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STUDY OF THE TEARCARE® SYSTEM IN DRY EYE DISEASE

PROTOCOL ID #:	06001
CURRENT REVISION:	C
REVISION DATE:	July 30, 2018
SPONSOR:	Sight Sciences, Inc. [redacted]

Agreement of Principal Investigator

I, _____ agree to conduct this trial in accordance with this clinical protocol and any amendments.

_____ _____
Signature Date

_____ _____
Center Name City, State, Country

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical investigation. It must be held confidential and maintained in a secure location.

Revision History

Revision	Date	ECO
A	June 5, 2018	2457
B	July 2, 2018	2485
C	July 30, 2018	2511

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1 PROTOCOL SYNOPSIS

Protocol Title	Study of the TearCare® System in Dry Eye Disease
Protocol ID Number	06001
Study Device	TearCare® System
Primary Objective	To evaluate the safety and effectiveness of a single TearCare® procedure to treat adult patients with dry eye disease.
Study Design	Prospective, single-arm, exploratory treatment study
Primary Effectiveness Endpoint	• Tear Break-Up Time (TBUT)
Secondary Effectiveness Endpoints	• Ocular Surface Disease Index (OSDI) score • Corneal staining scores • Conjunctival staining scores • Total Meibomian Gland Secretion Score
Safety Endpoints	• Device-related adverse events • Best spectacle corrected visual acuity (Snellen)
Inclusion Criteria	1. At least 22 years of age 2. Reports dry eye symptoms within the past 3 months 3. Reports having to use artificial tears or lubricants regularly over the past month to relieve dry eye symptoms. 4. OSDI Score of ≥23 5. TBUT of ≤7 seconds in both eyes 6. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤15 in each eye. 7. At least 15 glands in each lower eyelid should be expressible, with a sterile cotton swab, at the slit lamp. 8. Best spectacle corrected visual acuity of 20/100 or better in both eyes. 9. Willing and able to comply with the study procedures and follow-up 10. Willing and able to provide informed consent 11. English-speaking

Exclusion Criteria	1. Any active, clinically significant ocular or peri-ocular infection or inflammation 2. Recurrent clinically significant eye inflammation, other than dry eye, within 3 months prior to enrollment 3. History of eyelid, conjunctiva or corneal surgery (including refractive surgery) within the past year. In addition, subjects with any history of the following are excluded: chalazion surgery, surgery on the tarsal conjunctiva, radial keratotomy (RK), complicated blepharoplasty, lid reconstruction, or significant complications post-refractive surgery. 4. Any office-based dry eye treatment (e.g. IPL, thermal pulsation [Lipiflow], etc.) within 12 months prior to enrollment. In addition Blephex or debridement within 3 months prior to enrollment is an exclusion. 5. Meibomian gland expression within 6 months prior to enrollment. In addition, any history of meibomian gland probing is an exclusion. 6. In the clinical judgement of the investigator, meibomian glands have significant capping, atrophy, or are unable to be expressed, digitally or with a sterile cotton swab. 7. Contact lens use within the past 2 weeks (Subjects must refrain from wearing contact lenses for the duration of the study.) 8. Use of TrueTear device within the past 2 weeks (Subjects must refrain from using the TrueTear device for the duration of the study.) 9. History of Ocular Herpes Simplex or Ocular Herpes Zoster 10. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy, etc.) 11. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, notching of lid margin, distichiasis, trichiasis) 12. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded. 13. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area 14. Ocular trauma within 3 months prior to enrollment 15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis 16. Known history of diminished or abnormal facial, periocular,

Exclusion Criteria (continued)	ocular or corneal sensation 17. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea 18. Punctal occlusion or punctal plug placement within 30 days prior to enrollment 19. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.) 20. Allergies to silicone tissue adhesives 21. Use of Restasis or Xiidra within 60 days prior to enrollment. Subject must also be willing to remain off these drugs for the duration of the study. 22. Use of antihistamines (oral or topical) within 10 days prior to enrollment. Subject must also be willing remain off antihistamines for the duration of the study. 23. Subject is currently on a systemic medication(s) (other than anti-histamines) that is known to cause ocular dryness (e.g. diuretics, anti-hypertensives, anti-depressants, hormone therapy) and whose dose of this medication(s) has not been stable within 30 days prior to enrollment. There must be no anticipated adjustments to the dose of these medications for the duration of the trial. 24. Subject has taken or is currently taking Accutane 25. Subject requires chronic use (i.e. for any portion of the study) of topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications or who has been on any of these medications within 30 days prior to enrollment 26. Subject is currently using Retin A or Latisse 27. Participation in another ophthalmic clinical trial within one year prior to enrollment. Subject must also be willing to refrain from another ophthalmic study for the duration of the study. 28. Co-existing condition, either ocular or non-ocular that, in the judgement of the investigator could affect the safety or effectiveness of treatment or the compliance of the subject to the protocol. Subjects who are pregnant or nursing or have active, wet macular degeneration are excluded.
Number of Subjects	Up to 30

Number of Sites	2-3
Study Duration for Each Subject	1 month
Schedule of Visits	Baseline, Week 1, 1 Month
Treatments	TearCare procedure at Baseline

2 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of a single TearCare® procedure to treat adult patients with dry eye disease.

3 BACKGROUND AND JUSTIFICATION FOR THE STUDY

Dry Eye Disease (DED) is a chronic eye condition that can cause an array of symptoms in patients, ranging from periodic ocular discomfort to severe corneal inflammation, scarring, and vision loss.[1,2] Approximately 1/3 of patients visiting their eye doctor suffer from dry eye. The prevalence of dry eye disease increases with age, especially in postmenopausal women. It is estimated that dry eye disease affects more than 7 million Americans older 40 years of age[1], and approximately 1 million to 4 million Americans between 65 to 84 years of age.[3]

Each year in the U.S., billions of dollars are spent on topical lubricants, medications, tear duct occlusions, and other treatments to control the chronic condition of dry eye disease. Yu et al reported that the average annual cost of managing a patient with dry eye was $783 (range $757 – 809) from the payers' perspective.[4] When adjusted to the prevalence of DED nationwide, the overall burden of DED on the US healthcare system was estimated to be $3.84 billion. Moreover, there is a great cost to society in terms of decreased productivity due to the symptoms of dry eye. Yu, et al estimated the societal cost to be $11,302 per patient and $55.4 billion to the US society overall.[4] Essentially, not only do dry eye patients directly suffer, but there is also a burden to healthcare, employers, and society.

Historically, dry eye disease has been categorized into one of two forms, aqueous tear deficiency and evaporative tear deficiency. The current understanding is that evaporative dry eye is more common than aqueous deficient dry eye.[5] However, because the symptoms of aqueous-deficient dry eye are difficult to differentiate from those of evaporative dry eye, it is often impossible to truly separate patients into

[1] The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop. Ocul Surf. 2007;5:75–92.

[2] Lemp MA, Crews LA, et al. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study. Cornea. 2012: 31: 472-478.

[3] Fiscella RG. Understanding dry eye disease: a managed care perspective. Am J Manag Care 2011; 17 Suppl 16:S432-9.

[4] Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea 2011;30(4):379-87.

[5] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tusbota K, Stapleton F. TFOS DEWS II Definition and Classification Report. The Ocular Surface 2017;15:276-283.

distinct groups.[6] In fact, AAO guidelines state that these conditions coexist in the majority of the patients with the disease.[7]

In terms of the mechanism of action for dry eye disease, the International Dry Eye Workshop (DEWS)[1] explained that tear hyperosmolarity and the symptoms of dry eye result from water evaporation caused by low aqueous tear flow and/or excessive evaporation. This reduced, concentrated tear volume, in turn results in further inflammation and tear film instability creating a vicious cycle. The DEWS report concluded the following: "Since both aqueous tear deficiency and increased evaporative tear loss occur in most cases of dry eye disease and are linked by common pathogenetic mechanisms, expert clinicians are increasingly basing treatment decisions on an assessment of severity rather than discrete deficiencies."[8]

Normal tears coat the ocular surface and perform many functions, including lubrication of the ocular surface, protection from infection, nourishing the ocular surface cells, and providing an optically clear surface to properly refract light. Tears consist of three layers:

1. An underlying mucin layer which acts as a wetting agent to spread tears uniformly on the ocular surface to prevent beading or irregularity;
2. An aqueous layer to maintain an optically clear medium and to keep the ocular surface moist and healthy; and
3. A superficial lipid layer to retard evaporation of the aqueous layer.

When any of these layers is disturbed, tears may lose their protective and optical properties leading to a constellation of symptoms, a cascade of inflammatory processes, and the vicious cycle of dry eye.

