

# Johnson & Johnson Vision Care, Inc.

## Clinical Study Protocol

Clinical Evaluation of two marketed artificial tears in non-contact lens wearing patients

Protocol Number CR-6013 (J17-626)

Version: 3.0

Date: 03 January 2018

Investigational Products: blink® intensive TRIPLE ACTION 3 in 1 eye drops and Systane® BALANCE eye drops

Key Words: artificial tears, dispensing, Visual Analogue Scale (VAS) comfort, Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire (DEQ)-5, dry eye

**Statement of Compliance to protocol, GCP and applicable regulatory guidelines:**

This trial will be conducted in compliance with the protocol, ISO 14155,<sup>1</sup> the International Conference for Harmonization Good Clinical Practice E6 (ICH-GCP),<sup>2</sup> the Declaration of Helsinki,<sup>3</sup> and all applicable regulatory requirements.

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**PROTOCOL TITLE, NUMBER, VERSION**

Title: Clinical Evaluation of two marketed artificial tears in non-contact lens wearing patients  
Protocol Number: CR-6013 (J17-626)  
Version: 3.0  
Date: 03 January 2018

**SPONSOR NAME AND ADDRESS**

Johnson & Johnson Vision Care, Inc. (JJV)  
7500 Centurion Parkway  
Jacksonville, FL 32256

**MEDICAL MONITOR**

[REDACTED]

The Medical Monitor must be notified by the clinical institution/site by e-mail, fax, or telephone within 24 hours of learning of a Serious Adverse Event. The Medical Monitor may be contacted during business hours for adverse event questions. General study related questions should be directed towards your assigned clinical research associate.

The Medical Monitoring Plan is maintained as a separate document and included in the Trial Master File.

## AUTHORIZED SIGNATURES

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations,<sup>4</sup> ICH guidelines,<sup>2</sup> ISO 14155,<sup>1</sup> and the Declaration of Helsinki.<sup>3</sup>

Author/Study Responsible Clinician	See Electronic Signature Report	
	_____ Meredith Bishop, OD, MS, FAAO Principal Research Optometrist	_____ DATE
Clinical Operations Manager	See Electronic Signature Report	
	_____ [REDACTED] [REDACTED]	_____ DATE
Biostatistician	See Electronic Signature Report	
	_____ [REDACTED] [REDACTED]	_____ DATE
Data Management	See Electronic Signature Report	
	_____ [REDACTED] [REDACTED]	_____ DATE
Fellow Reviewer	See Electronic Signature Report	
	_____ [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	_____ DATE
Approver	See Electronic Signature Report	
	_____ [REDACTED] [REDACTED]	_____ DATE

## CHANGE HISTORY

Version	Originator	Description of Change(s) and Section Number(s) Affected	Date
1.0	Meredith Bishop OD, MS, FAAO	Original Protocol	27 Nov 2017
2.0	██████████	Correction to exclusion #13 and addition of electronic consent in pre-screening. Amended reasons for registering study on <a href="http://clinicaltrials.gov">clinicaltrials.gov</a> in section 21.	01 Dec 2017
3.0	██████████	Added note in Section 3.3 and Synopsis regarding exclusion of potential subjects with allergy or sensitivity to ingredients.  Updated Section 6.2 to include “alternative sponsor approved product” for ancillary supplies	20 Dec 2017



## SYNOPSIS

Protocol Title	Clinical Evaluation of two marketed artificial tears in non-contact lens wearing patients
Sponsor	JJV, 7500 Centurion Parkway, Jacksonville, FL 32256
Clinical Phase	Post Marketing, Phase 4
Trial Registration	This study will be registered on ClinicalTrials.gov based on the following: the study will be utilizing marketed products to assess endpoints related to comfort.
Test Article(s)	Two artificial tears products: <ul style="list-style-type: none"><li>• blink® intensive TRIPLE ACTION 3 in 1 eye drops (Test)</li><li>• Systane® BALANCE eye drops (Control)</li></ul>
Treatment dosage	Dosage: Instill 1-2 drops OU at least three times a day.
Objectives	The primary objective of this study is to gain clinical insights of the products with respect to ocular comfort after one week of use.
Study Endpoints	Primary endpoint: VAS comfort score Secondary endpoint: OSDI score Other endpoints: DEQ-5, LipiView II®, NITBUT, ocular physiology, subject's reported ocular symptoms, adverse events

Study Design	<p>The study design is a randomized, double-masked, bilateral, 2 treatment × 2 period, dispensing, 4-visit study:</p> <p><u>Visit 0:</u> pre-screening with completion of DEQ-5</p> <p><u>Visit 1:</u> Baseline and eligibility, randomization. Dispense first eye drop solution. LipiView II® measurement at approx.5 mins, 30 mins, 1 hour, and 2 hours post-drops. VAS comfort.</p> <p>Study drops used at least 3x per day for 7-9 days.</p> <p><u>Visit 2:</u> One-week follow-up - Questionnaires, LipiView II®, NITBUT, slit lamp findings. VAS comfort.</p> <p><u>Washout period:</u> 7-9 days (habitual artificial tear usage)</p> <p><u>Visit 3:</u> Baseline, confirm eligibility, dispense second eye drop solution. LipiView II® measurement at approx..5 mins, 30 mins, 1 hour, and 2 hours post drop. VAS comfort.</p> <p>Study drops used at least 3x per day for 7-9 days.</p> <p><u>Visit 4:</u> One-week follow up, Questionnaires, ®, NITBUT, slit lamp findings, final evaluation. VAS comfort.</p> <p>See the Summary of Visits table at the end of the synopsis for the schematic of the study visits and procedures of main observations.</p>
Sample Size	Approximately 60 non-contact lens wearing subjects are targeted to be enrolled and approximately 50 subjects are targeted to complete the study.
Study Duration	The study will last approximately 3 months and include a 2-month enrollment period.
Anticipated Study Population	Non-contact lens wearers 18-69 years of age with occasional symptoms of dry eye and/or signs based on a DEQ-5 score of greater than 6.

<p>Eligibility Criteria</p>	<p>Potential subjects must satisfy all the following criteria to be enrolled in the study:</p> <ol style="list-style-type: none"> <li>1. Subjects must be at least 18 years of age and no more than 69 years of age (inclusive)</li> <li>2. Subjects must be non-contact lens wearers</li> <li>3. Subjects must have a DEQ-5 score of &gt;6 at either Visit 0 (pre-screen) or Visit 1 (screening)</li> <li>4. Subjects must achieve visual acuity of 20/30 (equivalent to 0.18logMAR) or better in each eye, either unaided or best corrected</li> <li>5. Subjects must possess a functional/ usable pair of spectacles and bring them to the visit (only if applicable - to the investigators discretion).</li> <li>6. Subjects must read, understand, and sign the Statement of Informed Consent</li> <li>7. Subjects must appear able and willing to adhere to the instructions set forth in this clinical protocol</li> </ol> <p>Potential subjects who meet any of the following criteria <b><u>will be excluded</u></b> from participating in the study:</p> <ol style="list-style-type: none"> <li>1. Currently pregnant or breast-feeding</li> <li>2. Diabetes</li> <li>3. Any ocular or systemic allergies or disease which may interfere with the clinical trial (at the discretion of the investigator).</li> <li>4. Any systemic disease, autoimmune disease, or use of medication which may interfere with the clinical trial (at the discretion of the investigator),</li> <li>5. Any infectious diseases (e.g. hepatitis, tuberculosis) or a contagious immunosuppressive disease (e.g. HIV), by self-report</li> <li>6. Any Grade 3 or greater biomicroscopy findings (this includes, corneal edema, corneal staining, corneal vascularization, conjunctival injection, tarsal abnormalities, bulbar injection) on the FDA classification scale</li> <li>7. Any active ocular abnormalities/conditions that may interfere with the clinical trial (this includes, but not limited to, chalazia, recurrent styles, pterygium, infection, etc).</li> <li>8. Any corneal distortion due to previous rigid gas permeable lens wear, surgery or pathology.</li> </ol>
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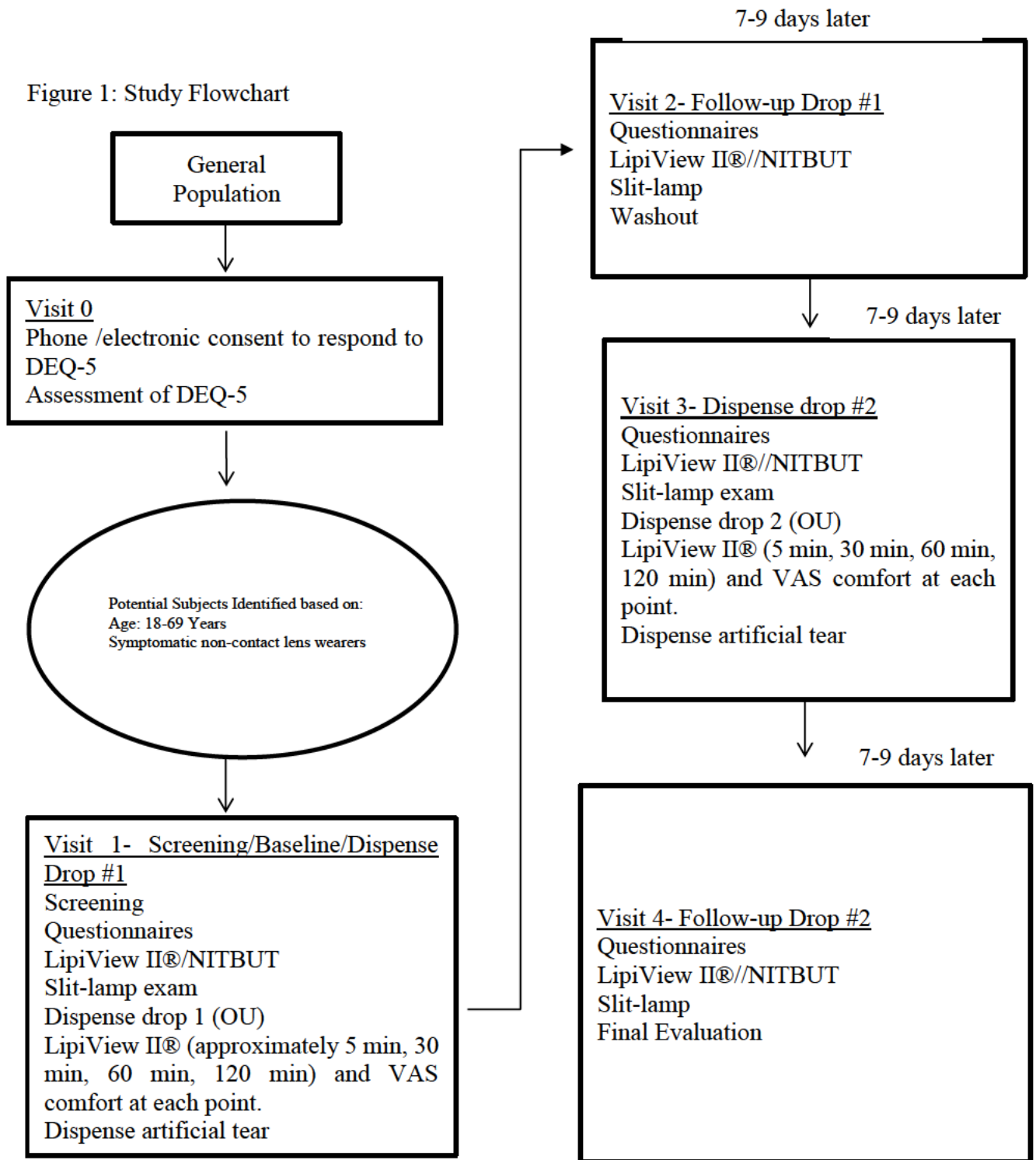
9. History of any ocular or corneal surgery (e.g. RK, PRK, LASIK)
10. Participation in any pharmaceutical or medical device related clinical trial within 14 days prior to study enrollment.
11. History of binocular vision abnormality or strabismus.
12. Habitual wearers of soft contact lenses within the past 1 month or rigid gas permeable lens within the past 3 months
13. Current habitual use of Prescription Only Medication (POM) to treat dry eye or ocular dryness symptoms that would interfere with the clinical study (at the discretion of the investigator)
14. Employees of investigational clinic (investigator, coordinator, and technician etc) or family members of an employee of the clinical site by self-report.

In addition to the above criteria, patients with any allergy or sensitivity to ingredients that this product may contain (liposomes, sodium hyaluronate, vitamin E polyethylene glycol succinate (TPGS), polyethylene glycol 400 (PEG 400), disodium edetate, polyhexanide methylbiguanide, propylene glycol, boric acid, dimyristoyl phosphatidylglycerol, edetate disodium, hydroxypropyl guar, mineral oil, polyoxyl 40 stearate, polyquaternium-1, sorbitan tristearate, sorbitol, hydrochloric acid and/or sodium hydroxide) should not participate in the study.

Disallowed Medications/Interventions	Current habitual use of Prescription Only Medicines (POM) to treat dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).
Measurements and Procedures	VAS Scale Comfort, OSDI, DEQ-5, ocular physiology, LipiView II®, and safety parameters.
Microbiology or Other Laboratory Testing	None
Study Termination	The occurrence of one or more Unanticipated Adverse Device Effect (UADE), or any SAE where relationship to study agent cannot be ruled out, will result in stopping further dispensing investigational product. In the event of a UADE or SAE, the Sponsor Medical Monitor may unmask the treatment regimen of subject(s) and may discuss this with the Principal Investigator before any further subjects are enrolled.
Ancillary Supplies/ Study-Specific Materials	BlueDot Saline Pods (or other sponsor-approved material), FluStips
Principal Investigator(s) and Study Institution(s)/Site(s)	A full list of Principal Investigators, clinical sites, and institutions is kept separately from the Study Protocol and is included in the study Trial Master File.



Figure 1: Study Flowchart



## COMMONLY USED ABBREVIATIONS AND DEFINITIONS OF TERMS

ADD	Plus Power Required For Near Use
ADE	Adverse Device Effect
AE	Adverse Event/Adverse Experience
BCVA	Best Corrected Visual Acuity
BSCVA	Best Spectacle Corrected Visual Acuity
CE	Conformité Européene
CFR	Code of Federal Regulations
COAS	Complete Ophthalmic Analysis System
COM	Clinical Operations Manager
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Center Thickness
CTP	Clinical Technical Procedure
D	Diopter
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
JJV	Johnson & Johnson Vision, Inc.
LC	Limbus Center
LogMAR	Logarithm of Minimal Angle of Resolution
MedDRA <sup>®</sup>	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIH	National Institutes of Health
OD	Right Eye
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
OS	Left Eye
OSDI	Ocular Surface Disease Index
OU	Both Eyes
PD	Protocol Deviation
PHI	Protected Health Information
PI	Principal Investigator
PIG	Patient Instruction Guide
PQC	Product Quality Complaint
PRO	Patient Reported Outcome
QA	Quality Assurance

QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VA	Visual Acuity

## 1. INTRODUCTION AND BACKGROUND

It is estimated that over 16 million US adults have been diagnosed with dry eye<sup>5</sup>. Artificial tears are often used to treat symptoms of ocular dryness and discomfort. Most of the major artificial tear companies have some type of lipid product to address lipid deficient tear films, however JJV CEH does not currently have a lipid-like drop in our portfolio. Additionally, JJV acquired TearScience Q3 2017 to address Meibomian gland disease resulting in lipid deficiencies.

This study will be conducted at a single clinical site (University of Manchester) in the United Kingdom (UK) and will include two marketed (CE marked) artificial tears (blink® intensive TRIPLE ACTION 3 in 1 and Systane® BALANCE) to gain clinical insights with respect to ocular comfort after 1 week of use. By exploring a lipid-like drop addition to the CEH portfolio it would continue to live into the JJV Eye Health Mission.

### 1.1. Name and Descriptions of Investigational Products

The products used in this clinical study are two CE marked/approved artificial tears eye drops:

- blink® intensive TRIPLE ACTION 3 in 1 eye drops (Test)
- Systane® BALANCE eye drops (Control)

### 1.2. Intended Use of Investigational Products

The products are marketed products, available over the counter (without a prescription). They will be used as indicated on-label to reduce symptoms of ocular dryness. Subjects will be required to use the 1-2 drops in both eyes at least 3 times a day. There is no maximum number of drops per day.

The proposed intended use of all the study artificial tears are subjects with symptoms of ocular dryness. For this study, we will use a cut off DEQ-5 score of 6. A score of greater than 6 indicates the presence of ocular discomfort and/or dryness and subject eligibility.

### 1.3. Summary of Findings from Nonclinical Studies

Not Applicable - Marketed products only.

### 1.4. Summary of Known Risks and Benefits to Human Subjects

The following risks/adverse events can be associated with using artificial tears, in general:

- There may be less comfort than when the drop was first placed on the eye.
- The eyes may burn, sting and/or itch.
- There may be a feeling of something in the eye (foreign body, scratched area).



- There may be the potential for some temporary impairment due to peripheral infiltrates, peripheral corneal ulcers and corneal erosion.
- There may be the potential for other physiological observations, such as local or generalized edema, corneal neovascularization, corneal staining, injection, tarsal abnormalities, iritis and conjunctivitis, some of which are clinically acceptable in low amounts.
- There may be excessive watering, unusual eye secretions, or redness of the eye.
- Poor visual acuity, blurred vision, rainbows or halos around objects, photo-phobia, or dry eyes may also occur if the drops are used continuously or for too long a time.

There is no direct benefit to the subject for participating in the study, although they will be able to try out new artificial tears. The information from this study will aid if the further development and design of new artificial tears.

For the most comprehensive clinical information regarding the artificial tears refer to the package inserts (Appendix C).

### **1.5. Relevant Literature References and Prior Clinical Data Relevant to Proposed Clinical Study**

All artificial tears evaluated in this study are CE marked/approved and marketed products. Refer to package inserts (Appendix C) for additional information.

## **2. STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES**

### **2.1. Objectives**

The primary objective of this study is to gain clinical insights of the products with respect to ocular comfort after 1 week of use.

### **2.2. Endpoints**

#### **Primary Endpoint:**

The primary endpoint is ocular comfort score at 1-week follow-up using Visual Analogue Scale (VAS) of comfort. VAS of comfort consists of a vertical line which represents continuous scale from 0 (extremely uncomfortable) to 100 (extremely comfortable).

#### **Secondary endpoint:**

The secondary endpoint is subjective assessment of dry eye symptoms at 1-week follow-up using Ocular Surface Disease Index (OSDI<sup>®</sup>) instrument. The OSDI<sup>®</sup> 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<sup>®</sup> is a reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function OSDI<sup>®</sup> questionnaire.<sup>6</sup>

#### **Other Endpoints:**

- DEQ-5 score at 1-week follow-up
- LipiView II<sup>®</sup> lipid layer measurement at 5 min, 30 min, 60 min, and 120 min post drop instillation.
- Non-invasive tear break-up time (NITBUT)

- Expanded corneal staining (██████████)
- Slit-Lamp findings (██████████)
- Subject's reported ocular symptoms (██████████)
- Adverse events

DEQ-5 questionnaire is a subset of Dry Eye Questionnaire (DEQ) items that discriminate across self-assessed severity and various diagnoses of dry eye. It is comprised of 5 items: frequency of watery eyes, discomfort, and dryness (0-4 scale) and late day discomfort and dryness intensity (0-5 scale). The DEQ-5 score is the sum of scores for frequency and late day intensity of dryness and discomfort plus frequency of watery eyes. DEQ-5 scores greater than 6 suggest dry eye is present and results greater than 12 may require further testing to rule out Sjögren's syndrome.<sup>7</sup>

### 2.3. Hypotheses

This is a pilot study and all the hypotheses are exploratory in nature.

#### Primary hypothesis:

The Test eye drop is superior to the Control eye drop with respect to ocular comfort as measured using VAS comfort at 1-week follow-up

#### Secondary hypothesis:

The Test eye drop is superior to the Control eye drop in reducing dry eye symptoms as measured using OSDI at 1-week follow-up.

## 3. TARGETED STUDY POPULATION

### 3.1. General Characteristics

The study populations will be healthy non-contact lens wearers between 18-69 years of age from a single site in the UK.

### 3.2. Inclusion Criteria

Potential subjects must satisfy all the following criteria to be enrolled in the study:

1. Subjects must be at least 18 years of age and no more than 69 years of age (inclusive)
2. Subjects must be non-contact lens wearers
3. Subjects must have a DEQ-5 score of >6 at either Visit 0 (pre-screen) and/or Visit 1 (screening).
4. Subjects must achieve visual acuity of 20/30 (equivalent to 0.18 logMAR) or better in each eye, either unaided or best corrected.
5. Subjects must possess a functional/usable pair of spectacles and bring them to every visit (only if applicable - to the investigators discretion).
6. Subjects must read, understand, and sign the Statement of Informed Consent.
7. Subjects must appear able and willing to adhere to the instructions set forth in this clinical protocol

### 3.3. Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Currently pregnant or breast-feeding.
2. Diabetes.
3. Any ocular or systemic allergies or disease which may interfere with the clinical trial (at the investigator's discretion).
4. Any systemic disease, autoimmune disease, or use of medication which may interfere with the clinical trial (at the investigator's discretion).
5. Any infectious diseases (e.g. hepatitis, tuberculosis) or a contagious immunosuppressive disease (e.g. HIV), by self-report
6. Any Grade 3 or greater biomicroscopy findings (this includes, corneal edema, corneal staining, corneal vascularization, conjunctival injection, tarsal abnormalities, bulbar injection) on the FDA scale
7. Any active ocular abnormalities/conditions that may interfere with the clinical trial (this includes, but not limited to, chalazia, recurrent styles, pterygium, infection, etc)
8. Any corneal distortion due to previous rigid gas permeable lens wear, surgery or pathology
9. History of any ocular or corneal surgery (e.g. RK, PRK, LASIK)
10. Participation in any pharmaceutical or medical device related clinical trial within 14 days prior to study enrollment.
11. History of binocular vision abnormality or strabismus.
12. Habitual wearers of soft contact lenses in the past 1 month or rigid gas permeable lens within the past 3 months
13. Current habitual use of Prescription Only Medicines (POM) to treat dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator.)
14. Employees of investigational clinic (investigator, coordinator, and technician etc) or family member of an employee of the clinical site by self-report.

In addition to the above criteria, patients with any allergy or sensitivity to ingredients that this product may contain (liposomes, sodium hyaluronate, vitamin E polyethylene glycol succinate (TPGS), polyethylene glycol 400 (PEG 400), disodium edetate, polyhexanide methylbiguanide, propylene glycol, boric acid, dimyristoyl phosphatidylglycerol, edetate disodium, hydroxypropyl guar, mineral oil, polyoxyl 40 stearate, polyquaternium-1, sorbitan tristearate, sorbitol, hydrochloric acid and/or sodium hydroxide) should not participate in the study.

### 3.4. Enrollment Strategy

Study subjects will be recruited from the University of Manchester, UK's subject database and/or utilizing Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved materials.

## **4. STUDY DESIGN AND RATIONALE**

### **4.1. Description of Study Design**

The study design is a randomized, double-masked, bilateral, 2 treatment × 2 period, dispensing, 4-visit study.

After a pre-screening assessment, eligible subjects will be invited to attend an initial visit. At study Visit 1, subjects will be consented and screened for inclusion/exclusion criteria. If a subject is found to meet all eligibility criteria, they will be dispensed with the first artificial tears eye drops based on the randomization scheme; otherwise, the subject will be discontinued from the study. After dispensing of the first eye drop solution; NITBUT, LipiView II® measurement at taken at approximately 5 mins, 30 mins, 1 hour, and 2 hours post drop

Subjects will be dispensed with their randomly assigned eye drops and instructed to use them OU at least 3 times a day over a 7-9 day period. The follow-up evaluation (Visit 2) will occur 7-9 days after the initial visit. At this visit questionnaires, LipiView II®, NITBUT, slit lamp findings will be captured.

After completion of Visit 2, there is a 7-9 day washout period during which subjects may use their habitual products, if any, but they will be advised not use any eye drops on the day of Visit 3

Following the washout period, the subject returns for Visit 3 and is dispensed with the second randomized eye drop with NITBUT, LipiView II® measurements at approximately 5 mins, 30 mins, 1 hour, and 2 hours post drop. Subjects will be dispensed with their second randomly assigned eye drops and instructed to use them OU at least 3 times a day over a 7-9 day period. Visit 4 takes place 7-9 days after visit 3, at which questionnaires, LipiView II®, NITBUT, slit lamp findings, final evaluation will take place.

### **4.2. Study Design Rationale**

Crossover designs are a well-established cost-effective study design in which subjects are exposed to multiple treatments during different time periods. This design was considered because patient-specific factors that might affect comfort are well controlled. A washout period of 7-9 days was implemented between each treatment exposure to reduce any potential carry-over effect that may bias the results.

### **4.3. Enrollment Target and Study Duration**

A total of up to 60 subjects will be enrolled (informed consent signed) at a single clinical site (University of Manchester) in the UK. The goal is for a sample size of approximately 50 subjects after subjects who withdraw or are lost to follow-up.

The Investigator is responsible for ensuring that all subjects entering the study conform to subject selection criteria. The number of subjects targeted for randomization and completion are as follows:

Table 1: Target number of subjects by arm and site

	Test/Control	Control/Test	Total
Randomization	30	30	60
Completion	25	25	50
Number of sites			1
Number of subjects/site Min-Max	25-30	25-30	50-60

The study will last approximately 3 months and include a 2-month enrollment period.

Once the informed consent has been signed the subject will be considered enrolled.

An additional subject may be enrolled if a subject discontinues from the study prematurely.

## 5. TEST ARTICLE ALLOCATION AND MASKING

### 5.1. Test Article Allocation

Eligible subjects will sequentially try the Test and Control eye drops in a random order. A computer-generated randomization scheme will be used to randomly assign subjects, in block size of 2, to one of the two possible treatment sequences: Test/Control or Control/Test.

The study site will follow the randomization scheme provided and will complete enrollment according to the randomization list and will not pre-select or assign subjects. The assignment of the subjects must be performed at the first baseline visit (Visit 1). The following must have occurred prior to randomization:

- Informed consent has been obtained
- Subject meets all the inclusion / exclusion criteria
- Subject history and baseline information has been collected

The randomization scheme will be generated using the PROC PLAN procedure from the SAS Software Version 9.4 or higher (SAS Institute, Cary, NC).

### 5.2. Masking

This is a double-masked study where subjects, investigators are masked to the identity of the eye drops during the study period. Every attempt will be made to keep the other clinical trial personnel involved in the study (e.g., Data management, Biostatistician) unaware of the identity of the test articles.

The identity of the investigational products will be masked by over labeling the eye drop bottles with a label containing the study number, expiration date and the randomization codes. Only the personnel involved in the over labeling and the Statistician generating the randomization scheme will have access to the decode information translating the randomization codes into Test and Control treatment. The medical monitor will also have access to the decode information in case breaking the mask is necessary for the urgent medical treatment of a subject.

### 5.3. Procedures for Maintaining and Breaking the Masking

Under normal circumstances, the mask should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the Investigator may, in an emergency, contact the medical monitor. In the event the mask is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unmasking must be documented in the subject record. The Investigator is also advised not to reveal the study treatment assignment to the clinical site or Sponsor personnel.

