temporal sequence of the event with the study device application exists or that the association of the event with study device application is unknown and the event is not reasonably supported by other conditions such that:

- There is a clinically plausible time sequence between onset of the AE and study device application a, and/or
- There is a biologically plausible mechanism for study application causing or contributing to the AE, and/or
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs or procedures.

6.3.4. Outcome

The clinical outcome of an AE should be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death

6.3.5. Treatment or Action Taken

The clinical treatment or action taken from an AE should be characterized as follows:

- None
- Medical intervention
- Surgical intervention
- Other

6.4. Anticipated Adverse Events

The following is a list of anticipated adverse events:

- Ocular discomfort or irritation
- Conjunctival injection
- Canaliculitis
- Subconjunctival hemorrhage
- Punctal stenosis
- Eyelid telangiectasia
- Eyelid edema

- Eyelid induration
- Eyelid erythema
- Epiphora
- Clinically significant decrease (>10 letters) in Corrected Distance Visual Acuity
- Clinically significant increase in corneal epithelial staining, e.g., an increase in corneal staining score of 2 or more in at least one corneal region or an increase in the sum for all corneal regions of 4 or more (using NEI grid and scale)

7. INVESTIGATOR QUALIFICATIONS AND RESPONSIBILITIES

7.1. Qualifications

The investigator is a licensed physician who has completed a residency in ophthalmology.

7.2. Responsibilities

The investigator has the following responsibilities:

- Ensure that the clinical study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155:2011, GCP, ICH guidelines, and any regional or national regulations as appropriate.
- Ensure that participants undergo no investigational procedures other than those described in this protocol and approved by the IRB, except those procedures deemed necessary to protect the health and well-being of the participants. Any such procedures will be documented in the participant's records and reported to the sponsor and the IRB.
- Report any use of the investigational device without first obtaining informed consent to the IRB and sponsor
- Assure that all participants entering the study conform to the participant selection criteria
- Assure that IRB approval of the study protocol and informed consent has been obtained and provided to the site prior to initiation of the study
- Perform the participant evaluations as described in the study protocol and not deviate from the study protocol unless protection of the health, safety or welfare of study participants requires prompt action
- Notify the IRB of unanticipated adverse device effects
- Ensure participant confidentiality

- Submit regular progress reports to the IRB as required
- Report any emergency deviations from the protocol that are necessary to protect study participants to the IRB within five working days of occurrence
- Submit a final report for the study to the IRB in a timely manner
- If any additional requirements are imposed by the IRB or regulatory authority, these requirements shall be followed.

7.3. Informed Consent Process

The site will submit the proposed informed consent to the IRB. Potential participants cannot be asked to sign the informed consent form until the study has been fully approved by the IRB. The following information should be provided in the informed consent:

- The study is research
- Purpose of the study, including the approximate duration of participation by the participant and a description of the procedures
- Possible side effects, risks or discomforts of the investigational device
- Reasonably expected benefits
- The existence of alternative therapy options and/or alternatives to participating in the study
- Confidentiality of records
- Costs and compensation or treatment for injury
- Person to contact regarding participant rights or for questions on research or research-associated injury
- That participation is voluntary
- The right to discontinue participation from the study at any time without disadvantage to the participant
- That the participant will be informed of new information learned during the study, which may affect the participant's decision to continue participation in the study

The investigator will obtain written informed consent from each participant prior to the initiation of any study-specific activities. Copies of the informed consent form used in the study should include the IRB-approved stamp (if applicable) and version date. The participant or participant's legally authorized representative (if applicable) will be allowed sufficient time to thoroughly read, or have read and explained to them, the informed consent form. The investigator will answer any questions that the participant or representative might have. If the participant agrees to participate in the study, all required parties should sign and date the informed consent form. The original signed

informed consent form will be retained by the site and a copy will be given to the participant for his/her records. The obtaining of informed consent and the date of that informed consent should be noted in the participant's medical record. It should also be noted in the participant's medical record that informed consent was obtained prior to conducting any study-specific activities.