With the most recent etiologies of dry eye disease in mind, multiple standard-of-care, therapeutic approaches are employed:

1. Supplementation of the tear film with artificial tears to address evaporation and maintain tear volume
2. Use of warm compress and lid massage to improve lipid production and flow on the tear film
3. Use of immunosuppressives (cyclosporine, corticosteroids, lifitegrast) to reduce inflammation

[6] Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthal-mol Vis Sci 2011;52:2050-64

[7] American Academy of Ophthalmology's Dry Eye Syndrome Preferred Practice Pattern 2013.

[8] Lemp M, Foulks, G. The Definition & Classification of Dry Eye Disease: Guidelines from the 2007 International Dry Eye Workshop. April 2008. http://www.tearfilm.org/pdfs/OM%20-%20Definition%20&%20Classification.pdf

4. Placement of punctal plugs to address evaporation and maintain tear volume

Recently, a great deal of evidence suggests that obstruction of the meibomian glands, which are the glands on the eyelid that produce the lipid layer of tears, is strongly associated with dry eye disease.[9,10,11,12] The DEWS II report states that meibomian gland disease is considered the leading cause of dry eye in clinic and population-based studies.[13] As these glands become either inflamed or obstructed, their ability to supply the essential lipids to the ocular surface is diminished. This, in turn, leads to rapid evaporation of tears and thus to the signs and symptoms of dry eye disease.[14] When this occurs, it can result in ocular discomfort and, in many cases, ocular surface disorders that can affect the quality of vision and/or visual acuity.

Sight Sciences has developed the TearCare™ System to provide a safe and effective treatment for the signs and symptoms of dry eye disease. The System is designed to conform to the eyelids to deliver controlled, precise heat to the tarsal plates and underlying meibomian glands of the eyelids for 15 minutes in the monitored setting of an ophthalmologist or optometrist office. In addition to blinking during TearCare™ treatment to naturally express melted meibum, the physician then uses physician gland clearing devices to further express the meibomian glands manually immediately (i.e., within 3 minutes) following the eyelid heat treatment.

The objective of this study is to evaluate the safety and effectiveness of the TearCare System to treat the signs and symptoms of dry eye disease.

[9] Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea. 2008;27: 1142–1147.
[10] Korb DR, Henriquez AS. Meibomian gland dysfunction and contact lens intolerance. J Am Optom Assoc. 1980;51:243–251.
[11] Blackie CA, Korb DR, Knop E, et al. Nonobvious obstructive meibomian gland dysfunction. Cornea. 2010;29:1333–1345.
[12] Maskin SL. Intraductal meibomian gland probing relieves symptoms of obstructive meibomian gland dysfunction. Cornea. 2010;29: 1145–1152.
[13] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tusbota K, Stapleton F. TFOS DEWS II Definition and Classification Report. The Ocular Surface 2017;15:276-283.
[14] Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf. 2004;2:149–165.

4 DESCRIPTION OF DEVICE

4.1 CURRENT INDICATION FOR USE

The TearCare System is a Class II exempt device that is listed with the FDA. It is commercially available in the US. It is currently labeled with the following indication for use:

> "The TearCare® System is indicated for the application of localized heat when the current medical community recommends the application of a warm compress to the eyelids. Such applications would include Meibomian Gland Dysfunction (MGD), Dry Eye, or Blepharitis."

4.2 DEVICE DESCRIPTION

The TearCare System is designed to deliver controlled, precise heat to the tarsal plates and underlying meibomian glands of the eyelids for 15 minutes, followed immediately by manual mechanical meibomian gland expression. The TearCare procedure takes place in the monitored setting of an ophthalmologist or optometrist office.

The Sight Sciences' TearCare System is comprised of the following components:

- iLid™ Devices
- SmartHub™ Kit, including SmartHub Nest, and charging adapter
- Express™ Forceps

The 4 iLid devices are custom designed to conform to the tarsal plate of each respective eyelid so that patients can blink normally throughout the treatment and naturally express melted meibum with every blink. Immediately following the thermal treatment (i.e., within 3 minutes after treatment), the physician uses the forceps to further express the meibomian glands manually to maximize the evacuation of melted meibum.

The iLid Devices, shown below in Figure 1, are single-use, flexible, sensor-controlled devices that adhere to each of the 4 eyelids. They contain flexible circuits, sensors and a microprocessor which provide accurate and precise thermal energy to the eyelids to melt oil in the meibomian glands (meibum). Medical grade adhesive on the skin-facing surface of the iLid devices allow them to be affixed to the external surface of the eyelids during the procedure and easily removed at the end of the procedure. The flexibility of the iLid devices permit them to remain attached to the eyelids throughout the procedure while patient blinks normally.

The iLid devices are connected to the TearCare SmartHub via a cable. The TearCare SmartHub, shown below in Figure 2, delivers electrical energy to the iLid Devices, which is subsequently converted into thermal energy. Embedded software and a closed loop sensor system ensures that the temperature delivered at the eyelids is maintained within a precise range (41 to 45˚C). A control button on the center of the SmartHub is used to turn the system on and off and to initiate or discontinue the TearCare session. Two buttons, "+" and "-", on the left side of the face of the SmartHub allow the user to adjust the temperature to a level that is comfortable for the patient. The current warmth setting is indicated by the warmth level indicators between the two adjustment buttons. The SmartHub also has a display on the right side of its face that indicates how much time is left in the session. The TearCare SmartHub is battery operated, with a built-in battery, and is recharged by placing it on the charging nest.

The Express Forceps (shown in Figure 3 below) is a single-use, sterile devices that are designed to facilitate manual expression of the meibomian glands after the application of heat by the TearCare iLid devices.

Figure 1: iLid Devices applied to the Eyelids

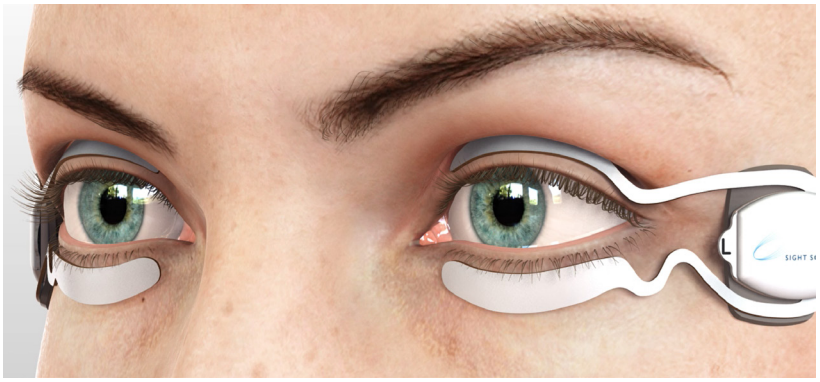


Figure 2: TearCare SmartHub

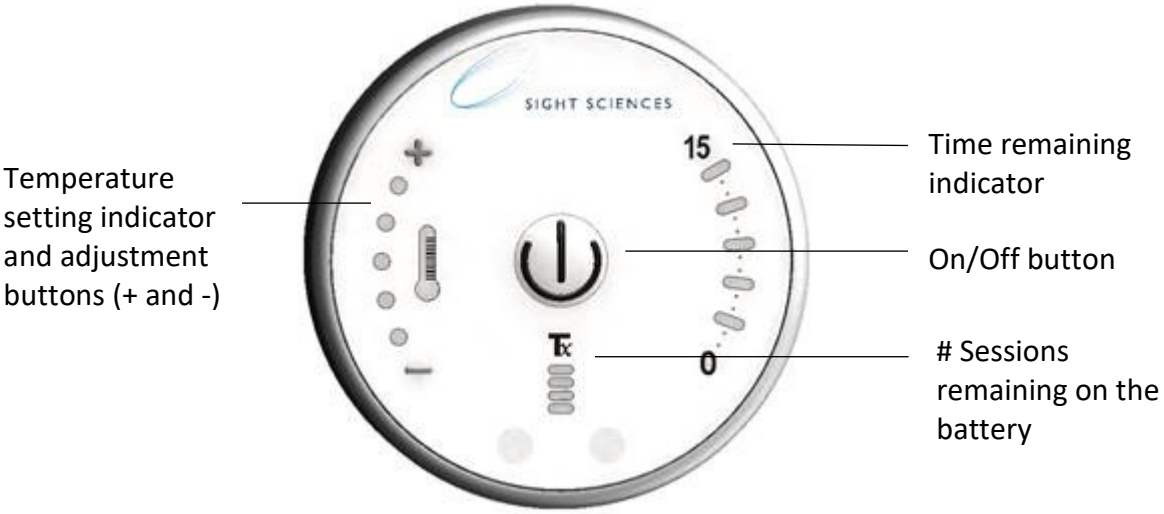
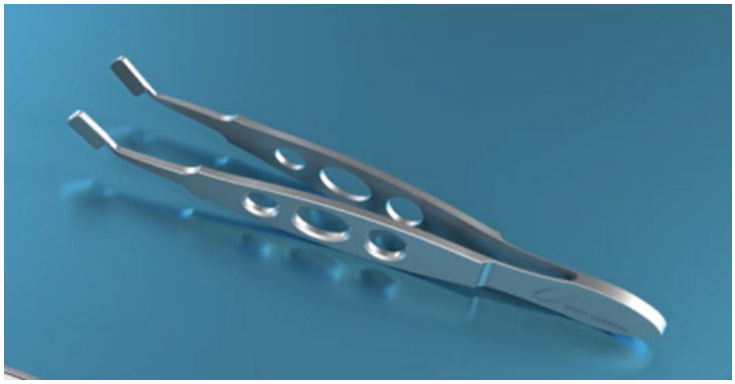


Figure 3: Express Forceps



To use the System, the flexible iLid devices are applied to the external surface of the upper and lower eyelids of the patient (Figure 1). The iLid devices are then connected to the TearCare SmartHub. When the SmartHub is turned on and the physician initiates the procedure, the TearCare System begins delivering heat to the eyelids. The system automatically and gradually increases the temperature over 2-3 minutes until it reaches the maximum set point temperature of 45°C. A complete TearCare session lasts 15 minutes.