When dispensing test articles, the following steps should be followed to maintain randomization codes:

1. Investigator or designee (documented on the Delegation Log) will consult the randomization scheme to obtain the test article assignment for that subject prior to dispensing
2. Investigator or designee will record the subject's number on the appropriate line of the randomization scheme
3. Investigator or designee will pull the appropriate test articles from the study supply. All test articles that are opened, whether dispensed (placed/fit on eye or dispensed outside the clinical site) or not, must be recorded on the Test Article Accountability Log in the "Dispensed" section

## 6. STUDY INTERVENTION

### 6.1. Identity of Test Articles

Table 2: Artificial Tears

	Test	Control
Solution Name/Description	blink® intensive TRIPLE ACTION 3 in 1 eye drops	Systane® BALANCE eye drops
Manufacturer	Johnson & Johnson Vision, Inc	Alcon
Ingredients	liposomes, sodium hyaluronate, vitamin E polyethylene glycol succinate (TPGS), polyethylene glycol 400 (PEG 400), disodium edetate, polyhexanide methylbiguanide and purified water.	Propylene Glycol 0.6%, boric acid, dimyristoyl phosphatidylglycerol, edetate disodium, hydroxypropyl guar, mineral oil, polyoxyl 40 stearate, POLYQUAD® (polyquaternium-1) 0.001% preservative, sorbitan tristearate, sorbitol and purified water. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.
Packaging Form	Over-Labeled	Over-Labeled

## 6.2. Ancillary Supplies/Products

The following solutions will be used in this study:

Table 2: Ancillary Supplies

Solution Name/Description	Solution	
	Saline Pods	Fluorescein Strips
Manufacturer	BlueDot (or alternative Sponsor-approved product)	Contacare Ophthalmics and Diagnostics (or alternative Sponsor-approved product)
Preservative	None	None
Other distinguishing items (dye, packaging, approval status, etc.)	NA	100 strips, CE marked



Sodium fluorescein dye will be used for biomicroscopy, as needed. Sterile, preservative-free, single-use eye wash (0.9% w/v sodium chloride solution) will be used in this clinical study to rinse each eye.

## 6.3. Administration of Test Articles

Test articles will be dispensed to subject meeting all eligibility requirements, including any dispensing requirements set forth in this clinical protocol. Subjects will be dispensed an adequate supply of test articles to complete the study. Lost or damaged test articles will not be replaced at the discretion of the Investigator and/or the Sponsor.

## 6.4. Packaging and Labeling

The test articles will be packaged in bottles as the primary packaging. The test article will be over-labeled to mask the subject to the identity. The test articles will be in investigational cartons sealed with a tamper evident seal, commercial cartons, or in plastic bags as the secondary packaging form. The labels for the primary and secondary packages will contain the following message, in accordance with JJV over-labeling procedures for masked studies involving marketed products: “For Use in Clinical Study CR-6013 Only, Not for Resale. Product Conforms to with CE Mark Requirements.” The labels will also contain the product code, lot number, expiration date and the clinical study number.

<p>For Use in Clinical Study CR-6013 Only Not For Sale Product Conforms with CE Mark Requirements</p> <p><b>Content:</b> 10 ml of artificial tears (eye drops) for the treatment of dry eye symptoms.</p> <p><b>Sponsored by:</b> Johnson &amp; Johnson Vision Care, Inc. Jacksonville, FL 32256, USA</p> <p style="text-align: center;">   </p> <p>LOT:                      EXP:                      RC:</p>		
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### **6.5. Storage Conditions**

Test articles will be maintained at ambient temperatures at the clinical site. Test articles must be kept under secure conditions.

### **6.6. Collection and Storage of Samples**

When possible, any test article associated with an Adverse Events and/or a Product Quality Complaint must be retained pending directions from the sponsor for potential return back to JJV.

### **6.7. Accountability of Test Articles**

JJV will provide the Investigator with sufficient quantities of study articles and supplies to complete the investigation. The Investigator is asked to retain all shipment documentation for the test article accountability records.

Test article must be kept in a locked storage room, accessible only to those assigned by the Investigator for dispensing. The Investigator may delegate this activity to authorized study site personnel listed on the Site Delegation Log. All test articles must be accounted. This includes:

1. What was dispensed for the subject
2. What was returned to the Investigator unused
3. The number and reason for unplanned replacements

The Investigator will collect all unused test articles from the subjects at the end of the subject's participation. Subject returned unused test articles must be separated from the clinical study inventory of un-dispensed test articles, and must be labeled with the subject number and date of return. Following final reconciliation of test articles by the monitor, the Investigator or monitor will return all unused test articles to JJV.

If there is a discrepancy between the shipment documents and the contents, contact the study monitor immediately.

Reference [REDACTED] Site Instructions for Test Article Receipt and Test Article Accountability for additional information.



## 7. STUDY EVALUATIONS

### 7.1. Time and Event Schedule

Table 3: Time and Events

Visit Information	Visit 0 Optional pre-screen	Visit 1 Baseline, dispense drop #1	Visit 2 Follow-up drop #1	Washout	Visit 3 Dispense drop #2	Visit 4 Follow-up drop #2
Time Point			7-9 days after V1	7-9 days	7-9 days after V2	7-9 days after V3
Estimated Visit Duration		3 hours	1.5 hours		3 hours	1.5 hours
Phone/ electronic consent	X					
Study Informed Consent		X				
Inclusion/Exclusion Screening Criteria		X				
Demographics		X				
Medical History & medication review		X	X		X	X
Habitual Artificial Tear usage		X				
DEQ-5	X	X	X		X	X
OSDI		X	X		X	X
Biomicroscopy		X	X		X	X
Eligibility		X				
Randomization		X				
LipiView II®		X	X		X	X
Pre-drop VAS comfort		X			X	
Drop #1 instillation		X				
Drop #2 instillation					X	
LipiView II® follow up (5 minutes, 30 minutes, 60 minutes, 120 minutes)		X			X	
Post-drop VAS comfort/questionnaires (5 minutes, 30 minutes, 60 minutes, 120 minutes)		X			X	
NITBUT		X	X		X	X
Ocular Symptoms		X	X		X	X
Drop Dispensing & Instruction		X			X	
Drop Usage questions		X	X		X	X
Follow-up VAS comfort/questionnaires			X			X
Exit Slit-lamp			X		X	X
Adverse Event Review			X		X	X
Final Evaluation						X

## 7.2. Detailed Study Procedures

### VISIT 0

Optional pre-screen that may occur

Visit 0: Pre-Screening			
Step	Procedure	Details	
0.1	Phone/electronic Consent	Obtain Consent from the subject utilizing an EC-approved consent	
0.2	Pre-screen DEQ-5	<p>The subject will respond to the DEQ-5.</p> <ul style="list-style-type: none"> <li>• If the DEQ-5 sum score is greater than 6 then schedule Visit 1 for screening</li> <li>• If DEQ-5 sum score is less or equal than 6, subject is not deemed eligible for further screening.</li> </ul>	

### VISIT 1

The subjects must present to Visit 1 wearing their spectacles (if applicable) having not used any artificial tears that day. Subjects will be asked to bring their habitual artificial tears with them to the visit (if applicable).

Visit 1: Screening			
Step	Procedure	Details	
1.1	Statement of Informed Consent	<p>Each subject must read, understand, and sign the Statement of Informed Consent and Privacy Statement before being enrolled into the study. The Principal Investigator or their designee conducting the informed consent discussion must also sign the consent form.</p> <p><b>Note:</b> The subject must be provided a signed copy of this document.</p>	
1.2	Demographics	Record the subject's date of birth, gender, race and ethnicity.	
1.3	Medical History and Concomitant Medications	Questions regarding the subjects' medical history and concomitant medications.	
1.4	Artificial Tear Use	The subject will be asked about their artificial tear use.	
1.5	DEQ-5 Questionnaires	The subject will respond to the DEQ-5 questionnaire.	Appendix A
1.6	Eligibility after Screening	All responses to Screening Inclusion Criteria questions must be answered "yes" and all responses to Exclusion Criteria must	

Visit 1: Screening			
Step	Procedure	Details	
		be answered “no” for the subject to be considered eligible.	

Visit 1: Baseline			
Step	Procedure	Details	
1.7	OSDI Questionnaire	The subject will respond to the OSDI questionnaire.	Appendix A
1.8	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	Appendix A
1.9	Entrance Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	EuroLens Research SOP
1.10	Tear film lipid layer thickness	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
1.11	Habitual tear film stability (Medmont)	Record the tear film stability (NITBUT), OD & OS	NITBUT Medmont Work Aid (Appendix E)
1.12	Slit Lamp Biomicroscopy	<p>The FDA slit lamp classification scale will be used to grade the findings and determine eligibility.</p> <p>If there are any Grade 2 or higher other slit-lamp findings, the subject is ineligible to continue at this time, but may return up to one additional time to determine eligibility. If discontinued a final examination must be completed.</p> <p>If there are no slit lamp findings, and the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.</p>	
1.13	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (FDA grading scale) will be assessed using a more detailed scale for internal purposes only.	

Visit 1: Baseline			
Step	Procedure	Details	
1.14	Eligibility after Baseline	All responses to Inclusion Criteria questions must be answered “yes” and all responses to Exclusion Criteria questions must be answered “no” for the subject to be considered eligible.	

Visit 1: Dispense Drop #1			
Step	Procedure	Details	
1.15	Randomization	Subjects will be randomized to an artificial tear order.	
1.16	Drop instillation	The subject will instill 1 drop in both eyes (or drops can be instilled by the investigator should the subject require drop installation training).  The investigator should observe the subject’s technique for drop instillation and recommend new techniques to improve subject safety, if necessary.	
1.17	Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	
1.18	Drop Settling	Allow the drop to settle for 5 minutes.	
1.19	Tear film lipid layer thickness-5 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
1.20	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
1.21	Tear film lipid layer thickness- 30 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
1.22	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
1.23	Tear film lipid layer thickness- 60 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)

Visit 1: Dispense Drop #1			
Step	Procedure	Details	
1.24	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
1.25	Tear film lipid layer thickness- 120 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
1.26	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
1.27	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP
1.28	Continuance	For the subject to continue in the study, they must meet both of the following criteria: <ul style="list-style-type: none"> <li>• Visual acuity is 20/30 (0.18logMAR) or better OD and OS</li> <li>• Subject willing to use the drop at least 3x a day OU for 7-9 days.</li> </ul>	
1.29	Instillation of drops training	Instruct and teach instillation of drops.	
1.30	Dispense	The artificial tears will be dispensed for a 7-9 day wearing period <ul style="list-style-type: none"> <li>• Dispense enough artificial tears to last the whole week.</li> <li>• A patient instruction guide will be provided.</li> <li>• Subjects will be scheduled for Visit 2 in approximately 7-9 days.</li> </ul>	

## VISIT 2

The subjects must present to visit 2 wearing their habitual spectacles (if applicable) having used the study drop in both eyes at least 2 times that day.

Visit 2: Follow-up on drop #1			
Step	Procedure	Details	
2.1.	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	

Visit 2: Follow-up on drop #1			
Step	Procedure	Details	
2.2.	Artificial Tear Use	The subject will be asked about their artificial tear use.	
2.3.	Collection of Study drops	The site will collect and discard the bottle of study eye drops.	
2.4.	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	
2.5.	DEQ-5 Questionnaires	The subject will respond to the DEQ-5 Questionnaires.	Appendix A
2.6.	OSDI questionnaire	The subject will respond to the OSDI questionnaire.	Appendix A
2.7.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
2.8.	Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP
2.9.	Tear film lipid layer thickness	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
2.10.	Habitual tear film stability (Medmont)	Record the tear film stability (NITBUT), OD & OS	NITBUT Medmont Work Aid (Appendix E)
2.11.	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings.  (All ocular AE's must be followed to resolution)  If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	
2.12.	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (1.0 scale units) will be assessed using a more detailed scale for internal purposes only.	
2.13.	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP

Visit 2: Follow-up on drop #1			
Step	Procedure	Details	
2.14.	Washout instructions	Instruct subject they may use any habitual drops during their washout of 7-9 days	

### VISIT 3

The subjects must present to visit 3 wearing their habitual spectacles (if applicable) having not used any artificial tears that day.

Visit 3: Dispense Drop #2			
Step	Procedure	Details	
3.1.	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
3.2.	Artificial Tear Use	The subject will be asked about their artificial tear use.	
3.3.	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	
3.4.	DEQ-5 Questionnaires	The subject will respond to the DEQ-5 Questionnaires.	
3.5.	OSDI questionnaire	The subject will respond to the OSDI questionnaire.	
3.6.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
3.7.	Entrance visual acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP
3.8.	Tear film lipid layer thickness	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
3.9.	Habitual tear film stability (Medmont)	Record the tear film stability (NITBUT), OD & OS	NITBUT Medmont Work Aid (Appendix E)
3.10.	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings.	

Visit 3: Dispense Drop #2			
Step	Procedure	Details	
		<p>If there are any Grade 3 or higher other slit-lamp findings, the subject is ineligible to continue at this time, but may return up to one additional time to determine eligibility. If discontinued a final examination must be completed.</p> <p>All ocular adverse events must be followed to resolution.</p> <p>If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.</p>	
3.11.	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (1.0 scale units) will be assessed using a more detailed scale for internal purposes only.	
3.12.	Confirm Eligibility	Confirm the subjects is still eligible to continue in the study.	
3.13.	Drop instillation	1 drop will be instilled in both eyes	
3.14.	Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	
3.15.	Drop Settling	Allow the drop to settle for 5 minutes.	
3.16.	Tear film lipid layer thickness-5 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
3.17.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
3.18.	Tear film lipid layer thickness- 30 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
3.19.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
3.20.	Tear film lipid layer thickness- 60 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)



Visit 3: Dispense Drop #2			
Step	Procedure	Details	
3.21.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	
3.22.	Tear film lipid layer thickness- 120 minutes	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
3.23.	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	EuroLens Research SOP
3.24.	Continuance	For the subject to continue in the study, they must meet both of the following criteria: <ul style="list-style-type: none"> <li>• Visual acuity is 20/30 or better OD and OS</li> <li>• Subject willing to use the drop at least 3x a day for 7-9 days.</li> </ul>	
3.25.	Dispense	The artificial tears will be dispensed for a 7-9 day wearing period <ul style="list-style-type: none"> <li>• Dispense enough artificial tears to last the whole week.</li> <li>• A patient instruction guide will be provided.</li> </ul> Subjects will be scheduled for Visit 4 in approximately 7-9 days.	Dispense

#### VISIT 4

The subjects must present to visit 4 wearing their habitual spectacles (if applicable) having used the study drop in both eyes at least 2 times that day.

Visit 4: Follow-up of Drop #2			
Step	Procedure	Details	
4.1.	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications from the previous study visit. Record any changes, and any adverse events.	
4.2.	Artificial Tear Use	The subject will be asked about their artificial tear use.	
4.3.	Collection of Study drops	The site will collect and discard the bottle of study eye drops.	

Visit 4: Follow-up of Drop #2			
Step	Procedure	Details	
4.4.	Subject Reported Ocular Symptoms	Subjects will respond to a verbal open-ended symptoms questionnaire.	██████████
4.5.	Modified DEQ-5 Questionnaires	The subject will respond to the modified DEQ-5 Questionnaires.	██████████ Appendix A
4.6.	OSDI Questionnaire	The subject will respond to the OSDI questionnaire.	██████████ Appendix A
4.7.	VAS Questionnaire	The subject will respond to the VAS comfort questionnaire	██████████
4.8.	Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP ██████████
4.9.	Tear film lipid layer thickness	Record the tear film lipid layer thickness, OD & OS	Measure per LipiView II® II manufacturer instruction (Appendix D)
4.10.	Habitual tear film stability (Medmont)	Record the tear film stability (NITBUT), OD & OS	NITBUT Medmont Work Aid (Appendix E)
4.11.	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings.  (All ocular AE's must be followed to resolution)  If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops or saline may be instilled.	██████████
4.12.	Expanded Sodium Fluorescein Corneal Staining	Corneal Staining Assessment (1.0 scale units) will be assessed using a more detailed scale for internal purposes only.	██████████

## FINAL EVALUATION

The final evaluation will ordinarily take place immediately following the last scheduled follow-up visit per the study protocol. It may also take place at any point the subject discontinues the study or is terminated from the study.

Final Evaluation			
Step	Procedure	Details	████
F.1	Final Exam Form	Indicate if the subject completed the study successfully. If subject discontinued from the study indicate the reason.	
F.2	Exit Distance Visual Acuity	Record the exit distance visual acuity OD, OS, OU with the subject's spectacles or unaided (the same method as used in Visit 1 Baseline entrance distance visual acuity).	EuroLens Research SOP █████

### 7.3. Unscheduled Visits

If, during the investigation, a subject requires an unscheduled visit to the clinical site, the following information will be collected at a minimum:

- Chief complaint prompting the visit. If the reason is an adverse event, the applicable eCRF for the adverse event must be completed and subject record completed as appropriate
- Date and time of the visit and all procedures completed at the unscheduled visit
- Review of adverse event and concomitant medications
- Documentation of any test article dispensed or collected from the subject, if applicable
- Slit lamp findings (using the Slit Lamp Classification Scale)

If the Investigator withdraws a subject from the study, the final study visit case report forms must be completed indicating the reason(s) why the subject was withdrawn. The subject record must be completed documenting the date and primary reason for withdrawal and the study CRA notified.

Any ocular and non-ocular adverse events that are ongoing at the time of the study visit will be followed by the Investigator, within licensure, until they have resolved, returned to pre-treatment status, stabilized, or been satisfactorily explained. If further treatment i.e., beyond licensure is required, the subject will be referred to the appropriate health care provider.

The following information will be collected during an unscheduled visit (when applicable)

Unscheduled Visit			
Step	Procedure	Details	████
U.1	Chief Complaints	Record the subject's chief complaints for reasons for the unscheduled visit.	
U.2	Adverse Events and Concomitant Medications Review	Review any changes to the subject's medical history or concomitant medications	

Unscheduled Visit			
Step	Procedure	Details	
		from the previous study visit. Record any changes, and any adverse events.	
U.3	Entrance VA	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP [REDACTED]
U.4	Dispensing	Dispensing of additional artificial tear drops, if necessary	
U.5	Slit Lamp Biomicroscopy	The FDA slit lamp classification scale will be used to grade the findings.  (All ocular AE's must be followed to resolution)  If the clearance of the fluorescein needs to be expedited, preservative-free rewetting drops may be instilled.	[REDACTED]
U.6	Exit Visual Acuity	Record the distance high contrast visual acuity to the nearest letter (OD, OS, and OU) with their habitual spectacle correction in place (or unaided if applicable).	Eurolens Research SOP [REDACTED]

#### 7.4. Laboratory Procedures

Not applicable.

### 8. SUBJECTS COMPLETION/WITHDRAWAL

#### 8.1. Completion Criteria

Subjects are considered to have completed the study if they:

- Provided informed consent;
- They are eligible;
- Completed all study visits;
- Have not withdrawn/discontinued from the study for any reason described in Section 8.2

#### 8.2. Withdrawal/Discontinuation from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Subject death during the study period
- Subject withdrawal of consent
- Subject not compliant to the study protocol including drop usage schedule
- Subject lost to follow-up
- Subject no longer meets eligibility criteria (e.g. the subject becomes pregnant)
- Subject develops significant or serious adverse events causing discontinuation of study drop
- Subjects who have experienced a Corneal Infiltrative Event (CIE)

- Investigator's clinical judgment regarding the subject safety reasons (that it is in the best interest of the subject to stop treatment)
- Subject not successfully dispensed due to lack of efficacy or safety

For discontinued subjects, the Investigator will:

- Complete the current visit (scheduled or unscheduled)
- Complete the Final Evaluation, indicating the reason that the subject was discontinued from the study
- Collect used test article(s) (brought to the visit) from the subject and discard them, unless otherwise stated in Section 7.2
- Collect all unused test article(s) from the subject

An additional subject may be enrolled if a subject discontinues from the study prematurely.

In cases where a subject is lost to follow-up, every possible effort must be made to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented including two written attempts and a certified letter (or equivalent) as the final attempt.

## **9. PRE-STUDY AND CONCOMITANT INTERVENTION/MEDICATION**

Concomitant medications will be documented during screening and updated during the study. Disallowed medications for this study include: Current habitual use of Prescription Only Medicines for dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).

Concomitant therapies that are disallowed include: Current habitual use of Prescription Only Medicines for dry eye or ocular discomfort, ocular steroids, or any medication (RX or OTC) that would interfere with the clinical study (at the discretion of the investigator).

## **10. DEVIATIONS FROM THE PROTOCOL**

Investigator will notify study sponsor upon identification of a protocol deviation. Major protocol deviations must be reported to the sponsor within 24 hours after discovery of the protocol deviation. The Investigator will report deviations per IRB/IEC requirements. All deviations will be tracked and corrective actions implemented as appropriate.

If it becomes necessary for the Investigator to implement a deviation to eliminate an immediate hazard to the trial subject, the Investigator may implement the deviation immediately without notification to the sponsor. Within 24 hours after the implemented deviation, the Investigator must notify and provide the rationale to the Sponsor and, as required, the IEC/IRB.

## **11. STUDY TERMINATION**

The occurrence of one or more Unanticipated Serious Adverse Device Effect (USADE), or any SAE where the relationship to study agent cannot be ruled out, may result in stopping further dispensing of test article. In the event of a USADE or SAE, the Sponsor may

unmask the treatment regimen for the subject(s) and will discuss this with the Investigator before any further subjects are enrolled.

The Sponsor will determine when a study will be stopped. The Principal Investigator always has the discretion to initiate stopping the study based on patient safety or if information indicates the study's results are compromised.

JJV reserves the right to terminate the study at any time for any reason. Additionally, the IEC/IRB reserves the right to terminate the study if an unreasonable risk is determined. The study can be terminated by the Principal Investigator at the individual clinical site due to specific clinical observations, if in their opinion, after a discussion with JJV, it is determined that it would be unwise to continue at the clinical site.

JJV (and the IEC/IRB and DMC, if applicable) will evaluate all adverse events. If it is determined that an adverse event presents an unreasonable risk, the investigation, or that part of the investigation presenting the risk, will be terminated, as soon as possible.

Should the study be terminated (either prematurely or as scheduled), the Investigator will notify the IEC/IRB and Regulatory Authority as required by local regulatory requirements.

## **12. PROCEDURE FOR HANDLING PRODUCT QUALITY COMPLAINTS**

A Product Quality Complaint (PQC) refers to any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of test articles after they have been released for clinical trial use.

Potential complaints may come from a variety of sources including but not limited to subjects, clinical research associates (CRA), clinical operations managers (COM), medical monitors, and site personnel, etc. The following are not considered product quality complaints:

- Subject satisfaction inquiries reported via “Subjective Questionnaires” and “Patient Reported Outcomes (PRO)”
- Clinical test articles that are stored improperly or damaged after receipt at the investigational site
- Artificial tear replacements that occur due to loss/run out
- Damage deemed by clinicians or clinical staff to be caused by handling by the user, and not indicative of a quality deficiency, only in situations where there is no deficiency alleged by the subject

Within 24 hours of site personnel becoming aware that a PQC has occurred, the PQC must be recorded in the EDC system, which will trigger an automatic email notification to the appropriate COM/CRA and Clinical QA representative. In cases where the EDC system in use is not configured to send automatic notifications or when an EDC system is not used, the COM/CRA is responsible for notifying Clinical QA upon discovery that a PQC has occurred.

Upon receipt of the EDC notification, the COM/CRA will contact the study site to collect additional information which will include:

- Date the complaint was received/recorded in the EDC System (Date of Sponsor Awareness)
- Who received the complaint
- Study number
- Clinical site information (contact name, site ID, telephone number)
- Lot number(s)
- Unique Subject Identifier(s)
- Indication of who first observed complaint (site personnel or subject)
- OD/OS indication, along with whether the drops were inserted
- Any related AE number, if applicable
- Detailed complaint description (scheduled/unscheduled visit, symptoms, resolution of symptoms, etc.)
- Eye Care Provider objective (slit lamp) findings if applicable
- Confirmation of product availability for return (and tracking information, if available), or rationale if product is not available for return (Refer to [REDACTED] [REDACTED] for test article return instructions)

Once a complaint is received, it will be assessed by the COM, CRA, or trained site personnel to determine if it is an Adverse Event/Serious Adverse Event (AE/SAE). If the complaint results in an AE/SAE, the COM/CRA, or trained site personnel will follow Section 13 of this protocol. If the AE/SAE was potentially the result of a product quality related deficiency, these procedures also applies and will be executed in parallel.

In some cases, a PQC form may be generated in EDC by the site in error. In this event, the PQC forms will be marked “Intentionally Left Blank” or “ILB”. Justification for ILB must be documented.

## 13. ADVERSE EVENTS

### 13.1. Definitions and Classifications

**Adverse Event (AE)** – An AE is “any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

*Note 1 to entry:* This definition includes events related to the investigational medical device or the comparator.

*Note 2 to entry:* This definition includes events related to the procedures involved.

*Note 3 to entry:* For users or other persons, this definition is restricted to events related to investigational medical devices.”<sup>1</sup>

An AE includes any condition (including a pre-existing condition) that:

1. Was not present prior to the study, but appeared or reappeared following initiation of the study
2. Was present prior to the study, but worsened during the study. This would include any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states
3. Pregnancy must be documented as an adverse event and must be reported to the clinical monitor and to the Sponsor immediately upon learning of the event

**Serious Adverse Event (SAE)** – An SAE is any untoward medical occurrence that:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (e.g., a sight threatening event, a significant persistent or permanent change, impairment, damage, or disruption to the subject's body)
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent permanent damage (the use of the test article resulting in a condition which requires medical or surgical intervention to preclude permanent impairment of the body structure or a body function). Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Diagnoses and conditions that are considered Ocular Serious Adverse Events include, but not limited to:

- Microbial Keratitis (MK)
- Iritis (including cells in the anterior chamber)
- Permanent decrease in best spectacle corrected visual acuity equivalent to 2 acuity lines or greater
- Central Corneal Opacity
- Central Corneal Neovascularization
- Uveitis
- Endophthalmitis
- Hypopyon
- Hyphemia
- Penetration of Bowman's Membrane
- Persistent Epithelial Defect
- Limbal cell Damage leading to Conjunctivalization

**Significant Adverse Events** – Those events that are usually symptomatic and warrant discontinuation (temporary or permanent) of the test article (excluding Serious Adverse Events).

Diagnoses and conditions that are considered Ocular Significant Adverse Events include, but not limited to the following:

- Significant Infiltrative Events (SIE)
- Keratoconjunctivitis (toxic or infectious)
- Chemical Keratitis
- Any Temporary Loss of >2 Lines of BSCVA
- Other Grade 3 or higher corneal findings, such as abrasions or edema
- Corneal events - e.g. Epidemic Keratoconjunctivitis (EKC)
- Asymptomatic Corneal Scar
- Any corneal event which necessitates temporary lens discontinuation >2 weeks



**Non-Significant Adverse Events** – Those conditions that are usually asymptomatic and usually do not warrant discontinuation (temporary or permanent) of the test article. However, the Investigator may choose to treat as a precautionary measure.

Diagnoses and conditions that are considered Ocular Non-Significant Adverse Events include, but not limited to the following:

- Non-significant Infiltrative Event (NSIE)
- Papillary Conjunctivitis
- Corneal abrasions
- Superficial Punctate Keratitis (SPK)
- Conjunctivitis: Bacterial, Viral, Allergic
- Blepharitis
- Meibomianitis
- Contact Dermatitis
- Localized Allergic Reactions or infections
- Temporary visual disturbances (blurriness)
- Any corneal event not explicitly defined as serious or significant adverse event, which necessitates temporary discontinuation of the drops <2 weeks

**Adverse Device Effect (ADE)** – An ADE is an “adverse event related to the use of an investigational medical device.

*Note 1 to entry:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

*Note 2 to entry:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.”<sup>1</sup>

**Unanticipated Adverse Device Effect (UADE)** – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the test article, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, Investigator’s Brochure or protocol, or any other unanticipated serious problem associated with the test article that relates to the rights, safety and welfare of subjects.

