Official Title : RANDOMIZED, CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFECTIVENESS OF THE TEARCARE® SYSTEM IN THE TREATMENT OF THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE (OLYMPIA)

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Sight Sciences, Inc.

RANDOMIZED, CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFECTIVENESS OF THE TEARCARE® SYSTEM IN THE TREATMENT OF THE SIGNS AND SYMPTOMS OF DRY EYE DISEASE (OLYMPIA)

PROTOCOL ID #:	06196
CURRENT REVISION:	B
REVISION DATE:	July 31, 2019
SPONSOR:	Sight Sciences, Inc. 3000 Sand Hill Road Building 3, Suite 105 Menlo Park, CA 94025 [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.
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Revision History

Revision	Date Issued	ECO
A	December 12, 2018	[redacted]
B	July 31, 2019	[redacted]

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1 PROTOCOL SYNOPSIS

Protocol Title	Randomized, Controlled Trial to Evaluate the Safety and Effectiveness of the TearCare® System in the Treatment of the Signs and Symptoms of Dry Eye Disease
Protocol ID Number	06196
Study Device	TearCare® System
Control Group	LipiFlow® Thermal Pulsation System
Primary Objective	To demonstrate the safety and effectiveness of a single TearCare® treatment compared to a single LipiFlow treatment to treat the signs and symptoms of dry eye disease in adult patients.
Study Design	Prospective, randomized, single-masked, multi-center non-inferiority, post-market study.
Primary Effectiveness Endpoints	Mean Change from baseline to 1 month in: o Tear Break-Up Time (TBUT) o Total Meibomian Gland Secretion Score
Secondary Effectiveness Endpoints	Mean Change from baseline to 1 month in: o Ocular Surface Disease Index (OSDI) score o Corneal staining scores o Conjunctival staining scores o Symptom Assessment in Dry Eye (SANDE) scores o Eye Dryness Score o Number of Meibomian Glands Yielding any liquid o Number of Meibomian Glands Yielding clear liquid
Primary Safety Endpoint	o Device-related adverse events
Secondary Safety Endpoints	o Discomfort/pain during treatment o Change in best corrected visual acuity (ETDRS) o Change in intraocular pressure (IOP)

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 23-79 5. TBUT of ≤7 seconds in both eyes 6. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤12 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 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. Use of any of the following medications: a) Restasis or Xiidra within 60 days prior to enrollment; b) Antihistamines (oral or topical) within 10 days prior to enrollment; c) 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; d) Accutane (at any time); e) Oral tetracyclines or azithromycin within 30 days prior to enrollment; or f) Topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications within 30 days prior to enrollment. **NOTE:** Use of any of the above medications (with the exception of 1c) is not permitted during the 1 month follow-up period. 2. Any of the following dry eye treatments: a) Office-based dry eye treatment (e.g. IPL, thermal pulsation [Lipiflow], etc.) within 12 months prior to enrollment; b) Meibomian gland expression within 6 months prior to enrollment; c) Blephex or debridement within 3 months prior to enrollment is an exclusion; d) Punctal occlusion or punctal plug placement within 30 days prior to enrollment; e) Use of TrueTear device within the past 2 weeks. (Subjects must refrain from using the TrueTear device for the duration of the study.); or f) Any history of meibomian gland probing 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. Contact lens use within the past 2 weeks. (Subjects must refrain from wearing contact lenses during the 1 month follow-up.) 5. History of Ocular Herpes Simplex or Ocular Herpes Zoster 6. Any active, clinically significant ocular or peri-ocular infection or inflammation 7. Recurrent clinically significant eye inflammation, other than dry eye, within 3 months prior to enrollment 8. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded. 9. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, distichiasis, trichiasis). 10. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area. 11. 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. 12. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy, Salzmann's nodules, etc.) 13. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea 14. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis. 15. Ocular trauma within 3 months prior to enrollment. 16. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation 17. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.) 18. Subject is currently using Retin A or Latisse. 19. Subject has permanent eyeliner/lid tattoos, eyelash extensions or wears false eyelashes.

	20. Subject is currently using Lash Boost. 21. Allergies to silicone tissue adhesives 22. 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. 23. 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. For example, subjects who are pregnant or nursing or have active, wet macular degeneration are excluded.
Study Cohorts	Cohort 1: Initial SmartLid design Cohort 2: Modified SmartLid design
Number of Subjects Enrolled and Randomized	Up to 100 in Cohort 1 + 138 Cohort 2 = Up to 238 subjects total
Randomization	1:1
Number of Centers	Up to 15
Study Duration for Each Subject	1 month
Total Study Duration	Approximately 9-12 months
Schedule of Visits	Baseline, Treatment (if not at Baseline Visit), Day 1, Week 2, Month 1

2 STUDY OBJECTIVE

The objective of this study is to demonstrate the safety and effectiveness of a single TearCare® treatment compared to a single LipiFlow treatment to treat the signs and symptoms of dry eye disease in adult patients. This objective will be met by demonstrating non-inferiority of the TearCare treatment for each of the primary effectiveness endpoints.