The SmartHub has 5 temperature set points (ranging from 41 to 45°C), which allow the user to manually adjust the temperature up or down to a level that is comfortable for the subject. The set points can be adjusted at any time during the treatment session. Subjects can blink naturally during the session.

The temperature range for the TearCare System was selected based on research that has shown that meibum will melt at temperatures between 32 to 45°C, but obstructed glands may require higher temperatures, around 45°C, to effectively melt meibomian obstructions.[15,16,17] The maximum temperature and 15 minute treatment duration is also well below the time-temperature threshold at which heat contacting the skin will first show signs of cutaneous damage and edema, and is within the safety limits specified for medical electrical equipment.[18,19,20]

Immediately following the TearCare session (i.e. within 3 minutes), the clinician uses the forceps to manually express the meibomian glands in all four eyelids.

4.3 INSTRUCTIONS FOR USE

Instructions for Use are provided with each TearCare System.

4.4 TRAINING

Prior to the start of the study, investigators and study staff who have not been previously trained in the proper use of the TearCare System will be trained in its use. All study staff will receive training on the protocol and execution of the study according to applicable regulations and Good Clinical Practices.

5 PRIOR INVESTIGATIONS

5.1 PRECLINICAL TESTING

The TearCare System has been tested extensively on the bench and in clinical validation testing to demonstrate that it meets all specified safety and performance requirements. The following testing and analyses was performed:

- Thermal Requirements: Bench testing was performed to demonstrate that the TearCare System meets the operational temperature requirements (range 41-

[15] Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf. 2004;2:149-165.
[16] Bron AJ, Tiffany JM, Gouveia SM, Yokoi N, Voon LW. Functional aspects of the tear film lipid layer. Exp Eye Res 2004;78:347–60.
[17] Jones et al. TFOS DEWS II Management and Therapy Report. The Ocular Surface 2017;15:575-628.
[18] Moritz AR, Henriques FC. Studies of thermal injury: the relative importance of time and surface temperature in the causation of cutaneous burns. Am J Pathol 1947;23:695–720.
[19] Despa F, Orgill DP, Neuwalder J, Lee RC. The relative thermal stability of tissue macromolecules and cellular structure in burn injury. Burns 2005;31:568–77.
[20] Medical electrical equipment Part 1: General requirements for basic safety and essential performance (IEC 60601-1).

45°C). Clinical validation testing was also performed in 15 human subjects to measure the temperature at the inner and outer surfaces of the eyelid during operation of the System and at the surface of the cornea immediately following the treatment. The testing confirmed that the system meets temperature-related performance and safety specifications. No adverse events were observed.

- Software Functionality: Testing was performed to demonstrate that the software in the TearCare SmartHub and iLid Devices meet all software design requirements.
- Electrical Safety: Testing was performed to demonstrate that the System meets the electrical safety requirements specified in IEC 60601-1.
- Electromagnetic Compatibility: Testing was performed to demonstrate that the System meets the electromagnetic requirements specified in IEC 60601-1-2.
- Biocompatibility: All patient-contacting materials were reviewed to confirm that that they are biocompatible for short-term (<24 hours), skin contact.
- Mechanical Strength: Testing was performed to demonstrate that the system meets mechanical strength requirements.
- Shipping, Storage, and Shelf-Life Testing: Testing was performed to demonstrate that the TearCare System continues to function properly after being exposed to environmental and shipping conditions specified in ASTM D4169. In addition, accelerated aging testing was performed to demonstrate the iLid devices have a minimum shelf life of 6 months.

5.2 PREVIOUS CLINICAL EXPERIENCE

The TearCare System has been studied in a single center pilot study conducted in 2017. The results were published in *Clinical Ophthalmology*[21] and are summarized below.

Objectives

The objective of this study was to evaluate the clinical utility, safety, and effectiveness of the TearCare™ System compared to standardized warm compress therapy.

Subjects

Twenty-four (24) subjects with symptoms of dry eye in the past 3 months were enrolled. The average age was 67.6 ± 13.5 years (range 29.7 – 89.8 years). All subjects were female, white and not Hispanic or Latino. All subjects had a SPEED score ≥6 at the Baseline visit. All subjects had a Tear Break-up Time (TBUT) of <10 seconds in at least one eye at baseline and 72% (17/24) had a Schirmer 1 score (non-anesthetized) of ≤10 mm in at least one eye at the Baseline visit.

[21] Badawi D. A novel system, TearCare, for the treatment of the signs and symptoms of dry eye disease. Clinical Ophthalmology. 2018;12:683-694.

Methods

This was a prospective, single-center, randomized, parallel-group, clinical trial. Subjects with DED were randomized to either a single TearCare treatment conducted at the clinic or 4 weeks of daily warm compress therapy. The TearCare procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual expression of the meibomian glands. Warm compress therapy consisted of once daily application of the compresses to the eyelids for 5 minutes. Subjects were followed to 6 months post-treatment. The primary effectiveness endpoint was defined as change from baseline to 4 weeks for Tear Break-up Time (TBUT). Secondary effectiveness endpoints included meibomian gland assessment, corneal and conjunctival staining scores, and assessment of dry eye symptoms using validated questionnaires. Safety was evaluated by collecting device-related adverse events, intraocular pressure, and best spectacle-corrected Snellen Visual acuity.

Results

Twenty-four subjects were enrolled and completed 6 months follow-up. Data are summarized in Table 1 below.

At 1 month follow-up, TearCare subjects demonstrated an improvement from baseline in mean (± SD) TBUT of 11.7 ± 2.6 seconds compared with an average worsening of -0.3 ± 1.1 seconds for subjects in the warm compress group ($p<0.0001$). Significantly greater improvements in the change from baseline in meibomian gland scores, as well as corneal and conjunctival staining scores were observed in the TearCare group. Subjects in the TearCare group also showed significantly greater improvement in dry eye symptoms as measured by the three questionnaires.

No adverse events were reported in either group.

Table 1: TearCare System – Pilot Study Results (2017)

	TearCare (n=24 eyes, 12 subjects)			Warm Compress control (n=24 eyes, 12 subjects)		
	Baseline	**4 weeks**	**6 months**	**Baseline**	**4 weeks**	**6 months**
Tear Break-up Time (sec) – Mean (SD)	3.1 (0.8)	14.8 (2.6)	7.9 (1.5)	3.3 (1.0)	3.1 (0.8)	3.0 (1.0)
Dry Eye Symptom Questionnaires						
Total **OSDI** Score (0 to 100)	41.0 (18.4)	15.7 (12.2)	30.3 (15.1)	33.0 (19.9)	24.6 (15.2)	30.3 (15.1)
Total **SPEED** Score (0 to 28)	15.7 (5.2)	7.8 (3.5)	8.2 (6.0)	14.4 (3.8)	12.6 (3.3)	12.2 (4.0)
Total **SANDE** Score	64.9 (25.9)	40.2 (18.8)	45.9 (30.5)	55.9 (31.5)	57.5 (25.7)	62.1 (21.8)
Meibomian Gland Assessment						
Total Meibomian Gland Score (0 to 45)	6.3 (3.6)	41.0 (2.1)	31.5 (5.5)	9.0 (4.3)	8.2 (4.0)	9.4 (3.5)
# Glands Secreting Any Liquid (0 to 15)	0.8 (0.9)	14.6 (0.8)	11.5 (2.4)	1.3 (1.7)	1.3 (1.6)	1.7 (1.5)
# Glands Yield Clear Liquid (0 to 15)	0.0 (0.0)	11.4 (1.6)	5.4 (3.0)	0.3 (0.7)	0.0 (0.0)	0.1 (0.4)
Corneal Staining Score (0 to 15)	3.5 (1.8)	0.2 (0.4)	3.2 (2.6)	3.4 (2.9)	3.2 (2.6)	3.2 (2.8)
Conjunctival Staining Score (0 to 15)	3.7 (2.5)	0.1 (0.3)	0.3 (0.7)	3.0 (3.4)	4.1 (3.5)	3.2 (3.1)

Conclusions

The TearCare Group consistently showed a significant improvement between the baseline and 4 weeks follow-up for all outcome measures, whereas the Warm Compress group did not. For all outcome measures, the TearCare Group's mean change between baseline and 4 weeks follow-up was better than the Warm Compress group. These results were maintained out to 6 months.