### 13.2. Assessing Adverse Events

In conjunction with the medical monitor, the Investigator will evaluate adverse events to ensure the events are categorized correctly. Elements of categorization will include:

- Seriousness/Classifications (see definition in Section 13.1)
- Causality or Relatedness – i.e. the relationship between the test article, study treatment or study procedures and the adverse event (not related; unlikely related; possibly related; related - see definition in Section 13.2.1)
- Adverse Event Severity – Adverse event severity is used to assess the degree of intensity of the adverse event (mild; moderate; severe for all events - see definition in Section 0)
- Outcome – not recovered or not resolved; recovering or resolving; recovered or resolved with sequelae; recovered or resolved; death related to adverse event; unknown
- Actions Taken – none; temporarily discontinued; permanently discontinued; other

### 13.2.1. Causality Assessment

**Causality Assessment** – A determination of the relationship between an adverse event and the test article. The test article relationship for each adverse event should be determined by the investigator using these explanations:

- Not Related- An adverse event that is not related to the use of the test article, study treatment or study procedures
- Unlikely Related – An adverse event for which an alternative explanation is more likely, e.g. concomitant treatment, concomitant disease(s), or the relationship of time suggests that a causal relationship is not likely
- Possibly Related – An adverse event that might be due to the use of the test article, or to the study treatment or study procedures. An alternative explanation, e.g. concomitant treatment, concomitant disease(s), is inconclusive. The relationship in time is reasonable. Therefore, the causal relationship cannot be excluded
- Related – An adverse event that is listed as a possible adverse effect (device) or adverse reaction (drug) and cannot be reasonably explained by an alternative explanation, e.g. concomitant treatment of concomitant disease(s). The relationship in time is very suggestive, e.g. it is confirmed by de-challenge and re-challenge

### 13.2.2. Severity Assessment

**Severity Assessment** – A qualitative assessment of the degree of intensity of an adverse event as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article, study treatment or study procedure relationship or seriousness of the event and should be evaluated according to the following scale:

- Mild – Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject’s daily activities
- Moderate – Event is bothersome, possibly requiring additional therapy, and may interfere with the subject’s daily activities
- Severe – Event is intolerable, necessitates additional therapy or alteration of therapy and interferes with the subject’s daily activities

### 13.3. Documentation and Follow-Up of Adverse Events

The recording and documenting of adverse events (ocular and non-ocular) begins when the subjects are exposed to the test article, study treatment or study procedure. Adverse events reported before the use of test article, start of study treatment, or study procedures will be recorded as medical history. However, if the condition deteriorates at any time during the study it will be recorded and reported as an AE. Untoward medical events reported after the subject’s exit from the study will be recorded as adverse events at the discretion of the Investigator.

Upon finding an adverse event, the Principal Investigator will document the condition in the subject record and in the eCRFs. He/she will complete the Adverse Event /eCRF.

Complete descriptions of all adverse events must be available in the subject record. All Adverse Events including local and systemic reactions not meeting the criteria for “serious adverse events” shall be captured on the appropriate case report form or electronic data system. All adverse events occurring while the subject is enrolled in the study must be documented appropriately regardless of relationship.

It is the Investigator's responsibility to maintain documentation of each reported adverse event. All adverse events will be followed in accordance with applicable licensing requirements. Such documentation will include the following:

- Adverse event (diagnosis not symptom)
- Drawings or photographs (where appropriate) that detail the finding (e.g., size, location, and depth, etc.)
- Date the clinical site was notified
- Date and time of onset
- Date and time of resolution
- Adverse event classification, severity, and relationship to test articles, as applicable
- Treatment regimen instituted, including concomitant medications prescribed, in accordance with applicable licensing requirements
- Any referral to another health care provider if needed
- Outcome, ocular damage (if any)
- Likely etiology
- Best corrected visual acuity at the discovery of the event and upon conclusion of the event

In addition, if an infiltrate(s) is present, he/she will complete the Corneal Infiltrate Assessment eCRF. Where necessary, a culture of the corneal lesion will be collected to determine if the infection is microbial in nature. If cultures are collected, the date of culture collection and laboratory utilized will be recorded.

Changes in the severity of an AE shall be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode. Changes in the assessment of relationship to the Test Article shall also be clearly documented.

Subjects who present with an adverse event shall be followed by the Investigator, within licensure, until all signs and symptoms have returned to pre-treatment status, stabilized, or been satisfactorily resolved. If further treatment beyond licensure is required, the patient will be referred to the appropriate health care provider. The Investigator will use his/her clinical judgment as to whether a subject reporting with an adverse event will continue in the study. If a subject is discontinued from the study, it will be the responsibility of the Investigator to record the reason for discontinuation. The Investigator will also document the adverse event appropriately and complete the Adverse Event eCRF. Any subjects with ongoing adverse events related to the test article, study treatment or study procedures, as of the final study visit date, should be followed to resolution of the adverse event or until referral to an appropriate health care provider, as recommended by the Investigator. Non-ocular adverse events that are not related to the test article, study treatment, or study procedures may be recorded as "ongoing" without further follow-up.

#### **13.4. Reporting Adverse Events**

The Investigator will notify the Sponsor of an adverse event by e-mail, facsimile, or telephone as soon as possible and no later than 24 hours from discovery for any serious /significant adverse events, and 2 days from discovery for any non-significant adverse event. In addition, a written report will be submitted by the Principal Investigator to the

IEC/IRB according to their requirements (Section 13.4.2). The report will comment whether or not the adverse event was considered to be related to the test article, study treatment or study procedures.

#### **13.4.1. Reporting Adverse Events to Sponsor**

##### **Serious/Significant Adverse Events**

The Investigator will inform the sponsor of all serious/significant adverse events occurring during the study period as soon as possible by e-mail, fax, or telephone, but no later than 24 hours following discovery of the event. The Investigator is obligated to pursue and obtain information requested by the Sponsor in addition to that information reported on the eCRF. All subjects experiencing a serious/significant adverse event must be followed up and all outcomes must be reported.

When medically necessary, the Investigator may break the randomization code to determine the identity of the treatment that the subject received. The Sponsor and study monitor should be notified prior to unmasking the test articles.

In the event of a serious/significant adverse event, the Investigator must:

- Notify the Sponsor immediately
- Obtain and maintain in the subject's records all pertinent medical information and medical judgment for colleagues who assisted in the treatment and follow-up of the subject
- Provide the Sponsor with a complete case history which includes a statement as to whether the event was or was not related to the use of the test article
- Notify the IEC/IRB as required by the IEC/IRB reporting procedure according to national regulations

##### **Unanticipated (Serious) Adverse Device Effect (UADE)**

In the event of an Unanticipated (Serious) Adverse Device Effect (UADE), the Investigator will submit a report of the UADE to the Sponsor and IEC/IRB as soon as possible, but no later than 24 hours after the Investigator first learns of the effect. This report is in addition to the immediate notification mentioned above.

The Sponsor must conduct an evaluation of the UADE and must report the results of the evaluation to FDA, the IEC/IRB and participating Investigators within 10 working days after the Sponsor first receives notification of the effect.

##### **Non-Serious Adverse Events**

All non-serious adverse events, including non-serious adverse device effects, will be reported to the sponsor by the Investigator no later than 2 days from discovery.

#### **13.4.2. Reporting Adverse Events to the Responsible IEC/IRB and Health Authorities**

Adverse events that meet the IEC/IRB requirements for reporting must be reported within the IEC/IRB's written guidelines. Each clinical site will refer to and follow any guidelines set forth by their Approving IEC/IRB. Each clinical site will refer to and follow any guidelines set forth by their local governing Health Authorities.

The Sponsor will report applicable Adverse Events to the local health authorities according the written guidelines, including reporting timelines.

### 13.4.3. Event of Special Interest

None.

### 13.5. Reporting of Pregnancy

Subjects reporting pregnancy (by self-report) during the course of the study will be discontinued after the event is recorded as an Adverse Event. Once discontinued, pregnant participants and their fetuses will not be monitored for study related purposes. At the Investigator's discretion, the study participant may be followed by the Investigator through delivery. However, this data will not be collected as part of the clinical study database. Pregnant participants are not discontinued from contact lens or solution related studies for safety concerns, but due to general concerns relating to pregnancy and contact lens use. Specifically, pregnant women are discontinued due to fluctuations in refractive error and/or visual acuity that occur secondary to systemic hormonal changes, and not due to unforeseen health risks to the mother or fetus.

## 14. STATISTICAL METHODS

### 14.1. General Considerations

Statistical Analysis will be undertaken by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be implemented in this clinical trial is outlined below.

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher (SAS Institute, Cary, NC). Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

### 14.2. Sample Size Justification

The plan is to enroll 60 subjects with a target of 50 subjects to complete the study. This is a pilot study and the sample size was not based on any empirical power calculation. The power analysis for different scenarios of size effects ( $\Delta$ ) and inter-subject correlation ( $\rho$ ), assuming a common VAS comfort score variance of 25, are summarized below:

Table 4: Power Analysis for VAS comfort

$\Delta$	$\rho$	Power (%)
5	.30	21.6
	.50	28.4
	.80	59.2
10	.30	64.9
	.50	79.2
	.80	99.2

The power analysis was conducted the SAS procedure PROC POWER procedure for paired tests.

### 14.3. Analysis Populations

#### **Safety Population:**

All subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation should be recorded.

#### **Per-Protocol Population:**

All subjects who have successfully completed all visits and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock (Per-Protocol Population). Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file.

#### **Intent-to-Treat (ITT) Population:**

All randomized subjects regardless of actual treatment and subsequent withdrawal from study or deviation from protocol. At least one observation should be recorded.

### 14.4. Level of Statistical Significance

All planned analysis for this study will be conducted with an overall type I error rate of 5%.

### 14.5. Primary Analysis

VAS comfort scores will be analyzed using a multivariate Bayesian model for repeated measures to test for the difference between the Test and Control eye drops. The regression model will include sequence and solution as fixed effects. The correlation between measurements across periods will be modeled using unstructured variance-covariance matrix.

#### **The Model:**

Let  $\mathbf{y}_{ijk} = (y_{1ij}, y_{2ij})^T$  denote the comfort scores for the  $i^{\text{th}}$  subject, from  $i^{\text{th}}$  site at 1week follow-up. The likelihood of  $\mathbf{y}_{ij}$  is constructed as follow:

$$\mathbf{y}_{ij} \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma}),$$

where  $\boldsymbol{\mu} = (\mu_1, \mu_2)^T$  and  $\boldsymbol{\Sigma}$  is a 2x2 variance-covariance matrix. Here  $\mu_i, i = 1, 2$ , are given by:

$$\begin{aligned}\mu_1 &= \mu_0 + \beta_1\text{BASE} + \beta_2\text{sequence} + \beta_3\text{Test}, \\ \mu_2 &= \mu_0 + \beta_1\text{BASE} + \beta_2\text{sequence} - \beta_3\text{Test},\end{aligned}$$

Other baseline characteristics such as age, gender DEQ-5 score will also be included as fixed effects when appropriate.

Non-informative prior distributions will be used for the coefficients in the models as well as for the error terms: Independent vague normal  $N(0,1000)$  priors for the regression

coefficients ( $\mu_0$  and  $\beta$ ) and inverse Wishart  $IW(R,2)$  for  $\Sigma$ .  $R$  is determined by  $S = E[\Sigma] = 4R$  where  $S$  is the sample variance-covariance matrix of the  $y_{ij}$ . The Metropolis sampler algorithm as implemented in the MCMC Procedure (SAS 9.4, SAS Institute, Cary, NC) will be used to estimate the posterior distributions of the unknown parameters. Inferences will be made based on a posterior credible interval for the relevant parameters. Results will be reported as regression coefficient mean estimates with 95% credible intervals.

#### **Hypothesis Testing:**

The null and alternative hypotheses for superiority is as follows:  $H_0: \beta_3 \leq 0$ ,  $H_a: \beta_3 > 0$ . Superiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between Test and Control is greater than 0:  $P(\beta_3 > 0|y) \geq 0.95$ .

#### **14.6. Secondary Analysis**

OSDI scores will be analyzed using the same model described in the primary analysis. The null and alternative hypotheses for superiority is as follows:  $H_0: \beta_3 \geq 0$ ,  $H_a: \beta_3 < 0$ . Superiority will be declared if the upper bound of the 2-sided 95% credible interval of the difference between Test and Control is less than 0:  $P(\beta_3 < 0|y) \geq 0.95$ .

#### **14.7. Other Exploratory Analyses**

If superiority cannot be concluded, the predictive probability of trial success (PPOS) will be calculated for different scenarios of sample size ( $n$ ) to support the planning for future studies.

Given the historical data from this pilot study, the PPOS will be estimated using a simulation based algorithm. We will simulate 1000 trials of 120 subjects from the predictive density function of  $y$ , then we will assess if success criterion  $\beta_3 > 0$  is met for each trial. The PPOS is estimated by the proportion of runs where the success criterion is met. The same algorithms will be used to calculate the PPOS for  $n = 150, 200$ .

Further exploratory analysis will be conducted on DEQ-5 scores, LipiView II® lipid layer measurements, non-invasive tear break-up time (NITBUT), corneal staining and subject's reported ocular symptoms (CTP-2009) at the discretion of the Study Responsible Clinician.

#### **14.8. Interim Analysis**

No interim analysis is planned.

#### **14.9. Procedure for Handling Missing Data and Drop-Outs**

Missing or spurious values will not be imputed. The count of missing values will be included in the summary tables and listings.

#### **14.10. Procedure for Reporting Deviations from Statistical Plan**

The analysis will be conducted according to that specified in above sections. There are no known reasons for which it is planned to deviate from these analysis methods. If for any reason a change is made, the change will be documented in the study report along with a justification for the change.

## **15. DATA HANDLING AND RECORD KEEPING/ARCHIVING**

### **15.1. Electronic Case Report Form/Data Collection**

The data for this study will be captured on electronic case report forms (eCRFs) using an EDC system (Bioclinica). An authorized data originator will enter study data into the eCRFs using the EDC system. Data collected on equipment that is not captured in EDC will be formatted to the specification of the JJV database manager and sent to JJV for analysis.

External Date Sources for this study include: Not Applicable

The clinical data will be recorded on dedicated eCRFs specifically designed to match the study procedures for each visit. Once completed, the eCRFs will be reviewed for accuracy and completeness and signed by the Investigator. The sponsor or sponsor's representatives will be authorized to gain access to the subject recordation for the purposes of monitoring and auditing the study.

Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection. Data will be transmitted from the clinical site to a secure central database as forms are completed or updated, ensuring information accuracy, security, and confidentiality. After the final database lock, the Investigator will be provided with Individual Patient Profiles (IPP) including the full audit trail on electronic media in PDF format for all of the study data. The IPP must be retained in the study files as a certified copy of the source data for the study.

The content and structure of the eCRFs are compliant with ISO14155:2011.<sup>1</sup>

### **15.2. Subject Record**

At a minimum, subject record should be available for the following:

- subject identification
- eligibility
- study identification
- study discussion
- provision of and date of informed consent
- visit dates
- results of safety and efficacy parameters as required by the protocol
- a record of all adverse events
- follow-up of adverse events
- medical history and concomitant medication
- test article receipt/dispensing/return records
- date of study completion
- reason for early discontinuation of test article or withdrawal from the study, if applicable

The subject record is the eCRF or an external record. The author of an entry in the subject record must be identifiable. The first point of entry is considered to be the source record.

Adverse event notes must be reviewed and initialed by the Investigator.



## **16. DATA MANAGEMENT**

### **16.1. Access to Source Data/Document**

The Investigator/Institution will permit trial-related monitoring, audits, IEC/IRB review and regulatory inspection(s) by providing direct access to source data/documents. Should the clinical site be contacted for an audit by an IEC/IRB or regulatory authority, JJV must be contacted and notified in writing within 24 hours.

### **16.2. Confidentiality of Information**

Information concerning the investigational product and patent application processes, scientific data or other pertinent information is confidential and remains the property of JJV. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that JJV will use information developed in this clinical study in connection with the development of the investigational product and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

### **16.3. Data Quality Assurance**

Steps will be taken to ensure the accuracy and reliability of data, include the selection of qualified investigators and appropriate clinical sites and review of protocol procedures with the Principal Investigator. The Principal Investigator, in turn, must ensure that all Sub-Investigators and clinical site personnel are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study article.

Training on case report form completion will be provided to clinical site personnel before the start of the study. The Sponsor will review case report forms for accuracy and completeness remotely during the conduct of the study, during monitoring visits, and after transmission to data management. Any data discrepancies will be resolved with the Investigator or designee, as appropriate.

Quality Assurance representatives from JJV may visit clinical sites to review data produced during the study and to access compliance with applicable regulations pertaining to the conduct of clinical trials. The clinical sites will provide direct access to study-related source data/documents and reports for the purpose of monitoring and auditing by JJV and for inspection by local and regulatory authorities.

## **17. MONITORING**

The study monitors will maintain close contact with the Principal Investigator and the Investigator's designated clinical site personnel. The monitor's responsibilities will include:

- Ensuring that the investigation is being conducted according to the protocol, any subsequent amendments, and regulatory requirements are maintained
- Ensuring the rights and wellbeing of subjects are protected
- Ensuring adequate resources, including facilities, laboratories, equipment, and qualified clinical site personnel

- Ensuring that protocol deviations are documented with corrective action plans, as applicable
- Ensuring that the clinical site has sufficient test article and supplies
- Clarifying questions regarding the study
- Resolving study issues or problems that may arise
- Reviewing of study records and source documentation verification in accordance with the monitoring plan

## **18. ETHICAL AND REGULATORY ASPECTS**

### **18.1. Study-Specific Design Considerations**

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. Subjects will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

### **18.2. Investigator Responsibility**

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the signed agreement, the investigational plan, Section 4 of the ICH E6 guidelines on Good Clinical Practice (GCP),<sup>2</sup> and applicable regulatory requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles of the Declaration of Helsinki 64<sup>th</sup> WMA General Assembly 2013<sup>3</sup> and that the clinical study data are credible. The Investigator must maintain clinical study files in accordance with Section 8 of the ICH E6 guidelines on Good Clinical Practice (GCP),<sup>2</sup> and applicable regulatory requirements.

### **18.3. Independent Ethics Committee or Institutional Review Board (IEC/IRB)**

Before the start of the study, the Investigator (or Sponsor when applicable) will provide the IEC/IRB with current and complete copies of the following documents (where applicable):

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruitment materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's curriculum vitae, clinical licenses, or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved.

During the study, the Investigator (or Sponsor when applicable) will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruitment materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB)
- Reports of adverse events that are serious, unanticipated, and associated with the test articles, according to the IRB's requirements
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Major protocol deviations as required by the IEC/IRB
- Report of deaths of subjects under the Investigator's care
- Notification if a new Investigator is responsible for the study at the clinical site
- Any other requirements of the IEC/IRB

For protocol amendments that increase subject risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will review and reapprove this clinical study. This request should be documented in writing.

At the end of the study, the Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion. Documentation of this notification must be retained at the clinical site and a copy provided to the CRO or Sponsor as applicable.

#### **18.4. Informed Consent**

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent is in accordance with principles that originated in the Declaration of Helsinki,<sup>3</sup> current ICH<sup>2</sup> and ISO 14155<sup>1</sup> guidelines, applicable regulatory requirements, and Sponsor Policy.

Before entry into the study, the Investigator or an authorized member of the clinical site personnel must explain to potential subject the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.

The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

### **18.5. Privacy of Personal Data**

The collection, processing and disclosure of personal data and medical information related to the Study Subject, and personal data related to Principal Investigator and any clinical site personnel (e.g., name, clinic address and phone number, curriculum vitae) is subject to compliance with the Health Information Portability and Accountability Act (HIPAA) in the United States<sup>9</sup> and other applicable personal data protection and security laws and regulations. Appropriate measures will be employed to safeguard these data, to maintain the confidentiality of the person's related health and medical information, to properly inform the concerned persons about the collection and processing of their personal data, to grant them reasonable access to their personal data and to prevent access by unauthorized persons.

All information obtained during the course of the investigation will be regarded as confidential. All personal data gathered in this trial will be treated in strictest confidence by Investigators, monitors, Sponsor's personnel and IEC/IRB. No data will be disclosed to any third party without the express permission of the subject concerned, with the exception of Sponsor personnel (monitor, auditor), IEC/IRB and regulatory organizations in the context of their investigation related activities that, as part of the investigation will have access to the CRFs and subject records.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor ensures that the personal data will be:

- processed fairly and lawfully
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

## **19. STUDY RECORD RETENTION**

In compliance with the ICH/GCP guidelines,<sup>2</sup> the Investigator/Institution will maintain all CRFs and all subject records that support the data collected from each subject, as well as all study documents as specified in ICH/GCP<sup>2</sup> and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or instructed by the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

If the Investigator has a question regarding retention of study records, he/she should contact JJV.

## **20. FINANCIAL CONSIDERATIONS**

Remuneration for study services and expenses will be set forth in detail in the Clinical Research Agreement. The Research Agreement will be signed by the Principal Investigator and a JJV management representative prior to study initiation.

JJV reserves the right to withhold remuneration for costs associated with protocol violations such as:

- Continuing an ineligible subject in the study
- Scheduling a study visit outside the subject's acceptable visit range

JJV reserves the right to withhold final remuneration until all study related activities have been completed, such as:

- Query resolution
- Case Report Form signature

- Completion of any follow-up action items

## 21. PUBLICATION

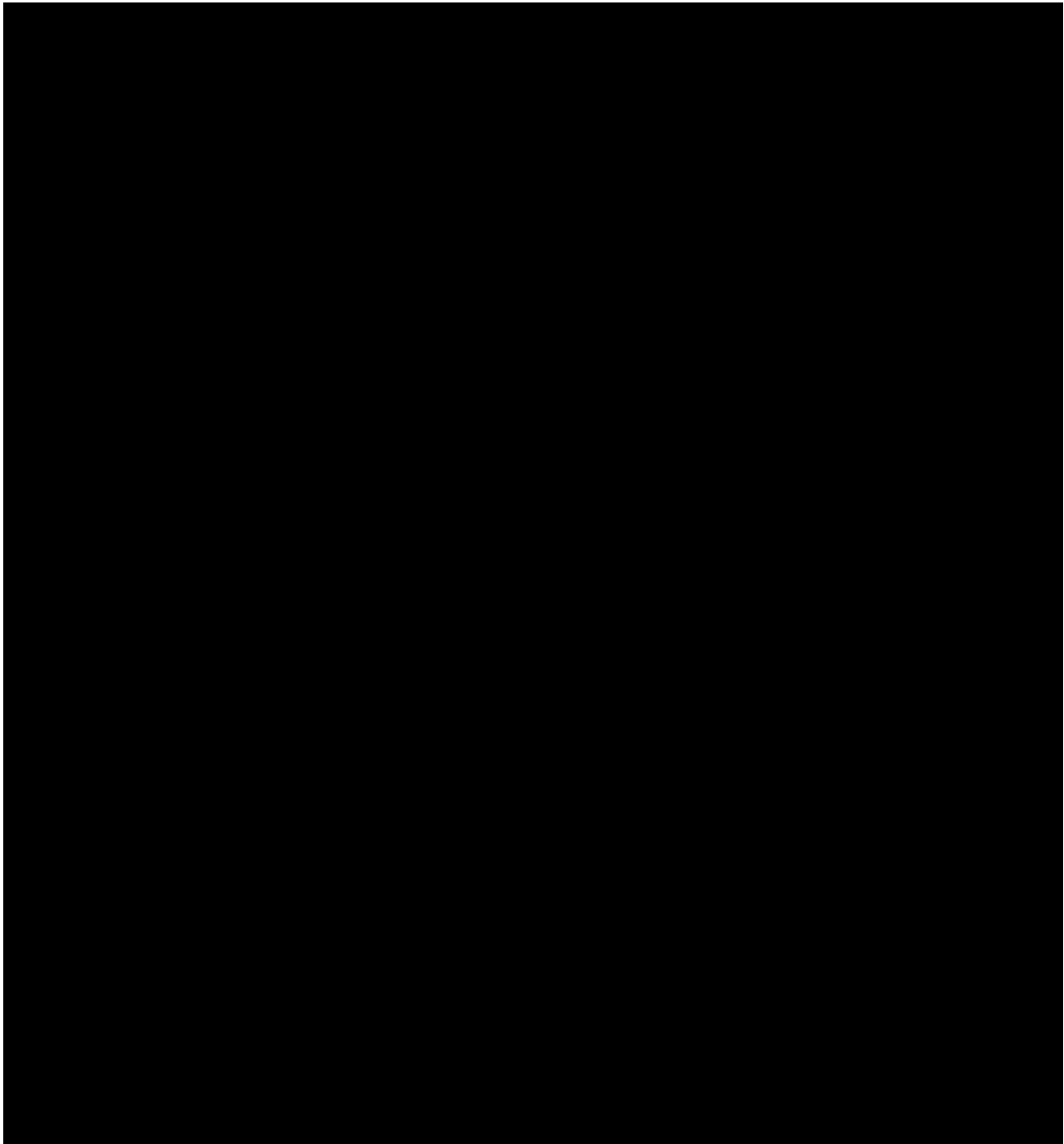
This study will be registered on ClinicalTrials.gov based on the following: This study is a post-market study with approved products assessing endpoints associated with ocular comfort. While the study is exploratory in nature, the data generated (for both the drops and the LipiViewII®) could be used for scientific materials.