7.4. Records

7.4.1. Source Documents

Source documentation for this study will be maintained to document the application and study course of each participant and to substantiate the integrity of the trial data. Source documentation will include, but may not be limited to, worksheets, hospital and/or clinic or office records documenting participant visits including study and other treatments or procedures, medical/ophthalmologic history and physical examination information, laboratory and special assessment results, pharmacy records, device accountability records, and medical consultations. In this study, case report forms can be used as source documents where appropriate.

The investigator is responsible for maintaining adequate case histories in the source documents of each participant. The following data will be reported by the investigator in the source medical records of each participant enrolled in the study:

- The date the participant entered the study and the participant number
- The study protocol number
- The date that informed consent was obtained
- Evidence that the participant met the study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study-related participant visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Occurrence and status of any adverse events
- The date the participant exited the study and a notation as to whether the participant completed the study or was discontinued, including the reason for discontinuation.

7.4.2. Case Report Forms

Case report forms will be filled out completely for each participant in accordance with instructions. The investigator should ensure that all data on the CRF is accurate and consistent with the source documents. Only the principal investigator may sign and date the designated CRF page(s).

7.4.3. Screening/Enrollment Log

The investigator will maintain a screening log that will record the date of screening, the enrollment status (enrolled/excluded), the date of informed consent and the reason for exclusion for all screen failures.

7.4.4. Device Accountability

The investigator will be responsible for maintaining a device accountability log that will track device usage for all study participants. Information tracked will include date of device application, lot number and the participant ID.

7.4.5. Record Retention

The investigator is responsible for maintaining adequate records to enable the conduct of the study to be fully documented. This includes:

- Signed protocol and amendments
- Signed and dated informed consents per institutional policy
- Signed, dated, and completed CRFs and documentation of CRF corrections
- Notification of SAEs and related reports
- All study device dispensing and accountability logs
- Shipping records of investigational device and trial-related materials
- Dated and documented IRB protocol approvals and all correspondence between the investigator and IRB
- *Curriculum vitae* and current medical license for principal investigator

The investigator must maintain a copy of all study documents for the period of time that is required by the regulatory authorities.

7.4.6. Deviations from the Investigational Plan

The investigator shall notify the IRB of any deviation from the Investigational Plan to protect the life or physical well-being of a participant in an emergency. Such notice shall be given as soon as possible, but in no event later than five (5) working days after the emergency occurred.

8. ETHICS

8.1. Study Conduct

The study will be performed in accordance with the relevant parts of the Code of Federal Regulations, ICH Guidelines for Good Clinical Practices, the Declaration of Helsinki and any other applicable regional and/or national regulations.

8.2. Ethics Review

Before any participant can be enrolled in this study, the IRB will review and approve the protocol and the Informed Consent Form to be used.

8.3. Confidentiality

Confidentiality of participants will be maintained throughout the study. A unique identification code will be assigned to each participant enrolled in this study. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique code and will not reveal the participant's identity.

8.4. Amendments to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the participants) must be approved by the IRB before it may be implemented. No change in the conduct of the study will be instituted without written approval from the Sponsor.

9. APPENDICES

9.1. Appendix A – Schedule of Assessments

Procedure/Assessments	Baseline Day -30 to 0	Application Day 0	Form 1 Day 3 ± 1	Form 2 Day 14 ± 2	Form 3 Day 42 ± 5
Informed Consent/HIPAA	X				
Demographics	X				
Eligibility	X				
OSDI Questionnaire (OD, OS separately)	X	X	X	X	X
CDVA	X	X	X	X	X
Slit Lamp Examination	X	X	X	X	X
Grading of Corneal Staining	X				X
Schirmer Test	X				X
Tear break-up time	X				X
Tear meniscus height	X				X
Application of device and control		X			
Removal of device					X
Adverse Events		X	X	X	X

9.2. Appendix B – Examinations and Procedures

9.2.1. Questionnaire

To minimize bias, participants will be asked to complete the questionnaire independently and in private after instructions have been provided by site personnel. The questionnaire should be completed twice and answered by the participant with reference to each eye individually.