This pilot study provided preliminary evidence of the safety and effectiveness of the TearCare device in relieving the signs and symptoms of dry eye.

6 STUDY ENDPOINTS

6.1 EFFECTIVENESS ENDPOINTS

The following endpoints will be assessed:

- **Primary effectiveness endpoint**
  - Mean Change from baseline in Tear Break-Up Time (TBUT)
- **Secondary effectiveness endpoints**
  - Mean Change from baseline in OSDI score[22]
  - Mean Change from baseline in the total Meibomian Gland Secretion Score[23]

[22] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118: 615-621.

[23] Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye 1991;5: 395–411.

- Mean Change from baseline in corneal staining scores
- Mean Change from baseline in conjunctival staining scores

6.2 SAFETY ENDPOINTS

Safety will be assessed by evaluating the following measures over time:

- Device-related adverse events (all adverse events will be recorded)
- Best spectacle-corrected visual acuity (Snellen)

7 STUDY DESIGN

This is a prospective, single-arm, exploratory treatment study. This is a post-market study intended to collect clinical data regarding the safety and effectiveness of the TearCare System. To reduce potential bias in the study, study staff performing the endpoint assessments will be independent of the clinician performing the TearCare procedure.

In this study, all subjects will receive the TearCare procedure. The TearCare procedure includes an in-office 15 minute treatment session with the TearCare System immediately (i.e. within 3 minutes) followed by manual expression of the meibomian glands using the Express Forceps. Subjects will receive one in-office TearCare procedure at the baseline visit and will then have follow-up visits at 1 week and 1 month.

This study will be conducted at 2-3 sites in the United States.

8 STUDY SELECTION CRITERIA

8.1 INCLUSION CRITERIA

For inclusion in this study, subjects must meet all of the following criteria:

1. At least 22 years of age
2. Reports dry eye symptoms within the past 3 months
3. Reports having to use artificial tears or lubricants regularly over the past month to relieve dry eye symptoms.
4. OSDI Score of ≥23
5. TBUT of ≤7 seconds in both eyes
6. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤15 in each eye.

7. At least 15 glands in each lower eyelid should be expressible, with a sterile cotton swab, at the slit lamp.
8. Best spectacle corrected visual acuity of 20/100 or better in both eyes.
9. Willing and able to comply with the study procedures and follow-up
10. Willing and able to provide informed consent
11. English-speaking

8.2 EXCLUSION CRITERIA

A subject who meets any of the criteria listed below (in either eye) will be excluded from the study:

1. Any active, clinically significant ocular or peri-ocular infection or inflammation
2. Recurrent clinically significant eye inflammation, other than dry eye, within 3 months prior to enrollment
3. History of eyelid, conjunctiva or corneal surgery (including refractive surgery) within the past year. In addition, subjects with any history of the following are excluded: chalazion surgery, surgery on the tarsal conjunctiva, radial keratotomy (RK), complicated blepharoplasty, lid reconstruction, or significant complications post-refractive surgery.
4. Any office-based dry eye treatment (e.g. IPL, thermal pulsation [Lipiflow], etc.) within 12 months prior to enrollment. In addition Blephex or debridement within 3 months prior to enrollment is an exclusion.
5. Meibomian gland expression within 6 months prior to enrollment. In addition, any history of meibomian gland probing is an exclusion.
6. In the clinical judgement of the investigator, meibomian glands have significant capping, atrophy, or are unable to be expressed, digitally or with a sterile cotton swab.
7. Contact lens use within the past 2 weeks (Subjects must refrain from wearing contact lenses for the duration of the study.)
8. Use of TrueTear device within the past 2 weeks (Subjects must refrain from using the TrueTear device for the duration of the study.)
9. History of Ocular Herpes Simplex or Ocular Herpes Zoster
10. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy, etc.)
11. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, notching of lid margin, distichiasis, trichiasis)
12. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded.
13. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area

14. Ocular trauma within 3 months prior to enrollment
15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis
16. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation
17. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea
18. Punctal occlusion or punctal plug placement within 30 days prior to enrollment
19. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.)
20. Allergies to silicone tissue adhesives
21. Use of Restasis or Xiidra within 60 days prior to enrollment. Subject must also be willing to remain off these drugs for the duration of the study.
22. Use of antihistamines (oral or topical) within 10 days prior to enrollment. Subject must also be willing remain off antihistamines for the duration of the study.
23. Subject is currently on a systemic medication(s) (other than anti-histamines) that is known to cause ocular dryness (e.g. diuretics, anti-hypertensives, anti-depressants, hormone therapy) and whose dose of this medication(s) has not been stable within 30 days prior to enrollment. There must be no anticipated adjustments to the dose of these medications for the duration of the trial.
24. Subject has taken or is currently taking Accutane
25. Subject requires chronic use (i.e. for any portion of the study) of topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications or who has been on any of these medications within 30 days prior to enrollment
26. Subject is currently using Retin A or Latisse
27. Participation in another ophthalmic clinical trial within one year prior to enrollment. Subject must also be willing to refrain from another ophthalmic study for the duration of the study.
28. Co-existing condition, either ocular or non-ocular that, in the judgement of the investigator could affect the safety or effectiveness of treatment or the compliance of the subject to the protocol. Subjects who are pregnant or nursing or have active, wet macular degeneration are excluded.

9 STUDY PROCEDURES

9.1 STUDY SCHEDULE

The Study Schedule is shown below in Table 2.

Table 2: Study Visit Schedule

Visit (Visit Window)	**Baseline** (Day 0)	**Wk 1** (Day 5-9)	**1 Mo** (Day 21 – 35)
Informed Consent	X		
Demographics, Ocular & Medical History	X		
Medication use	X	X	X
OSDI*	X	X	X
Best Spectacle corrected visual acuity (Snellen)*	X	X	X
Slit Lamp Exam*	X	X	X
Tear Breakup Time*	X	X	X
Corneal Staining*	X	X	X
Conjunctival Staining*	X	X	X
Meibomian Gland Secretion Scoring*	X	X	X
TearCare Treatment	X		
AE Assessment*	X	X	X
Lubricant Drops Log			X

* Endpoint assessment should be performed by an independent study staff who does not perform the TearCare procedure on study subjects.

9.2 NUMBER OF SUBJECTS AND DURATION OF FOLLOW-UP

Up to 30 subjects will be enrolled and treated in the study. All subjects will be followed for 1 month.

9.3 MATERIAL AND EQUIPMENT

A listing of general equipment and materials required at the investigational site for the study is provided below.

- TearCare System (including a SmartHub, SmartHub Nest, and charging adapter)
- TearCare iLid Devices and Physician Gland Clearing Devices
- Snellen Visual Acuity System
- Wratten filter (yellow)
- Meibomian Gland Evaluator (TearScience, Inc.)
- Fluorescein sodium strips or compounded fluorescein (0.5 – 2%) preservative-free ophthalmic solution
- Lissamine green strips
- 0-10µL & 20-200 uL micropipettes and sterile tips
- Microcentrifuge tubes
- Preservative-free sterile saline
- Proparacaine 0.5% or tetracaine 0.5% ophthalmic drops
- Akten® (lidocaine hydrochloride ophthalmic gel) 3.5% or equivalent

- Stopwatch
- Makeup remover wipes
- Sterile scissors

9.4 INFORMED CONSENT AND POINT OF ENROLLMENT

The IRB-approved informed consent will be presented and explained to each prospective subject by the investigator or a trained clinical professional. Once the subject has had ample time to read the consent form, has been informed of all aspects of the study, and has had an opportunity to ask questions, the subject will be given a choice to voluntarily confirm his or her participation in the study as documented by completion of the Informed Consent. After signing the Informed Consent and the HIPAA (Health Insurance Portability and Accountability Act) authorization, the subject can then proceed with the baseline visit. The subject has the right to withdraw from the study at any time without consequences, as indicated in the Informed Consent Document.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. Subjects are enrolled upon signing the ICD even if they subsequently fail to meet the eligibility criteria.

The principal investigator(s) must retain the original, signed written Informed Consent Document. A copy of the written Informed Consent Document must be given to the subject.