## 22. REFERENCES

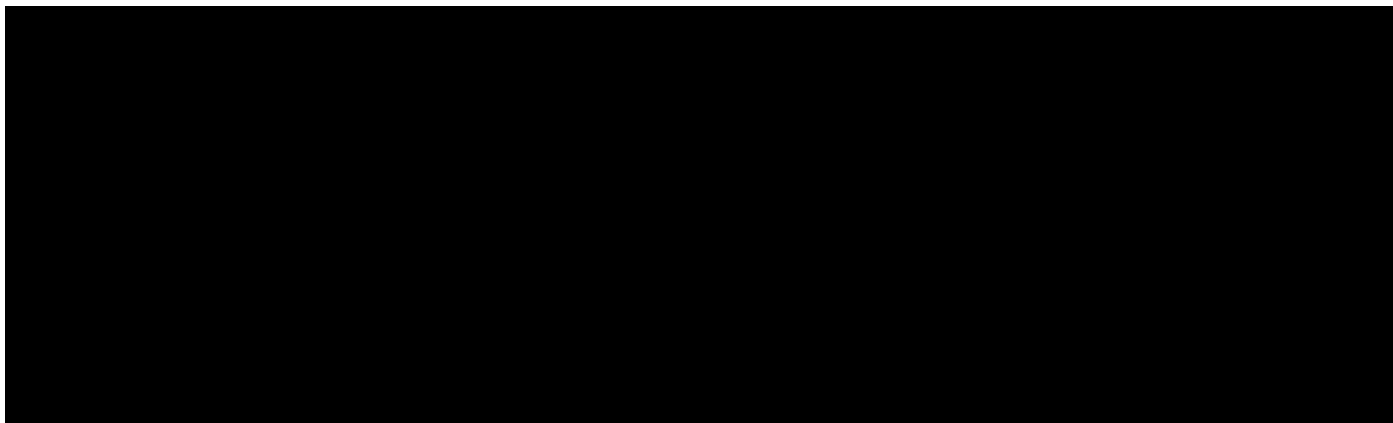
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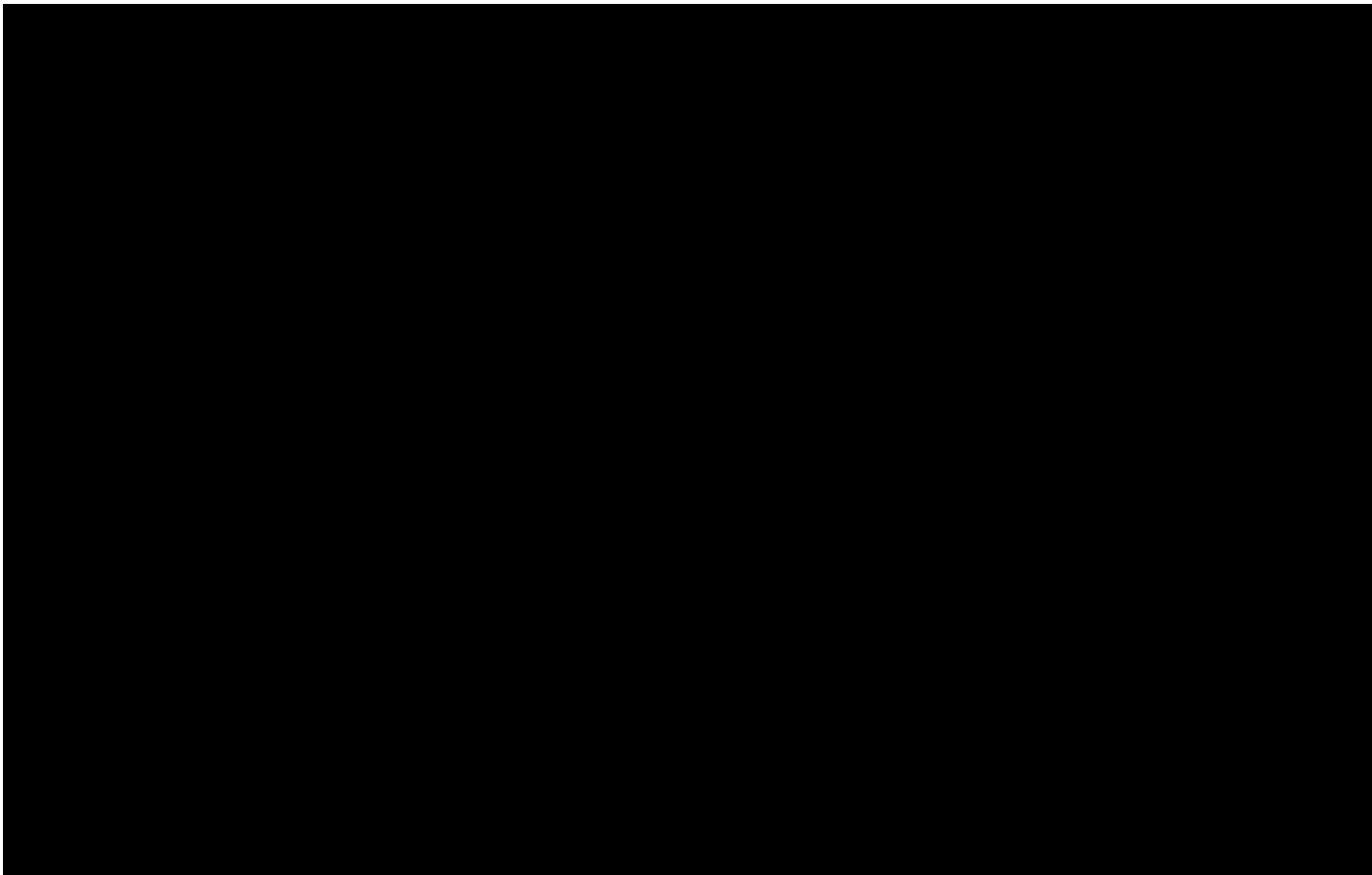
**APPENDIX A: PATIENT REPORTED OUTCOMES (STUDY QUESTIONNAIRES)**

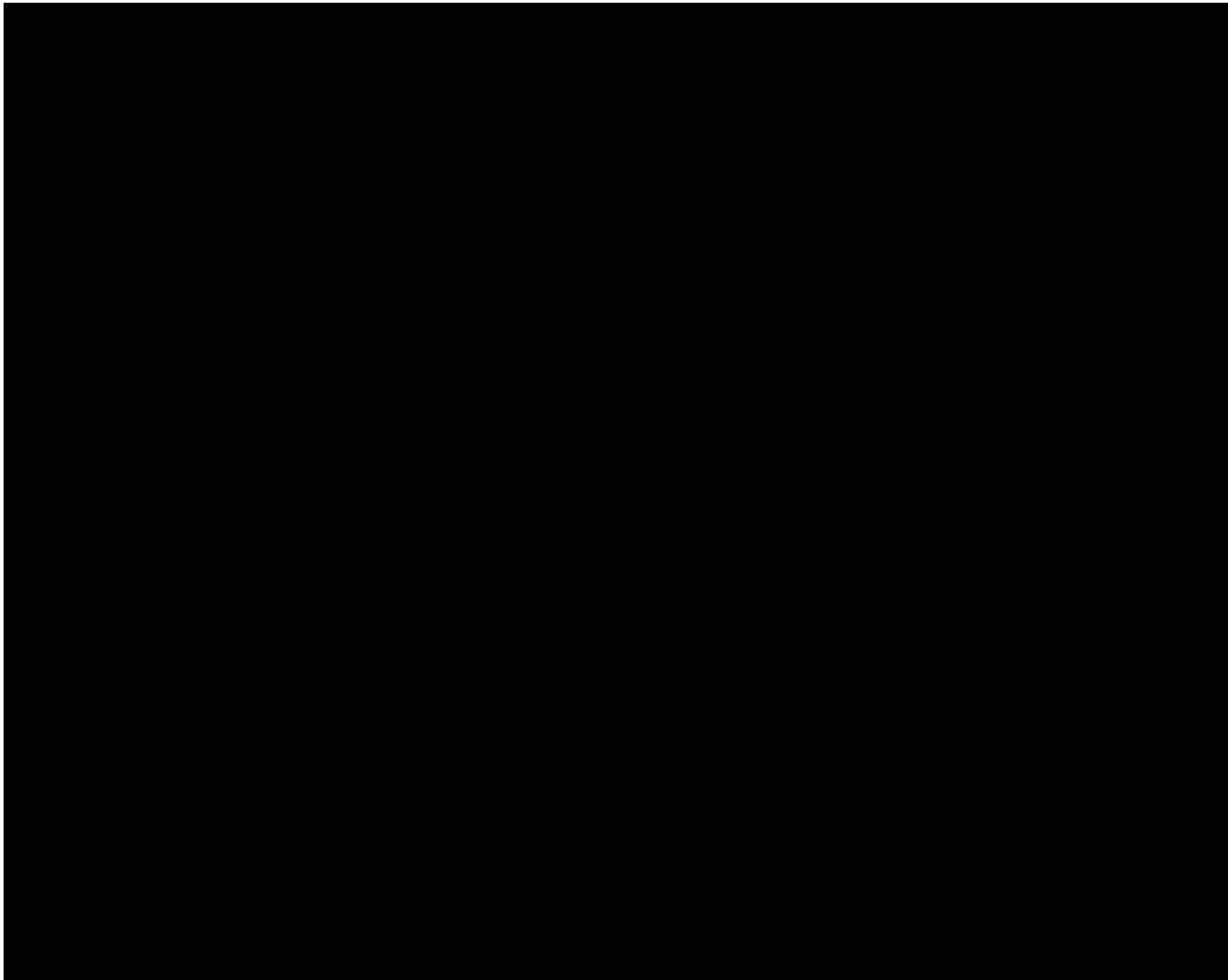


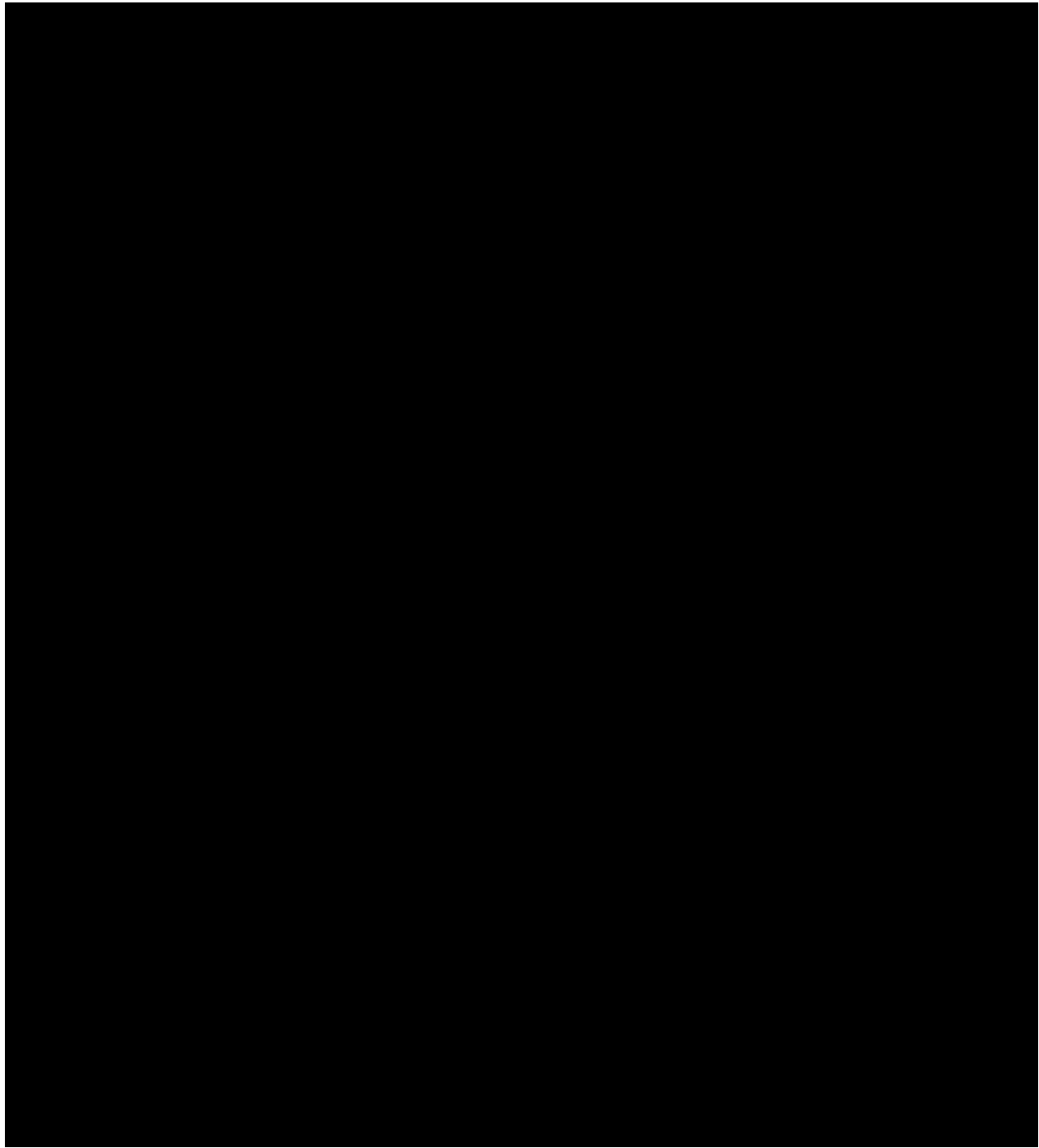












**APPENDIX B: PATIENT INSTRUCTION GUIDE**

Patient Instruction Guide will be provided separately.



**APPENDIX C: PACKAGE INSERT (APPROVED PRODUCT)**









**APPENDIX D: LIPIVIEW II® II ASSESSMENT PROCEDURE**





# **LIPIVIEW<sup>®</sup> II**

*Ocular Surface Interferometer*

## *Instructions for Use*

Model LVI-2000

running Software Version 3.X

**Manufactured by:**

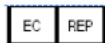
TearScience, Inc.

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Morrisville, NC 27560

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<b>Revision History</b>			
<b>Revision</b>	<b>Date</b>	<b>Description of Changes</b>	<b>ECR # or PCR #</b>
A	19 Nov 2014	Initial release of Instructions for Use for LipiView II/3.x software.	P1407211
B	31 July 2015	Made updates for software version 3.11. Replaced Figure 6. Fixed minor typographical and formatting errors.	P1502121
C	1 February 2016	<p>Previous revisions of this document were numbered 012051-ENG. To accommodate the release of varied English versions, this document is now numbered as 012051-US with the following applicable changes:</p> <p>Removed phrase "All of these image types can be photographically documented and visually monitored" from Indications for Use.</p> <p>Removed information pertaining to Model LVI-1001.</p> <p>Updated phototoxicity warning with ISO 15004-2 required information.</p> <p>Clarified patient contact components and added disinfection of Lid Everter to Device Description and Warning sections (already described in Cleaning and Instructions sections of the manual).</p> <p>Added inspection of Lid Everter to Device Description and Instructions.</p> <p>Added USB mouse and keyboard to Accessory Support.</p> <p>Updated recording time from 10 to 5 seconds in Capture Ocular Images procedure.</p> <p>Updated document copyright date to 2016.</p>	P1601281



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# 1 Introduction

This manual provides the indications, contraindications, warnings, precautions, potential adverse effects and instructions for use for the *TearScience® LipiView® II Ocular Surface Interferometer*. **Carefully read this manual in its entirety before using LipiView II. Failure to follow these instructions may result in improper use of the device.**

This manual provides essential information for safe and proper use of LipiView II.

- Section 2 (Important Device Information: indications, contraindications, warnings, precautions, potential adverse effects, device description, storage and transport, service and maintenance, cleaning, disposal and warranty)
- Section 3 (Instructions for Use for Start-up, First Time Setup, Lipid Imaging, Gland Imaging and Ocular Imaging)
- Section 4 (Troubleshooting Guide)

The *LipiView II Administrator's Guide* contains information about the setup and administration of LipiView II.

- **Prior to initial use of LipiView II, refer to Section 3.2 of this manual and/or the Administrator's Guide to ensure proper setup** (including requirements for operator (user) names, passwords, network connections and file storage.)

**NOTE:** LipiView II has a firewall and disabled remote access to protect the device and ensure privacy of patient records over a network. However, if LipiView II is connected to a non-secure wireless network, exported patient data will not be protected from unauthorized access. TearScience recommends the LipiView II be connected to a password-protected wireless router utilizing the WPA or WPA2 security protocols to ensure protection of the device and patient records.

Strong passwords do not contain words that appear in a dictionary, are at least six characters long, and consist of a mixture of letters and numbers. TearScience recommends that you choose a strong password and change it regularly (for example, every 90 days.)

Contact TearScience (in North America, at +1 919 459 4891 or by email at [customerservice@tearscience.com](mailto:customerservice@tearscience.com)) with any questions about the information contained in this manual or for additional information on the safe and proper operation of LipiView II.



## 2 Important Device Information

### 2.1 *Indications for Use*

The LipiView II Ocular Surface Interferometer is an ophthalmic imaging device intended for use by a physician in adult patients to capture, archive, manipulate and store digital images of:

- Specular (interferometric) observations of the tear film. Using these images, LipiView II measures the absolute thickness of the tear film lipid layer.
- Meibomian glands under near-infrared (NIR) illumination
- The ocular surface and eyelids under white illumination

### 2.2 *Contraindications*

Contraindications are conditions in which the device should not be used because the risk of use clearly outweighs any benefit. No contraindications have been identified for LipiView II.

### 2.3 *Precautions*

The following patient conditions may affect the interferometry assessment of a patient's tear film using LipiView II:

- **Use of ophthalmic drops such as artificial tear lubricants, ointments, and medications.** Advise patients not to instill oil-based ophthalmic drops (e.g., Soothe<sup>®</sup>, Restasis<sup>®</sup>, Systane Balance<sup>®</sup>) for at least 12 hours prior to device use and not to instill ointments for at least 24 hours prior to device use. Wait at least 4 hours after instillation of all other ophthalmic drops prior to device use.
- **Soft or rigid contact lens wear.** Advise patients to remove contact lenses at least 4 hours prior to device use.
- **Use of oil-based facial cosmetics around the eye.**
- **Eye rubbing.**
- **Recent swimming in a chlorinated pool.** Advise patients not to swim for at least 12 hours prior to device use.
- **Any ocular surface condition** that affects the stability of the tear film. These conditions include disease, dystrophy, trauma, scarring, surgery, or abnormality.

### 2.4 *Warnings*

Review the warnings in Table 1 prior to using LipiView II.

**Table 1: General and Operation Warnings**

	<b>GENERAL WARNINGS</b>
<b>WARNING:</b> No modification of this equipment is allowed.	
<b>Caution: Power Requirements.</b> The LipiView II is a continuous operation device which requires a power source of 100-240 Volts AC $\pm$ 10%, 50/60 Hz single phase, 4 Amps. Connection to a power supply other than a supply mains with protective earth may result in electric shock.	
	<b>Caution:</b> The LipiView II has protection against electric shock of applied part classified as Type B. This device is classified as an IEC Class 1 product.
<b>Caution: Voltage Protection and Fuse Selection.</b> Contact TearScience to replace a blown fuse. TearScience personnel must replace only with a 5 x 20 mm, 4 A, 300 ms, 40 A breaking capacity fuse to avoid risk of fire. TearScience personnel must disconnect from power before servicing to avoid risk of electrical shock.	
<b>Caution:</b> Backup Battery Replacement. Backup battery cannot be replaced.	
<b>Caution:</b> Keep the LipiView II away from strong magnetic fields as it could damage the device's hard drive, but is not a safety hazard to the user or patient.	
<b>Caution:</b> This equipment is intended for use by healthcare professionals only. This equipment may cause radio interference or may disrupt the operation of nearby equipment. It may be necessary to take mitigation measures, such as re-orienting or relocating the LipiView II or shielding the location.	
<b>Caution:</b> Portable and mobile RF communications equipment can affect MEDICAL ELECTRICAL EQUIPMENT.	
<b>Caution:</b> The use of ACCESSORIES, transducers and cables other than those specified, with the exception of transducers and cables sold by the manufacturer of the EQUIPMENT or DEVICE as replacement parts for internal components, may result in increased EMISSIONS or decreased IMMUNITY of the EQUIPMENT or DEVICE.	
<b>Caution:</b> The EQUIPMENT or DEVICE should not be used adjacent to or stacked with other equipment and if adjacent or stacked use is necessary, the EQUIPMENT or DEVICE should be observed to verify normal operation in the configuration in which it will be used.	
<b>Caution:</b> Degree of protection against harmful ingress of liquid: IPX0. This equipment has no protection against ingress of liquids.	
<b>Caution:</b> This device is not suitable for use in the presence of flammable mixtures.	
<b>Caution:</b> This device is not suitable for use in oxygen rich environments.	
<b>Caution:</b> The device monitor and base unit may exceed 41°C. Device will remain within safe momentary contact temperature, below 51°C.	







**OPERATION WARNINGS**

**Caution:** Federal law restricts this device to sale by or on the order of a physician.

**Caution:** The chin and forehead rest surfaces and Handheld Near IR Lid Everter must be disinfected with alcohol immediately prior to use and prior to storage.

**Caution: Photo-toxicity hazard.** No acute optical radiation hazards have been identified for LipiView II under intended use conditions. Since prolonged intense light exposure can damage the retina, the use of the device for ocular examination should not be unnecessarily prolonged. The retinal exposure dose for a photochemical hazard is a product of the radiance and the exposure time. Aphakes and persons with diseased eyes will be at greater risk. The risk may also be increased if the person being examined has had any exposure with the same instrument or any other ophthalmic instrument using a visible or near-infrared light source during the previous 24 hours.

**Caution:** The light emitted from this instrument is potentially hazardous. The longer the duration of exposure, the greater the risk of ocular damage. Exposure to light from the instrument when operated at maximum intensity will exceed the safety guideline after 8 hours.

**Caution:** To prevent pinching, do not put fingers near illuminator, lens or chin rest during focusing. Instruct patient not to place hands on LipiView II during operation, and not to put fingers near illuminator, lens or chin rest.

**Caution:** If a problem occurs with LipiView II, identify the symptom then attempt to resolve the problem as indicated in Section 4, *Troubleshooting Guide*. If the problem cannot be resolved, stop using the device and contact TearScience.

**Caution:** To prevent electric shock or performance alteration, do not attempt to service the device or remove the cover. No maintenance is required for LipiView II, and the device and all of its associated parts are not serviceable by the user.

**Caution:** In order to isolate this equipment from supply mains the equipment must be unplugged from the wall. Do not position the equipment in a location which would prevent the unit from being unplugged in an emergency.

**Caution:** Do not store this instrument in conditions where the temperature may rise above 55°C or fall below -10°C.

**Caution:** When lifting or handling LipiView II, caution should be taken to prevent injury or damage to the device. Prior to moving the device, put the monitor arm into a locked position and unplug the power cord from the wall. If an external monitor is attached, disconnect the external monitor prior to moving the device.

**Caution:** Shock hazard. Do not touch patient and device under top cover simultaneously.






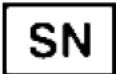



## 2.5 Potential Adverse Effects





There are no known or anticipated adverse effects associated with use of this device.

## 2.6 Labeling

Table 2 provides a description of the symbols used on LipiView II labeling.

**Table 2. Symbols Used on LipiView II Labeling**

Label Symbol	Symbol Description
	Type B applied part
	Consult operating instructions
	Device transmits radiofrequency (RF) energy
	Text consists of a warning or precaution relating to safety. Read the text carefully and use the equipment as instructed to ensure safety.
	Reference Number
	Serial Number
	<b>CAUTION:</b> Federal law restricts this device to sale by or on the order of a physician.
	Mandatory conformity mark for medical device products in the European Economic Area (EEA). The <b>CE marking</b> certifies that a product has met consumer safety, health or environmental requirements. "0086" is the Notified Body Number.
	This model/product is Listed in Intertek's Directory of Listed Products.

Label Symbol	Symbol Description
	Date of Manufacture
	Manufacturer
	Temperature Limitation, defining upper and lower temperature limits; used for storage or shipping temperatures.
	Authorized Representative in the European Community
P/N	Part Number
Rev	Revision Level

## 2.7 Device Description and Overview

The LipiView II is a bench-top device used as an ophthalmic camera for imaging the lipid layer of the tear film, meibomian glands, ocular surface and eyelids. There are three imaging modes: Lipid, Gland and Ocular.

In Lipid Imaging Mode, LipiView II operates on the principle of white light interferometry and provides an interferometry color assessment of the tear film by specular reflection. The patient's eye is positioned in front of an illumination source directed toward the tear film on the corneal surface. Light from the illumination source passes through the tear film and is specularly reflected into a camera. The light reflecting back through the lens in the camera forms an interference pattern, called an "interferogram." A video image file is recorded over time since the interference pattern changes as the tear film is distributed across the cornea during blinking.

The computer system captures and enhances the interference pattern and displays a profile corresponding to an interferometry color scale. This color scale has been validated to a known standard for measurement of thin film thickness, demonstrating that LipiView II has the ability to make absolute thickness measurements of the tear film lipid layer by the imaging interferometric colors. The measured lipid layer thickness may range from 10 to 240 nanometers (nm), with a precision of 1 nm and an accuracy of  $\pm 10$  nm. The conformance factor of the measured interference pattern is displayed as a "C-factor," which is equal to the proportion of measured colors that match the predicted interferometric color scale. The video image of the ocular surface may be viewed on the computer screen display and in a printed report.

In Gland Imaging Mode, LipiView II uses near infrared (NIR) illumination and an NIR-sensitive camera mounted on a motion control system to image the meibomian glands. The tissue between the meibomian glands and the surface of the eyelid are transparent to NIR light; the glands reflect NIR wavelengths, allowing them to be imaged.

In Ocular Imaging mode, LipiView II captures high-resolution still images or video to record relevant findings on the ocular surface and/or eyelids. The images can be taken using room light only or the device's built-in white light.

LipiView II contains the following components, which are identified in Figure 1 (Front/Patient View) and Figure 2 (Rear/User View):

- Base with Computer System and Electronics
- 2-position Forehead and Chin Rest with Fluted Roller (for height adjustment)
- Motion Stage
- Camera and Attached Lens
- Illuminator
- Pushbutton Controls
- Touchscreen Display with Pivoting Arm
- USB Ports
- Handheld Near Infrared (IR) Lid Everter, shown in Figure 3
- Connections for an External Monitor, the Near Infrared (IR) Lid Everter, and the power cord, shown in Figure 4.



**Figure 1. Front (Patient) View of LipiView II**

Key	
1	Forehead Rest

2	Camera and Attached Lens
3	Illuminator
4	Chin Rest
5	Fluted Roller (adjusts chinrest height)
6	Chin Rest Base -- 2-position (toward/away from device) adjust
7	Motion Stage
8	Back of Touchscreen Display
9	Pushbutton Controls (on top of unit)
10	Base (contains Computer System and Electronics)

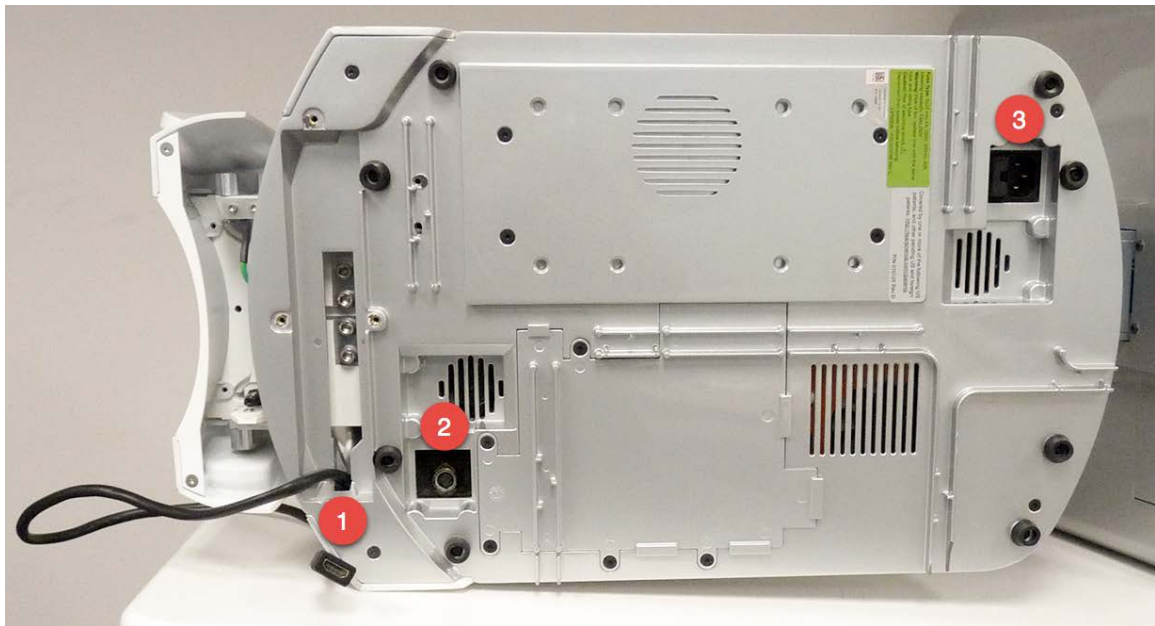


**Figure 2. Rear (User) View of LipiView II**

Key	
1	Touchscreen Display
2	USB Port (another is on the other side, and a third is above the power switch)
3	Power Switch
4	Motion Stage
5	Chinrest --2-position (toward/away from device) adjust
6	Base (contains Computer System and Electronics)
7	Pivoting Arm



**Figure 3. Handheld Near Infrared (IR) Lid Everter**



**Figure 4. External Connectors on Underside of Base**

Key	
1	Hardwired HDMI connection for external monitor
2	Connector for Handheld Near IR Lid Everter
3	Connector for Power Cord

### 2.7.1 Base with Computer System and Electronics

The base houses the power connection and computer hardware. The base connects with the forehead and chin rest, motion stage and touchscreen display. The on/off power switch (Figure



2) is located on the base opposite the chin rest. An external monitor connection is hardwired into the base, as is a connection point for the Near IR lid everter.

### **2.7.2 Forehead and Chin Rest with Fluted Roller**

The adjustable forehead and chin rest is designed to allow proper positioning of the patient's head to capture images. To ensure a properly focused image, the patient must place his/her forehead and chin firmly against the forehead and chin rests. The chin rest may be raised or lowered to accommodate different facial dimensions by spinning the fluted roller. The chin rest has a 2-position adjust (toward the device for Lipid imaging and away from the device for Gland and Ocular Imaging.)

Two canthus alignment marks are located on the left and right sides of the forehead rest. Adjusting the chin rest to position the lateral canthus of the patient's eye at these marks will optimize the range of camera motion.

The forehead and chin rest come in contact with the patient. Disinfect the forehead and chin rest surfaces with alcohol immediately prior to use and prior to storage.

