



**Protocol 2020-03
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***Randomized Comparison between iLux™ and LipiFlow® in the Treatment
of Meibomian Gland Dysfunction***

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1 STUDY SYNOPSIS

Study Name	Randomized Comparison between iLux™ and LipiFlow® in the Treatment of Meibomian Gland Dysfunction
Design	<ul style="list-style-type: none"> Randomized, open-label, multisite trial comparing the iLux System to LipiFlow Thermal Pulsation System to test for non-inferiority 142 subjects (284 eyes), 128 required for analysis (256 eyes) at ≥ 7 clinical sites
Objective	Determine the safety and effectiveness of the iLux System in adults with meibomian gland dysfunction (MGD)
Co-Primary Effectiveness Endpoints	Changes from baseline to the 4-week exam in Meibomian Gland Score (MGS), as assessed by a masked rater, and Tear Break-Up Time (TBUT)
Secondary Effectiveness Endpoint	Change from baseline in subject symptoms using Ocular Surface Disease Index (OSDI) at 4-week exam
Primary Safety Endpoint	Comparison of the incidence of device-related adverse events (e.g., changes in the lid margin, development of floppy eyelids, entropion or ectropion; and lash integrity) for the two treatments
Secondary Safety Endpoint	<ul style="list-style-type: none"> The evaluation of discomfort and pain during treatment Changes from baseline following treatment for the test and control devices for the following assessments: <ul style="list-style-type: none"> Ocular Surface Staining Intraocular Pressure Best Spectacle Corrected Visual Acuity (BSCVA)
Population	Adult patients with symptoms of evaporative dry eye/MGD
Inclusion Criteria	<ul style="list-style-type: none"> Age 18 years and older of any gender or race Written informed consent to participate in the study Willingness and ability to return for all study visits Positive history of self-reported dry eye symptoms for three months prior to the study using OSDI with a score of ≥ 23 at the baseline visit Evidence of meibomian gland (MG) obstruction, based on total MGS of ≤12 in lower eyelids for each eye as assessed by a clinician not involved in the study procedure Tear break-up time <10 seconds Agreement/ability to abstain from dry eye/MGD medications for the time between the screening visit and the final study visit (ocular lubricants are allowed if no changes are made during the study)
Exclusion Criteria	<ul style="list-style-type: none"> History of ocular or corneal surgery including intraocular, oculo-plastic, corneal or refractive surgery within 1 year Subjects with giant papillary conjunctivitis Subject with punctal plugs or who have had punctal cautery Ocular injury or trauma, chemical burns, or limbal stem cell deficiency within 3 months of the baseline examination Active ocular herpes zoster or simplex of eye or eyelid or a history of these within the last 3 months Subjects who are aphakic Cicatricial lid margin disease identified via slit lamp examination, including pemphigoid, symblepharon, etc. Active ocular infection Active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months Ocular surface abnormality that may compromise corneal integrity Lid surface abnormalities that affect lid function in either eye

	<ul style="list-style-type: none"> • Anterior blepharitis (staphylococcal, demodex or seborrheic grade 3 or 4) • Systemic disease conditions that cause dry eye • Unwillingness to abstain from systemic medications known to cause dryness for the study duration • Women who are pregnant, nursing, or not utilizing adequate birth control measures • Individuals who have either changed the dosing of systemic medications or non-dry eye/MGD ophthalmic medications within the past 30 days prior to screening • Individuals who are unable or unwilling to remain on a stable dosing regimen for the duration of the study • Individuals using isotretinoin (Accutane) within 1 year, cyclosporine-A (Restasis) or lifitegrast ophthalmic solution 5% (Xiidra) within 3 months, or any other dry eye or MGD medications within 2 weeks of screening (ocular lubricants are allowed if no changes are made during the study) • Individuals wearing contact lenses at any time during the prior three months or during the study period • Eyelid tattoos, including permanent eyeliner makeup • Individuals that were treated with LipiFlow in either eye in the last 24 months • Individuals using another ophthalmic investigational device or agent within 30 days of study participation • Individuals who are unable to complete the required patient questionnaires in English
<p>Clinical Sites</p>	<ul style="list-style-type: none"> • Dishler Laser Institute, Greenwood Village, CO • Tauber Eye Center, Kansas City, MO • Gordon Schanzlin New Vision Eye Institute, La Jolla, CA • Eyecare Consultants – Vision Source, Engelwood, CO • Barnet-Dulany-Perkins Eye Center, Phoenix, AZ • Schwartz Laser Eye Center, Scottsdale, AZ • Pepose Vision Institute, Chesterfield, MO • Other sites TBD
<p>Procedure</p>	<p>Treatment of eyes per Instructions for Use (IFU) for the device to which the subject was randomized</p>
<p>Statistical Analysis</p>	<p>Categorical or binary endpoints will be summarized by count and percentage. Analysis of covariance (ANCOVA) will be used to assess the treatment effect between baseline and 4 weeks for iLux and LipiFlow treatments for the primary and secondary effectiveness endpoints. For each endpoint analyzed, the baseline value will be used as a covariate. Given that non-inferiority is demonstrated for the iLux endpoints, success will not be claimed unless the mean change from baseline in the test arm is clinically significant and significantly different from zero.</p>
<p>Schedule of Evaluations</p>	<p><u>Screening (Day -7 to Day 0)</u></p> <ul style="list-style-type: none"> • Informed Consent • Demographics/medical/ocular history • Concomitant systemic and ophthalmic meds <hr/> <p><u>Pre-Treatment/Baseline (Day 0)</u></p> <ul style="list-style-type: none"> • Pain and Discomfort Questionnaires (self-assessed after treatment but prior to any clinical assessment) • OSDI • Uncorrected visual acuity • Keratometry • Manifest refraction • BSCVA • Slit Lamp for Anterior Segment Health

	<ul style="list-style-type: none"> • Lid Margin Abnormalities • Eyelid Margin Assessment (including development of entropion or ectropion, floppy eyelids, lash integrity assessment) • TBUT • Corneal Fluorescein Staining Slit Lamp Evaluation • Meibomian Gland Assessment and Scoring (must be performed by a masked rater) • Intraocular pressure <p><u>Treatment (Day 0)</u></p> <ul style="list-style-type: none"> • Treatment with assigned device per IFU • Assessment for adverse events <p><u>Post-Treatment (Day 0)</u></p> <ul style="list-style-type: none"> • Pain and Discomfort questionnaires • BSCVA • Uncorrected visual acuity • Slit Lamp for Anterior Segment Health • Lid Margin Abnormalities • Eyelid Margin Assessment • Corneal Fluorescein Staining Slit Lamp Evaluation • Intraocular Pressure • Assessment for Adverse Events one hour following treatment, including changes to eyelid margins (development of entropion or ectropion, floppy eyelids, lash integrity assessment)
	<p><u>1-Day (Day 0-1) Office Visit Follow-Up</u></p> <ul style="list-style-type: none"> • Pain and Discomfort Questionnaires (self-assessed prior to clinical assessment) • Uncorrected visual acuity • BSCVA • Slit Lamp for Anterior Segment Health • Lid Margin Abnormalities • Eyelid Margin Assessment (including development of entropion or ectropion, floppy eyelids, lash integrity assessment) • Corneal Fluorescein Staining Slit Lamp Evaluation • Assessment for Adverse Events
	<p><u>2-Week (Day 12-16) Office Visit Follow-Up</u></p> <ul style="list-style-type: none"> • Pain and Discomfort Questionnaires (self-assessed prior to clinical assessment) • OSDI • Uncorrected visual acuity • Keratometry • Manifest Refraction • BSCVA • Slit Lamp for Anterior Segment Health • Lid Margin Abnormalities • Eyelid Margin Assessment (including development of entropion or ectropion, floppy eyelids, lash integrity assessment) • TBUT • Corneal Fluorescein Staining Slit Lamp Evaluation • Meibomian Gland Assessment and Scoring (must be performed by a masked rater) • Intraocular Pressure • Assessment for Adverse Events
	<p><u>4-Week (Day 21-35) Office Visit Follow-Up</u></p> <ul style="list-style-type: none"> • Pain and Discomfort Questionnaires (self-assessed prior to clinical assessment) • OSDI • Concomitant systemic and ophthalmic meds • Uncorrected visual acuity

	<ul style="list-style-type: none">• Keratometry• Manifest Refraction• BSCVA• Slit Lamp for Anterior Segment Health• Lid Margin Abnormalities• Eyelid Margin Assessment (including development of entropion or ectropion, floppy eyelids, lash integrity assessment)• TBUT• Corneal Fluorescein Staining Slit Lamp Evaluation• Meibomian Gland Assessment and Scoring (must be performed by a masked rater)• Intraocular Pressure• Assessment for Adverse Events
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2 INTRODUCTION

Meibomian glands are located in the tarsal plate of the upper and lower eyelids, where they terminate along the interior rim (or margin) of the eyelids. These glands secrete meibum, which is a lipid-rich essential component of a healthy tear film. When sufficient meibum is not present in the tear film, the aqueous layer of the tear film is disrupted and readily evaporates causing irritation, redness, and inflammation of the lid margin and surrounding tissues. Meibomian Gland Dysfunction (MGD) is associated with a failure of these glands to produce adequate quantities of meibum due to atrophy, inflammation, or obstruction, and is thought to be the most common cause of evaporative dry eye disease [1].