Ocular Surface Disease Index (OSDI)

The OSDI is a 12-item questionnaire generated by the Outcomes Research Group at Allergan (Irvine, CA),[14] which asks participants to describe the severity and the nature of their irritation symptoms. The participant will answer the 12 questions by circling the number that best represents each answer: 4 (all of the time), 3 (most of the time), 2 (half of the time), 1 (some of the time), or 0 (none of the time). The final score for the questionnaire is calculated as follows:

Add subtotals from Sections I, II, and III = A

Determine total number of questions answered from Sections I, II, and III (do not include N/A) = B

Final OSDI score = A x 25 divided by B

An example of the questionnaire is as follows:

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)

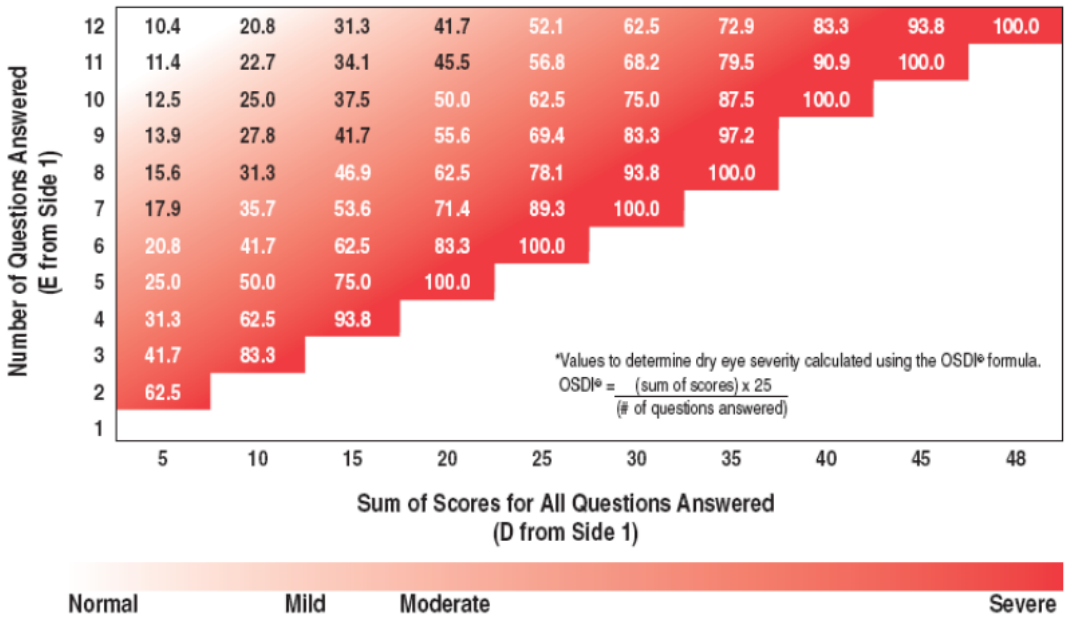
Please turn over the questionnaire to calculate the patient's final OSDI® score.

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

9.2.2. Corrected Distance Visual Acuity

Corrected distance visual acuity (CDVA) should be recorded with the participant's current spectacle correction or with the most current spectacle correction in a trial frame using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The number of letters read correctly will be recorded. The CDVA should be collected at the screening examination and on the application day, both before and after the three randomized applications are administered, using the same spectacle correction used during the screening examination. If the CDVA is not believed to be maximal during the screening visit, pinhole visual

acuity should be recorded for this reading throughout the study or a manifest refraction should be performed.

Note: Repeated use of topical anesthetic and Schirmer testing may result in a transient decrease in CDVA.

Early Treatment Diabetic Retinopathy Study (ETDRS) Corrected Distance Visual Acuity

The equipment used will include a set of two Lighthouse Distance Visual Acuity Test charts (ETDRS Charts 1 and 2; Lighthouse Low Vision Products Precision Vision, Long Island, New York) and a retroilluminated box providing standardized chart illumination. Most of the room lights should be turned off during the visual acuity test as the box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. With the box light off, not more than 15 foot-candles of light should fall on the center of the chart. A distance of exactly 4 meters is required between the participant's eyes and the visual acuity chart for the 4-meter test and a distance of exactly 1 meter is required for the 1-meter test.