### **2.7.3 Motion Stage**

The motion stage contains the camera, illuminator and motor controls used to adjust the camera and illuminator. The height of the motion stage is adjusted as part of the image capture process, to position the camera correctly.

### **2.7.4 Camera and Attached Lens**

The camera is located inside the motion stage and is not visible externally. The height of the camera is adjusted as part of the motion stage. The camera can also be adjusted left and right and backwards and forwards with separate controls.

### **2.7.5 Illuminator**

The grid-like fixture attached to the motion stage is the illuminator. The height of the illuminator is adjusted as part of the motion stage. There are no separate controls for the illuminator.

### **2.7.6 Pushbutton Controls**

LipiView II includes a pushbutton control keypad on top of the unit that may be used in all modes, to make it easier for the operator to capture images.

### **2.7.7 Touchscreen Display with Pivoting Arm**

The touchscreen display is on a pivoting arm, which allows it to be positioned  $\pm 45$  degrees or  $\pm 90$  degrees from its location shown in Figure 1. To reposition the screen, press the button under the pivoting arm while moving the arm left or right to the approximate 45 or 90 degree location. Release the button and continue moving the arm until it locks into place.

In addition to displaying images and information to the operator, the screen functions as a touchscreen user interface to the LipiView II. The operator touches the screen to operate the motion stage and camera controls and capture images.

### 2.7.8 USB Ports

The lower base of the touchscreen display contains three USB ports, located as shown in Figure 2. These ports may be used to connect a printer or storage device.

### 2.7.9 Handheld Near Infrared (IR) Lid Everter

The Handheld Near Infrared (IR) Lid Everter is both a near-infrared light source and a shaped instrument that aids in the proper eversion of the lower eyelid. The Near IR Lid Everter contacts the patient's lower eyelid. Inspect the Near IR Lid Everter to ensure it is intact prior to use. Disinfect the Near IR Lid Everter with alcohol immediately prior to use and prior to storage. Place the Near IR Lid Everter slightly below the lash line and move the instrument slightly inward and upward to evert the entire length of the lower eyelid.

### 2.7.10 Operating Environment and Specifications

System and environmental specifications are displayed in Table 3.

**Table 3. System and Environmental Specifications**

Input Voltage	100 – 240 VAC, 50 – 60 Hz
Product Safety Classification	Type B Applied Part
IEC 60601-1— Medical electrical equipment—Part 1: General requirements for safety	
IEC 60601-1-2 — Medical electrical equipment—Part 1: General requirements for safety—Section 2: Collateral standard—Electromagnetic compatibility—Requirements and tests;	CISPR 11 (Class A, Group 1)
Accuracy of lipid layer thickness measurement	±10 nm
Operating Temperature	10°C to 35°C
Operating Relative Humidity	Up to 90% non-condensing
Atmospheric Pressure	700 hPa to 1060 hPa
Storage Temperature	-10°C to 55°C
Transport Temperature	5°C to 60°C

### 2.7.11 Accessory Support

LipiView II may be used with the following USB accessories that are compatible with Windows 7 and USB 2.0:

- USB printer (Printer Support)
- USB external hard drive (External Backup Support)



- USB flash drive (USB / Thumb Drive Support)
- USB mouse and keyboard (support for optional alternative to touchscreen controls)

LipiView II is designed to operate wirelessly with other network devices, such as a printer. Placement of LipiView II should be within range of the network, if a network system is used.

LipiView II may be used with an external monitor. The hardwired connection in the base will support HDMI or DVI inputs for an off-the-shelf external monitor, which has at least 1280 x 1024 resolution and supports 60Hz frame rates.

## 2.8 Storage and Transport

Before storage, ensure the power switch is off, and the chin and forehead rest surfaces, as well as the Near IR Lid Everter, are cleaned according to the instructions in Section 2.10, *Cleaning*. Store LipiView II in a way that prevents contamination and damage between uses.

For transport, ensure power cord is unplugged and secured off the ground. Grip onto metal portion of the device in two locations: 1) under the base or under the head containing the motion stage; and 2) monitor arm behind the screen. Carefully lift and move the device in an upright position.

## 2.9 Installation, Maintenance and Servicing

There are no specific installation requirements for LipiView II, other than unpacking the device from its carton and connecting power and accessories (the external monitor and Near IR Lid Everter.) The device is installed and ready to use safely and correctly if it passes its Power-On Self Test with no system errors.

LipiView II performs a calibration process at startup. LipiView II does not require preventive maintenance or scheduled calibration. If the touchscreen gets out of calibration, refer to the *LipiView II Administrator's Guide* for instructions on how to recalibrate the touchscreen using the built-in utility.

Expected life of LipiView II is 5 years. Note that no user serviceable components are inside the unit. For Field Service, contact TearScience in North America at +1 919 459 4891 or by email at customerservice@tearscience.com.

## 2.10 Cleaning

Table 4 identifies the components of LipiView II that require cleaning. For each component, the frequency and method of cleaning is provided.

**Table 4: LipiView II Cleaning Information**

Component	Frequency	Method
Chin rest and forehead rest	Immediately prior to use and prior to storage	Alcohol

surfaces		
Handheld Near IR Lid Everter	Immediately prior to use and prior to storage	Alcohol
Camera lens and Illuminator	Monthly	Wipe with a lint-free photographic quality lens cloth
Touchscreen Display Monitor	When soiled or as needed	<ul style="list-style-type: none"> <li>• Power off the device.</li> <li>• Apply window or glass cleaner to a cloth rag and wipe the screen</li> <li>• <b>Do not apply cleaner directly to the screen</b></li> <li>• <b>Do not clean the monitor with alcohol, paint thinner, benzene or compressed air</b></li> </ul>
LipiView II exterior, including keypad	When soiled or as needed	<ul style="list-style-type: none"> <li>• Wipe down exterior of the device with a mild soapy cloth</li> <li>• <b>Do not use bleach, chlorine or acetone-based solutions</b> to clean any part of the chin rest or the system enclosure</li> </ul>
External monitor	Follow manufacturer's cleaning instructions	Follow manufacturer's cleaning instructions

## 2.11 Disposal

LipiView II consists of an ABS plastic enclosure, aluminum chassis, circuit boards, and electrical components. In the unlikely event that the device is damaged and cannot be repaired, never dispose of the device. Return LipiView II to TearScience using the contact information on the first page of this manual.

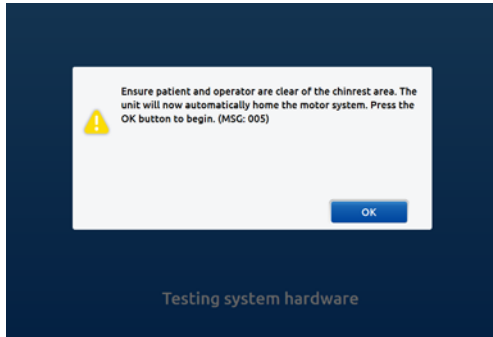
## 2.12 Warranty

TearScience, Inc. warrants that each LipiView II: 1) is free from defects in materials and workmanship; and 2) conforms to TearScience Inc.'s official specifications. The warranty period for each LipiView II is one year commencing on the date of purchase. *Any tampering or modifications to the device by the user will void the warranty.*

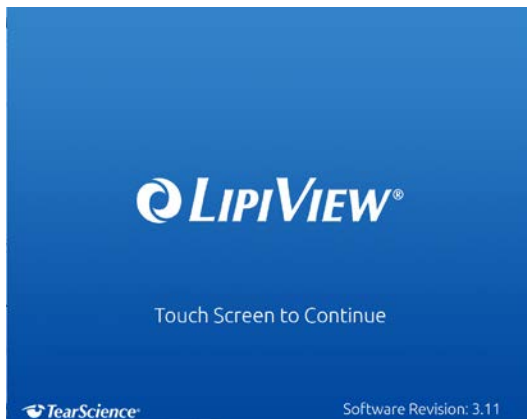
## 3 Instructions for Use

### 3.1 Startup and Login

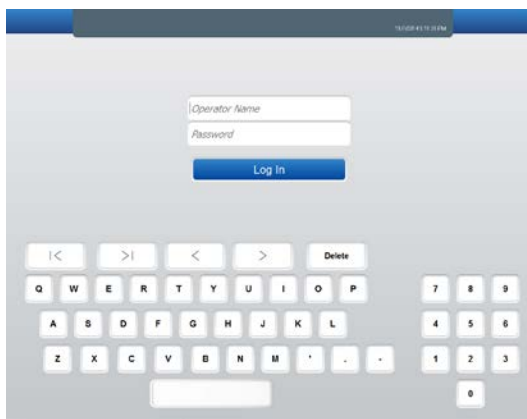
At startup, LipiView II performs a self-test, confirms camera connection, verifies system voltages, checks remaining hard drive space, and calibrates camera motors.



**Figure 5. Warning Screen**



**Figure 6. Initialization Screen**

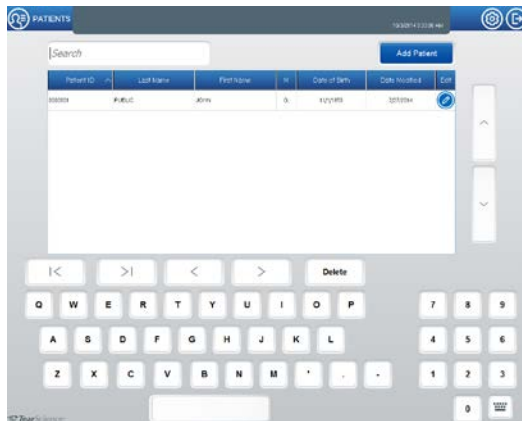


**Figure 7. Login Screen**

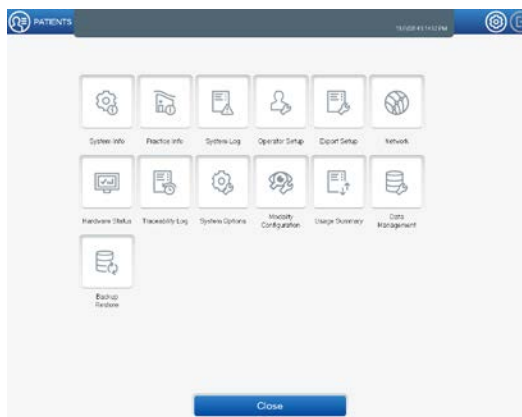
1. Ensure the power cord is plugged into an electrical outlet. The power cord connection is located underneath the base of the device.
2. Power on LipiView II by pressing the rocker switch on the device base (refer to Figure 2). The touchscreen display is initially blank and then displays a “Welcome” message and other messages related to self-test and initialization.
3. Press the OK button to acknowledge the warning (Figure 5) after ensuring the patient and operator are clear of the chinrest area. The motion stage moves during system hardware self-test, which takes about 20 seconds.
4. Touch the screen to continue when Figure 6 is displayed indicating that the device is ready for use. (Note that the software version displayed may differ from Figure 6.)
5. When the Login screen (Figure 7) is displayed, enter the operator name and password using the onscreen keyboard. (Operator name and password are provided by the Administrator or TearScience trainer.) Press *Log In*.

## 3.2 First Time Device Setup

Prior to initial use, ensure that the following instructions are completed by an Administrator. Other administrative functions, detailed in *LipiView II Administrator's Guide*, can be completed at the discretion of the Administrator. LipiView II has been set up with a default Operator Name (LIPIVIEW) and Password (LIPIVIEW) that has administrator privileges. After initial login, it is recommended but not required that the Administrator reset the password.



**Figure 8. Patient Records Screen**



**Figure 9. Main Admin Screen**

1. Power on the system.
2. When the Login screen (Figure 7) is displayed, enter LIPIVIEW for both the Username and Password. (The onscreen keyboard only supports uppercase characters.) Press *Log In*. The Patient Records screen (Figure 8) is displayed.
3. Press the Gear icon [⚙️] on Menu bar (Figure 10) located in the upper right corner of the screen. The Main Admin screen (Figure 9) is displayed.
4. Press *Operator Setup*. Add additional operator usernames and set or change passwords as needed.

Before capturing images, it is also recommended that the following items be set up using the functions on the Main Admin screen (Table 5).

From Main Admin screen (Figure 9):

5. Press *Practice Info* to enter Practice Information.
6. Press *System Info*, then Press *Set Date and Time* to set System Date and Time.
7. Press *Network* to set up network connections.
8. Press *Close* to return to the Patient Records screen (Figure 8).

**Table 5. Main Admin Functions**

<b>System Info</b>	System information, including software versions and important utilities (Calibrate Touchscreen, Set Date and Time, Set Up System for Packaging, Launch Remote Support, Software Update, Save Changes and Shut Down, Save as PDF)
<b>Practice Info</b>	Enter the name and business information for the medical practice
<b>System Log</b>	View the system log, which collects information about key system events and errors (useful for troubleshooting and technical support)
<b>Operator Setup</b>	Add or delete Operators (users) and/or Administrator
<b>Export Setup</b>	Select file formats for records export
<b>Network</b>	View network information
<b>Hardware Status</b>	See comprehensive status information for the hardware and software
<b>Traceability Log</b>	View records of all traceable events to ensure data integrity (e.g., users added/deleted, treatment records moved from one patient to another)
<b>System Options</b>	Set the automatic logout timer, choose display options
<b>Modality Configuration</b>	Set options for Lipid Imaging or Gland Imaging modes
<b>Usage Summary</b>	View statistics about use, selected by configurable criteria
<b>Data Management</b>	Delete or move patient records (creates a permanent record in the Traceability Log)
<b>Backup/Restore</b>	Backs up or restores LipiView II patient and treatment data to networked drive or other media

### 3.3 Menu Bar

The menu bar (Figure 10), shown at the top of the screen, has the following icons.

**Figure 10. Menu Bar**

Key	
1	<b>Patients Button</b> – Touch to return to Patient Records screen (Figure 11)
2	<b>Drawer Dropdown</b> – Contains information on current patient and active imaging session (if any). Pull down to access patient history. When on Image Capture screens or Review Image screens, press <b>Capture/View Button</b> on menu bar to return to Capture/View screen (Figure 13).
3	<b>Admin</b> – Touch to access Administrator screens (requires access privileges)
4	<b>Log Out</b>

### 3.4 Enter and Select a Patient and Imaging Mode

After Login, enter a new patient or search for an existing patient. Select the patient to capture new images or view prior images. Then, select an imaging mode.

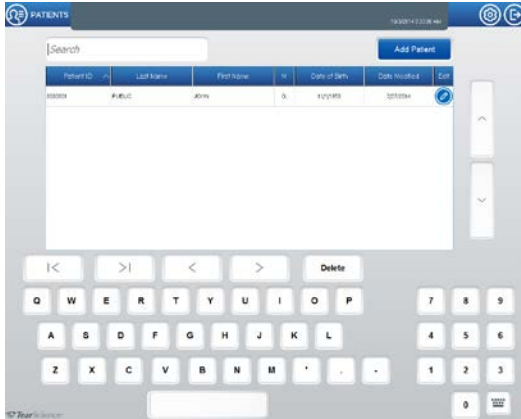


Figure 11. Patient Records Screen

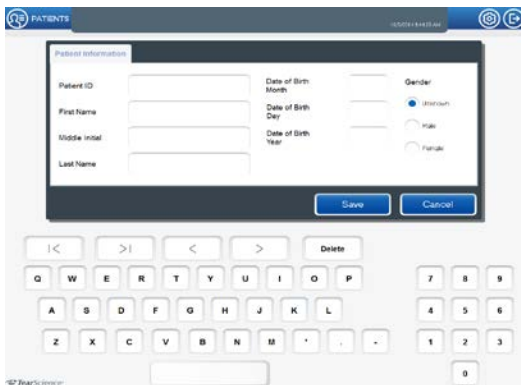


Figure 12. Patient Entry Screen



Figure 13. Capture/View Screen

1. For a **New Patient**, select **Add Patient** on Patients Records screen (Figure 11) to display Patient Entry screen (Figure 12).
  2. Using onscreen keyboard, enter patient information, then press **Save**. Patient records must include at a minimum:
    - 1) Patient ID or
    - 2) Last Name, First Name and Date of Birth (enter the month and date as two-digit numbers, and the year as a four-digit number: MM/DD/YYYY).
  3. For an **Existing Patient**, enter patient data (patient ID or name) in Search field on Patient Records screen (Figure 11) to locate the record. To edit patient data, press Pencil icon to the right of the list.
  4. Select the desired patient record from the patient listing table.
- NOTE:** The step keys can be used to move backwards or forwards through the table. When the list spans multiple pages, sort the table by pressing the header field by the desired column. Press the same header a second time to sort the table in the reverse order. A small triangle in the column header indicates the table is being displayed by this column. The triangle points down or up to specify the sorting direction.
5. When Capture/View screen (Figure 13) displays, select an imaging mode (Lipid Imaging, Gland Imaging or Ocular Imaging) to capture new images or view prior images for that patient. Select **All Exams** to view all images in the patient's history.

### 3.5 Capture Tear Film Images (Lipid Imaging Mode)

1. To image the tear film lipid layer by specular reflection of light, select Lipid Imaging from the Capture/View screen (Figure 13) and press *New*.
2. Disinfect the forehead and chin rest with alcohol prior to use.
3. Ensure the chin rest is in closest position toward the device.
4. Place the patient's chin fully forward into chin rest and forehead firmly against forehead rest. Adjust the height of the chin rest by spinning the fluted roller until the temporal canthus is aligned with the marks on the left and right sides of the forehead rest. Instruct the patient to look at the orange fixation light.

**CAUTION: To prevent pinching, do not put fingers near illuminator, lens or chin rest during focusing. Instruct patient not to place hands on LipiView II during operation, and not to put fingers near illuminator, lens or chin rest.**

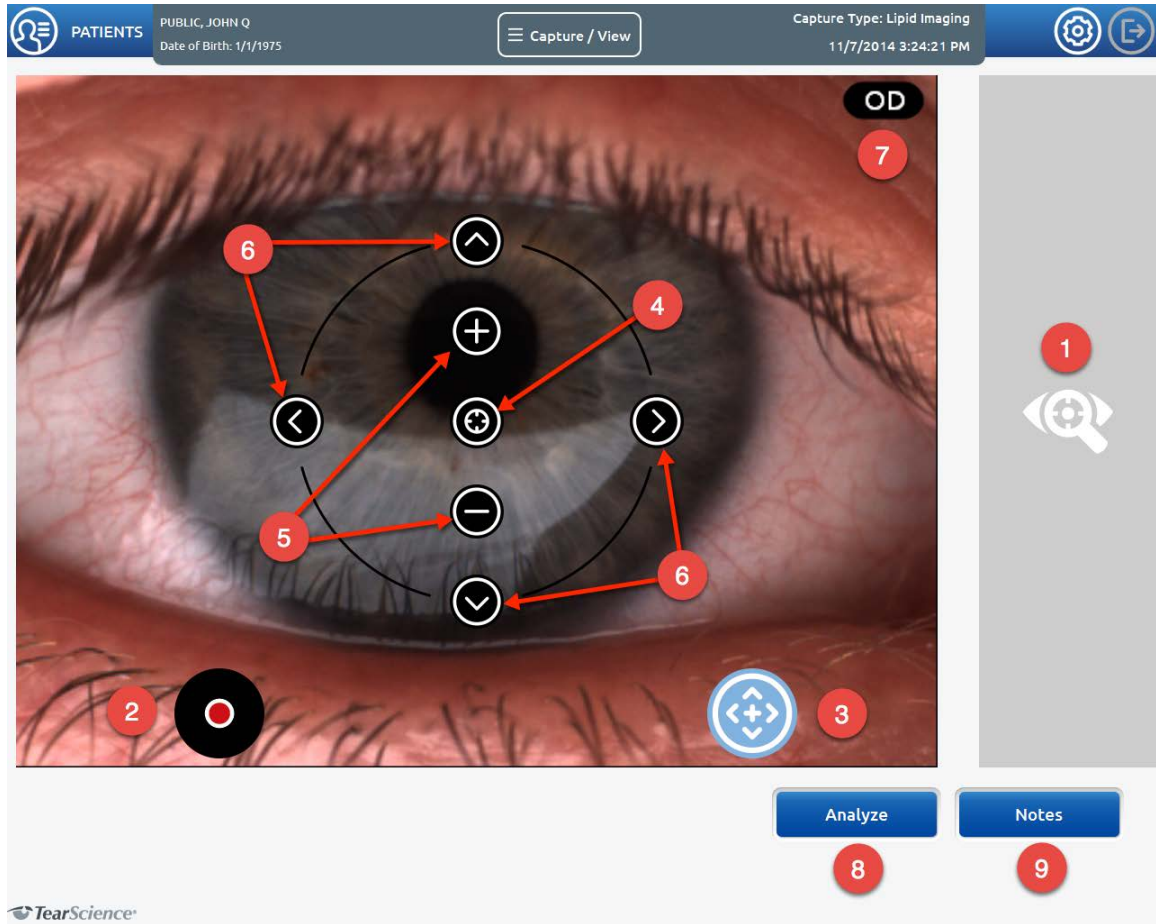
5. Select OD (right eye) or OS (left eye) to image by touching the right or left side of the Lipid Image Capture screen (Figure 14).
6. Position the camera using one or a combination of methods: 1) If the pupil is visible on screen, press autoposition reticle to automatically center the camera on the pupil. 2) Touch the desired location (toward pupil) on screen, which will automatically move the camera and center on the location. 3) Press the manual position buttons, as needed, until the pupil appears in the center of the screen. (You may also use the keypad to position the camera.)

**NOTE:** Ensure the lower lid margin is visible to evaluate partial blinking

7. Focus the camera using one or a combination of methods: 1) Press autofocus reticle to focus (*not necessary if reticle was already pressed to position camera*); 2) press fine focus buttons to adjust the focus until the tear film image is clear. (You may also use the keypad to focus the camera.)

**NOTE:** If the tear film image is not in focus, invalid video data may be saved.

8. Press *Capture* button to begin recording approximately 20 seconds of video. The blinking red light indicates LipiView II is recording. Press *Capture* button again to stop recording prior to 20 seconds, if desired.
9. Instruct the patient to blink naturally or to perform a squeezed blink, as desired.
10. When recording is complete, the illuminator turns off. Press *Notes* to add any notes to images, if desired.
11. Review video using onscreen playback button. If image quality is suboptimal, delete video using Trashcan icon and recapture another image.
12. Repeat steps 5 to 11 to capture an image of the other eye, if desired.
13. Press *Analyze* to save and process the image(s).



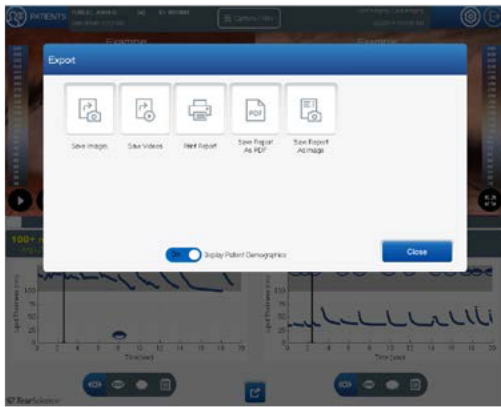
**Figure 14. Lipid Image Capture Screen with Labeled Controls**

Key	
1	<b>Magnify View Icon</b> - OD (right eye) is currently in view. OS (left eye) side is currently greyed out. Touch icon to capture images for OS (left eye).
2	<b>Capture Video Button</b> – Press to begin recording. Appears as a rectangle during recording; press rectangle to stop recording before 20 seconds.
3	<b>Select Position/Focus Button</b> – Press to toggle display of manual focusing and positioning button controls on or off.
4	<b>Autoposition/Autofocus Reticle</b> – Once the pupil is visible on screen, press the reticle to automatically center and focus the image.
5	<b>Manual Fine Focus Buttons</b> - Press plus or minus to focus image
6	<b>Manual Positioning Buttons</b> – Press to move camera left, right, up or down
7	<b>Eye Position Indicator</b> – Indicates the eye being imaged (OD in figure)
8	<b>Analyze Button</b> – Press to save, process and analyze captured imagery
9	<b>Notes Button</b> – Press to open notes field for text entry



### 3.6 Review Tear Film Images (Lipid Imaging Mode)

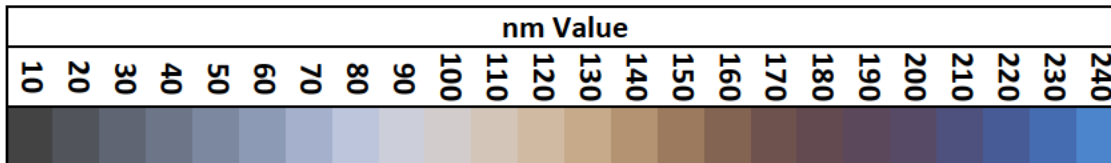
1. After pressing *Analyze* on the Lipid Image Capture screen (Figure 14), the Review Lipid Images screen (Figure 17) appears with the tear film lipid layer images.
2. *To review prior tear film lipid images for an existing patient:*
  - a. Select the patient from the Patient Records screen (Figure 11).
  - b. On the Capture/View screen (Figure 13), select Lipid Imaging to view prior lipid images or select All Exams to view all prior images.
  - c. A list of prior images is displayed on the Capture/View screen (Figure 13). Drag and drop the desired images from the list to the sides of the screen marked "Drop Here". Touch the image again to display the Review Lipid Images screen (Figure 17).



**Figure 15. Export Dialog**

3. Playback the video using onscreen controls.
4. If desired, press Export icon on the Review Lipid Images screen (Labeled 8 in Figure 17) to export or print images or report.
5. From the Export dialog (Figure 15), press the button to save images, video or report to an external medium or network, or print a report. Exported images can be displayed with or without patient demographics.

The Review Lipid Images screen (Figure 17) displays numerical and graphical analysis of the measured lipid layer thickness in nanometers (nm) from 10 (thinnest) to 240 (thickest), with a precision of 1 nm and an accuracy of 10 nm. The interferometric color scale (Figure 16) has been validated to a known standard for measurement of thin film thickness. By comparison to this known standard, the lipid layer thickness values are absolute thickness measurements of the tear film lipid layer.



**Figure 16. Interferometric Colors**

**NOTE:** If analysis cannot be performed, a message *NO VALID ANALYSIS DATA FOR VIDEO* replaces the graph, and the numerical information shows as dashes (---).