A common clinical treatment to restore normal gland function in patients with obstructive MGD involves the application of heat and pressure therapy to the eyelids to express the meibomian gland obstruction and other material from the gland [2]. Warming the eyelid tissue softens or melts the meibum, which is known to facilitate expression using pressure.

3 DEVICE DESCRIPTION

The iLux™ System is a medical device intended for use by Eye Care Professionals (ECP) to apply localized heat and pressure therapy to a patient's eyelids. The system consists of a handheld instrument coupled to a single-use, sterile Disposable component that is positioned behind the eyelid. The iLux device allows an ECP to view the eyelid margin through a magnifier, then warm the eyelid tissue to a range of 40 to 42°C, and then apply compression to the eyelid in order to express melted meibum from obstructed glands.

3.1 iLux Indications for Use

The iLux System is indicated for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye.

3.2 iLux Components

The iLux system is shown in Figure 1.



Figure 1: The iLux system shown with a Disposable attached to the Instrument

3.2.1 iLux Disposable

The iLux Disposable is a sterile component used for a single patient treatment, and then disposed. The main parts of the Disposable are shown in Figure 2. During a treatment, the Inner Eyelid Pad is inserted behind the eyelid in the fornix and is intended to contact the inner mucosal lining (i.e., the palpebral conjunctiva). The Outer Pad, which opposes the Inner Pad, contacts the skin on the outer surface of the eyelid. Light produced by the Instrument is transmitted through the clear Outer Pad to warm the eyelid tissue. The Outer Pad is used to apply pressure to the eyelid by moving this component towards the Inner Pad by means of a mechanism in the Instrument. Temperature sensors in the Outer and Inner Pads monitor eyelid temperature during a treatment.

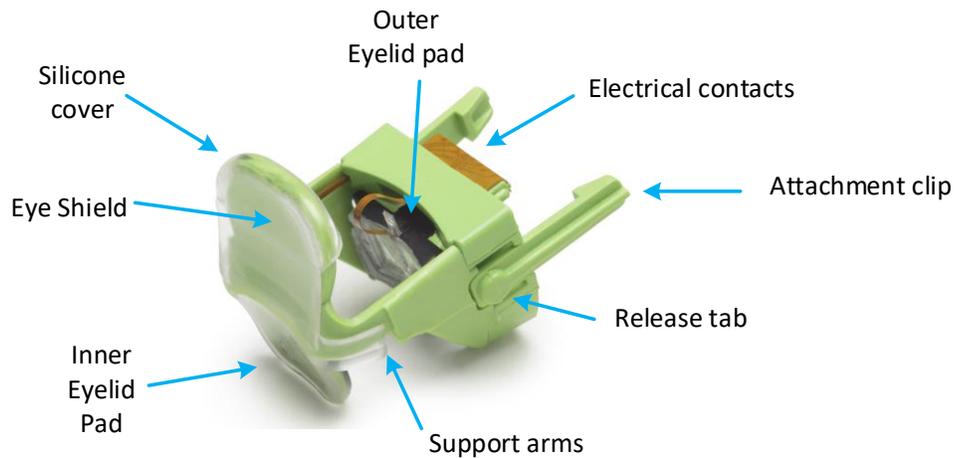


Figure 2 The main parts of the iLux Disposable are shown in this rendering. Not shown are the temperature sensors.

3.2.2 iLux Instrument

The iLux Instrument is a handheld, electronic instrument used together with the iLux Disposable to apply heating and pressure to the eyelid. The Instrument includes electronic circuits that read sensors in the Inner and Outer Eyelid Pads to measure temperatures representative of inner and outer eyelid temperature, respectively. Warming is accomplished using light energy emitted from LEDs in the Instrument. A mechanism in the Instrument allows the operator to apply pressure to the eyelid by controlling the movement of the Outer Pad using finger pressure applied to the Compression Control button. The force applied to the Compression Control is measured by a sensor in this mechanism. A graphic Screen displays information for operating the Instrument during a treatment. A magnifier allows the operator to view the eyelid margin during treatment.

Eyelid temperature is measured using sensors in the Disposable including two sensors in the Outer Pad and two in the Inner Pad. When the Disposable is attached to Instrument, spring loaded pins mounted above the Shroud make an electrical connection to the pads in the Disposable. Electronic circuitry in the Instrument reads the sensors and determines temperatures more than 20 times a second. The accuracy of the temperature measurement system is ± 1 °C. The circuitry performs self-test checks to ensure the sensors are operating properly. If the electronics detect a failure, an error code is displayed and the heat source is disabled.

The Instrument features an integrated Display Screen shown in Figure 3. The Display Screen shows the elapsed warming time that the temperature is above 38 °C (in seconds), the compression force applied by the user, the highest of the two temperature sensors located in the Inner Eyelid Pad, and status of the rechargeable batteries as indicated by a battery icon. The Display also provides messages regarding status or conditions that require the operator's attention.

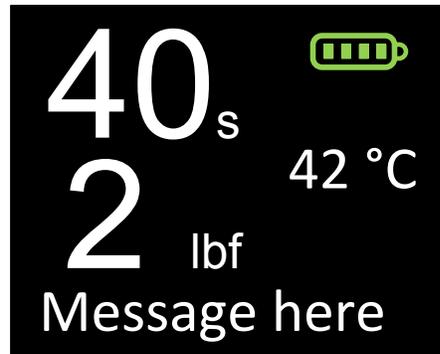


Figure 3: The information displayed on the screen. Any operating message is displayed on the bottom row.

Pressure applied to the eyelid is controlled by the ECP depressing the Compression Control button using their thumb or finger, which causes the Outer Pad to move towards the opposing Inner Pad. The mechanism that connects the Compression Control button to the Outer Eyelid Pad is shown in Figure 4. When the Disposable is attached to the Instrument, the Outer Eyelid Pad automatically attaches to the front of the Shroud. The Compression Control button is connected to the movable Shroud by a linkage, which reduces the force applied to the Compression Control button by at least 50%. The ECP can retract or advance the Outer Eyelid Pad and Shroud combination as well as control the amount of pressure applied using the Compression Control button. A sensor is mounted in this mechanism to measure the force applied by the user to Compression Control button. Electronic circuitry monitors the sensor output and then displays the compression force on the Screen to provide feedback for the user during a treatment.