9.5 BASELINE VISIT

9.5.1 SCHEDULING THE BASELINE VISIT

Since dry eye drops and lubricants can affect the endpoint assessments, instruct subjects not to use any of these products within 2 hours of the Baseline visit.

9.5.2 BASELINE EXAMS AND QUESTIONNAIRES

After the subject has signed the informed consent form and agreed to participate in the study, the exams, tests and questionnaires listed in the Baseline column of Table 2 should be performed. Refer to Appendix A for instructions for performing the exams and administering the questionnaire.

At this visit, subjects should undergo the following tests and exams, performed in the order indicated below, to screen them for the study qualification and to record baseline data. Endpoint assessments (indicated with a *) should be performed by independent study staff who does not perform the TearCare procedure on study subjects.

1. OSDI Questionnaire
2. Demographics, medical and ocular history
3. Medication use: ocular and systemic
4. Best-spectacle corrected visual acuity*
5. Slit Lamp Exam*
6. Tear Breakup Time*
7. Corneal staining*
8. Conjunctival staining*
9. Meibomian Gland Secretion Scoring*

If, at any point during the visit the subjects fails to meet a subject selection criterion, then the visit can be terminated. Subjects who fail to meet all the selection criteria will be considered a screen failure and will be withdrawn from the study. Screen failures will not count toward the total enrolled and treated number of subjects.

NOTE: Questionnaire and exam data collected on subjects prior to enrollment as part of the routine clinical practice may be used to pre-screen patients for the study. However, once the subject signs the consent form and is enrolled in the study, these questionnaires and exams must be repeated following the protocol procedures.

After all required measurements have been obtained and it has been confirmed that the subject meets all the Subject Selection Criteria, then the subject will receive the TearCare procedure.

9.5.3 TEARCARE PROCEDURE

The TearCare procedure should be performed by a clinician who did not perform the Baseline endpoint assessments. Refer to the TearCare Instructions for Use for detailed instructions for operating the TearCare System.

1. Obtain a new set of iLid devices and a TearCare SmartHub with enough battery left for at least one procedure.
2. Wipe the subject's eyelids and temple with the makeup removal wipe provided by the Sponsor. Allow the skin to dry or pad dry with a tissue. Use care not to allow any of the wipe to get into the eye.
3. Place a pair of iLid devices on the subject's eyelids and affix the temple housing to the subject's temple. Use the clip to secure the cables behind the subject's head.
4. Connect the iLid devices to the SmartHub.
5. Inform the subject that the iLid devices will heat up very quickly once the TearCare procedure is started.

6. Start TearCare procedure. Subjects should be encouraged keep their eyes open and blink naturally during the TearCare procedure.
7. If the subject indicates the temperature is too hot, decrease the temperature set point to a setting that is comfortable for the subject.
8. Following the thermal portion of the TearCare treatment, remove the iLid devices from the subject and position the subject at the slit lamp to perform expression of the meibomian glands. Begin performing expression within 3 minutes of completion of the thermal portion of the procedure.
9. Apply 1 drop of proparacaine or tetracaine into each eye. Apply Akten® (lidocaine hydrochloride ophthalmic gel) 3.5% or equivalent into the lower eyelid fornices.
10. Using the Express Forceps, express the meibomian glands in all 4 eyelids using the following technique:
    a. Think of each eyelid as having 3 zones: nasal, central & temporal.
    b. For each zone, start at the fornix and work your way up to the margin.
    c. Position the forceps horizontal, parallel to the margin.
    d. Apply moderate continuous pressure and adjust based on the gland output.
    e. Perform a second pass on the same eyelid to further express the glands.
    f. After treating the lower and upper eyelids, repeat expression on all 4 lids to ensure complete expression.
    g. Should the subject experience discomfort, it is reasonable to apply additional topical anesthetic.
    h. The goal is to express each zone until the meibum coming out is clear. Typically, complete expression takes approximately 5 minutes/eye.

9.5.4 MANAGEMENT OF DRY EYE SYMPTOMS DURING FOLLOW-UP

During follow-up, if subjects require relief of their dry eye symptoms, they should only use Refresh® Plus drops. Other types of over-the-counter lubricants should not be used. Subjects should record their daily use of lubricants on the Lubricant Drop log.

Subjects **should not use** any other method of relieving dry eye symptoms, including any of the following:

- Warm compress
- Restasis or Xiidra
- Other dry eye treatments (e.g. Lipiflow, TrueTear, iLux, punctal plugs, etc.)
- Lubricants other than Refresh Plus

NOTE: If a subject had a punctal plug at the baseline visit and it falls out during the study, it should be replaced.

Review these instructions with subjects at the end of the Baseline visit and provide them with the Lubricant Drop log. They should complete the log each day and bring it back to the clinic at the 1 month follow-up visit.

9.6 FOLLOW-UP VISITS

Prior to the Visit: Reminder Call

Since dry eye drops and lubricants can affect the endpoint assessments, it is important to call subjects a few days before their follow-up visits to remind them that on the day of the Follow-up visit, they should not to use any of these products before the Follow-up visit.

Order of Procedures During the Follow-Up Visit

Follow-up exams should not be performed by the clinician who performed the TearCare procedure.

Follow-up procedures will be performed per the Study Schedule provided in Table 2 (page 25) and the methods included in Appendix A. Since certain tests/exams can impact the ability to perform other tests/exams, the following tests and exams should be performed in this order:

1. OSDI
2. Best spectacle-corrected visual acuity
3. Slit Lamp Exam
4. Tear Breakup Time
5. Corneal staining
6. Conjunctival staining
7. Meibomian Gland Secretion Scoring
8. Assessment of adverse events

The following activities can be performed in any order:

- Medication Use
- Collection of Lubricant Drop Log (1 month visit only)

9.7 WITHDRAWAL AND DISCONTINUATION

All subjects have the right to withdraw at any point during the treatment without prejudice. The investigator can discontinue any subject at any time if continued participation in the study would result in harm to the subject. All efforts should be

made by the investigator to retain the subject in the study. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) the subject discontinued the study. The reason must be recorded in the subject's file and on the Study Exit Form.

10 ADVERSE EVENTS (AEs)

Adverse Events are defined below. Adverse events that occur in the eye during the trial, whether they are considered to be device related or not, must be documented in the subject's records. Date of the event, its severity, treatment (if any) and the assessed relationship of the event to the study device will be recorded on the Adverse Event Form. Conditions which exist at the time the subject is enrolled do not need to be recorded as adverse events unless they increase in severity during the study.

10.1 DEFINITIONS OF AE, SAE, SADE, USADE

Adverse Event	Any untoward medical occurrence in a subject who has been treated with the device that does not necessarily have causal relationship with the treatment.
Adverse Device Effect	Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is possibly related to the study device.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • Results in death • Is life-threatening • Requires in-patient hospitalization or prolongs existing hospitalization • Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure • Sight threatening
Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). Any sight-threatening

	event, whether listed in the protocol or not, is considered to be reportable as a UADE

10.2 LIST OF ANTICIPATED POTENTIAL ADVERSE EVENTS

Anticipated potential adverse events include those that might reasonably be expected to occur in this study because they are associated with dry eye disease, the risk analysis for TearCare System (albeit remote likelihood), study testing methods or potential risks associated with warm compresses and lid massage.

- Burn, erythema, or swelling of the eyelids
- Conjunctival injection (Moderate or severe)
- Conjunctival abrasion
- Corneal abrasion
- Corneal deformation
- Allergic or inflammatory reaction to medical adhesive on the iLid device
- Formation of a chalazion or stye
- Loss in BSCVA of 2 lines or greater from baseline BSCVA
- Increased discomfort or pain of ocular surface (grittiness, foreign body sensation, etc.)
- Discomfort or pain of eyelids or orbit: Transient discomfort or pain during the TearCare procedure is not considered an adverse event. Persistent pain or discomfort may represent an adverse event, if judged so by the investigator.

10.3 REPORTING ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

Identification, collection and reporting of adverse event information is the responsibility of the principal investigator. The investigator records the date of the event, its severity, treatment (if any) and the assessed relationship of the event to the study device on the Adverse Event Case Report Form (AE CRF).

Any ocular-related **serious adverse event** (SAE) should be reported to the study sponsor within one working day of learning of the event. Non-ocular-related SAEs should be

reported to the study sponsor within two working days of learning of the event. Email the AE CRF to [redacted].

Any **unanticipated adverse device effects (UADE)** must be reported to the following two entities:

1. The study sponsor – Within one working day of the investigator first learning of the event, e-mail the AE CRF to [redacted]; and
2. The reviewing IRB – As soon as possible, but no later than 10 working days after the investigator first learns of the event, report per the IRB's instructions.

The sponsor will conduct an evaluation of unanticipated adverse device effects. If the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, parts of the investigation presenting risks will be terminated. Termination will occur no later than 5 working days after the sponsor makes such a determination and no later than 15 working days after the sponsor first received notice of the effect.