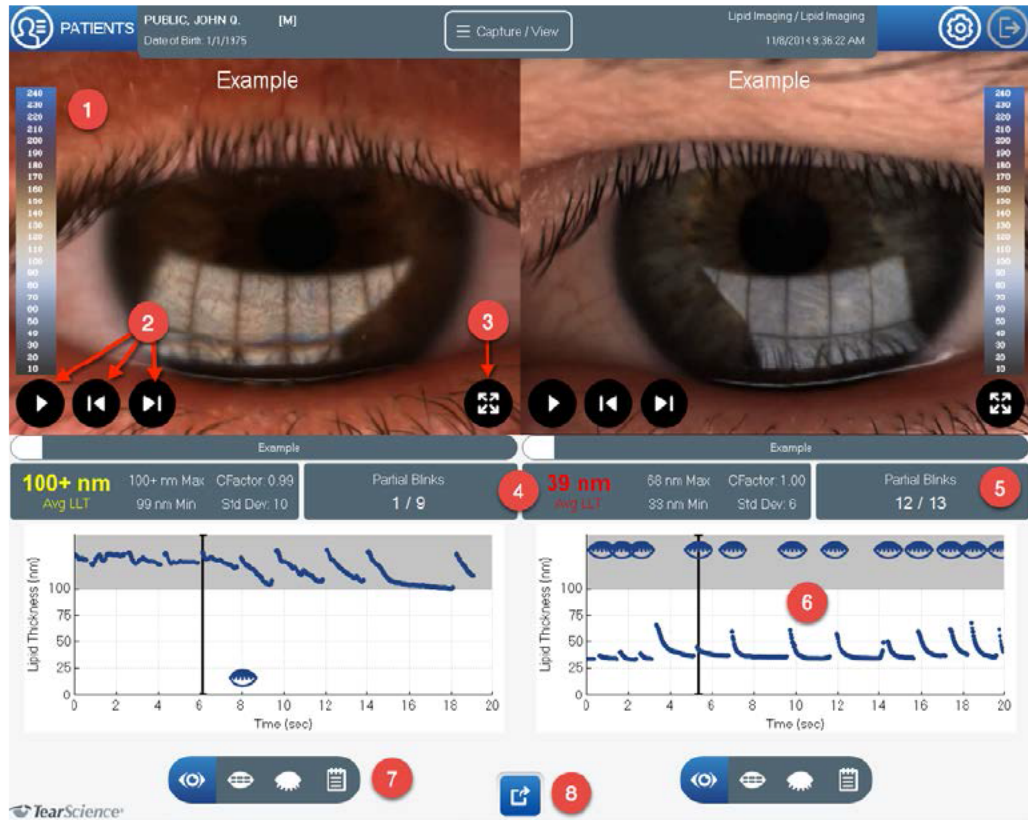


Figure 17. Review Lipid Images Screen with Labeled Controls

Key	
1	<b>Interferometric Color Scale</b> - Corresponds to lipid layer thickness value in nm
2	<b>Video Playback Controls</b> – Press to play, pause, forward step, reverse step
3	<b>Full Screen Mode</b> – Press to view screen in full screen mode
4	<p><b>Numerical Analysis:</b></p> <ul style="list-style-type: none"> <li>• <b>Avg LLT:</b> Average lipid layer thickness in nm displayed in colored font corresponding to thickest (yellow), medium thickness (orange) and thinnest (red).<sup>1</sup></li> <li>• <b>Max:</b> Maximum lipid layer thickness in nm recorded for a given video frame.</li> <li>• <b>Min:</b> Minimum lipid layer thickness in nm recorded for a given video frame.</li> <li>• <b>C-Factor:</b> Conformance factor is the ratio of image pixels that fall on the interferometric color spectrum. C-factor of 1.0 indicates every tear film pixel throughout the entire video has found a close match to an interferometric color.</li> <li>• <b>St Dev:</b> Standard deviation of the frame averages for lipid layer thickness.</li> </ul> <p><b>NOTE:</b> Since most tear film images have an average thickness well below 100, the maximum thickness values displayed are 100 with values above 100 represented as “100+”.</p>
5	<b>Partial Blinks Count</b> - Presented as a fraction with the number of partial blinks (numerator) over the number of total blinks (denominator). In this OD example, 1 partial blink/9 total blinks.
6	<p><b>Graphical Analysis:</b></p> <ul style="list-style-type: none"> <li>• Blue line shows average lipid layer thickness values over video sampling time.</li> <li>• Partial Blink Eye icon represents video frame where partial blink occurred.</li> </ul>
7	<b>Select View Mode:</b> Press to toggle between Full Eye View (Eyeball icon), Isolated Tear Film View (Tiled icon), Blinking Frames Only View (Closed Eye icon) or Notes (Notepad icon).
8	<b>Export Icon</b> – Export saved images, video or report to external medium or print report

<sup>1</sup> Finis D, Pischel N, Schrader S, Geerling G. Evaluation of lipid layer thickness measurement of the tear film as a diagnostic tool for Meibomian gland dysfunction. *Cornea*. 2013; 32(12):1549-53.

The first images, labeled as “Example” on the Capture/View screen (Figure 13), are standard reference video images of eyes with different lipid layer thickness values, provided for purposes of comparison. These videos allow the physician to observe differences in interference colors for a variety of tear films. As shown in Figure 18, the thin lipid example image is an example of an average tear film lipid layer thickness of 39 nm, which is relatively thinner lipid layer with very little color appearing mostly gray. Conversely, the thick lipid example image (Figure 19) is an example of an average tear film lipid layer thickness above 100, where brown and blue colors are visible indicating a relatively thicker lipid layer.



**Figure 18. Example OD Image – Average Lipid Layer Thickness 39 nm**

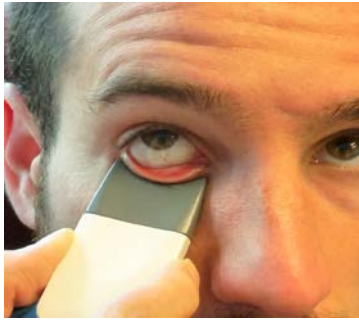


**Figure 19. Example OS Image – Average Lipid Layer Thickness 100+ nm**

### 3.7 *Capture Gland Images (Gland Imaging Mode)*

**NOTE:** One person can both evert the lids and operate the device, using the pushbutton controls on the top panel with an external monitor positioned behind the patient where the operator can easily see it. Alternatively, imaging the meibomian glands can be easier to perform as a two-person procedure: one person everting the eyelids, and one person operating and focusing LipiView II.

1. To image the meibomian glands, select Gland Imaging from the Capture/View screen (Figure 13) and press *New*.
2. **Turn the room lights off** (or down sharply) prior to imaging to ensure good contrast in the image quality.
3. Disinfect the forehead and chin rest and Handheld Near IR Lid Everter with alcohol prior to use. Inspect Handheld Near IR Lid Everter to ensure it is intact prior to use.
4. Ensure the chin rest is in the extended position away from the device (closer to the patient).
5. Place the patient's chin fully forward into chin rest and forehead firmly against forehead rest. Adjust the height of the chin rest by spinning the fluted roller until the temporal canthus is aligned with the marks on the left and right sides of the forehead rest.
6. Select the upper or lower eyelid of the OD (right eye) or OS (left eye) to image by touching the magnify view icon in the applicable quadrant on Gland Image Capture screen (Figure 22). (You may also use the buttons on the keypad.)
7. Carefully evert the eyelid and ensure that the full extent of the meibomian glands is visible over the entire nasal to temporal length of the eyelid.
  - a. Evert entire length of lower eyelid: place Handheld Near IR Lid Everter (Figure 20) slightly below lash line; while maintaining contact, pull the lid down and then roll instrument slightly inward and upward.
  - b. Evert upper lid at the top of the tarsal plate: use a cotton swab, finger or other handheld instrument (Figure 21). Ensure the fingertip or cotton swab is not blocking the inner surface of the eyelid before capturing the image.



**Figure 20. Everting Lower Eyelid using Handheld Near IR Lid Everter**



**Figure 21. Everting Upper Eyelid using Cotton Swab**

8. Position the camera using onscreen or pushbutton controls (Figure 23) on top of the unit to center the image of the everted eyelid on the screen. Alternatively, when using the touchscreen, touch the desired location to center the image on the screen and the device will automatically center the image in that location.
9. Press the autofocus reticle to focus the image using onscreen or pushbutton controls. If needed, press fine focus onscreen controls until the image is clear. (The F3 and F4 buttons on the keypad can also be used for fine focus.)

**NOTE:** Ensure full extent of the glands is visible over entire nasal to temporal length of the eyelid. When imaging lower eyelid, toggle between **Reflected IR** and **Trans IR** views (Figure 24) to ensure both views are of good image quality.

10. Press *Capture* button using onscreen or pushbutton controls to capture image.
11. Review gland image to ensure good image quality, including in both Reflected IR and Trans IR views for lower lid images (as shown in Figure 24). If the image is suboptimal (e.g., blurred focus, poor centration, only a partial lid eversion, finger obscuring view, washed out), delete image by selecting the Trashcan icon and recapture the image. Press *Notes* to add any notes to images, if desired.
12. Repeat steps 6 to 11 to capture the remaining images of other eyelid locations until all four eyelid images (i.e., upper and lower eyelid of the right and left eyes) are captured for the patient, if desired.
13. Press *Analyze* to save the image(s).

**NOTE: PRESSING ANALYZE IS REQUIRED TO SAVE ALL IMAGES.**

If *Analyze* is not pressed before exiting the imaging screen, a message will appear as a reminder to save the images.

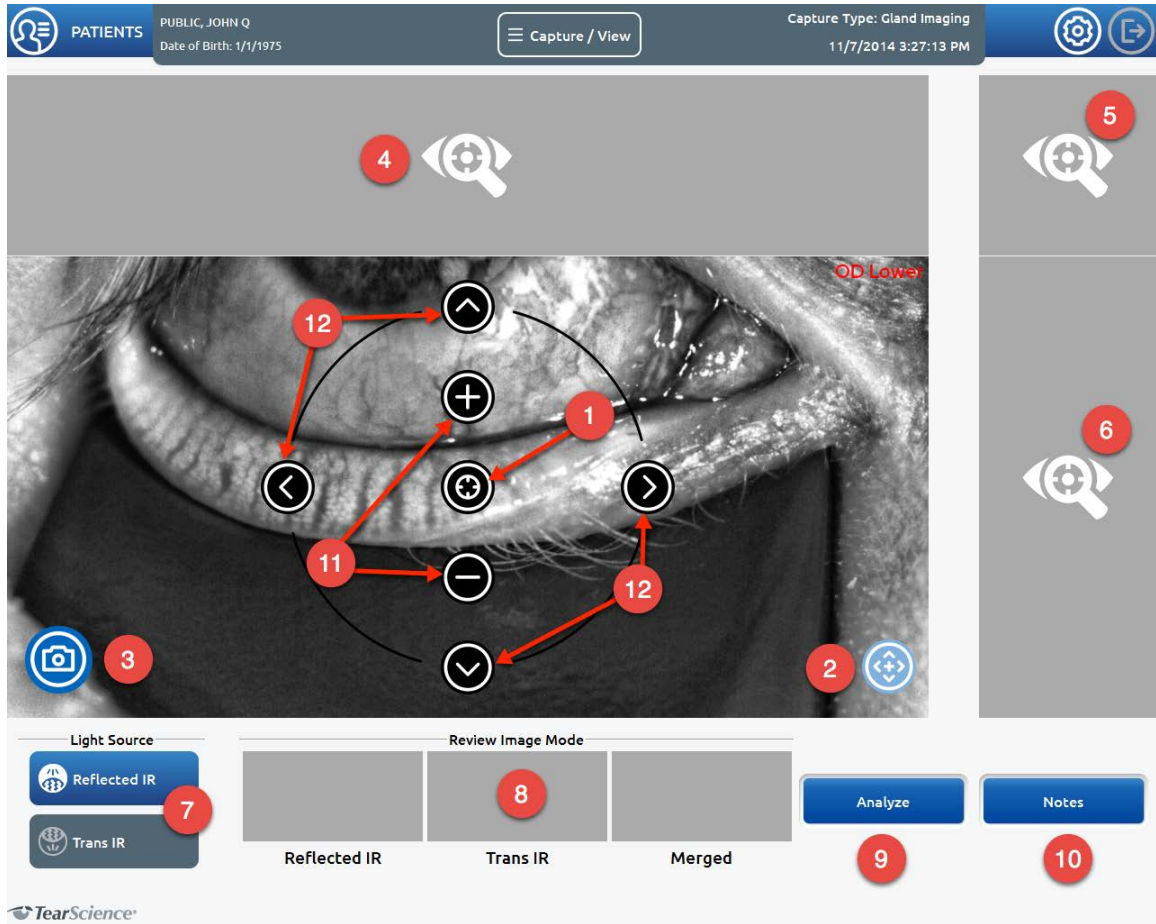
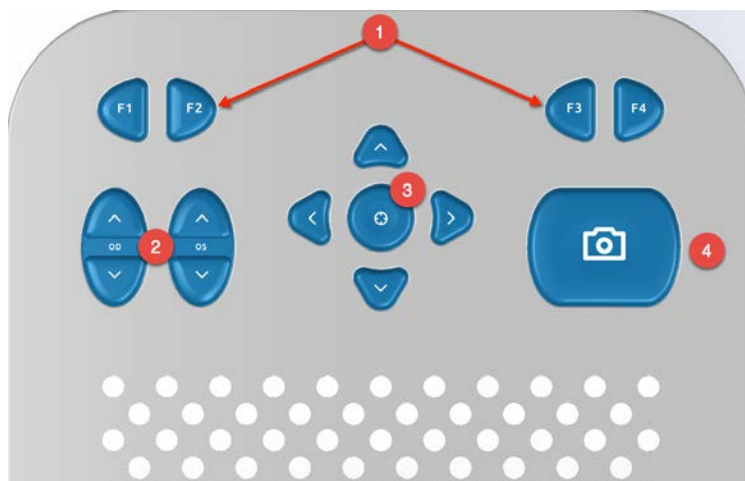


Figure 22. Gland Image Capture Screen with Labeled Controls

Key	
1	<b>Autofocus Reticle</b> - Press the reticle to automatically focus the image
2	<b>Select Position/Focus Button</b> – Press to toggle display of manual focusing and positioning button controls on or off
3	<b>Camera Button</b> – Press to capture still image
4	<b>Magnify View Icon</b> - OD (right eye) lower lid is currently in view Touch to image OD (right eye) upper lid.
5	<b>Magnify View Icon</b> - Touch to image OS (left eye) upper lid
6	<b>Magnify View Icon</b> - Touch to image OS (left eye) lower lid
7	<b>Light Source</b> - Toggle between Reflected IR and Trans IR illumination views to image lower lid. Only Reflected IR illumination is used for upper lid.
8	<b>Review Image Mode</b> - Preview Captured Reflected IR, Trans IR and Merged images (after image capture, these small windows are populated with thumbnails of the different images)
9	<b>Analyze Button</b> – Press to save captured imagery
10	<b>Notes Button</b> – Press to open notes field for text entry
11	<b>Manual Fine Focus Buttons</b> - Press plus or minus to focus image
12	<b>Manual Positioning Buttons</b> – Press to move camera left, right, up or down

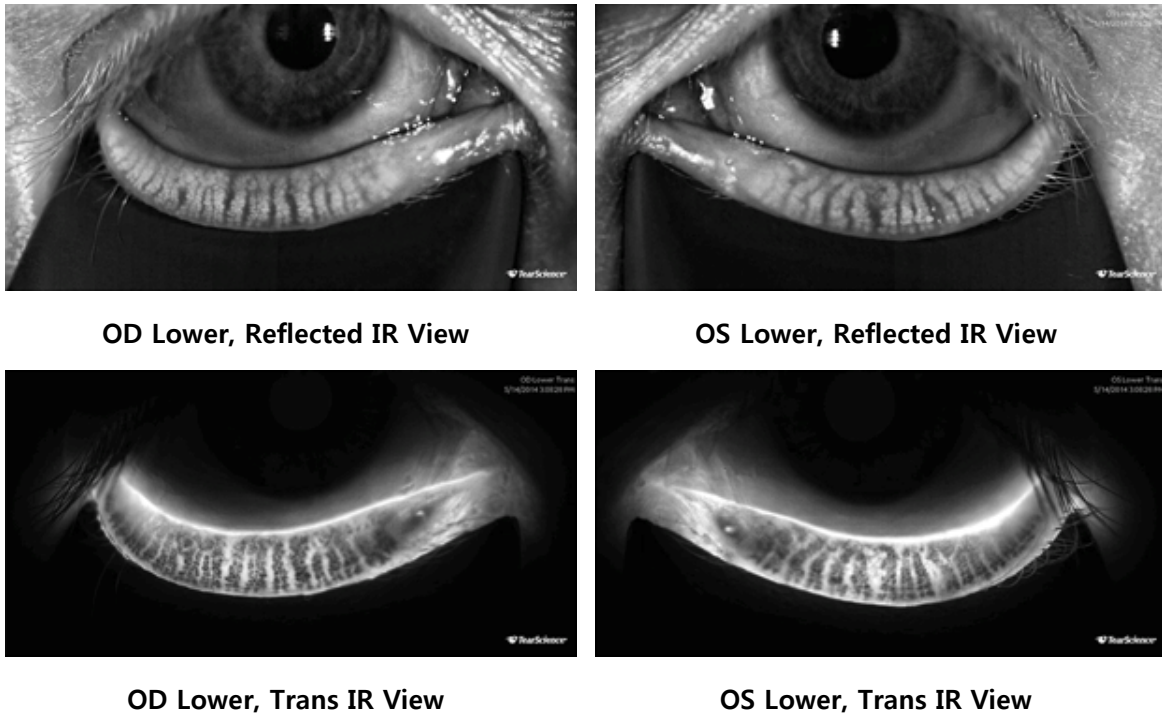
**Gland Image Modes:**

- **Reflected IR view** is shown for both upper and lower eyelid gland images.
- **Trans (Transillumination) IR view** is shown only for lower eyelid gland images, if images were captured using Handheld Near IR Lid Everter.
- **Merged view** is the combination of the Reflected IR and Trans IR views and is shown only for the lower eyelid gland images.



**Figure 23. Pushbutton Controls (on top of unit)**

Key	
1	<p><b>Function Keys</b></p> <p><b>F1:</b> In pre-capture view, toggles between Reflected IR and Trans IR mode</p> <p><b>F2:</b> In post-capture review, changes view mode to captured Reflected IR image</p> <p><b>F3:</b> In pre-capture mode, focuses in; post-capture review, changes view mode to captured Trans IR image</p> <p><b>F4:</b> In pre-capture mode, focuses out; In post-capture review, changes view mode to captured Merged image</p>
2	<p><b>Select Eye/Lid</b> - OD for right eye or OS for left eye and upper or lower lid</p>
3	<p><b>Position/Autofocus Buttons</b> – Press up, down, right and left buttons to center on the desired lid. Tap to move in small increments or hold button down to move until released. Once lid is positioned, press reticle to autofocus.</p>
4	<p><b>Camera Button</b> – Press to capture an image</p>



**Figure 24. Properly Focused Lower Lid Images: Reflected IR and Trans IR**

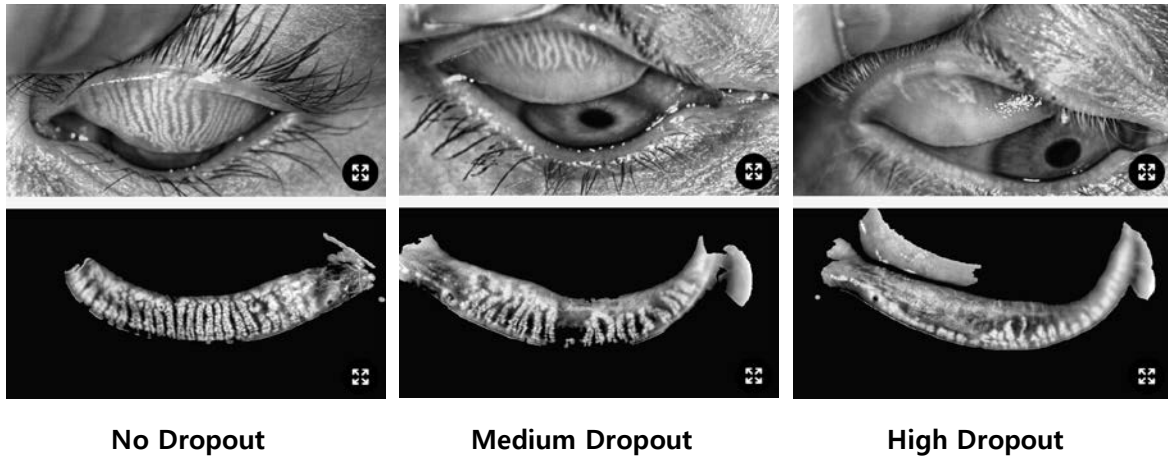
### **3.8 Review Gland Images (Gland Imaging Mode)**

1. *To review prior gland images for an existing patient:*
  - a. Select the patient from the Patient Records screen (Figure 11).
  - b. On the Capture/View screen (Figure 13), select Gland Imaging to view prior gland images or select All Exams to view all prior images.
  - c. A list of prior images is shown on the Capture/View screen (Figure 13). Drag and drop the desired images from the list to the sides of the screen marked “Drop Here”. Touch the image again to display the Review Gland Images screen (Figure 27).
2. If desired, press the Export icon at the bottom of the Review Gland Images screen (Labeled 4 in Figure 27) to export or print images or report.
3. From the Export dialog (Figure 15), press the button to save images or report to an external medium or network, or print a report. Exported images can be displayed with or without patient demographics.

The first images, labeled as “Example” on the Capture/View screen (Figure 13), are standard reference images of upper and lower eyelids with different gland findings, provided for purposes of comparison. As shown in Figure 25, the image set labeled high dropout is an example of an eye with severely truncated meibomian glands. The image set labeled as medium dropout is an example of an eye with some evidence of gland loss. The image set labeled as no dropout is an



example of an eye with no signs of gland loss. In Figure 26, the lower lid image labeled as dilation is an example of glands that appear dilated (enlarged), indicating a possible structural change or blockage.



**Figure 25. Gland Example Images:  
No Dropout, Medium Dropout, High Dropout**



**Figure 26. Gland Dilation Example, Lower Lid**

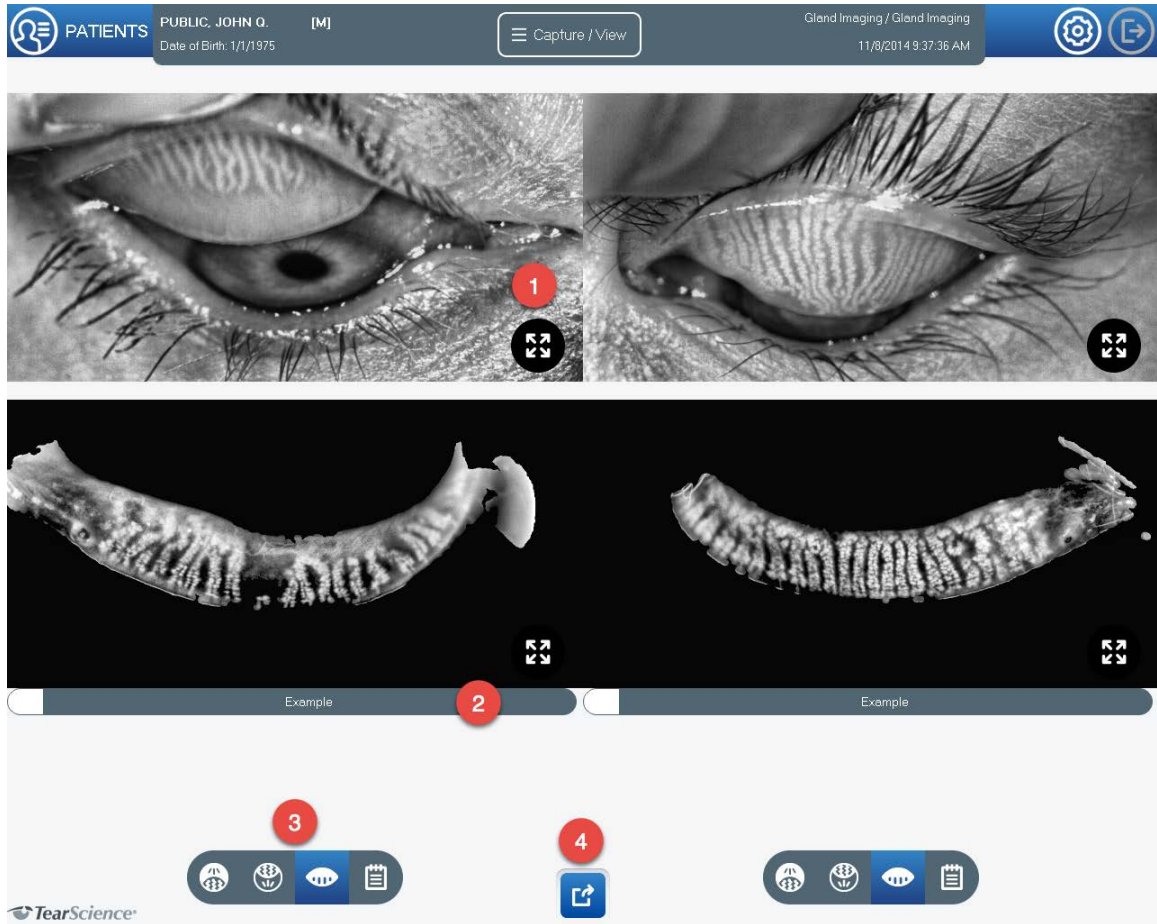


Figure 27. Review Gland Images Screen with Labeled Controls

Key	
1	<b>Full Screen Mode</b> – Press to view screen in full screen mode
2	<b>Image Details</b> – Timestamp date of image collection and Operator name
3	<b>Select View Mode:</b> Press to toggle between views; <ul style="list-style-type: none"> <li>• <b>Reflected IR view</b> (Light from above icon)</li> <li>• <b>Trans IR view</b> (Light from below icon) – only displayed for lower lid images captured using Handheld Near IR Lid Everter</li> <li>• <b>Merged view</b> (Lower Eyelid icon) – only displayed for lower lid images captured using Handheld Near IR Lid Everter</li> <li>• <b>Notes</b> (Notepad icon)</li> </ul>
4	<b>Export Icon</b> – Export saved images or report to external medium or print report

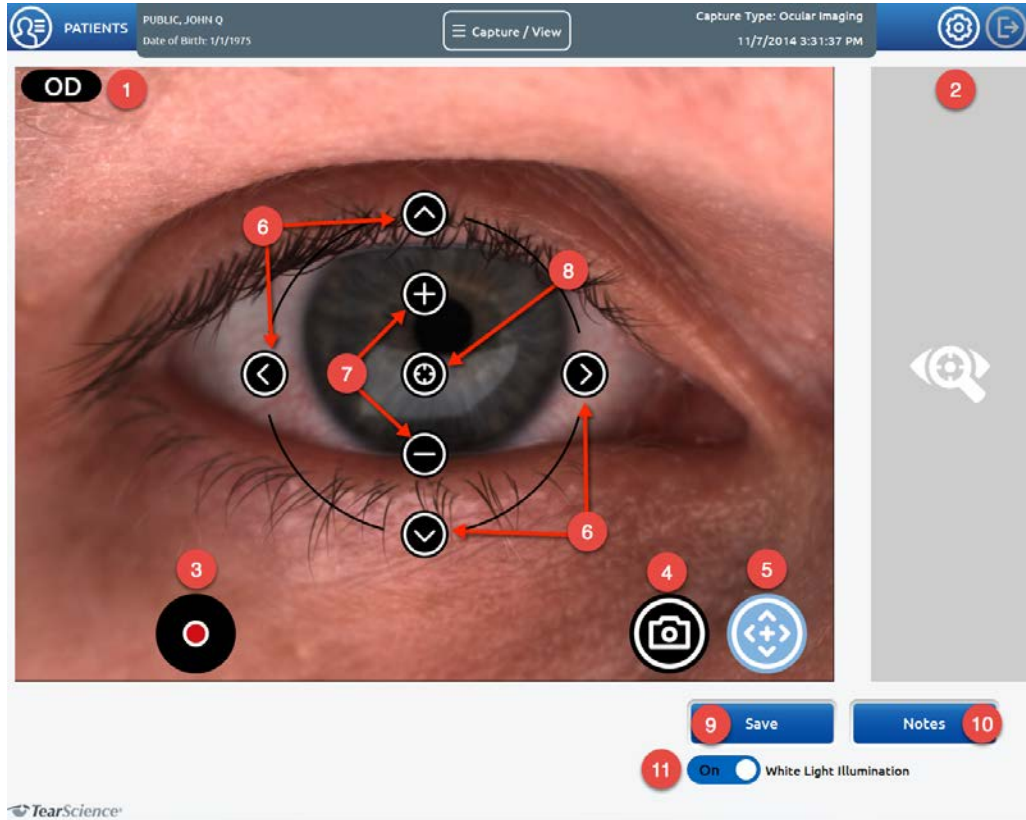
### 3.9 Capture Ocular Images (Ocular Imaging Mode)

In Ocular Imaging mode, high-resolution images of the surface of the eye or the eyelids can be taken. White-light illumination may be switched on or off.