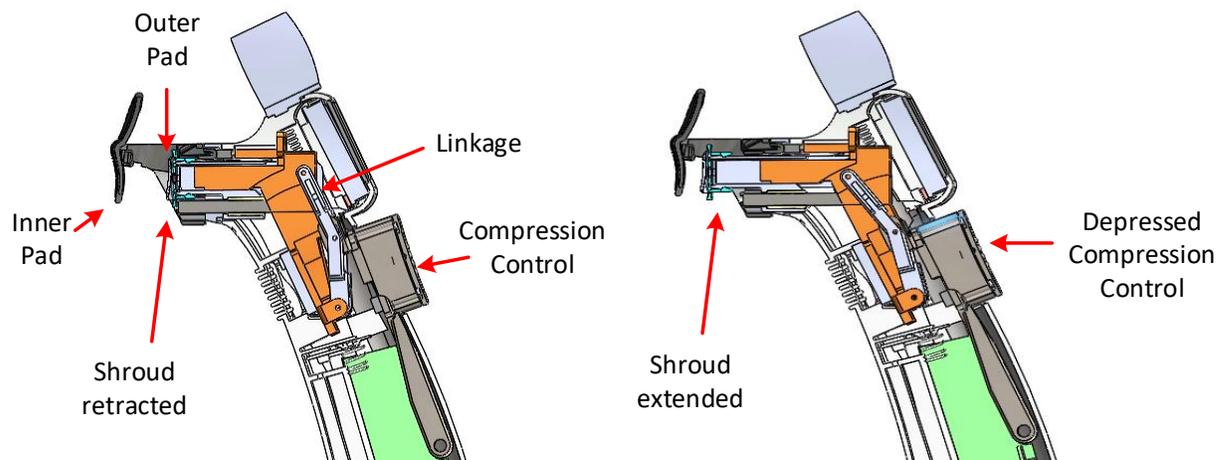


Figure 4 A mechanism in the Instrument allows the eye care professional to control the pressure applied to the eyelid. Depressing the Compression Control button causes the Outer Pad attached to the Instrument Shroud to advance towards the Inner Pad. A spring-return feature causes the Outer Pad and Shroud to retract when the Compression Control is released.

The eyelid tissue is warmed by light energy produced by LEDs in the Instrument and transmitted through the clear Outer Pad. The LEDs are located behind a clear window on the open end of the Shroud. Two wavelengths of light are used: lime-green (568 nm) and near-infrared (850 nm). Chromophores in the eyelid absorb the light energy and heat the surrounding tissue [3]. Similarly, chromophores in the black plastic of the Inner Pad absorb the light energy and warm nearby tissue of

the inner eyelid. A small fan, which creates an audible sound, provides cooling for the LEDs by drawing air through slotted openings in the housing.

The system is designed to protect against unintended exposure to the light. The Inner Pad and Eye Shield block light transmission directly into the eye during a treatment. The Instrument is designed to prevent heat source operation without a Disposable attached. To minimize stray light, the heat source cannot be operated without the user advancing the Outer Pad to within 4 to 6 mm of the Inner Pad by depressing the Compression Control.

The top surface of the Compression Control has a Heater Control switch that is slid forward by the operator's thumb or forefinger to turn on the warming LEDs. This switch has a spring-return feature, so that when it is released, or when the ECP's thumb or forefinger is relaxed, the Heater Control switch returns to its normal "off" position. The highest temperature measured by the Inner Eyelid Pad sensors is shown on the LCD. When the heater is turned on by the ECP, circuitry adjusts power to the LEDs to raise eyelid temperatures to 40 to 42 °C. At any time during heating, if any of the measured eyelid temperatures exceeds 42 °C, the high-temperature alert symbol is displayed and the light source is dimmed. If any one of the temperatures exceeds 44 °C, the attention required symbol is displayed the Instrument automatically turns off the light source until the temperature drops below 40 °C. The elapsed time that the tissue is warmed above 38°C is displayed on the screen. The duration that the LEDs can be operated is limited to 90 seconds from initial activation; after this period, sliding the Heater Control switch forward will no longer turn on the LEDs. Momentarily depressing the Instrument power ON/OFF switch resets the 90 second LED timer and the elapsed warming timer.

The instrument records temperature and force along with other operating data in internal memory. Data. The performance data can be downloaded to an external computer by Tear Film for the purposes of troubleshooting or other data needs.

3.2.3 Device Operation

The Instrument is turned ON by depressing the ON/OFF button for four seconds. The instrument first verifies proper operation of the internal electronics and beeps once if no errors are detected. Without a Disposable attached, the Screen displays the "Attach Disposable" message. If the Screen displays an error message, the operator should refer to the Troubleshooting section of this manual. If the battery power is low, which is indicated by a flashing battery icon with a single bar, the Instrument should be turned OFF and the batteries removed and placed in the charging stand. When the Instrument is ready, the Disposable is removed from the packaging immediately before a treatment and attached to the Instrument by means of snap clips on the two sides. The Screen now displays the elapsed time, which is "0", the compression force, and the highest Inner Pad temperature.

After the patient is prepared, the Inner Eyelid Pad is placed adjacent to the region of the palpebral conjunctiva containing the meibomian glands to be treated. Figure 5 illustrates the Inner Pad placement for a lower eyelid and Figure 6 shows Inner Pad placement for an upper eyelid. The orifices of the targeted glands should be visible through the Magnifier. The Outer Eyelid Pad is then moved against the outer surface of the eyelid by depressing the Compression Control on the Instrument. Since the Outer Eyelid Pad opposes the Inner Eyelid Pad, this action applies pressure to the eyelid that

can be varied by the force applied to the Compression Control. This force is displayed on the Screen to provide feedback to the user. If compressing the glands using a gentle pressure (force < 3) does not produce secretions, then the tissue should be warmed to approximately 40 to 42 °C to melt the meibum and facilitate expression. Sliding the heater control switch forward causes the Instrument to energize the LEDs.

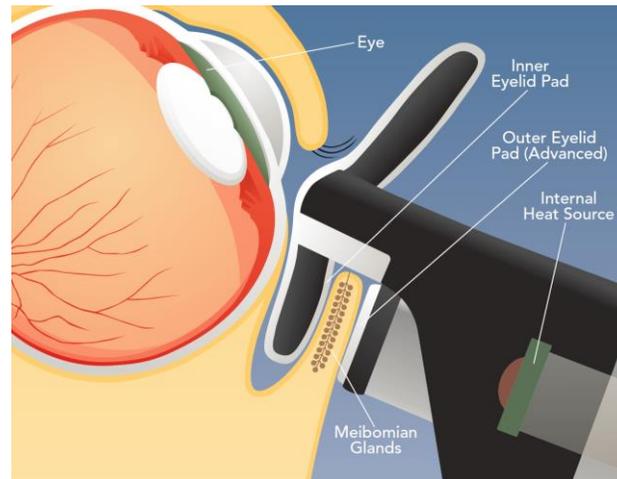


Figure 5: To treat a lower eyelid, the patient is instructed to look up and the Inner Eyelid Pad is placed in the inferior fornix adjacent to the blocked meibomian glands. The Compression Control is then depressed causing the Outer Eyelid Pad to apply pressure against the outer eyelid.

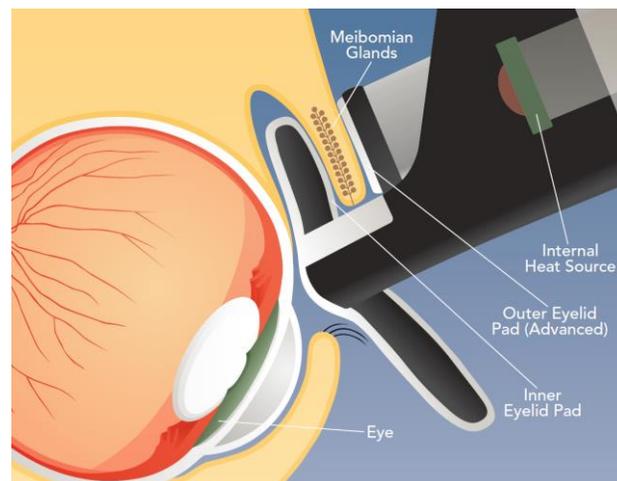


Figure 6: Treatment of an upper lid is illustration. The patient is instructed to look down and the Inner pad is placed in superior fornix adjacent to the blocked meibomian glands. The screen content is automatically re-oriented to remain upright when the Instrument is inverted.

3.3 LipiFlow System

The LipiFlow Thermal Pulsation System is a commercially available device used in the treatment of MGD. It is cleared to be marketed by the United States Food and Drug Administration and will be used as the control device in this study.

3.4 LipiFlow Indications for Use

The LipiFlow Thermal Pulsation System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye or lipid deficiency dry eye.