11 RISK-BENEFIT ANALYSIS

11.1 ANTICIPATED CLINICAL BENEFITS

The TearCare™ procedure will be performed with the aim of reducing the signs and symptoms of dry eye. The goal of the procedure is to provide a safe, reproducible, and effective treatment for dry eye disease, a disease for which there is an unmet need for effective therapies.

11.2 ANTICIPATED ADVERSE DEVICE EFFECTS

Anticipated adverse effects associated with the TearCare System have been described above in Section 10.2.

11.3 RESIDUAL RISKS ASSOCIATED WITH THE TEST DEVICE, AS IDENTIFIED IN THE RISK ANALYSIS REPORT

Sight Sciences believes that there are no Intolerable residual risks from this non-invasive, controlled heat treatment device that can be easily and quickly removed by the subject or by the supervising ophthalmologist, in the event of a complication during a TearCare treatment session.

11.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

All anticipated study risks are listed in Section 10.2.

11.5 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

It is anticipated that there will be no interactions with concomitant medical treatments.

11.6 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

The major risks to the subjects and the steps taken to control or mitigate them are described below:

1. Overheating of the eyelids: All TearCare treatments will be done in the investigator's office under direct supervision of the investigator. The device delivers heat to the eyelids at a temperature ranging from 41-45°C. This temperature range was selected because it is both safe for eyelid heating and effective for melting obstructions in the meibomian glands.[24,25,26,27] The user can adjust the temperature up or down to a level that is comfortable, and may also shut off the System at any time if it is too uncomfortable or painful. In addition, the TearCare System continuously monitors and regulates the temperature at the tissue-contacting surface of the iLid devices and has been designed to not exceed the maximum allowable temperature.

2. Corneal abrasion: If the iLid devices are not positioned properly or come loose during the treatment, there is the potential for a corneal abrasion. To mitigate this, the supervising physician will apply the strips to the subject and will monitor their position during the treatment to ensure they remain in place and secure.

   In addition, there is the possibility of corneal abrasion or abrasion of the eyelid surface during expression of the meibomian glands. To reduce the chance of abrasion, the forceps have been designed with smooth surfaces (i.e. no rough edges) and only trained users will perform expression.

[24] Lane SS, DuBiner H, Epstein RJ, et al. A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. Cornea. 2012: 31 : 396-404

[25] Blackie CA, Solomon JD, Greiner JV, Holmes M, Korb DR. Inner Eyelid Surface Temperature as a Function of Warm Compress Methodology. Optom Vis Sci 2008;85:675-683.

[26] Moritz AR, Henriques FC. Studies of thermal injury: the relative importance of time and surface temperature in the causation of cutaneous burns. Am J Pathol 1947;23:695–720.

[27] Medical electrical equipment Part 1: General requirements for basic safety and essential performance (IEC 60601-1).

3. Worsening of dry eye symptoms: It is possible that subjects will experience a worsening of dry eye symptoms during the study. Subjects will undergo a complete eye exam at each visit and if any untoward or worsening signs of ocular surface disease are observed, they will be treated appropriately.

In addition to the above, the following mitigation steps have also been taken to reduce the risks in this study:

- The device has been tested to demonstrate that it meets performance and safety specifications, as described in Section 5.1.
- Instructions for Use are provided with each device.
- The clinician using the device will be trained in how to safely and correctly apply and remove the iLid devices, and operate the TearCare System.

12 STATISTICAL CONSIDERATIONS

12.1 HYPOTHESIS

This exploratory study is not a hypothesis-driven study.

12.2 SAMPLE SIZE CALCULATION

Given that this is not a hypothesis-driven study, no sample size was calculated for the study. A sample size of up to 30 subjects was chosen for the study as a reasonable number of subjects for this exploratory study to evaluate of the safety and effectiveness of the TearCare System.

12.3 PASS/FAIL CRITERIA

No pass/fail criteria are defined for the study.

12.4 EVALUABILITY

All subjects on whom the TearCare device is attempted will be considered evaluable for the safety analysis. All eyes that have at least one follow-up visit and have no major protocol deviations will be evaluable for the per protocol analysis.

12.5 ANALYSIS POPULATIONS

The per-protocol analysis population includes all subjects who have at least one post-treatment visit and have no major protocol deviations, including specifically no use of dry-eye medications (Xiidra, Restasis). The primary and secondary endpoint analyses will be carried out on the per-protocol population. The primary analysis population will be per-protocol.

12.6 SUBJECT ACCOUNTABILITY

A complete accounting of subjects by visit will be provided, including reasons for dropout, if known.

12.7 STATISTICAL DESIGN, METHOD & ANALYTICAL PROCEDURES TO BE USED

Only basic descriptive statistics will be used to analyze data from the study.

12.8 INTERIM ANALYSIS AND EARLY TERMINATION CRITERIA

No interim analysis or early termination criteria are planned for this study.

12.9 DEVIATION FROM THE STATISTICAL PLAN

Any deviations from the statistical plan will be noted in the final report.

13 MONITORING PROCEDURES

Sight Sciences or contract research organization (CRO) personnel will monitor the study in a manner consistent with FDA regulations, good clinical practices and the clinical research standards adopted by Sight Sciences. Study monitoring will involve the following elements:

- Site Qualification: For sites that have not already been qualified for another Sight Sciences study, Sight Sciences or CRO personnel will meet with investigators and clinical study staff prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.

- Site Initiation: Sight Sciences or CRO personnel will meet with the investigator(s) and clinical study staff when the site is ready to begin enrolling subjects in order to train them in how to properly select subjects, perform the study procedure, and record study data. This visit will include, but not be limited to a review of the following:
  - Detailed review of the protocol
  - Informed consent procedures
  - Instruction in how to use the TearCare System
  - Records and reports
- Interim Monitoring: Due to the small sample size and one month study duration, interim monitoring may not be required. Sight Sciences or CRO personnel may visit the clinical site during the study to review charts and to perform source document verification, to ensure proper adherence to the study protocol, and to review regulatory documents.
- Study Closure: At the conclusion of the trial there will be a study closure visit during which several actions, including but not limited to the following, will be performed:
  - A final inspection of the study binder
  - Accountability and return of all devices and study materials to the sponsor
  - Discussion of record retention requirements with the investigator
  - Close-out notification to the IRB

14 DATA AND QUALITY MANAGEMENT

All study-related data will be recorded on Case Report Forms. When subjects are enrolled in the study, they will receive a unique study identifier, which will be used to identify them on all Case Report Forms. The Enrollment log containing the subject identifying information and the subject study id will be maintained under the investigator's control at all times. No subject-identifying information will leave the site.

14.1 DATABASE MANAGEMENT

Data Management will be performed by Sight Sciences who will create a database or spreadsheet in which the study data will be entered.

14.2 CONFIDENTIALITY

All medical records associated with the clinical investigation will be made available for review by Sight Sciences personnel, its contract research organization (CRO) and

governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area at the investigator's facility, the CRO, the data management firm and at Sight Sciences, Inc.

14.3 SOURCE DATA AND CASE REPORT FORMS

Data will be collected directly on the study worksheets provided by the sponsor and these study worksheets will serve as the source data.

Source data and study worksheets are to be maintained at the site in the subject records or in the medical records. All entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. All source documents must be completed and signed by the authorized study personnel (e.g., study coordinator). No "white-out" is to be used on the source documents.

14.4 RETENTION PERIOD

Clinical sites are to retain any and all clinical trial material (documentation, photographs, etc.) for a period of two years from the date the marketing application is approved or two years after the investigation has been discontinued, or as directed by their institutional document retention requirements, whichever is the longest. After that time, the items must be returned to Sight Sciences for archiving. Unused medical devices are to be returned to the sponsor at the conclusion of the enrollment period.

15 PROTOCOL MODIFICATIONS AND DEVIATIONS

Protocol modifications may occur during the study. Each will be approved by the sponsor before implementation. Each will undergo Institutional Review Board (IRB) review and approval, as necessary.

Any deviations from this protocol intended to protect the life or physical well-being of a subject in an emergency are to be reported to Sight Sciences, Inc. as well as the IRB as soon as possible, and no later than 5 working days after the emergency occurred.

All protocol deviations will be documented using the Protocol Deviation form.

16 DEVICE FAILURES AND MALFUNCTIONS

All device failures or malfunctions should be recorded on the Device Deficiency Form and reported to Sight Sciences Customer Service [redacted]

If the TearCare procedure cannot be completed due to a product failure or malfunction, the procedure may be rescheduled for a different day. Every effort should be made to reschedule the procedure within the next 7 calendar days of the Baseline visit.

17 ETHICAL CONSIDERATIONS

17.1 DECLARATION OF HELSINKI

This study shall be conducted in accordance with the Declaration of Helsinki (Appendix B).