1. To image the ocular surface or eyelids, select Ocular Imaging from the Capture/View screen (Figure 13) and press *New*.
2. Disinfect the forehead and chin rest with alcohol prior to use.
3. Ensure the chin rest is in the extended position away from the device.
4. Place the patient's chin fully forward into chin rest and forehead firmly against forehead rest. Adjust the height of the chin rest by spinning the fluted roller until the temporal canthus is aligned with the marks on the left and right sides of the forehead rest. Instruct the patient to look at the orange fixation light.

**CAUTION: To prevent pinching, do not put fingers near illuminator, lens or chin rest during focusing. Instruct patient not to place hands on LipiView II during operation, and not to put fingers near illuminator, lens or chin rest.**

5. Select OD (right eye) or OS (left eye) to image by touching the right or left side of the Ocular Image Capture screen (Figure 28).
6. Select to turn white light illumination on, or turn off to capture images using room illumination only.
7. Position the camera by touching the desired location to be imaged on screen, which will automatically move the camera and center on the location. Press the position keys, as needed, until the location appears in the center of the screen.
8. Press the reticle to autofocus, or press the fine focus buttons to adjust the focus until the image is clear.
9. Press *Camera* icon to capture a still image. Press *Capture Video* button to begin recording approximately 5 seconds of video. The blinking red light indicates LipiView II is recording video. Press *Capture Video* button again to stop recording prior to 5 seconds, if desired. You can capture up to 10 still images and one video per eye.
10. When recording is complete, the illuminator turns off (if white illumination was turned on during imaging). Press *Notes* to add any notes to images, if desired.
11. Review still image or video using onscreen playback button. If image quality is suboptimal, delete image using Trashcan icon and recapture another image.
12. Repeat steps 5 to 11 to capture an image of the other eye, if desired.
13. Press *Save* to save the video or image(s).

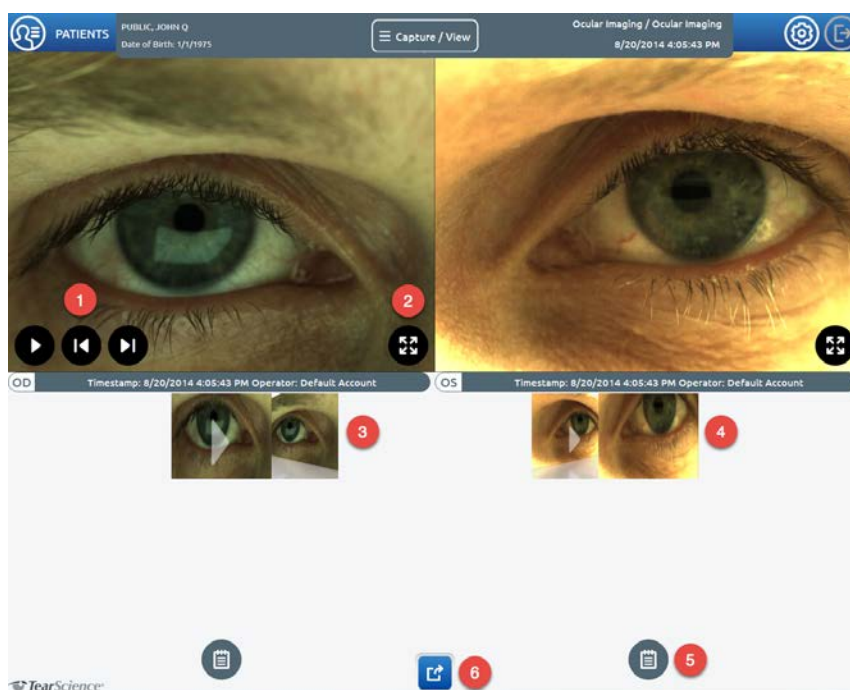


**Figure 28. Ocular Image Capture Screen with Labeled Controls**

Key	
1	<b>Eye Position Indicator</b> – Indicates the eye being imaged (OD in figure)
2	<b>Magnify View Icon</b> – OD (right eye) is currently in view. OS (left eye) side is currently greyed out. Touch icon to capture images for OS (left eye).
3	<b>Capture Video Button</b> – Press to begin recording. Appears as a rectangle during recording; press rectangle to stop recording before 10 seconds.
4	<b>Camera Button</b> – Press to capture still image
5	<b>Full Screen Mode</b> – Press to view screen in full screen mode
6	<b>Manual Positioning Buttons</b> – Press to move camera left, right, up or down
7	<b>Manual Fine Focus Buttons</b> - Press plus or minus to focus image
8	<b>Autofocus Reticle</b> - Press the reticle to automatically focus the image
9	<b>Save Button</b> – Press to save captured imagery
10	<b>Notes Button</b> – Press to open notes field for text entry
11	<b>White Light Illumination</b> – Press to toggle illuminator on or off

### 3.10 Review Ocular Images (Ocular Imaging Mode)

1. **To review prior ocular images or video for an existing patient:**
  - a. Select the patient from the Patient Records screen (Figure 11).
  - b. On the Capture/View screen (Figure 13), select Ocular Imaging to view prior ocular images or select All Exams to view all prior images.
  - c. A list of prior images is shown on the Capture/View screen (Figure 13). Drag and drop the desired images from the list to the sides of the screen marked “Drop Here”. Touch the image again to display the Review Ocular Images screen (Figure 29).
2. If desired, press the Export icon on the Review Ocular Images screen (Labeled 6 in Figure 29) to export or print images or report.
3. From the Export dialog save, (Figure 15), press the icon to save images, video or report to an external medium or network, or print a report. Exported images can be displayed with or without patient demographics.



**Figure 29. Review Ocular Images with Labeled Controls**

Key	
1	<b>Video Playback Controls</b> – Press to play, pause, forward step, reverse step (for captured video only)
2	<b>Full Screen Mode</b> – Press to view screen in full screen mode
3	<b>Video Preview</b>
4	<b>Image Preview</b>
5	<b>Notes Button</b> – Press to open and view notes field for text entry
6	<b>Export Icon</b> – Export saved images, video or report to external medium or print report

### ***3.11 Log Out and Power Off***

Press the Log Out tab (Labeled 4 in Figure 10) on the menu bar to log out when the device is not in use.

Power off LipiView II overnight to allow the device to cool down. The device does not need to be powered off between patient examinations during the day.



## 4 Troubleshooting Guide

Table 6 lists the troubleshooting actions for Unexpected Events. For technical support, contact TearScience in North America at +1 919 459 4891 or by email at [customerservice@tearscience.com](mailto:customerservice@tearscience.com).

**Table 6: Troubleshooting Unexpected Events**

Event	Action to Take
Device will not power up (after pressing the power switch, the screen remains dark)	Ensure device is connected to a power outlet and the connection into the device is secure, then press the power switch again. If the problem persists, contact TearScience.
Problem reported during Power On Self Test (POST)	Turn the device off then on again. If the problem persists, contact TearScience.
Touch Screen does not respond	Turn the device off then on again. If the problem persists, contact TearScience.
Illuminator does not light during lipid image capture	Turn the device off then on again. If the problem persists, contact TearScience.
Camera stops working	Turn the device off then on again. If the problem persists contact TearScience
Disk Space Indicator shows internal disk drive is full	Contact the Administrator to archive data. If the problem persists, contact TearScience.
The system works except the Capture screen will not respond (for Lipid, Gland, or Ocular Imaging)	An error was detected during power on self-test, which affects image acquisition. Turn the device off then on again. If the error persists, contact TearScience.
Device will not process images after acquisition	The internal hard drive is full. Contact the site Administrator to archive data. If the problem persists, contact TearScience.
Device no longer allows image acquisition	A power on self-test problem has been found. If the problem persists, contact TearScience.
The Review Lipid Images screen does not display a numerical lipid layer thickness value	The patient's head may not have been pushed forward, the patient's forehead may not have been firmly pressed against the forehead rest, or the tear film image may have been out of focus. Collect another video of the patient after ensuring that the patient's head is positioned properly and that the image is clearly focused.
Network is not connected	Contact the Administrator. If the problem persists, call TearScience.

Event	Action to Take
External monitor does not work	Ensure the monitor is powered on before LipiView II. Ensure connections to the DVI or HDMI are made, and proper video input is selected. Ensure the Administrator has activated and properly configured the monitor on the Computer Info screen in the Admin interface.
Administrator forgets password after resetting it	Contact TearScience.
When accessing options on the System Information Administration screen, this message displays: "Too much time has elapsed since system startup to access this function"	Selected options on the System Information Administration screen cannot be accessed after more than 10 minutes has elapsed since the system was started. Turn the device off then on again. Then, attempt to access the option again on the System Information Administration screen.
When accessing the Capture/View screen, a message displays stating disk space usage has surpassed the warning level	The system's disk drive usage is beyond the level specified in the Networking/Backup Administration screen. Contact the Administrator to perform a system backup.
When accessing the Capture/View screen, a message displays stating disk space usage has surpassed the critical level	The system's disk drive usage is beyond the maximum level specified by TearScience. Contact the Administrator to perform a system backup. Video capture is disabled until system backup is performed.

Table 7 describes the Operational System Messages categorized by type as: "E" for Error Message; "C" for User Confirmation Message; and "I" for Information Message Requiring User Attention. For a list of system messages related to System Administrative functions, refer to *LipiView II Administrator's Guide*.

System messages are generated when something unexpected occurs, when the user attempts to perform an invalid operation, or to confirm completion of an event. These messages may instruct the user on a particular action to take (e.g., enter a missing field, or correct the format of a date field). When a system message is displayed, it requires a response from the user by pressing a button (e.g., Close or OK) on the message before any other input from the screen is accepted. System messages related to Windows error codes will also be listed in the System Log.

**Table 7. Operational System Messages and Descriptions**

ID	Type	Displayed Text	Description
1	E	You must enter a user name and password.	Displayed on Login screen if operator touches Login button without entering a username or a password
2	E	Invalid user name or password.	Displayed on Login screen if operator enters and invalid username and/or password and attempts to login to the system.
3	E	An internal system error was	Displayed on Login screen if the system database is corrupt



ID	Type	Displayed Text	Description
		encountered when attempting to log operator into system. Consult the system log for details.	and the system is unable to log an operator into the system. Service call or remote support is required to fix.
4	E	An internal system error was encountered when attempting to access the patient list. Consult the system log for details.	Displayed on Patient Records screen if the system database is corrupt and the system is unable to obtain a list of patients. Service call or remote support is required to fix.
5	I	Ensure patient and operator are clear of the chinrest area. The unit will now automatically home the motor system. Press the OK button to begin.	Displayed on Warning Screen during the system power-on self-test before the system performs initialization.
6	E	An error was encountered obtaining the list of network adapters. Consult the system log for details.	Displayed on Networking Administrator screen if the system is unable to obtain a list of network adapters from the operating system. Service call or remote support is required to fix.
7	E	An error was encountered obtaining the status of a network adapter. Consult the system log for details.	Displayed on Networking Administrator screen if the system is unable to obtain the status of the network adapters from the operating system. Service call or remote support is required to fix.
8	E	Image capture functionality has been disabled due to a system error. Consult the system log for details.	Displayed on Capture Screen if a system error has prevented new images from being captured. Reboot the system to see if the error clears. If the error does not clear, service call or report support is required.
9	E	The Capture screen is not configured correctly. Contact TearScience for technical support.	Displayed on Capture screen if the system database is corrupt and the Capture screen cannot reads its configuration. Service call or remote support is required to fix.
10	E	Unable to set up the system for image capture. Consult the system log for details.	Displayed on Capture screen if an error was encountered from the system hardware while attempting to configure the system to capture images. Try to enter the Capture screen again to see if the error clears. If the error does not clear, a service call or remote support is required to fix.
11	E	The live video stream from the camera has been interrupted. Please exit the Capture screen and try again. Consult the system log for details.	Displayed on Capture screen if an error was encountered from the camera during live video streaming. Try to enter the Capture screen again to see if the error clears. If the error does not clear, a service call or remote support is required to fix.
12	E	A motion control error was encountered. Consult the system log for details.	Displayed on Capture screen if an error was encountered trying to move a motion control axis. Try to enter the Capture screen again to see if the error clears. If the error does not clear, a service call or remote support is required to fix.
13	E	An error was encountered during video capture. Consult the system log for details.	Displayed on Capture screen if an error was encountered during video capture. Try to enter the Capture screen again to see if the error clears. If the error does not clear, a service call or remote support is required to fix.
14	E	The patient's date of birth is invalid. Please enter a valid date of birth.	Displayed on Patient Records screen if a patient is added or edited and an invalid date of birth in entered for the patient.
15	E	A first name must be entered for the patient.	Displayed on Patient Records screen if a patient is added or edited and the first name is omitted without a patient ID having been entered.
16	E	A last name must be entered for the patient.	Displayed on Patient Records screen if a patient is added or edited and the last name is omitted without a patient ID having been entered.

ID	Type	Displayed Text	Description
17	E	A first and last name plus a date of birth, OR a Patient ID, must be entered for the patient.	Displayed on Patient Records screen if a patient is added or edited and the patient ID is omitted.
18	E	The entered Patient ID already exists for another patient.	Displayed on Patient Records screen if a patient ID is entered for a patient and the patient ID is already used by another patient in the system.
19	E	An internal system error was encountered when attempting to add the patient to the system. Consult the system log for details.	Displayed on Patient Records screen if a system database error prevented system from adding a new patient. Service call or remote support is required to fix.
20	E	An internal system error was encountered when attempting to update the patient demographics. Consult the system log for details.	Displayed on Patient Records screen if a system database error prevented the system from editing an existing patient. Service call or remote support is required to fix.
21	E	An internal system error was encountered when attempting to perform the analysis. Consult the system log for details.	Displayed on Capture screen if the system is unable to perform an analysis when the Analyze button is pressed on the Capture screen. Service call or remote support is required to fix.
22	C	No data has been collected for either eye. Are you sure you wish to exit the Capture screen?"	Displayed on Capture screen if the operator pressed the Analyze/Save button without having collected any data on the capture screen.
23	C	Data has been collected for only one eye. Are you sure you wish to exit and analyze?	Displayed on Capture screen if the operator pressed the Analyze/Save button and has only collected data for one eye.
24	C	Are you sure you wish to discard the collected video?	Displayed on Capture screen if the operator clicked the Trash button in an attempt to discard the collected video.
25	C	Are you sure you wish to discard the collected image?	Displayed on Capture screen if the operator clicked the Trash button in an attempt to discard a collected still frame image.
26	E	The View Analysis screen is not configured correctly. Contact TearScience for technical support.	Displayed on View Analysis screen if it is unable to display the View Analysis sub-screen for a modality. Service call or remote support is required to fix.
27	E	An internal system error was encountered processing the data analysis. Consult the system log for details.	An internal system error was encountered during the processing of an analysis. Service call or remote support is required to fix.
28	E	An internal system error was encountered loading the analysis data. Consult the system log for details.	An internal system error was encountered attempting to load analysis data from disk into memory for display. Service call or remote support is required to fix.
29	E	The data storage disk space used has reached a critical level. Please perform a data archival operation. Image capture has been disabled until this problem is resolved.	Displayed on Capture screen when the data disk used space is greater than 95%. Further image capture has been disabled. Site administrator must either perform a system backup or delete some imaging sessions to gain free space.
30	I	The data storage disk space usage is above the warning threshold. Please perform a data archival operation when convenient.	Displayed on Capture screen when the data disk used space is above the warning threshold specified in the Backup/Restore Administration screen (default 75%). This message is to remind the operator to perform a backup in the near future.

ID	Type	Displayed Text	Description
37	C	There is unsaved data collected on the Capture Screen and the requested operation will discard this data. Are you sure you wish to proceed?	Displayed on Capture Screen if the operator attempts to exit the Capture screen with unsaved/unanalyzed data present.
38	E	The operating system encountered an error obtaining a list of drives on the system. Consult the system log for details.	Displayed when the Destination Drive list dialog is displayed but the system is unable to get a list of removable/networked drives from the operating system. Service call or remote support is required.
39	C	Please select one or more destinations for the output:	Displayed on the Destination Drive list dialog is displayed informing the operator of the intent of the drive list.
40	E	The output file '%1' is unable to be opened. The operating system error code is '%2'.	The system attempted to output a file of some type (e.g. video or still image) to an external USB or network drive and was unable to write the file. Check health and status of the storage location and try again.
44	I	No available drives are detected on the system.	Displayed by the Destination Drive dialog to inform the operator the system did not detect any external storage locations (either USB or networked).
54	E	An internal error was encountered accessing the notes database. Please contact TearScience for technical support.	The operator attempted to access the Notes Editor screen but a system internal error prevented the notes data from being accessed. Service call or remote support is required to fix.
55	C	Are you sure you wish to delete the selected note?	The operator has clicked the Delete Note icon and this message asks the operator to confirm the deletion.
56	C	Note information exists that has not been saved. Are you sure you wish to exit without saving the information?	The operator has entered text into a new note but has not clicked the Save Note button and is attempting to exit the Notes screen.
60	C	Please select the destination drive(s) for the exported images:	The operator clicked the Export Images button on the Export Screen and this message appears on the Destination Drive selection dialog to inform the operator of the function of the drive selection dialog.
62	E	An error was encountered producing the requested output. Please check the system log for details.	An internal system error occurred while producing export images or videos. Check the system log for more details. Service call or remote support is likely required.
63	E	An error was encountered producing the requested output. The error information from the operating system is '%1' (%2).	An error occurred with an external storage location in attempting to export images or videos to the storage location. Evaluate the error information given and resolve the problem. Examples of problems would be insufficient disk space to store the output, etc.
64	E	An error was encountered attempting to load the web page. The error information is '%2' (Code: %3).	An error occurred attempting to load a web page in the internal web browser (e.g. the Remote Support login screen). Attempt to access the page and ensure connectivity to the Internet.
76	C	Please select the destination drive(s) for the exported videos:	Displayed on Destination Drive selection dialog to prompt user to select destination for exported videos.
96	C	Data has not been collected for all eye and lid combinations. Are you sure you wish to exit the Capture screen?	Displayed on the Gland Image Capture screen if the operator has not collected image for both lids on both eyes.
109	C	Please select the destination printer for the report:	Displayed on the Printer Selection list when the operator chooses the Print Report feature from the Export screen.
110	E	The operating system encountered an error obtaining a list of printers.	The system was unable to get a list of printers from the operating system. Turn the device off then on again, and try to

ID	Type	Displayed Text	Description
		Consult the system log for details.	print the report again.
111	I	Video Data File Not Found On System	Displayed in the video pane of an analysis view screen if the source video file could not be located on the system or attached external storage.
112	I	Image Data File Not Found On System	Displayed in the still frame pane of an analysis view screen if the source image file could not be located on the system or attached storage.
113	C	Please select the destination drive for the PDF:	Displayed on the Drive Select list dialog after the operator has chosen to Save a PDF file of the report by touching the Save PDF button from the Export screen.
114	I	No printers are installed on the system	Displayed on the Printer Selection list dialog when no printers are installed on the system. Install a printer before attempting to print.
125	I	The entered password is not correct.	Displayed where an operator is required to enter a password and enters an incorrect password.
127	I	Please check the position of the chinrest and ensure it is in the rear position.	Displayed when the chinrest is not in the correct position for imaging.
128	I	The maximum number of images has been captured. To capture additional images, delete one or more of the existing images.	Displayed on the Ocular Image Capture screen when the operator has captured the maximum number of still images and then attempts to capture another.

## Appendix: Electromagnetic Compatibility Requirements


**Table 8: Guidance and Manufacturers Declaration-Electromagnetic Emissions**

LipiView II is intended for use in the electromagnetic environment specified below. The customer or the user of LipiView II should assure that it is used in such an environment.		
<b>Emissions Test</b>	<b>Compliance</b>	<b>Electromagnetic Environment-Guidance</b>
RF emissions CISPR 11	Group 1	LipiView II uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions CISPR 11	Class A	NA
Harmonic emissions IEC 61000-3-2	Class A	NA
Voltage fluctuations Flicker emissions IEC 61000-3-3	Complies	LipiView II is suitable for use in all establishments <b>other than</b> domestic and those directly connected to the public low-voltage power supply network that supplies buildings for domestic purposes.

**Table 9: Guidance and Manufacturers Declaration-Electromagnetic Immunity (part 1)**

LipiView II is intended for use in the electromagnetic environment specified below. The customer or the user of LipiView II should assure that it is used in such an environment.			
<b>Immunity Test</b>	<b>IEC 60601 Test Level</b>	<b>Compliance Level</b>	<b>Electromagnetic Environment-Guidance</b>
Electrostatic discharge (ESD) IEC 61000-4-2	$\pm 6$ kV contact $\pm 8$ kV air	$\pm 6$ kV contact $\pm 8$ kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%
Electrical fast transient/burst IEC 61000-4-4	$\pm 2$ kV for power supply lines $\pm 1$ kV for input/output lines	$\pm 2$ kV for power supply lines $\pm 1$ kV for input/output lines	Mains power quality should be that of a typical commercial or hospital environment
Surge IEC 61000-4-5	$\pm 1$ kV differential mode $\pm 2$ kV common mode	$\pm 1$ kV differential mode $\pm 2$ kV common mode	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	$< 5\% U_T$ ( $> 95\%$ dip in $U_T$ for 0,5 cycle $40\% U_T$ ( $60\%$ dip in $U_T$ ) for 5 cycles  $70\% U_T$ ( $30\%$ dip in $U_T$ ) for 25 cycles  $< 5\% U_T$ ( $> 95\%$ dip in $U_T$ ) for 5 sec	$< 5\% U_T$ ( $> 95\%$ dip in $U_T$ for 0,5 cycle $40\% U_T$ ( $60\%$ dip in $U_T$ ) for 5 cycles  $70\% U_T$ ( $30\%$ dip in $U_T$ ) for 25 cycles  $< 5\% U_T$ ( $> 95\%$ dip in $U_T$ ) for 5 sec	Mains power quality should be that of a typical commercial or hospital environment. If the user of the equipment requires continued operation during power mains interruptions, it is recommended that the equipment be powered from an uninterruptible power supply or a battery.
Power frequency (50/60 Hz) magnetic field IEC 61000-4-8	3 A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
*NOTE: $U_T$ is the a.c. mains voltage prior to application of the test level.			

**Table 10: Guidance and Manufacturers Declaration-Electromagnetic Immunity (part 2)**

LipiView II is intended for use in the electromagnetic environment specified below. The customer or the user of LipiView II should assure that it is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment-Guidance
Conducted RF IEC 61000-4-6	3 Vrms 150 kHz to 80 MHz	10 V	<p>Portable and mobile RF communications equipment should be used no closer to any part of the LipiView II, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.</p> <p><b>Recommended Separation Distance</b></p> $d = [3.5/\sqrt{V1}] \sqrt{P}$ $d = [3.5/E1] \sqrt{P} \text{ 80MHz to 800MHz}$ $d = [7.0/E1] \sqrt{P} \text{ 800MHz to 2.5GHz}$ <p>Where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, are determined by an electromagnetic site survey,<sup>a</sup> should be less than the compliance level in each frequency range.<sup>b</sup> Interference may occur in the vicinity of equipment marked with the following symbol:</p> 
Conducted RF IEC 61000-4-3	3 Vrms 80 MHz to 2,5 GHz	3 V/m	
NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies.			
NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			
<p><sup>a</sup> Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the LipiView II is used exceeds the applicable RF compliance level above, the LipiView II should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the LipiView II.</p> <p><sup>b</sup> Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.</p>			



**Table 11: Recommended Separation Distances Between Portable and Mobile RF Communications Equipment and LipiView II**

<p>LipiView II is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of LipiView II can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and LipiView II as recommended below, according to the maximum output power of the communications equipment.</p>			
	<p><b>Separation distance according to frequency of transmitter</b> <b>m</b></p>		
<p><b>Rated maximum output power of transmitter</b> <b>W</b></p>	<p><b>150 kHz to 80 MHz</b> <b><math>d=[3.5/V_1]\sqrt{P}</math></b></p>	<p><b>80 MHz to 800 MHz</b> <b><math>d=[3.5/E_1]\sqrt{P}</math></b></p>	<p><b>800 MHz to 2,5 GHz</b> <b><math>d=[7/E_1]\sqrt{P}</math></b></p>
0,01	0.12	0.12	0.23
0,1	0.37	0.37	0.74
1	1.2	1.2	2.3
10	3.7	3.7	7.4
100	12	12	23
<p>For transmitters rated at a maximum output power not listed above, the recommended separation distance <math>d</math> in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where <math>P</math> is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.</p> <p>NOTE 1 At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.</p> <p>NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.</p>			



## **APPENDIX E: MEDMONT ASSESSMENT PROCEDURE**

## **WORK AID: NON-INVASIVE TEAR BREAK-UP TIME (NIBUT) MEASUREMENT USING THE MEDMONT E300 CORNEAL TOPOGRAPHER**

### **1.0 OBJECTIVES**

Tear break-up time is a standard clinical measurement used to indicate the stability of the pre-ocular tear film. An individual with an unstable tear film can experience symptoms of visual disturbances or discomfort. The Medmont videokeratoscope is one type of instrument which may be used to view the regularity of the tear film, since it displays a live video image of a set of illuminated rings reflected by the eye surface. Disturbances to the tear film can be visualized as disruptions to the reflected ring pattern. This measurement is a form of non-invasive tear break-up time (NIBUT), since the instrument does not touch the eye and there is no use of topical dyes.

### **2.0 MATERIALS**

The Medmont E300 Corneal Topographer is a computerized videokeratometer which uses Placido rings to map the surface of the human cornea.

#### **SOFTWARE VERSION**

The E300 Software is part of the Medmont Studio integrated software environment. The instructions in this Appendix apply to Medmont Studio 4 software *version 4.14.1*. Other versions of the software are unlikely to have substantial difference in basic function or data integrity.

### **3.0 DATA MANAGEMENT**

The Medmont videokeratoscope consists of a light source made up of a series of concentric rings, and a video camera for recording the reflected image of these rings. For tear break-up time measurement, it is not necessary to save the series of images, but this may be done as an optional step for proof of performance or if needed for further analysis. Tear break-up time is measured with a stopwatch and the results are recorded on paper CRF forms or an eCRF data entry screen.

### **4.0 PROCEDURES**

#### **MEDMONT SOFTWARE SETUP**

If videokeratoscope images are not being saved, it is not necessary to enter a new patient name or date of birth. Selecting video data collection mode will ensure that a continuous live video view of the participant's eye is shown on the computer monitor.

**Figure 1. Selecting Normal (single frames) or Video capture control**

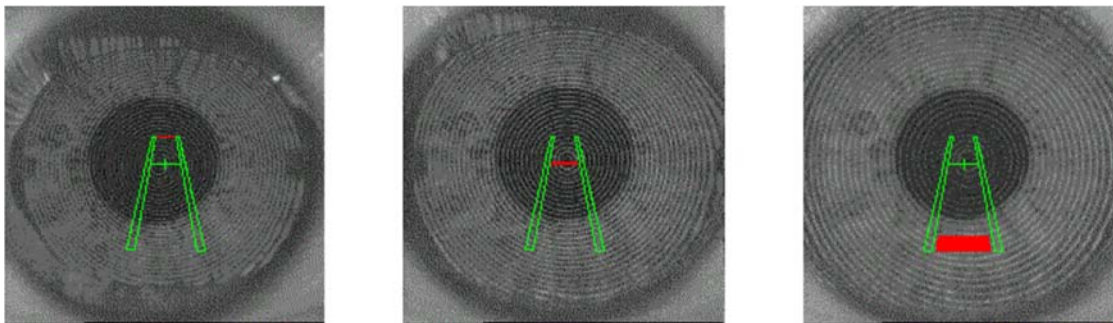


**PARTICIPANT SETUP**

While instrument and participant alignment is being set up, the participant should be instructed to continue blinking normally.

The patient should sit comfortably in the chair. Ask the participant to put their chin onto the chinrest and put their forehead firmly against the forehead rest. Adjust the chinrest height until the eye is approximately level with the mark on the vertical bar of the headrest. The participant should push their chin forward slightly on the chinrest. Ask the participant to look into the centre of the green central illuminated ring and keep their gaze on this target during the measurement. The investigator will use the instrument joystick to move the instrument to the correct distance from the eye, and to align the instrument axis (shown as a green cross overlay) with the reflection of the central reflected ring. A red line indicates whether the instrument is too close or too far away from the participant’s eye.