3.5 LipiFlow Components

The LipiFlow Console provides the user interface and control elements of the system, including all software, algorithms and control elements. The Activator, a single-use sterile device, delivers automated therapeutic energies to each meibomian gland. Its contoured design vaults the cornea and protects the eye allowing a maximum therapeutic temperature of 43 degrees Celsius to reach glands from the inner eyelid, without damaging the eyelid or delicate structures of the globe. Insulation protects the cornea from exceeding a safe 39.5 degrees Celsius, while a pressure feedback loop sends pulsed sequences to expel blockages. Force equalization protects the globe from pressure transmission by focusing energy only on the eyelid. Delivered through the LipiFlow Activator, Vectored Thermal Pulse™ (VTP) technology applies a combination of heat and pressure to the inner eyelid to safely remove gland obstructions and stagnant gland content. Vectored heat and adaptive force equalization targets the pulse, heat, and pressure on the meibomian glands to maximize effectiveness. Therapeutic motion provides proximal-to-distal parastalsis to clear gland contents.



Figure 7: The LipiFlow Console and Activator disposable

4 CLINICAL STUDY DESIGN

4.1 Objective

The objective of this trial is to evaluate the safety and effectiveness of the iLux System for adults with meibomian gland dysfunction (MGD).

4.2 Description of the Study

This study is a randomized, open-label, multisite clinical trial comparing the iLux System to an active control, which will be the LipiFlow® Thermal Pulsation System. The goal of this study is to verify that technological differences between the iLux System and the LipiFlow System do not adversely affect safety and effectiveness. The comparison between the two systems will determine if the iLux System is non-inferior to the LipiFlow System. The proposed sample size is 256 eyes (128 subjects) to demonstrate non-inferiority of treatment with iLux relative to treatment with LipiFlow for the two coprimary effectiveness endpoints. A total of 142 subjects is requested to allow for 10% fallout during patient screening. One hundred twenty-eight subjects will be randomized for bilateral treatment and will be assigned in a 1:1 ratio into the iLux treatment group or the control group at least 7 study sites.

4.3 Non-Significant Risk

The iLux device is a non-significant risk device because it does not meet the criteria for a significant risk device.

The criteria for a significant risk device are as follows¹:

1. The device is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. The device is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. The device is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. The device otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

4.4 Outcome Measures

4.4.1 Co-Primary Effectiveness Endpoints

The co-primary effectiveness endpoints are the changes from baseline to the 4-week exam in total Meibomian Gland Score (MGS) and Tear Break-Up Time (TBUT). MGS must be assessed by a masked

¹ "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies", FDA CDRH, January 2006.

rater. Clinical and statistically significant improvements from baseline for each parameter are required to achieve success for these co-primary endpoints.

The MGS is determined for the lower eyelids using a device that applies a standardized pressure to an area including 5 glands (Meibomian Gland Evaluator, Model MGE-1000, TearScience, Inc.) while viewing the eyelid margin using a slit lamp microscope to determine the presence and quality of the gland secretions. A total of 15 glands in three lower eyelid zones (nasal, medial, temporal) will be evaluated. Each gland is graded from 0 to 3 (0 = no secretion, 1 = inspissated, 2 = cloudy, 3 = clear liquid). The maximum MGS score is 45 in each eye. This endpoint has been used in previous studies evaluating the LipiFlow device [5, 6]. The clinician performing the MGS must not be involved in the study procedure and must be blinded to which arm of the study the subject is randomized.

TBUT is evaluated using the fluorescein method [4]. This measurement provides an aggregate assessment of the effectiveness of treatments to both the lower and upper eyelids.

4.4.2 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint will be the change from baseline in patient symptoms using the Ocular Surface Disease Index (OSDI) at the 4-week exam. OSDI is a scoring that evaluates patient symptoms based on a validated questionnaire [7]. This assessment has been used in several clinical studies for treating MGD with the LipiFlow [5, 6].

4.4.3 Primary Safety Endpoint

The primary safety endpoint will be a comparison of the incidence of device-related adverse events (e.g., changes in the lid margin, development of floppy eyelids, entropion or ectropion; and lash integrity) for the two treatments.

4.4.4 Secondary Safety Endpoint

A secondary safety endpoint will be following assessments:

- The evaluation of discomfort and pain during treatment
- Changes from baseline following treatment for the test and control devices for the following assessments:
 - Ocular Surface Staining
 - Intraocular Pressure
 - Best Spectacle Corrected Visual Acuity (BSCVA)

5 PATIENT POPULATION

The study will include adult subjects with symptoms of MGD/evaporative dry eye

5.1 Inclusion Criteria

1. Age 18 years and older of any gender or race.
2. Provision of written informed consent prior to study participation.
3. Willingness and ability to return for all study visits.
4. A positive history of self-reported dry eye symptoms for three months prior to the study using the Ocular Surface Disease Index (OSDI) questionnaire, and a score of ≥ 23 at the baseline visit.

5. Evidence of meibomian gland (MG) obstruction, based on a total Meibomian Gland Score (MGS) of ≤ 12 in the lower eyelids for each eye. A total of 15 glands are evaluated using a standardized pressure device (Meibomian Gland Evaluator, Model MGE-1000, TearScience Inc.) in the nasal, medial, temporal zones of the lower eyelid of each eye (5 glands each zone). Glands expressed and graded from 0 to 3 (0 = no secretion, 1 = inspissated, 2 = cloudy, 3 = clear liquid). The maximum MGS score is 45 for each eye. The rater of MGS must not be involved in the study procedure.
6. Tear break-up time < 10 seconds
7. Agreement/ability to abstain from dry eye/MGD medications for the time between the treatment visit and the final study visit. Ocular lubricants are allowed if no changes are made during the study.

5.2 Exclusion Criteria

1. History of ocular surgery including intraocular, oculo-plastic, corneal or refractive surgery within 1 year
2. Subjects with giant papillary conjunctivitis
3. Subject with punctal plugs or who have had punctal cautery
4. Ocular injury or trauma, chemical burns, or limbal stem cell deficiency within 3 months of the baseline examination
5. Active ocular herpes zoster or simplex of eye or eyelid or a history of these within the last 3 months
6. Subjects who are aphakic
7. Cicatricial lid margin disease identified via slit lamp examination, including pemphigoid, symblepharon, etc.
8. Active ocular infection (e.g., viral, bacterial, mycobacterial, protozoan, or fungal infection of the cornea, conjunctiva, lacrimal gland, lacrimal sac, or eyelids including a hordeolum or sty))
9. Active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months (e.g. retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis)
10. Ocular surface abnormality that may compromise corneal integrity (e.g., prior chemical burn, recurrent corneal erosion, corneal epithelial defect, Grade 3 corneal fluorescein staining, or map dot fingerprint dystrophy)
11. Lid surface abnormalities (e.g., entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis) that affect lid function in either eye
12. Anterior blepharitis (staphylococcal, demodex or seborrheic grade 3 or 4)
13. Systemic disease conditions that cause dry eye (e.g., Stevens- Johnson syndrome, vitamin A deficiency, rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, leukemia, Riley-Day syndrome, systemic lupus erythematosus, Sjogren's syndrome)
14. Unwillingness to abstain from systemic medications known to cause dryness for the study duration.
15. Women who are pregnant, nursing, or not utilizing adequate birth control measures.
16. Individuals who have either changed the dosing of systemic or non-dry eye/MGD ophthalmic medication within the past 30 days prior to screening
17. Individuals who are unable or unwilling to remain on a stable dosing regimen for the duration of the study.
18. Individuals using isotretinoin (Accutane) within 1 year, cyclosporine-A (Restasis) or lifitegrast ophthalmic solution (Xiidra) within 3 months, or any other dry eye or MGD medications (antibiotics, non-steroidals anti-inflammatory drugs and corticosteroids) for at least 2 weeks and

to maintain abstinence throughout the duration of the study (ocular lubricants are allowed if no changes are made during the study).

19. Individuals wearing contact lenses at any time during the prior three months
20. Individuals that were treated with LipiFlow in one or two eyes in the last 24 months.
21. Eyelid tattoos, including permanent eyeliner makeup
22. Individuals using another ophthalmic investigational device or agent within 30 days of study participation.
23. Individuals who are unable to complete the required patient questionnaires in English.