The participant can be standing or sitting and will be asked to focus on an ETDRS visual acuity chart. Testing of all eyes should begin at the 4 meter test distance. The examiner should ensure that the head does not move forward or backward during testing. After careful instruction, testing should begin with the right eye using Chart 1.

The participant should be told (and reminded if appropriate) that the chart has letters only and no numbers. The participant should be asked to read at a steady pace, at a rate no faster than about one letter per second, and not to proceed until providing a definitive response. Examiners should not point to specific letters on the chart or read any of the letters during testing. If the participant says s/he cannot read a letter, s/he should be encouraged to guess. If the participant identifies a letter as one of two or more letters, s/he should be asked to choose one letter. When it becomes evident that no further meaningful readings can be made despite encouragements to read or guess, the examiner should stop the test for that eye.

Each letter is scored as right or wrong. Once a participant has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter should not be accepted. If the participant changes a response aloud (e.g. "That was a 'C,' not an 'O') before s/he has read the next letter aloud, then the change should be accepted. If the participant changes a response after beginning to read the next letter, the change is not accepted. The test is repeated for the left eye using Chart 2. Chart 1 should not be exposed to the left eye and Chart 2 should not be exposed to the right eye, even when switching charts and occlusion.

1-Meter Test

Eyes reading 19 or fewer letters correctly at 4 meters should be tested at 1 meter. If the spectacles or trial frame is to be removed when changing the test distance

from 4 meters to 1 meter, the testing chart should first be removed from view to prevent the participant from reading the chart with the fellow eye. Before testing at 1 meter, a +0.75 D sphere should be added to the 4-meter correction already in the trial frame to compensate for the closer testing distance. The avoidance of any head movement forward to backward is particularly important during the 1-meter test. The participant should be asked to read only the first six lines at 1 meter, making 30 the maximum score attainable at that distance.

Light Perception

If visual acuity is so poor that the participant cannot read any of the largest letters at 1 meter (i.e., the number of letters read correctly at 1 meter is zero), light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope light should be in focus at 3 feet with the rheostat set at maximum voltage. From a distance of 3 feet, the beam should be directed in and out of the eye at least four times and the participant should be asked to respond when s/he sees the light. If the examiner is convinced that the participant perceives the light, vision should be recorded as "light perception," and, if not, vision should be recorded as "no light perception."

Corrected Distance Visual Acuity Scoring Instructions

The ETDRS visual acuity worksheets are for clinic use only. The examiner records each letter identified correctly by circling the corresponding letter on the appropriate worksheet. The examiner records letters read incorrectly with an 'X' and leaves letters for which the participant makes no guesses unmarked. Each letter read correctly is scored as one point. After testing is completed, the score for each line (which is zero if no letters are read correctly) and the total score for each eye are recorded on the visual acuity worksheet. If testing at 1 meter is not required, 30 points are automatically scored for the 1-meter test. The total combined score (i.e., the sum of the 4- and 1-meter scores) are entered on the worksheet as the final visual acuity letter score.

Note: A clinically significant visual acuity decrease (defined as an increase of 0.22 or greater in logMAR score from Day 0) at a Follow-up visit will be considered an adverse event.

9.2.3. Slit Lamp Biomicroscopy

A slit lamp examination will be performed at the screening and twice during the application visit, once prior to the first application and once following the completion of all three applications. Biomicroscopy will be used to assess the following structures for pathology:

- Eyelids (i.e., Meibomian glands, lid margin, puncta, lashes)
- Cornea (the presence or absence of corneal edema will be noted)
- Conjunctiva
- Anterior chamber
- Lens

9.2.4. Ocular Surface Staining – Corneal Staining Using Fluorescein

Ocular surface staining using fluorescein will be assessed and recorded in the schematic representation of 5 corneal regions per eye on the case report form using the NEI grading system.[15]

First, corneal staining should be assessed using 1.0 mg sodium fluorescein strips. After moistening the tip of the strip with sterile buffered saline, the excess is shaken into a waste bin with a sharp flick. The lower lid is then pulled down and the flat end of the tip should be gently applied to the inferior tarsal conjunctiva with the intent of not inducing reflex tearing and instilling a very small volume of dye. The patient will be instructed to blink naturally several times without forced closure of the eyelid to distribute the fluorescein. After allowing fluorescein to remain on the eye for at least one minute, 5 corneal regions will be graded using a cobalt (blue) filter to maximize the view of the fluorescence. The upper eyelid is lifted slightly to grade the entire corneal surface.