17.2 INSTITUTIONAL REVIEW BOARDS (IRB)

The study shall not begin at a site until approval has been obtained from the reviewing IRB. It is the Investigators' responsibility to obtain and maintain written approval of the study protocol and Informed Consent documents from the appropriate IRB. It is also the Investigators' responsibility to notify that body about any amendments to these documents and to follow the IRBs rules regarding the reporting of Adverse Events and Protocol Deviations related to the device and/or this study. Copies of all written approvals (identifying the study, the submitted and approved documents and the date reviewed) and the approved versions of the documents must be provided to Sight Sciences or its CRO.

The Investigators must file all correspondence with the IRB and forward copies of such correspondence to Sight Sciences.

17.3 INFORMED CONSENT FORM (ICF)

An Informed Consent template that covers all protocol procedures and follows GCP Guidelines will be prepared by Sight Sciences and made available to each Investigator. The Investigator may adapt these templates to the requirements of the local IRB and of the institution where the study is conducted, but any revisions made to the ICF must be submitted to the sponsor for review prior to submission to the IRB. A copy of each IRB-approved ICF version is to be made available to Sight Sciences and its CRO. The approved, IRB-stamped ICF is to be kept in its full length in the study Regulatory Binder.

Original, signed ICFs are to be maintained in the subject's study records and must be made available for monitoring review.

17.4 PUBLIC LISTING OF STUDY

The study will be listed on the NIH website www.clinicaltrials.gov.

18 STUDY ADMINISTRATION

18.1 DEVICE ACCOUNTABILITY

With each shipment of study devices, Sight Sciences will include a Packing List that will give the amount shipped and the lot numbers. This packing list must be reconciled by the investigational site with the contents of the shipment and then recorded on the Device Accountability Logs (these logs are contained within the regulatory binder at the site). All study products at the site must be stored in a secured/locked area. When study devices are used, returned or disposed of, their disposition (including the disposition and date of disposition) must be recorded on the Device Accountability log.

Device reconciliation activities will also be conducted periodically in conjunction with site monitoring visits. The investigator must maintain accurate records of the receipt and disposition of all devices shipped by Sight Sciences.

18.2 EARLY TERMINATION OR SUSPENSION OF AN INVESTIGATION

Sight Sciences may terminate the study, in which case the investigators and associated IRBs will be notified in writing. Possible reasons for study termination include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the study subjects implanted with the device
- Inability to enroll the study in a reasonable amount of time
- Withdrawal of FDA listing of the TearCare product.

Sight Sciences reserves the right to stop the study at a center any time after the initiation visit if there have been no subject enrollments.

Likewise, a principal investigator may terminate the study at his/her institution. This decision must be followed by written notification to Sight Sciences within five working days, stating the reasons for termination.

If the study is terminated, every effort should be made to obtain final follow-up from all subjects.

In the event that there are significant human use issues with the device, the investigator will be consulted to make a determination of whether the study should be terminated or not.

18.3 INVESTIGATOR RESPONSIBILITIES

18.3.1 GENERAL RESPONSIBILITIES OF INVESTIGATORS

An Investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the Investigator's care, and for the control of devices under investigation. An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

18.3.2 SPECIFIC RESPONSIBILITIES OF INVESTIGATORS

1. Awaiting approval - An Investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB approval.
2. Subject Qualification -The Investigator is responsible for ensuring that all subjects entering the study conform to the patient selection criteria.
3. Compliance - An Investigator shall conduct an investigation in accordance with the signed agreement with the Sponsor, the investigational plan, all applicable FDA regulations, and any conditions of approval imposed by an IRB.

18.3.3 INVESTIGATOR RECORDS

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for the period specified in Section 14.4:

1. All correspondence with another Investigator, an IRB, the Sponsor, a monitor, or FDA, including required reports.
2. Records of each subject's case history and exposure to the device. Case histories include the study CRF's/worksheets and supporting data including, for example, signed and dated consent forms and medical records. Such records shall include:
    a) Documents evidencing informed consent.

b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

3. The protocol, with documents showing the dates and reasons for each deviation from the protocol.

4. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

18.3.4 INVESTIGATOR REPORTS

An Investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

2. Withdrawal of IRB Approval - An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.

3. Progress - An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

4. Deviations from the Investigational Plan - An Investigator shall document and report to the Sponsor any deviation from the investigational plan.

5. Informed Consent - If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.

6. Final Report - An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB.

7. Other - An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

18.4 INVESTIGATOR AGREEMENT

The principal investigators in each center shall agree to the clinical protocol and any amendments and indicate their approval and agreement by signing and dating the cover page of the study protocol and the Investigator Responsibility Agreement.

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16. Lane SS, DuBiner H, Epstein RJ, et al. A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. Cornea. 2012: 31 : 396-404
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20 APPENDIX A – METHODS FOR EXAMS, TESTS AND QUESTIONNAIRES

20.1 OSDI

The subject should complete the OSDI at the beginning of each visit before conducting other clinical testing. Provide a paper copy of the questionnaires and a blue or black ink pen to the subject. Review the instructions for the questionnaire with the subject and answer any questions they have about how to complete them. Then allow the subject to complete the questionnaires on their own (i.e. self-administered). The study staff should strictly restrain from interpreting the questions, using suggestive comments and writing on the questionnaires.

Study staff should review the completed questionnaire before the subject leaves the office to check for missing or multiple answers on a given question. If these are found, please point this out to the subject and allow them to revise their response(s) to the specific question(s). Please confirm initials and date of the subject on the last page of the questionnaire. Do not allow the subject to take the questionnaires home.

The OSDI has 12 questions. Based on the answers provided by the subject, study staff calculate the overall OSDI Total score (from 0-100) and scores for the three subscales according to the OSDI instructions. Based on the recommended cutoffs for OSDI Total score, the severity of the subject's dry eye symptoms will be categorized as follows:

- Normal – 0-12
- Mild – 13-22
- Moderate – 23-32
- Severe – 33 or higher

20.2 MEDICATIONS

When recording medications that the subject is taking, be sure to ask the subject to list any over-the-counter medications and supplements they are taking that could affect dry eye disease including, for example, cold medicines, Benadryl, fish oil supplements and Omega 3 products, retinol products, Latisse, etc.

20.3 SLIT LAMP EXAM

A standard slit-lamp examination shall be performed including inspection of the cornea at a magnification of 10X and 16X for the presence or active inflammation or structural

change, the iris and anterior chamber for inflammation, and the eyelids for crusts, collarettes, or scales.

20.4 TEAR BREAKUP TIME (TBUT)

TBUT is an indicator of tear film instability.

Methods for Preparing and Administering Fluorescein into the eye

Any of the following methods may be used to administer fluorescein into the subject's eye. Whenever possible, the same method should be used for follow-up visits that was used for the baseline visit for a particular subject. In addition, whenever possible, the same method should consistently be used at a site on all subjects.

1. DET Strips:

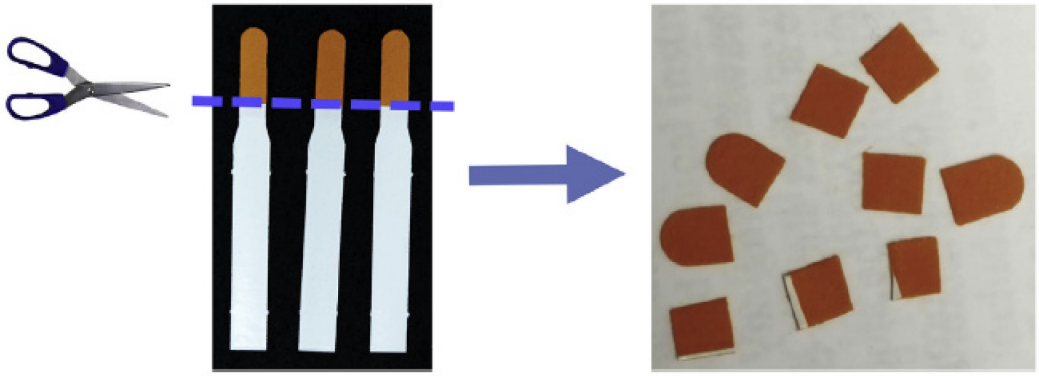
The Dry Eye Test (DET) method should be followed using DET test strips (Amcon Laboratories). While holding a fluorescein impregnated DET strip suspended in air, use a micropipette to apply 10uL of sterile saline onto the dyed end of the strip. Do not allow the saline to drip off and do not shake the strip. Instill the dyed tip of strip into the lower conjunctival fornix.

2. Compounded Fluorescein Solution

Obtain 0.5%, 1.0% or 2.0% preservative-free fluorescein ophthalmic solution from a compounding pharmacy. Using a micropipette, instill 5uL of the solution into the lower conjunctival fornix.