6 STUDY PROCEDURES

6.1 Subject Enrollment

Patients will be screened, assessed, treated and followed according to the schedule in Appendix A. Patients must have the study explained to them by a member of the site study team, they must be provided sufficient time to consider their participation in the study and provided an opportunity to ask questions of the study team. Subjects must sign the most current version of an informed consent form (ICF) approved by an Institutional Review Board (IRB). All patients who sign an ICF are considered enrolled subjects in the study. Therefore, patients should be screened to the extent possible prior to signing an ICF but patients should not undergo any study-specific assessments until they have signed the ICF.

Enrolled subjects will be assigned a unique study identification (ID) number. No subject-specific information (e.g., initials) will be used in the ID number. Only the study ID number will be used to identify subjects once they are enrolled.

6.2 Subject Withdrawal

Subjects may withdraw their consent to participate in the study at any time, for any reason. Investigators may also withdraw subjects from the study at their discretion in order to protect the rights, safety, or welfare of the subject. All withdrawn subjects will be included in study analyses but they will not be replaced. No missing data will be imputed.

6.3 Screening

The following steps and information will be performed/completed up to 7 days prior to the treatment day:

- Informed Consent
- Demographics/Medical/Ocular history
- Concomitant Systemic and Ophthalmic Meds

6.4 Pre-Treatment/Baseline Assessment

The following assessments will be performed on Day 0, **prior to** treatment (**Note: the OSDI, Discomfort, and Pain Questionnaires must be administered prior to clinical evaluations**):

Table 1: Subject Assessments

Assessment	Description
Discomfort and Pain Questionnaires	The Pain Questionnaire (provided in Appendix C) is a Linkert scale questionnaires using a scale of 0-10 with anchored descriptions for the scale. The Discomfort Questionnaire is a visual analog scale (VAS) questionnaire using a scale from 0-100% to assess eye discomfort. Both questionnaires are to be self-assessed by the subject prior to any clinical assessment.
OSDI	Scoring that evaluates patient symptoms based on a validated questionnaire [7] using a Linkert scale. (see questionnaire provided in Appendix B). OSDI questionnaires include 12 questions in 3 categories asked of the subjects by clinicians who circle a number next to a description that best represents the subject's answer on a paper form. The numbers for each category are totaled and the total OSDI score is calculated by the formula: sum of scores x 25/# of questions answered. Dry eye severity is then assessed using the chart on the 2 nd page of the questionnaire.
Uncorrected Visual Acuity	Single letter scoring with an ETDRS high contrast test face at the test distance corresponding to the ETDRS chart used
Keratometry	Test of corneal curvature conducted using a manual keratometer or using simulated keratometry from corneal topography
Manifest Refraction	Manual test of refraction to determine optimum prescriptive lenses required by the subject to obtain 20/20 vision
BSCVA	Single letter scoring with an ETDRS high contrast test face at the test distance corresponding to the ETDRS chart used
Slit Lamp for Anterior Segment Health	Using biomicroscopy to examine anterior segment including lids, adnexa, conjunctiva, sclera, corneal clarity, and surface integrity, anterior chamber, and iris Grading system: <ul style="list-style-type: none"> • 0=No clinical findings • 1=Non-clinically significant positive findings (including pterygium, pinguecula, corneal scar, conjunctival pigment, corneal arcus, verucca, non-visual significant lens changes) • 2=Abnormal findings
Lid Margin Abnormalities	Scored 0-4 based on the number of the following present in each eye: <ul style="list-style-type: none"> • irregular lid margin • vascular engorgement • plugged meibomian gland orifices • anterior or posterior replacement of the mucocutaneous junction
Eyelid Margin Assessment	Development of any of the following: <ul style="list-style-type: none"> • entropion or ectropion • floppy eyelids • loss of lash integrity

<i>Assessment</i>	<i>Description</i>
Tear Break-Up time	<ul style="list-style-type: none"> • Use AMCON 0.12mg Fluorescein strips • Apply one or two drops of non-preserved saline to the impregnated paper tip. Excess fluid will automatically fall off. Shaking is neither required nor desirable. • Ask the patient to look down and in. • Gently touch the strip to the superior temporal bulbar conjunctiva for one or two seconds • Ask the patient to blink three times and open eyes naturally • Immediately measure the time between the last blink and the first appearance of a dark spot on the cornea (formation of dry area) • Time shall be recorded in seconds and shall be the average of three consecutive measurements • Repeat with a new strip for the second eye
Corneal Fluorescein Staining Slit Lamp Evaluation	<p>National Eye Institute (NEI) corneal grading scale evaluating five corneal regions:</p> <ul style="list-style-type: none"> • superior • inferior • central • temporal • central <p>Each graded on a 0-3 scale (0=normal-no staining; 1=mild-superficial stippling micropunctate staining; 2=moderate-macropunctate staining with some coalescent areas; 3=severe-numerous coalescent macropunctate areas and/or patches) [8]</p>
Meibomian Gland Assessment and Scoring	<p>Note: Meibomian Gland Assessments must be made by a rater not involved in the study procedure and blinded to the arm to which the subject is randomized</p> <ul style="list-style-type: none"> • Assess lower eyelids using Meibomian Gland Evaluator while viewing the eyelid margin using slit lamp microscope • Evaluate 15 glands in 3 zones (nasal, medial, temporal) • Each gland graded from 0 to 3 • Maximum MGS score=45 in each eye [5, 6]
Intraocular Pressure	Measured by a Goldmann tonometer and recorded in mmHg

6.5 Randomization

Prior to randomization it must be determined that the subject meets all entrance criteria. This includes the completion of all screening tests to determine eligibility. The randomization schedules with subjects allocated to the iLux or control LipiFlow group in a 1:1 ratio will be prepared for each site. Each envelope will have a sequential envelope number on the outside, and contain the assigned treatment procedure inside. Before the treatment, the assigned personnel will open the lowest numbered envelope. The envelope number will be documented on the study source documents and in the EDC. Randomization will take place at the treatment visit prior to subject treatment. There are no criteria for crossover in this study, so all subjects must be treated according to the arm to which they are randomized.

6.6 Treatment

The study procedure shall be performed on both eyes on the same day.

1. Eye makeup shall be removed.
2. The device shall be prepared for use in accordance with the Instructions for Use (IFU)/User Manual for the device to which the subject is randomized. An IFU/User Manual is packaged with each device that will be used in the study.

3. Anesthetic eye drops shall be instilled in both eyes.
4. Therapy shall be delivered in accordance with the IFU/User Manual for the device to which the subject is randomized.
5. For iLux device treatment, the following zones will be treated in the following order:
 - 5.1. upper lid, medial-nasal region
 - 5.2. lower lid, medial-nasal region
 - 5.3. lower lid, medial-temporal region
6. Representatives from the Sponsor may be present during the treatment but are not required.
7. Throughout the treatment visit, subjects will be assessed for any adverse events. Subjects will also be assessed for adverse events one hour following treatment, including for development of entropion or ectropion, floppy eyelids, and lash integrity assessment.
8. Following treatment, subjects will be assessed for the following:
 - Pain and discomfort using the questionnaires in Appendix C. These questionnaires must be self-assessed prior to any clinical evaluation.
 - Uncorrected Visual Acuity
 - BSCVA
 - Slit Lamp for Anterior Segment Health
 - Lid Margin Abnormalities
 - Eyelid Margin Assessment
 - Corneal Fluorescein Staining Slit Lamp Evaluation
 - Intraocular Pressure

6.7 1-Day Office Visit Follow-Up

Subjects will be required to be seen in person 1 day after the procedure for the following assessments:

- Discomfort and Pain Questionnaires (self-assessed prior to clinical evaluation)
- Uncorrected Visual Acuity
- BSCVA
- Slit Lamp for Anterior Segment Health
- Lid Margin Abnormalities
- Eyelid Margin Assessment
- Corneal Fluorescein Staining Slit Lamp Evaluation

Assessment for adverse events must include assessment for changes to eyelid margins (development of entropion or ectropion, floppy eyelids, and lash integrity assessment).