9.2.5. Schirmer Test

The Schirmer test with topical anesthetic[16] will be used to assess tear production using the following steps:

1. Topical anesthetic drops such as 0.5% proparacaine hydrochloride or equivalent should be instilled in both eyes of the participant.
2. As soon as the anesthetic drop has been instilled, the participant will be instructed to keep the eyes gently closed for one minute. The closed eyes can be gently blotted.
3. After opening the eyes and allowing the eyes to recover for approximately one additional minute, excess moisture in the inferior fornix is gently removed with a spear.
4. Schirmer strips (35 mm x 5 mm size filter paper strip) will be placed in each eye at the junction of the middle and lateral thirds of the lower eye lid.
5. Under ambient light, the participant will be instructed to look forward and to blink normally during the course of the test. The test should be performed in a room with no direct air on the participant's face.
6. After five minutes, strips will be removed from both eyes and the amount of wetting will be recorded. The strips should be taped to the CRF.

Note: Should the Schirmer score reach maximum prior to the five minute endpoint, the time it took to reach maximum should be recorded for each individual strip.

9.2.6. Tear Break-up Time Test

A non-invasive tear break-up time test will be performed with the Keratograph 5M according to the manufacturer's directions, as reproduced below.

Non-Invasive Keratograph Break-Up Time (NIKBUT)

Placido rings are reflected on the corneal surface. The software analyzes different segments and a distortion in the reflected mires is recorded as a break in the tear film. The results are displayed in a color-coded map, where red/orange segments correspond with a faster break-up time. A break-up characteristics map shows the total area (%) of the cornea affected during the measuring time. The time when the first break in the tear film occurred is displayed, as well as the average time of all the break-ups that occurred during the measurement. The software automatically grades the level according to the JENVIS grading scale, see below figures.

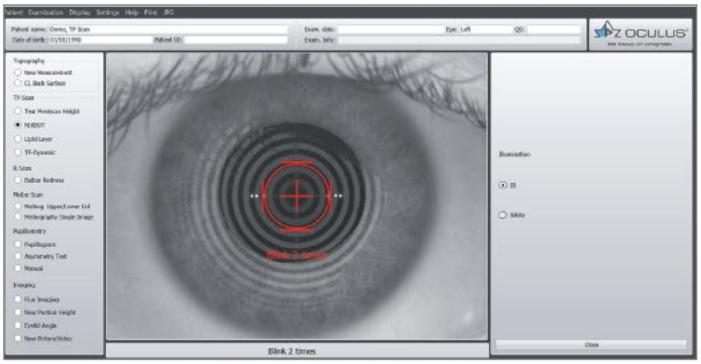


Figure 14: Keratograph 5M NIKBUT acquisition window

Important: Ask the patient to blink twice when prompted by the software!