**Figure 2: Focus examples showing Too Far, In Focus, and Too Near**



If it is not possible to move the instrument in to best focus due to obstruction by the eyebrow, instruct the participant to move their chin slightly further forward on the chinrest, or their forehead slightly back from the headrest. If the instrument is obstructed by the side of the nose, ask the participant to turn their head so that their nose moves further away from the instrument.

**MEASURING TEAR BREAK-UP TIME**

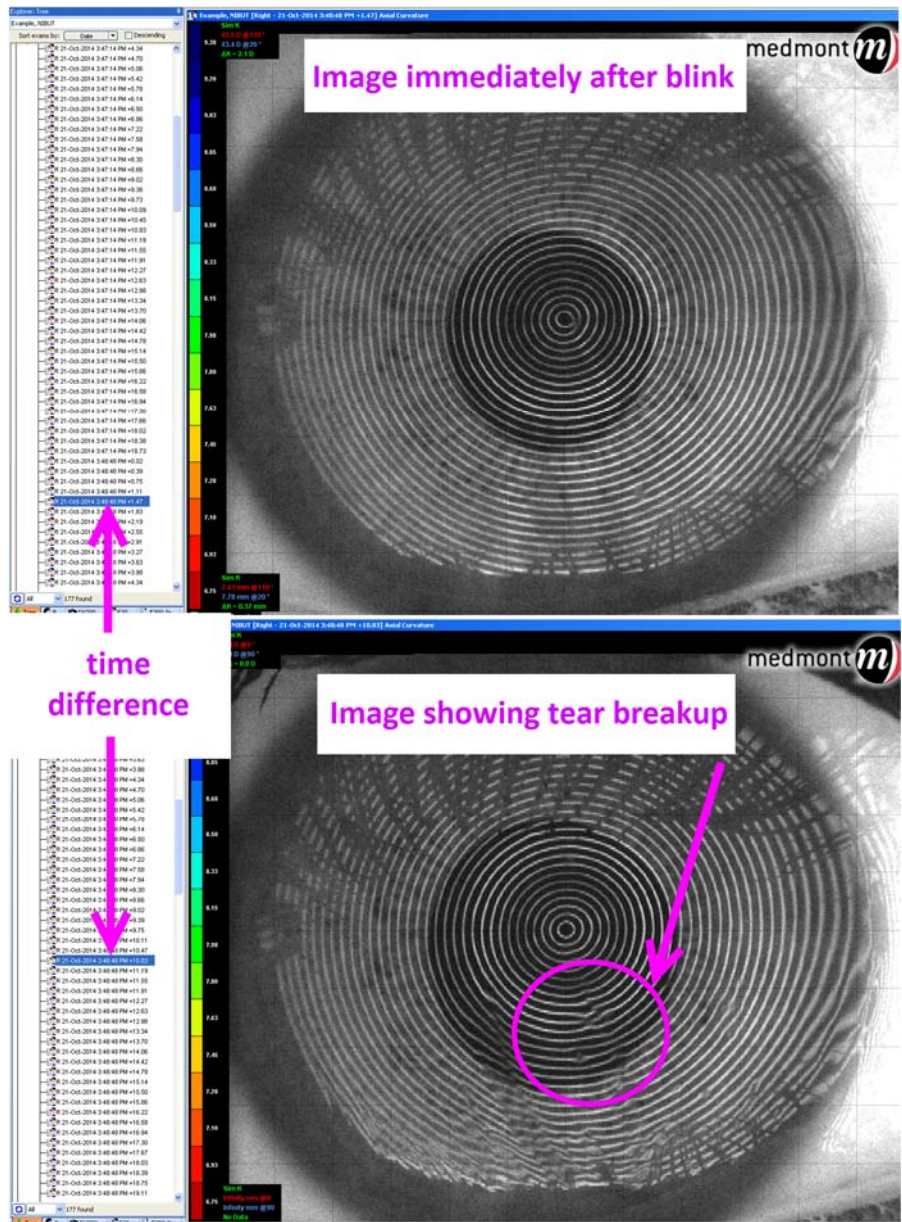
When the examiner is ready to commence the measurement, the participant is instructed to have a final blink (the blink should be natural, not forceful) and then to stop blinking for as long as possible and continue to look straight ahead at the central green ring. NIBUT is measured as the time interval in seconds after the final blink to the first appearance of distortion in the reflected rings; or to the time that the participant has to blink due to discomfort. The investigator must



watch for a change in the appearance of the ring pattern compared to the immediate post-blink appearance. Events that are considered distortions and thus endpoints include: debris that causes a break in the grid pattern, localized bending or blurring of a section of the ring pattern, or a distinct doubling of any lines.

The standard measurement of tear film break-up time involves three measurements on each eye. Between measurements, ask the participant to sit back from the chinrest for at least 30 seconds and to blink naturally. Taking measurements too rapidly without a sufficient rest period can result in a gradually worsening (ie. decreasing) tear film break-up time.

**Figure 3: An example of the appearance of tear breakup**



## SAVING THE SERIES OF IMAGES (OPTIONAL)

The raw images may be saved using “*File/Save All Images*”.

In order to also save the series of topography maps, click on “*File/Analyze All*” before “*File/Save All Images*”.

### 5.0 PHOTODOCUMENTATION

Not applicable

### 6.0 ADDITIONAL INFORMATION

Not applicable

### 7.0 TRAINING REQUIREMENTS

Read only

### 8.0 CASE REPORT FORM MODULE

The standard Bioclinica eCRF screen will record three measurements of NIBUT (in seconds) for each eye.

## DOCUMENT CHANGE HISTORY

<u>Originator</u>	<u>Change Description</u>	<u>Effective Date</u>
R. Franklin	New specification.	October 21, 2014

## **APPENDIX F: CLINICAL TECHNICAL PROCEDURES (CTP)**

- [REDACTED] Expanded Corneal Staining assessment
- [REDACTED] Subject reported Ocular Symptoms/Problems
- [REDACTED] Determination of Distance Spherocylindrical Refractions
- [REDACTED] Biomicroscopy Scale
- EUROLENS RESEARCH SOP [REDACTED] (DISTANCE AND NEAR VISUAL ACUITY EVALUATION)
- [REDACTED] Patient Reported Outcomes

**██████████ EXPANDED CORNEAL STAINING ASSESSMENT**

**Expanded Sodium Fluorescein Corneal Staining**

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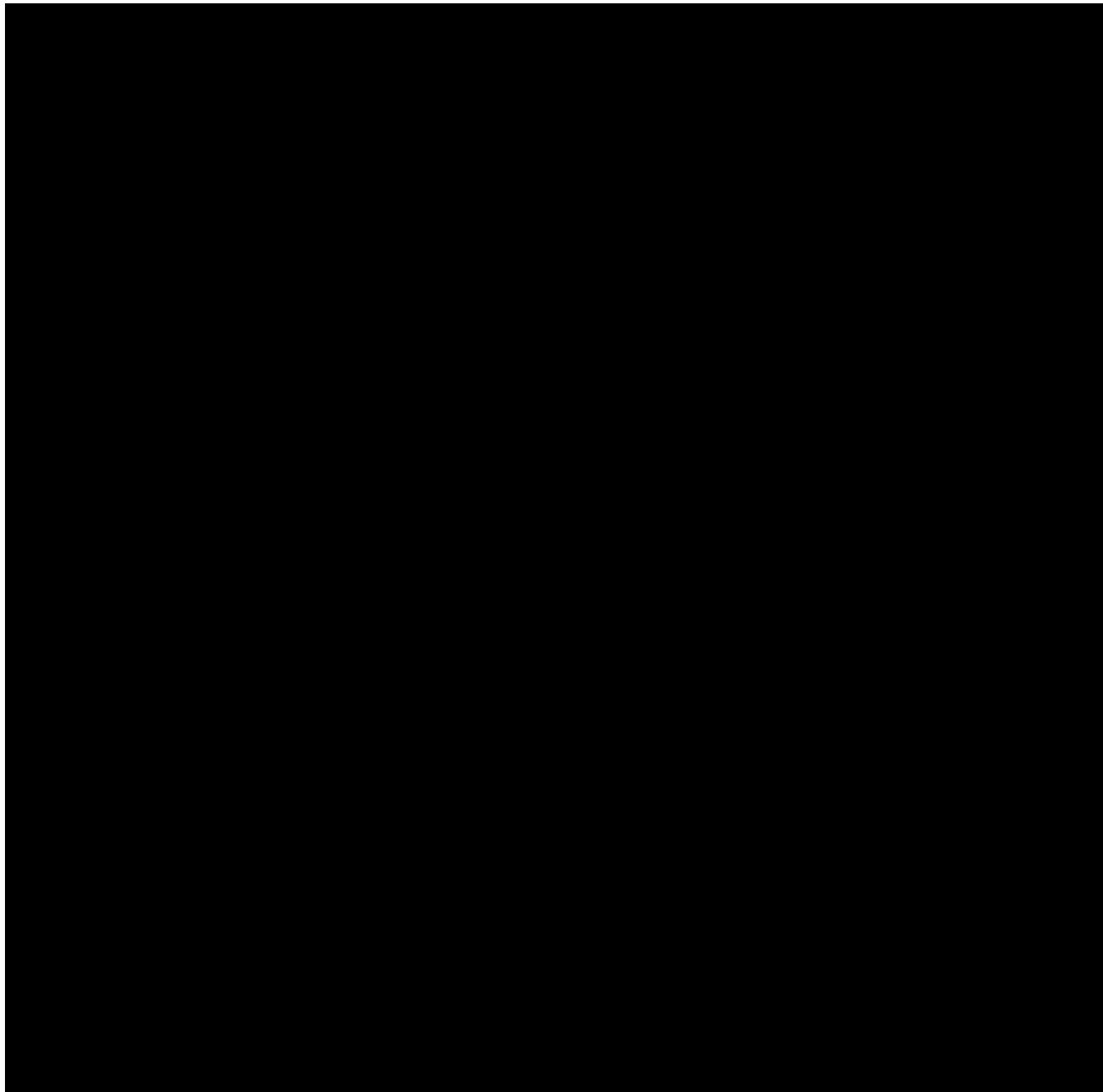
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**██████████ SUBJECT REPORTED OCULAR SYMPTOMS/PROBLEMS**

[REDACTED]

## Subject Reported Ocular Symptoms/Problems

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**Determination of Distance Spherocylindrical Refractions**

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**██████████ BIOMICROSCOPY SCALE**

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## Biomicroscopy Scale

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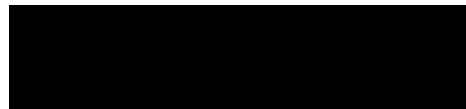


**EUROLENS RESEARCH SOP [REDACTED] (DISTANCE AND NEAR VISUAL ACUITY EVALUATION)**

**EuroLens Research**

**Clinical**  
**Standard Operating Procedure**

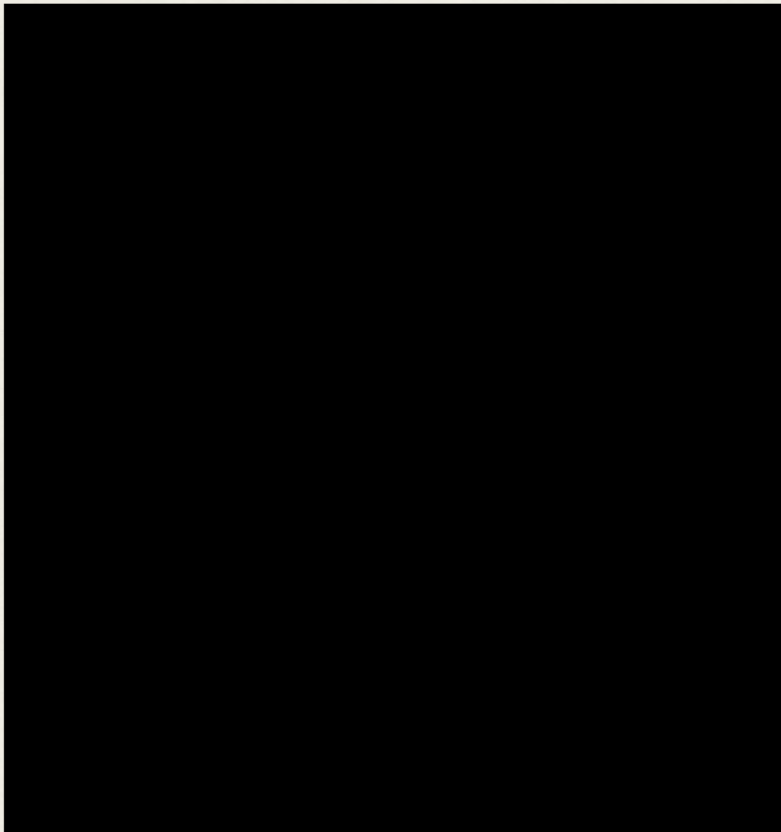
**The set up, measurement of visual acuity and  
procedures for carrying out an over refraction  
using the EuroLens computerised logMAR  
VA chart**



**First issued: v0; July 8, 2009**  
**Reviewed (with changes): v1; February 7, 2014**  
**Reviewed (no changes): v1; February 2, 2016**

### Document control

Title: The set up and measurement of visual acuity using  
the EuroLens computerised logMAR VA chart  
Document type: Clinical standard operating procedure  
Number of pages: 11

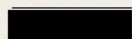


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## Summary

This document contains details of:

1. Overview of chart design.
2. The procedure of calibration and set up of the Eurolens computerised logMAR chart.
3. A method of measurement of VA using the Eurolens chart.
4. A method of carrying out an over refraction for clinical study contact lenses when visual performance is being measured using the Eurolens chart at 6m.

## Responsibilities

Study investigators/research optometrists

## Definitions/Acronym

*logMAR* - logarithmic value of the minimum angle of resolution.

The MAR relates to the resolution required to resolve the elements of a letter. logMAR is the  $\log_{10}$  of the MAR. (Table 1)

Snellen	Decimal	MAR	logMAR
6/60	0.10	10	1.00
6/24	0.25	4	0.602
6/12	0.50	2	0.301
6/6	1.00	1	0.000
6/4	1.50	0.667	-0.176

Table 1. The relationship between different acuity measurements

*Optotype* – A standardised symbol for testing vision

*Over refraction* – the amount, in Dioptres (D), that will be accepted by a subject over a contact lens in order to obtain the optimum visual performance when viewing a visual acuity test chart.

## Chart design

1. The Eurolens computerised logMAR visual acuity chart (hereafter referred to as Eurolens chart) is a logMAR chart designed to run on an Apple Macintosh with

Microsoft Excel software. The chart is displayed through an external LCD monitor connected to the Apple Mac via its monitor socket and appropriate cable.

2. The Eurolens chart is similar in design to the traditional Bailey-Lovie logMAR chart, however uses a reversed Sloan font as the optotype. The need for the reversed font is due to the chart being viewed indirectly in a mirror in a 3m consulting room. The chart is mounted on an adjustable mount, above the subject's head.
3. The indirect viewing makes the effective distance of the chart 6m from the subject. This 6m distance is the standard testing distance in optometric practice.
4. High (100%) and low (10%) contrast VA measurements can be taken with the chart.
5. The VA measurement from the Eurolens chart is intended to be equivalent to that obtained from the traditional Bailey-Lovie logMAR charts at 6m. The Eurolens chart has two advantages over the Bailey-Lovie. The Eurolens chart does not fade or discolour (which reduces legibility). Further, unlike the fixed Bailey-Lovie chart, the letters can be randomised on the Eurolens chart, which reduces the effect of memory influencing the subject's VA score.

### **Initial computer set up**

1. The Apple Macintosh should have the following installed:
  - a. Reversed Sloan font (otf file, which should be copied to the Macintosh HD/Library/Fonts/ folder)
  - b. Microsoft Office 2008 or later
  - c. Eurolens chart v5 software
2. The external monitor should be connected to the Mac. It will require the use of a DVI adaptor and cable.
3. The additional monitor should be recognised automatically by the Mac. The Mac should configure the monitor as a second desktop. To verify this, move the mouse pointer across the screen. It should be possible to move the mouse pointer off the edge of the main screen and it should appear on the external monitor.
4. The Eurolens Chart software is an Excel file called Eurolens Research chart.xls. This, for convenience, is located on the desktop.
5. To run the chart, open the Excel file. Click on "enable macros".
6. The chart should be displayed on the external monitor and the chart's control panel should appear on the Mac's main screen (**Figure 1**).

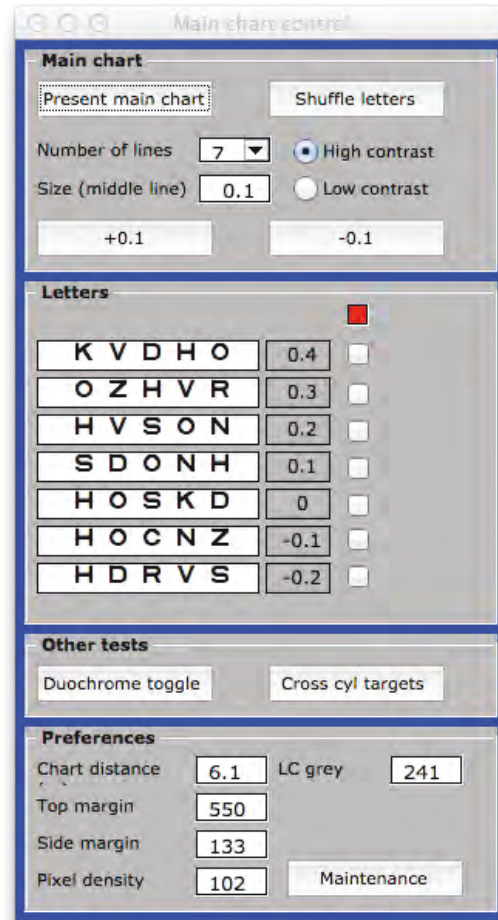


Figure 1. Chart control panel

7. If the letter chart appears on the Mac's main screen, it will need to be "dragged" onto the external monitor. To do this the chart control box must be closed. The main chart can now be dragged onto the second screen and maximised.
8. To restart the control panel, click on the Excel icon in the dock. Then in Excel's menu, select.: Tools -> Macro-> Macros. A macro box should appear, select the macro entitled 'showform' and click on run. The chart's control panel can be reopened if closed (e.g. accidentally) by repeating this step.

### Chart calibration procedure

1. It is important the charts are calibrated before first use, to ensure the optotypes are of the correct size and contrast. Minute adjustments of monitor contrast or brightness can affect the contrast of the letters (especially low).



2. If the chart distance is set to 6m, the 0.8 letter on the computer chart should be the same height as that on the Bailey-Lovie chart, measuring just under 55mm high.
3. The chart distance should then be set to the distance of the subject's head to the chart.
4. The monitor should be inclined downwards at an angle of approximately five degrees from the vertical. The reason being the contrast of an LCD monitor can vary with tilt. At five degrees of inclination, the monitor will be 'straight on' for the subject sat on the chair below. (see Appendix A)
5. The monitor should then be calibrated using a Datacolor Spyder 4. Whilst calibrating, the room lights should be on full illumination and the monitor set to factory default values (all setting "standard"). The corresponding monitor profile file generated should be saved and then used as the profile for the external monitor.
6. The contrast of the low contrast chart should be measured. The test spreadsheet (low contrast grey test.xlsx) should be displayed on the monitor with room lights on. Measurements of the luminance of the grey and white halves are taken with the spyder. The luminance measurements are then averaged. The contrast of the grey to white backgrounds is calculated as follows:

$$\% \text{ contrast} = \frac{\text{white lum} - \text{grey lum}}{\text{white lum}} \times 100$$

7. The RGB vales of the grey background should be altered until the contrast is calculated to be approximately 10%. This value is usually between 240 and 245 units.
8. Acuity measurements on the freshly calibrated chart should then be compared to those taken with two already calibrated charts. This is done by measuring high and low contrast visual acuity with all three charts (in a randomised order on around eight subjects). The acuity measurements of the three charts should all agree to within 95% confidence on the t-test.
9. If the high contrast acuity on the test chart does not agree with that of the control charts, then the "chart distance" value should be altered on the test chart, until it is in agreement with the controls.

10. Once the high contrast acuity values are in agreement, the test chart's low contrast acuity should be in agreement with the control. If not then the "LC grey" value should be altered on the test chart until agreement is reached.
11. Final settings for each monitor on 1/10/13 are contained in Appendix B.

## Measurement of VA using the Eurolens chart

### General instructions

1. The subject should be seated in the chair 3m from the mirror. This will place the chart at a 6m testing distance.
2. The default test chart for standard testing should be a 7-line chart ranging from 0.4 to -0.2 (Figure 1).
3. The subject's acuity can be tested monocularly and/or binocularly according to the study protocol.
4. If the subject cannot read the top line then increase letter size in 0.1 steps until the subject can see the top line.
5. Adjusting the "number of lines" box can alter the number of rows of letters displayed on the chart. Please note to display larger letters (over 0.4), then only one or three rows should be selected.
6. Letters can be increased in size by 0.1 steps, by clicking on the "+0.1" box. Letters can be increased in size to a maximum of 1.0.
7. Letters can be decreased in size by clicking on "-0.1".
8. The control panel displays information on the optotypes currently displayed on the chart and their size in logMAR.
9. The VA score is calculated using the same method as a traditional Bailey-Lovie chart, with each letter scoring 0.02 units and each complete line scoring 0.1 (see below).
10. To display the high contrast chart select "high contrast", similarly to display the low contrast chart select "low contrast". This will display letters of 100% and 10% contrast respectively
11. The Mac generates the sequence of letters used in the chart randomly. Clicking on "shuffle letters" can change the sequence of letters.
12. Letters should be shuffled after each VA measurement to avoid the subject learning the chart.

13. As the chart is at 6m, any over-refraction performed can be considered to be equivalent to that performed on a 6m Snellen chart i.e. at infinity.
14. The 6m testing distance should also be taken into account when comparing logMAR scores obtained with the Bailey-Lovie chart at 3m. The Bailey-Lovie scores should differ by -0.3.

### Subject instructions (standard chart display)

After positioning the subject at the desired test distance, initiate the testing as follows:

1. Ask the subject to read the smallest line where they feel they can easily read all the letters. If the subject reads all the letters on the initial line, encourage them to continue reading the smaller lines until three or more letters on a 5-letter line are incorrectly identified.
2. If the subject identifies one letter incorrectly on the initial line, ask them to read the line(s) above until one complete line has been identified correctly. Then encourage the subject to continue reading the smaller lines/letters until three or more letters on a 5-letter line are incorrectly identified. *Note: The subject is to be encouraged to read and even guess at the letters until three or more letters are incorrectly identified.*

### Scoring

To determine the VA unit score for a given line: Take the maximum VA for the last line read (i.e. the line on which three or more letters were missed) and add +0.02 for every letter missed on the chart.

For example:

- |      |            |                  |                    |
|------|------------|------------------|--------------------|
| i)   | 0.00 line  | 3 letters missed | logMAR score +0.06 |
| ii)  | +0.20 line | 0 letters missed |                    |
|      | +0.10 line | 2 letters missed |                    |
|      | 0.00 line  | 3 letters missed | logMAR score +0.10 |
| iii) | -0.20 line | 0 letters missed |                    |
|      | -0.30 line | 2 letter missed  |                    |
|      | -0.40 line | 4 letters missed | logMAR score -0.28 |

## Over-refraction

Unless the clinical study protocol states otherwise the following procedures should be carried out:

1. Visual acuity using the Eurolens chart will be measured with no over-refraction in place. The study protocol may require that this be carried out monocularly or binocularly.
2. A binocular over-refraction should be carried out using the chart at 6m. This procedure will control accommodation and allow accurate assessment of the subject's visual status. These results will allow the Investigator to judge whether or not the contact lens BVP is acceptable.

## Bailey Lovie chart

LogMAR visual acuity can also be measured on a card-based Bailey-Lovie chart. The use of this chart is covered in more detail in the relevant SOP<sup>1</sup>. In summary the differences are:

1. Unless specified the Bailey-Lovie chart is used at a testing distance of 3m as it is viewed directly.
2. The font used is that defined in BS 4274, a 5x5 sans-serif font.<sup>2</sup>
3. If the Bailey-Lovie is used at 3m, then it should not be used as a target to determine over-refraction. Instead an alternative chart (e.g. Snellen) positioned at 6m should be used.

## References

1. Eurolens Research Standard Operating Procedure. Assessment of visual performance using the Bailey-Lovie logMAR visual acuity test chart and procedures for carrying out an over-refraction.
2. BS 4274-1:2003. Visual acuity test types. Test charts for clinical determination of distance visual acuity – Specification.

**Appendix A. Screen inclination calculation**

To calculate chart inclination

$$\text{Tan (angle of chart inclination)} = \frac{\text{Subject's distance below chart}}{\text{Subject to chart distance (parallel to floor)}}$$

Room	1.015	1.014	1.013	1.012
Subject's distance below chart (eye to top of monitor) (cm)*	50	65	65	65
Subject to chart distance (parallel to floor) (cm)	600	605	610	600
Calculated chart inclination (degrees)	4.7	6.1	6.1	6.2

Table 2: Eurolens clinic room screen inclination.

\* Subject used was Subject AM, (Eurolens ID 2023) of average UK male height (175cm, ONS data)



**Appendix B. Chart settings on 1/10/2013**

	1.015	1.014	1.013	1.012
Monitor number	1	3	5	4
Clinic computer	iMac 9.1	iMac 4.2	iMac 4.2	iMac 5.2
Chart distance (m)	6	6.05	6.1	6
LC grey	240	241	240	240

Table 3: Eurolens clinic room chart settings

All monitors calibrated were a BenQ G2255 displaying the chart at native resolution (1920x1080).

**Appendix C. Revisions to chart software**

2008

Initial clinic version of computer chart software

01/02/2013 v5

2013 version of chart software was rewritten for compatibility with Office 2011 and Mac OSX10.8. Contains the following amendments:

- Colours of the control box have been altered for better legibility with office 2011
- Chart letter display was updated for 16:9 monitors
- Letter size is calculated correctly for chart distance
- Low contrast letters contrast adjustable from chart control panel.

**██████████ PATIENT REPORTED OUTCOMES**

[REDACTED]

## Patient Reported Outcomes

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[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

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[REDACTED]

- | [REDACTED]
  - | [REDACTED]
- 

[REDACTED]

[REDACTED]

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**PROTOCOL COMPLIANCE INVESTIGATOR(S) SIGNATURE PAGE**

Protocol Number and Title: CR-6013 (J17-626) Clinical Evaluation of two marketed artificial tears in non-contact lens wearing patients

Version and Date: 3.0 03 January 2018

I have read and understand the protocol specified above and agree on its content.

I agree to conduct this study according to ISO 14155,<sup>1</sup> GCP and ICH guidelines,<sup>2</sup> the Declaration of Helsinki,<sup>3</sup> United States (US) Code of Federal Regulations (CFR),<sup>4</sup> and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations. The Principal Investigator is responsible for ensuring that all clinical site personnel, including Sub-Investigators adhere to all ICH<sup>2</sup> regulations and GCP guidelines regarding clinical trials during and after study completion.

I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

I am responsible for ensuring that all clinical site personnel including Sub-Investigators adhere to all ICH<sup>2</sup> regulations and GCP guidelines regarding clinical trials during and after study completion.

All clinical site personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all clinical site personnel involved in the conduct of this study are informed about their obligations in meeting the above commitments.

I shall not disclose the information contained in this protocol or any results obtained from this study without written authorization.

Principal Investigator:

\_\_\_\_\_  
Signature Date

\_\_\_\_\_  
Name and Professional Position  
(Printed)

Institution/Site:

\_\_\_\_\_  
Institution/Site Name

\_\_\_\_\_  
Institution/Site Address