6.8 2-Week Office Visit Follow-Up

Subjects will be required to be seen in person 2 weeks (day 10-16) after the procedure for the following assessments:

- Discomfort and Pain Questionnaires (self-assessed prior to clinical evaluation)
- OSDI
- Uncorrected Visual Acuity
- Keratometry
- Manifest Refraction

- BSCVA
- Slit Lamp for Anterior Segment Health
- Lid Margin Abnormalities
- Eyelid Margin Assessment
- TBUT
- Corneal Fluorescein Staining Slit Lamp Evaluation
- Meibomian Gland Assessment and Scoring (must be performed by a masked rater)
- Intraocular Pressure

Assessment for adverse events must include assessment for changes to eyelid margins (development of entropion or ectropion floppy eyelids, and lash integrity assessment).

6.9 4-Week Follow-Up

Subjects will undergo the same screening assessments identified in Table 1 above at the 4-week visit. Specifically, the following tests will be performed:

- Discomfort and Pain Questionnaires (self-assessed prior to clinical evaluation)
- OSDI
- Uncorrected Visual Acuity
- Keratometry
- Manifest Refraction
- BSCVA
- Slit Lamp for Anterior Segment Health
- Lid Margin Abnormalities
- Eyelid Margin Assessment
- TBUT
- Corneal Fluorescein Staining Slit Lamp Evaluation
- Meibomian Gland Assessment and Scoring (must be performed by a masked rater)
- Intraocular Pressure

Assessment for adverse events must include assessment for changes to eyelid margins (development of entropion or ectropion floppy eyelids, and lash integrity assessment).

7 DATA ANALYSIS

Descriptive statistics will be provided to summarize outcomes at each visit as well as for change from baseline. Continuous endpoints will be summarized with N, mean, standard deviation, minimum, maximum, and median. Categorical or binary endpoints will be summarized by count and percentage. Analysis of covariance (ANCOVA) will be used to assess the treatment effect between baseline and 4 weeks for iLux and LipiFlow (LF) treatments for the primary and secondary effectiveness endpoints. For each endpoint analyzed, the baseline value will be used as a covariate.

Given that non-inferiority is demonstrated for the iLux endpoints, success will not be claimed unless the mean change from baseline in the test arm is clinically significant and significantly different from

zero. For any endpoints for which non-inferiority is demonstrated and mean changes from baseline are clinically significant and significantly different from zero, a test for superiority will be performed.

All subjects enrolled and treated in the study shall be included as part of the safety analysis.

Subjects who are randomized but not treated for any reason will be included in the intent-to-treat analysis as part of the arm to which they are randomized but they will be excluded from the per-protocol analysis.

7.1 Clinically Significant Effects

The values for clinical significance are used to establish the non-inferiority margins.

7.1.1 Meibomian Gland Score (MGS)

The clinical significance of the MGS score change both from baseline and in comparing study arms is based on a severity ranking using an alternative scoring method established by the consensus of clinical experts in the Diagnosis Subcommittee of the International Workshop on Meibomian Gland Dysfunction [4]. A difference in score of 5 changes the staging of the severity of MGD, and therefore represents a clinically significant level.

7.1.2 Tear Break-Up Time

The clinical significance for a change in TBUT both from baseline and in comparing study arms has not been reported in any of the published LipiFlow studies or other studies of MGD diagnosis and treatment. As a result, the clinical significance of the TBUT is based on labeling for the DET test strip (Table 2). The diagnosis of dry and abnormal tear stability is determined by a span of 5 seconds. If we use a moderate change in effect of 50%, then a difference in TBUT of 2.5 seconds is determined to be clinically significant. Based on this determination of a clinically significant change, a value of 2.5 seconds for the non-inferiority margin is used for TBUT primary endpoint.

Table 2: AMCON DET strip labeling

TBUT (seconds)	Significance
≥ 10	Normal
> 5 to < 10	Borderline dry eye
< 5	Dry eye

7.1.3 OSDI

A change in score of 7 is the minimal clinically significant difference for patients with moderate and severe dry eye established in a clinical study by Miller [9] using an anchor-based method. For this study, this value is being used both from baseline and in comparing study arms.

7.2 Non-Inferiority Compared to Control

7.2.1 Primary Effectiveness Endpoints Hypothesis

7.2.1.1 MGS

The co-primary effectiveness endpoint, MGS, will be tested for non-inferiority against LipiFlow using a 5-point non-inferiority delta (δ) in a one-tailed test.

It is hypothesized that the MGS mean score from the iLux group will not be lower than (not inferior to) the MGS mean score from the LipiFlow group at the 4-week exam:

Null Hypothesis: $\mu (\text{iLux-MGS} - \text{LF-MGS}) + \delta \leq 0$

Alternate Hypothesis: $\mu (\text{iLux-MGS} - \text{LF-MGS}) + \delta > 0$

Where $\mu (\text{iLux-MGS} - \text{LF-MGS})$ is the mean difference in the MGS between iLux and LipiFlow from baseline to week 4 and $\delta = 5$.

The MGS was found to be highly correlated across eyes in the previously completed pilot study data (correlation of 0.68); consequently, OD and OS values will be averaged to form an overall person score. An ANCOVA model, with baseline MGS as a covariate, will be used to assess the difference between the LipiFlow System and the iLux System results. The lower boundary of the least square means group confidence interval will be tested against the non-inferiority boundary of 5 points. To be successful, the lower boundary of the confidence interval must exceed -5.

7.2.1.2 TBUT

The co-primary endpoint, Tear Break-Up Time (TBUT) will be tested for non-inferiority against LipiFlow using a 2.5-second non-inferiority delta (δ) in a one-tailed test. A similar ANCOVA model will be used to compare TBUT between devices, with covariate adjustment for baseline TBUT. It is hypothesized that the TBUT mean time for the iLux group will not be less than (not inferior to) the TBUT mean time for the LipiFlow group at the 4-week exam:

Null Hypothesis: $\mu (\text{iLux-TBUT} - \text{LF-TBUT}) + \delta \leq 0$

Alternate Hypothesis: $\mu (\text{iLux-TBUT} - \text{LF-TBUT}) + \delta > 0$

Where $\mu (\text{iLux-TBUT} - \text{LF-TBUT})$ = mean difference in the TBUT between iLux and LipiFlow from baseline to week 4 and $\delta = 2.5$.

7.2.2 Secondary Effectiveness Endpoint Analysis

If the co-primary effectiveness endpoints demonstrate non-inferiority, the secondary effectiveness endpoint, change from baseline in Ocular Surface Disease Index (OSDI) at the 4-week exam, will be compared against the control device to test for non-inferiority. A similar ANCOVA model will be used to compare OSDI between devices, with covariate adjustment for baseline OSDI.

It is hypothesized that the OSDI mean score from the iLux group will not be lower than (not inferior to) the OSDI mean score from the LipiFlow group at the 4-week exam:

Null Hypothesis: $\mu (\text{iLux-OSDI} - \text{LF-OSDI}) - \delta \geq 0$

Alternate Hypothesis: $\mu (\text{iLux-OSDI} - \text{LF-OSDI}) - \delta < 0$

Where $\mu (\text{iLux-OSDI} - \text{LF-OSDI})$ = mean difference in the OSDI between iLux and LipiFlow from baseline to week 4 and $\delta = 7$.

7.2.3 Multiplicity

Both co-primary endpoints, MGS and TBUT, must be successful to demonstrate non-inferiority. The secondary endpoint is only tested if the co-primary effectiveness endpoints are non-inferior.

7.2.4 Sample Size Justification

The proposed sample size is 256 eyes (128 subjects) for this open-label, prospective multicenter trial designed to demonstrate non-inferiority of treatment with iLux relative to treatment with LipiFlow for the primary effectiveness endpoint. A total of 142 subjects is requested to allow for 10% fallout during patient screening. This study design provides a combined power of 88% to demonstrate non-inferiority given the following primary endpoint assumptions:

- MGS non-inferiority delta of 5 points and standard deviation of 8 points, provides a MGS primary endpoint power of 93.9%.
- TBUT non-inferiority delta of 2.5 seconds and standard deviation of 4 seconds, provides a TBUT primary endpoint power of 93.9%
- Power that both endpoints are significant, assuming independence, is $0.939^2 = 0.882$, or 88.2% power.