3. Prepare Fluorescein Solution Per the Gyau Method[29]

   a) Put on a pair of sterile gloves.
   b) Cut three (3) 1.0 mg Fluorescein Sodium Ophthalmic strips at the end of the colored portion of the strip using sterile scissors and tear each portion into 3 pieces. You should have 9 pieces.



c) Place the 9 pieces into a disposable microcentrifuge tube. Make sure the pieces of the strips are lying at the bottom part of the tube. Pipette 200µL of sterile saline into the tube containing the cut strips. Gently shake the tube to make sure the fluid is covering all the pieces of the cut strips and cover with the lid.

d) Wait 3-15 minutes before using the Fluorescein solution.
e) Using a micropipette, instill 5uL of the solution into the lower conjunctival fornix.
f) After use, discard the remaining solution and microcentrifuge tube.

Measuring Tear Breakup Time

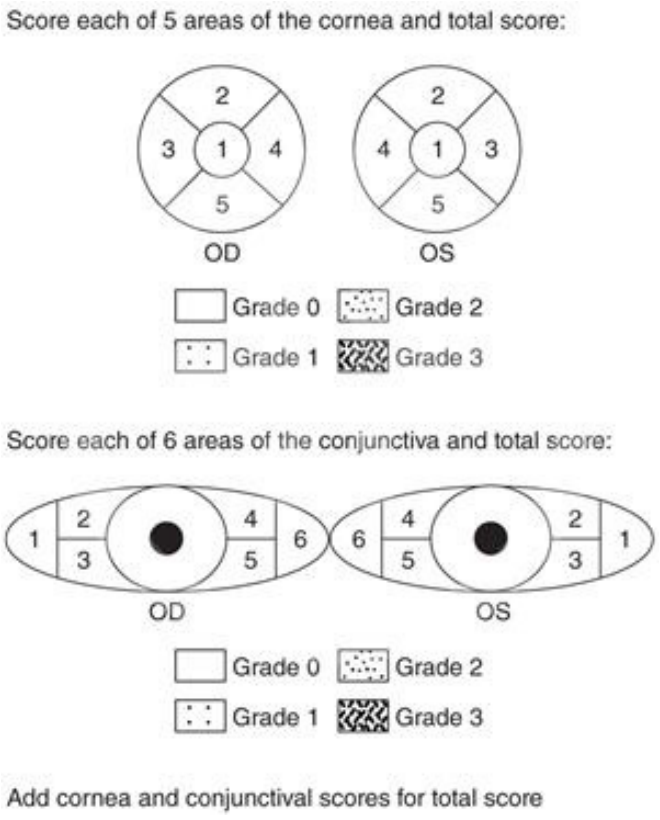
Under the cobalt blue illumination of the slit lamp, tear break-up time should be assessed. Tear Break-up Time is defined as the number of seconds between a blink and the appearance of a first dry spot or negative staining in the tear film.

Ask the subject to blink several times before taking the TBUT measurements. TBUT measurements should be done quickly thereafter, since in the presence of epithelial defects, the fluorescein will diffuse into the tissue and the borders of staining become indistinct, as does the intensity of staining of both tear film and cornea. Record the break-up time using a stopwatch. Repeat the test 3 times and take the average of the 3 measurements.

20.5 CORNEAL STAINING

Corneal staining should be assessed immediately following TBUT measurements (i.e. within 1-4 minutes after instillation of fluorescein dye) to assure the dye does not diffuse into stroma, blurring the discrete margin of any staining defects. A yellow Wratten filter should be used to improve any visualization of corneal staining. Grade the corneal staining using the NEI/Industry Grading System provided in Figure 4 below.[28]

Figure 4: NEI/Industry Grading System for Corneal and Conjunctival Staining



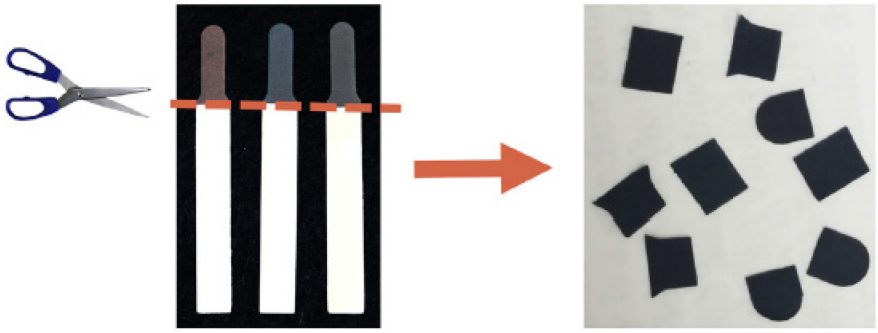
20.6 CONJUNCTIVAL STAINING

Preparation of Lissamine Green Solution[29]:

[28] Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J 1995;21: 221–232.

[29] Gyau DA, Begley CF, Nelson JD. A simple cost effective method for preparing FL and LG solutions. Ocular Surface. 2018;16:139-145.

g) Put on a pair of sterile gloves.
h) Cut three (3) Lissamine Green strips at the end of the colored portion of the strip using sterile scissors and tear each portion into 3 pieces. You should have 9 pieces.



i) Place the 9 pieces into a disposable microcentrifuge tube. Make sure the pieces of the strips are lying at the bottom part of the tube. Pipette 200µL of sterile saline into the tube containing the cut strips. Gently shake the tube to make sure the fluid is covering all the pieces of the cut strips and cover with the lid.

j) Wait 5-15 minutes before using the Lissamine Green solution. After use, discard the remaining solution and microcentrifuge tube.

Conjunctival staining: Instill 10µL of Lissamine Green solution into the lower conjunctival fornix. The conjunctival staining grading should be performed 1 minute after instillation of stain and within 4 minutes of staining. Perform a slit lamp exam to score the conjunctival staining per the NEI grading system shown above in Figure 4. Start with a low illumination and increase the level until the lissamine green staining is most visible. The use of an optional red barrier filter between the slit lamp eyepieces and the ocular surface highlights the staining pattern.

20.7 MEIBOMIAN GLAND SECRETION SCORING

The Meibomian Gland Secretion Scoring is an assessment of the quality of the secretions produced by the meibomian glands in the lower eyelids. The Meibomian Gland Secretion Scoring should be performed using the Meibomian Gland Evaluator (TearScience, Inc.). Ensure that the instrument has been cleaned using alcohol prior to each use.

Grade the quality of secretions in the lateral, central and temporal thirds of the lower eyelids. Grade the 5 central glands in each region, for a total of 15 glands per eye.

Per the method described by Korb et al, [30] place the part of the instrument's contact surface onto the skin immediately inferior to the eyelashes of the lower eyelid so that the long dimension is parallel to the eyelid margin. Once full contact is achieved between the instrument and the skin immediately below the lash line of the lower lid, rotate the shaft of the instrument downward approximately 15 to 45 degrees. Then, depress the shaft midway (~3mm) and roll the lower eyelid margin slightly outward.

Hold the instrument in place over each third of the lid for a minimum of 10 and a maximum of 15 seconds while grading the quality of secretion of the 5 glands in the center of the instrument (15 glands total per eye). Grade the quality of the secretions per the following scale described by Lane et al[31]:

- 0 = nothing
- 1 = toothpaste
- 2 = cloudy
- 3 = clear

From this assessment the following endpoints will be calculated:

- Total Meibomian Gland Secretion Score: Sum of the grade (0 – 3) for each of the 15 glands. Range for this score is 0-45.
- Count of the number of Meibomian glands yielding clear liquid secretions. Range for this count is 0-15.
- Count of the number of glands secreting any liquid (clear or cloudy). Range for this count is 0-15.

[30] Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea. 2008;27: 1142–1147.

[31] Lane SS, DuBiner H, Epstein RJ, et al; A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. Cornea. 2012: 31 : 396-404.

21 APPENDIX B - DECLARATION OF HELSINKI

I. PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

II. GENERAL PRINCIPLES

1. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

2. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. Medical progress is based on research that ultimately must include studies involving human subjects.

4. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

5. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

6. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

7. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

8. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

9. Medical research should be conducted in a manner that minimizes possible harm to the environment.

10. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

11. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

12. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

13. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

III. RISKS, BURDENS AND BENEFITS

- In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

- All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

  Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

  When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

IV. VULNERABLE GROUPS AND INDIVIDUALS

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

  All vulnerable groups and individuals should receive specifically considered protection.

- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

V. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

  The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

  In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

VI. RESEARCH ETHICS COMMITTEES

- The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

  The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

VII. PRIVACY AND CONFIDENTIALITY

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

VIII. INFORMED CONSENT

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

  After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

  All medical research subjects should be given the option of being informed about the general outcome and results of the study.

- When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

IX. USE OF PLACEBO

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

  Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

  Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo,

or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

X. POST-TRIAL PROVISIONS

- In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

XI. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

XII. UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to

evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.