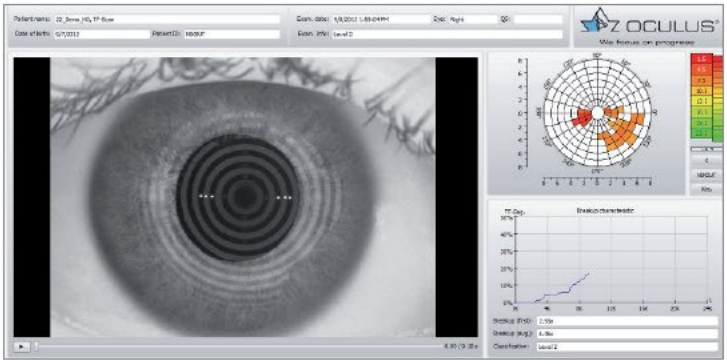


Figure 15: Keratograph 5M NIKBUT result map

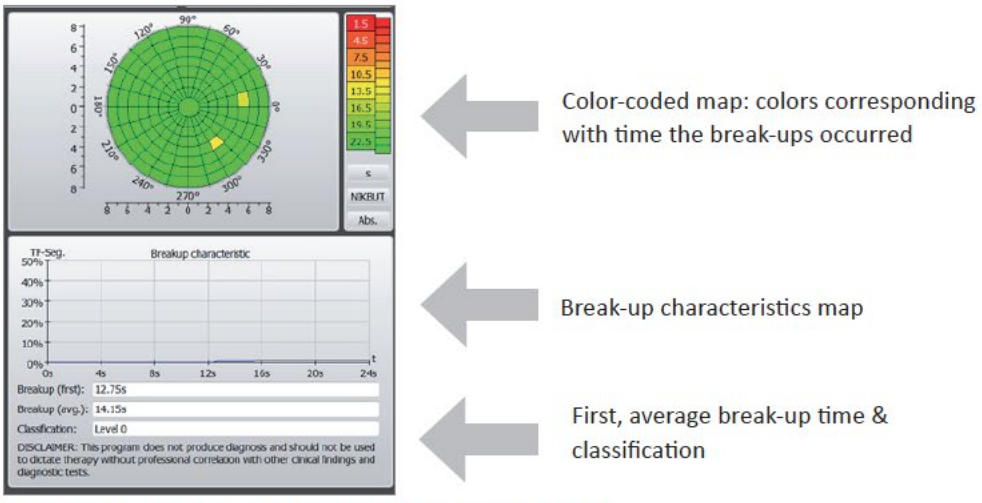


Figure 16: Detailed NIKBUT and automatic classification, here 'Level 0'

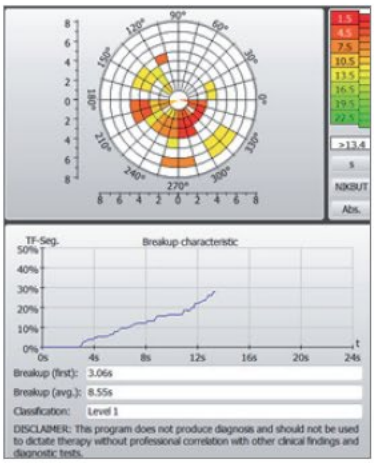


Figure 17: Detailed NIKBUT and automatic classification, here 'Level 1'

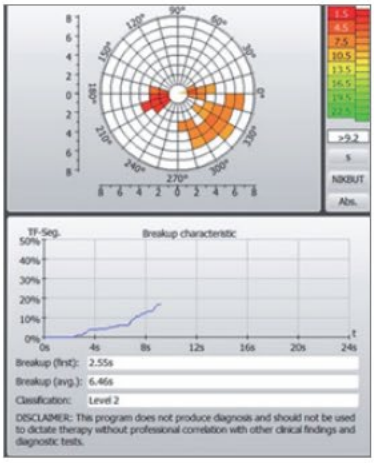


Figure 18: Detailed NIKBUT and automatic classification, here 'Level 2'

- Objective

  To evaluate the quality (stability) of the tear film

- Method
  - Instruct the patient to blink naturally. Avoid unnatural/forced/double blinks.
  - When device is aligned, notice will be given to instruct patient to blink twice. After the second blink, measurement will automatically begin.
  - Instruct and motivate the patient to keep his/her eyes open without blinking.
  - Measurement is automatically terminated if the patient blinks, moves strongly, or the tear film significantly breaks up.
  - A break-up characteristics map display total area of the cornea being affected by breaks in the tear film.
  - First and average break-up time is displayed in the results display.

- Reported values:

  9.7 ± 6.7 seconds for normal eyes and 4.6 ± 1.3 seconds for dry eyes[12] (Study from Japan).

  4.3 ± 0.3 seconds for normal eyes and 2.0 ± 0.2 seconds for dry eyes[13] (Study from China).