For the secondary endpoint, a standard deviation of 14 is assumed based on pilot data and the non-inferiority delta is set to 7. The chosen sample size and $\alpha = .025$ provides 80% power for this endpoint.

7.2.5 Safety Endpoints

The primary safety endpoint is the comparison of the incidence of device-related adverse events (e.g., changes in the lid margin, development of floppy eyelids, entropion or ectropion; and lash integrity) for the two treatments. The reporting period is from baseline through the last study visit.

The secondary safety endpoint is the evaluation of discomfort and pain during treatment and changes from baseline following treatment for the test and control devices for the following assessments:

- Ocular Surface Staining
- Intraocular Pressure
- BSCVA

Adverse events and other findings shall be summarized by presenting the percentages of subjects with each event type. Continuous endpoints shall be summarized using summary statistics such as means, medians, standard deviations, minima, maxima, and relevant percentiles. Definitions of adverse events, serious adverse events, and categorizations of events can be found in Appendix D.

All adverse events shall be evaluated beginning with onset, and evaluation shall continue until resolution is noted, or until the investigator determines that the subject's condition is stable.

All AEs shall be characterized by the following criteria (see Adverse Event Definitions in Appendix D):

- Event diagnosis
- Intensity or severity (*mild, moderate, severe*)
- Expectedness (anticipated, unanticipated)
- Relatedness to study treatment (*related, not related*)
- Treatment (none, medication, non-drug treatment/procedure, ER visit/hospitalization)
- Action taken (none, study procedure interrupted, study procedure discontinued)
- Outcome (resolved without sequelae, resolved with sequelae-specify, ongoing at time of assessment, death, unknown)

If more than one distinct adverse event occurs, each event shall be recorded separately.

7.2.5.1 Anticipated Adverse Events

- Eyelid/eye Pain
- Eyelid Irritation or Inflammation
- Ocular Surface Irritation or Inflammation
- Ocular Symptoms – Burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light.

7.2.5.2 Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

SAEs and unanticipated adverse device effects (UADE) must be reported to the study sponsor as soon as possible and no later than 48 hours after the investigator first learns of the event.

For initial reports, Investigators shall record all case details that can be gathered within the reporting timeframe. The contact information for Tear Film Innovations, Inc. below:

Study Sponsor:

Tear Film Innovations, LLC
Rob Thornhill, Chief Executive Officer
12625 High Bluff Drive, Suite 107
San Diego, CA 92130
PHONE: (858) 755-3333
E-Mail: rthornhill@tearfilm.com

Relevant follow-up information shall be submitted to the sponsor as soon as it becomes available and/or upon request. For some events, the sponsor or designee may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

7.2.6 Poolability Analysis

Subject demographic characteristics and background variables shall be summarized. To ensure poolability, primary effectiveness endpoints will be compared across site and gender. Analysis of variance will be used to test mean effects and interaction of stratification variables of treatment. A p-value of 0.15 will be used for these assessments.

7.2.7 Missing Data

Primary and secondary effectiveness endpoints will be imputed when missing to preserve the randomization in the intent-to-treat analysis population. The primary method of imputation used will be by multiple imputation. Ten imputations will be produced for each endpoint using SAS PROC MI. The seed used to begin random number generation will be 11142016. The Markov chain Monte Carlo method will be used to compute with the following predictor variables: baseline tear break-up time, baseline MGS score, gender, and age. Alternate imputation methods used to assess sensitivity to the presence of missing data will be last observation carried forward (LOCF), best case (a test subject's best prior value and a predicate subject's worst prior value is imputed) and worst case (a test subject's worst prior value and a predicate subject's best prior value is imputed). If best case and worst case

conclusions differ, a tipping point analysis will be performed. In the absence of post-treatment data, baseline values will be used for imputation for alternate imputation methods.

8 RISK ANALYSIS

Risks associated with using the iLux 2020 were assessed in accordance with ISO 14971, which is an international standard for medical device risk management that is recognized by the FDA. Most of the potential hazards identified in the analysis are common to many medical devices and are addressed by compliance with international standards. Other potential hazards unique to the iLux were addressed by assessing risk using Failure Modes Effects and Criticality Analysis (FMECA) and identifying controls to reduce residual risks to acceptable levels.

The iLux is used in the eye and the sterile disposable may come in contact with the conjunctiva and or cornea during the treatment of each lid. The sterile disposable is covered with a biocompatible silicone similar to a contact lens. There is nothing implanted either temporarily or permanently in the eye related to the iLux and the risk is similar to other meibomian gland treatments. Testing demonstrated that the disposable meets the requirements for biocompatibility (ISO 10993) and sterilization and packaging (ISO 1135, ISO 11607).

9 MEDICAL MONITOR

David Hardten, MD will serve as Medical Monitor for this study to oversee the overall safety and conduct of the study. There are no formal stopping rules for this study but the Medical Monitor is responsible for notifying the Sponsor of any circumstances in which he believes the rights, safety, and/or welfare of study subjects or potential future study subjects is compromised. The Sponsor is responsible for supplying the Medical Monitor with timely, complete, and accurate accounts of all adverse events in the study as well as regular progress reports that provide information such as enrollment rate, study compliance, and/or any other issues that may impact the scientific integrity of the study. The Medical Monitor will meet periodically with the Sponsor to review study status and any issues with study conduct and/or subject safety.

10 UNSCHEDULED VISITS

Unscheduled visits will be recorded by the site and data will be collected relating to any adverse events, device-related events, or any endpoint of the study. Data will be recorded on the most appropriate CRF depending on when the unscheduled visit occurs relative to the procedure. Any unscheduled visit should not replace or be in lieu of any scheduled visit unless agreed to by the Sponsor and documented in the site regulatory file.

11 STUDY DISCONTINUATION

The study sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete.

12 RECORD RETENTION

The investigator shall maintain all subject records for a period of two years after the latter of the conclusion or termination of the investigation or the time it is determined that the information is no longer needed to support a regulatory submission for market clearance.

The investigator must maintain accurate records of the receipt of all investigational material shipped by the sponsor, including the date and lot numbers received. In addition, accurate records must be kept on the amount and date that the investigational material, by lot number, was used and for each subject.

The investigator must assure that study supplies are used only in conjunction with subjects enrolled in the study and under the direct supervision of the investigator or co-investigators.

13 STUDY MONITORING REQUIREMENTS

It is the responsibility of the study Sponsor to ensure proper monitoring of the investigation and to see that all the clinical requirements are met. Either sponsor personnel or a contracted third party will perform monitoring. In general, monitoring will consist of an initiation visit to train the site on the proper use of the device and execution of the protocol. Ongoing monitoring will consist of periodic visits to the site to compare study eCRF data with site source data. The frequency of these visits will depend on site enrollment and observations during prior visits. During monitoring visits, the monitor may review the subject records to verify that all records and files are current and to assure compliance with all requirements of this protocol as well as with applicable IDE regulations. The final monitoring visit may also serve as the study close-out visit.

14 PROTOCOL DEVIATIONS/AMENDMENTS

An investigator may deviate from the protocol to protect the life or physical well-being of a subject in an emergency, and must notify the sponsor and the reviewing IRB within 5 working days after the emergency occurred. Except in such an emergency, an investigator may not deviate from the protocol

unless he/she obtains the prior approval of the sponsor. Depending on the specifics of the deviation, IRB approval may also be required.

15 DEVICE ACCOUNTABILITY

All investigational devices will be tracked during the study by either lot number or serial number depending on the device. The Sponsor will track all device shipments and all device returns. An accountability log will be maintained at each site to record the date and number of devices received by the site as well as the date and number of devices used, returned to the Sponsor, and/or disposed of during the study. This log will be included in the review of documentation during monitoring visits. Overall accountability for all devices will be maintained by the Sponsor.