- Tips and advice
  - Perform measurement of NIKBUT after TMH measurement
  - Dry eye patients: First break-up area recordet with NIKBUT shows a tendency of occuring in the inferior cornea. First tear film break-up area during fluorescein BUT is also generally observed in these areas

- Step by step
  1. Enable 'NIKBUT' button
  2. Select infrared or white light
  3. Adjust camera if necessary
  4. When aligned, prompt "Blink twice" appears on the screen
  5. Instruct patient to blink twice
  6. Measurement automatically activated after second blink

[12] Koh S, et al. Upper and lower difference in tear film stability and meibomian glands in dry eye. Eye & Contact Lens. In press
[13] Hong J, et al. Assessment of tear film stability in dry eye with a newly developed keratograph. Cornea. 2013;32:716-721.

9.2.1. Tear Meniscus Height

A tear meniscus height test will be performed with the Keratograph 5M according to the manufacturer's directions, as reproduced below.

Tear Meniscus Height (TMH)

A camera image is taken with either infrared or white illumination allowing measurement of the TMH.

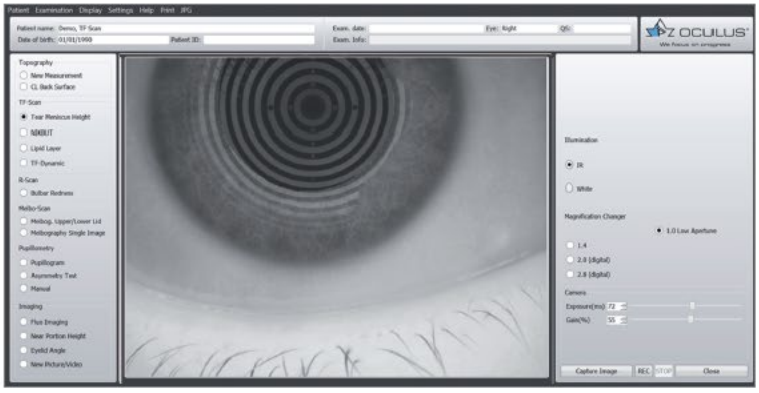


Figure 4: Keratograph 5M TMH using the infrared acquisition function

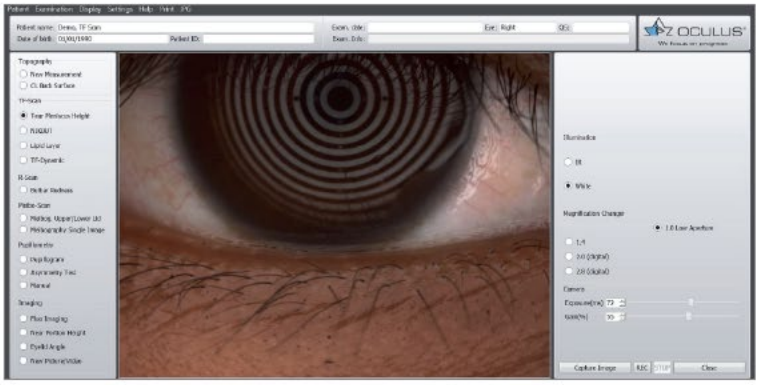


Figure 5: TMH using the white light acquisition function

- Objective

  To evaluate the quantity of the tear film

- Method
  - TMH image recorded
  - TMH measured with a built-in ruler. Generally, TMH is measured in line with the pupil center.
  - Normal TMH > 0.20mm
  - Irregular TMH can be evaluated along the lid margin
  - Magnification changer assists with image evaluation

- Tips and advice
  - To avoid artificial high readings due to reflex tearing from other tests, the first test performed during tear film assessment should be the TMH measurement
  - It may be better to measure TMH a few seconds after the blink to avoid post-blink TMH change
  - If conjunctival chalasis or lid parallel conjunctival folds (LIPCOF) exist, accurate TMH measurement can be difficult
- Step by step
  1. Enable 'TMH' button
  2. Select IR or white light
  3. Magnification, exposure and gain can be changed if necessary
  4. Adjust the camera image to display tear meniscus centrally
  5. Focus on the lower tear meniscus
  6. Record image by pressing 'Image" button or alternatively using the foot switch

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