16 REFERENCES

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- [8] Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eye. *CLAO J.* 1995;21:221-32.
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APPENDIX A: STUDY ASSESSMENTS

All subjects shall be assessed according to the following schedule unless otherwise specified:

<i>Assessment</i>	<i>Screening</i>	<i>Pre-Treatment (Baseline)</i>	<i>Treatment</i>	<i>Post-Treatment</i>	<i>Day 1</i>	<i>Week 2</i>	<i>Week 4</i>
<i>Treatment Window</i>	<i>Day -7 to Day 0</i>	<i>Day 0</i>	<i>Day 0</i>	<i>Day 0</i>	<i>Day +1</i>	<i>Days 10-16</i>	<i>Days 21-35</i>
Informed Consent	x						
Demographics/Medical/Ocular history	x						
Concomitant Systemic and Ophthalmic Meds	x						x
Discomfort and Pain Questionnaires		x		x	x	x	x
OSDI		x				x	x
Uncorrected Visual Acuity		x		x	x	x	x
Keratometry		x				x	x
Manifest Refraction		x				x	x
BSCVA		x		x	x	x	x
Slit Lamp for Anterior Segment Health		x		x	x	x	x
Lid Margin Abnormalities		x		x	x	x	x
Eyelid Margin Assessment		x		x*	x	x	x
Tear Break-Up Time		x				x	x
Corneal Fluorescein Staining Slit Lamp Evaluation		x		x	x	x	x
Meibomian Gland Assessment and Scoring (assess by a masked rater)		x				x	x
Intraocular Pressure		x		x		x	x
iLux OR LipiFlow Treatment per IFU/User Manual			x				
Adverse Events			x	x*	x	x	x

* 1 hour post-treatment

**APPENDIX B: OCULAR SURFACE DISEASE INDEX (OSDI)
QUESTIONNAIRE**

APPENDIX C: DISCOMFORT AND PAIN QUESTIONNAIRES

To be asked at Baseline

Place a vertical line on the following scales at the point that indicates the discomfort in or around your eyelids, or face over the past week. Discomfort includes feelings of pressure, tightness, heaviness, burning, and other negative sensations.

To be asked immediately post-procedure:

Place a vertical line on the following scales at the point that indicates the discomfort in or around your eyelids, or face during the procedure. Discomfort includes feelings of pressure, tightness, heaviness, burning, and other negative sensations.

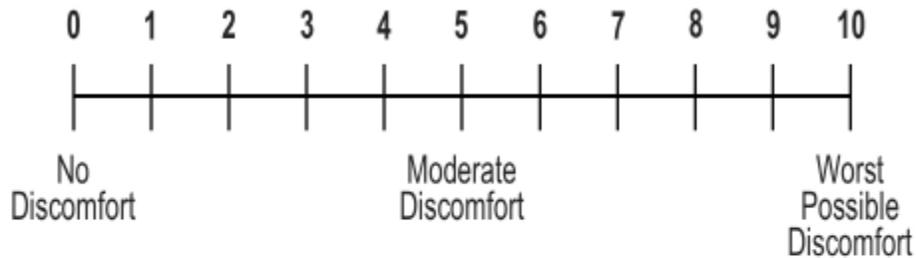
To be asked at 2 weeks & 4 weeks:

Place a vertical line on the following scales at the point that indicates the discomfort in or around your eyelids, or face over the past week. Discomfort includes feelings of pressure, tightness, heaviness, burning, and other negative sensations.

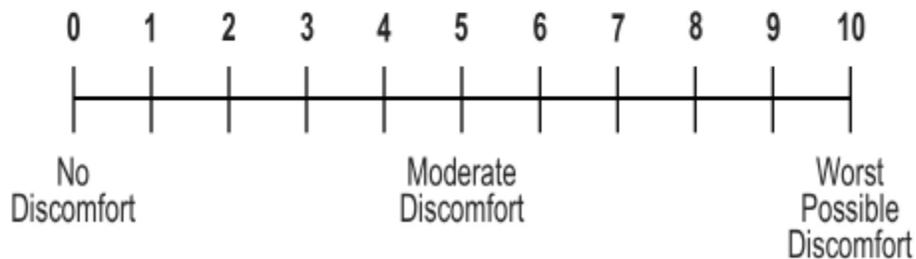
To what degree do you feel the discomfort is due to the treatment you received as part of this study:

- 1) Entirely due
- 2) Partially due
- 3) Not due

Right Eye



Left Eye



To be asked at Baseline

Using the faces below as a guideline, place a vertical line on the following scales at the point that indicates the intensity of pain in or around your eyelids, or face over the past week.

To be asked immediately post-procedure:

Using the faces below as a guideline, place a vertical line on the following scales at the point that indicates the intensity of pain in or around your eyelids, or face during the procedure.

To be asked at 2 weeks & 4 weeks:

Using the faces below as a guideline, place a vertical line on the following scales at the point that indicates the intensity of pain in or around your eyelids, or face over the past week.

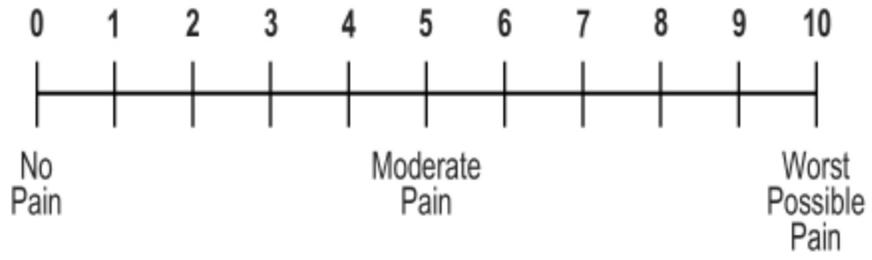
To what degree do you feel the discomfort is due to the treatment you received as part of this study:

- 1) Entirely due
- 2) Partially due
- 3) Not due

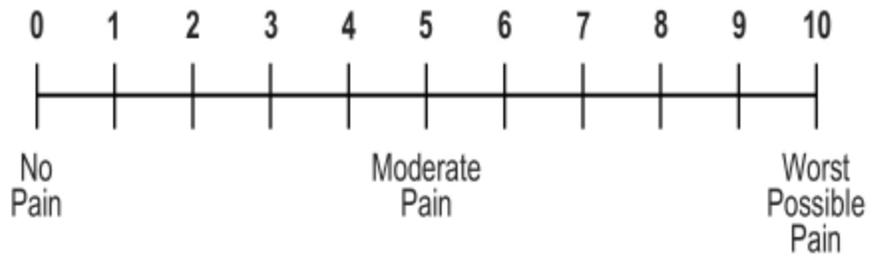


Pain Scale

Right Eye



Left Eye



APPENDIX D: ADVERSE EVENT DEFINITIONS

Adverse Event (AE)	<p>Any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational drug or device, or other protocol-imposed intervention, regardless of the suspected cause</p> <ul style="list-style-type: none"> • Chronic but stable conditions or diseases are not AEs • Changes in a chronic condition or disease consistent with natural disease progression are not AEs
Serious Adverse Event (SAE)	<p>SAEs are AEs that:</p> <ul style="list-style-type: none"> • Led to death • Led to serious deterioration in the health of the patient that resulted in: <ul style="list-style-type: none"> ○ A life-threatening illness or injury ○ A permanent impairment of a body function ○ In-patient or prolonged hospitalization ○ Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
AE Severity	<p><i>Mild:</i> Awareness of sign or symptom, but easily tolerated <i>Moderate:</i> Discomfort enough to cause interference with usual activity <i>Severe:</i> Incapacitating with inability to work or do usual activity</p> <ul style="list-style-type: none"> • Severity is irrespective of procedure relationship or seriousness of the event • Severity is a measurement of intensity but not seriousness; thus, a severe reaction is not necessarily a SAE
AE Expectedness	<p><i>Anticipated:</i> The nature, severity, or degree of incidence was previously described, including those anticipated events listed in the protocol and/or IFU/User Manual of the device. <i>Unanticipated:</i> The nature, severity, or degree of incidence was not previously described.</p>
AE Relatedness	<p><i>Not related:</i> Clearly related to other factors such as subject’s clinical state, therapeutic interventions, concomitant disease or therapy administered to the subject, and does not follow a known response pattern to the procedure <i>Related:</i> Follows a reasonable, temporal sequence from the time of procedure and/or follows a known response pattern to the study procedure and cannot be reasonably explained by other factors such as subject’s clinical state, therapeutic interventions, or concomitant therapy administered to the subject</p>