This study is being conducted to collect data to support a modification to the TearCare indication for use to read as follows, "The TearCare® System is indicated for the treatment of the signs and symptoms of dry eye disease (DED)."

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.

[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.

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 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:

[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.

[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

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
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 vision.

To address this, use of warm compresses and lid massage are recommended for the treatment of dry eye by the AOA, AAO, and the International Workshop on Meibomian Gland Dysfunction.[15,16,17] It is believed that the heat helps melt the oily obstructions in the meibomian glands and helps reduce gland inflammation, thereby helping to restore the ability of the meibomian glands to effectively secrete oil onto the tear film and prevent rapid tear evaporation.

[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.
[15] American Academy of Ophthalmology's Dry Eye Syndrome Preferred Practice Pattern 2013.
[16] American Optometric Association's Clinical Practice Guidelines for Ocular Surface Disorders, updated 2010.
[17] 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

It has been shown that warm compress therapy can lead to improved lipid production and flow on to the tear film.[18,19,20] This improved lipid delivery is associated not only with an improvement in the profile of the tear film but also an improvement in patient symptoms.[21,22,23] The tear film is demonstrably thicker and more stable with an increased contribution of lipid to its surface.[24,25,26]

While warm compress and lid massage can be an effective treatment for dry eye disease, it has several shortcomings, including the fact that the warm compress may not be sufficiently warm or it may cool too quickly. In addition, use of warm compresses on a daily basis is time-consuming and labor-intensive which leads to poor patient compliance. As a result, , various alternative approaches to heating the eyelids have been proposed. [27,28,29,30,31]

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™

[18] Goto E, Monden Y, Takano Y, et al. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. Br J Ophthalmol. 2002;86:1403–1407.
[19] Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011;52:1922–1929.
[20] Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. CLAO J. 1995;21:221–232.
[21] Korb DR, Blackie CA. Restoration of meibomian gland functionality with novel thermodynamic treatment device–a case report. Cornea. 2010;29:930–933.
[22] Friedland BR, Fleming CP, Blackie CA, et al. A novel thermodynamic treatment for meibomian gland dysfunction. Curr Eye Res. 2011;36: 79–87.
[23] Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. Eye Contact Lens. 2003;29:96–99.
[24] Mitra M, Menon GJ, Casini A, et al. Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects. Eye (Lond). 2005;19:657–660.
[25] Craig JP, Blades K, Patel S. Tear lipid layer structure and stability following expression of the meibomian glands. Ophthalmic Physiol Opt. 1995;15:569–574.
[26] Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. Adv Exp Med Biol. 1994;350:293–298.
[27] Lemp MA, Bardfield L, Blackie CA, et al. Evaluation of a novel method of treatment of dry eye. Invest Ophthalmol Vis Sci. 2008; 127/A154.
[28] Majmudar PA. LipiFlow Study Group. A novel thermal pulsation treatment for obstructive meibomian gland dysfunction: applying heat to the inner eyelid surfaces. Invest Ophthalmol Vis Sci. 2010; 6281/D909.
[29] Mori A, Oguchi Y, Goto E, et al. Efficacy and safety of infrared warming of the eyelids. Cornea. 1999;18:188–193.
[30] Matsumoto Y, Dogru M, Goto E, et al. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. Cornea. 2006;25:644–650.
[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.

treatment to naturally express melted meibum, the physician then uses the Clearance Assistant device to further express the meibomian glands manually immediately following the eyelid heat treatment.

In this study, the TearCare System will be compared with the LipiFlow Thermal Pulsation System[27] in patients with dry eye disease. The objective is to demonstrate that the TearCare System is safe and effective in relieving the signs and symptoms of dry eye disease and that it is non-inferior to treatment with the LipiFlow System.

The TearCare System is a Class II-exempt device that is currently listed and commercially available in the US. This post-market study is being conducted to collect data to update the indication for use for the TearCare System to read as follows, "The TearCare® System is indicated for the treatment of the signs and symptoms of dry eye disease (DED)."

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 PROPOSED INDICATION FOR USE

This study is being conducted to collect data to support a modification to the TearCare indication for use to read as follows:

> "The TearCare® System is indicated for the treatment of the signs and symptoms of dry eye disease (DED)."

4.3 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:

- SmartLid™ devices
- SmartHub™ Kit, including SmartHub, SmartHub Nest, and charging adapter
- Clearance Assistant™ devices

The SmartLid 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, the physician uses the Clearance Assistant device to further express the meibomian glands manually to maximize the evacuation of melted meibum.

The SmartLid 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. Medical grade adhesive on the skin-facing surface of the SmartLid 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 SmartLid devices permit them to remain attached to the eyelids throughout the procedure while patient blinks normally.

The SmartLid devices are connected to the SmartHub via a cable. The SmartHub, shown below in Figure 2, delivers electrical energy to the SmartLids, and this energy 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. 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 SmartHub is battery operated, with a built-in battery, and is recharged by placing it on the charging nest.

The Clearance Assistant device (shown in Figure 3 below) is single-use, sterile device that is designed to facilitate manual expression of the meibomian glands after the application of heat by the TearCare SmartLid devices.

Figure 1: SmartLid Devices applied to the Eyelids

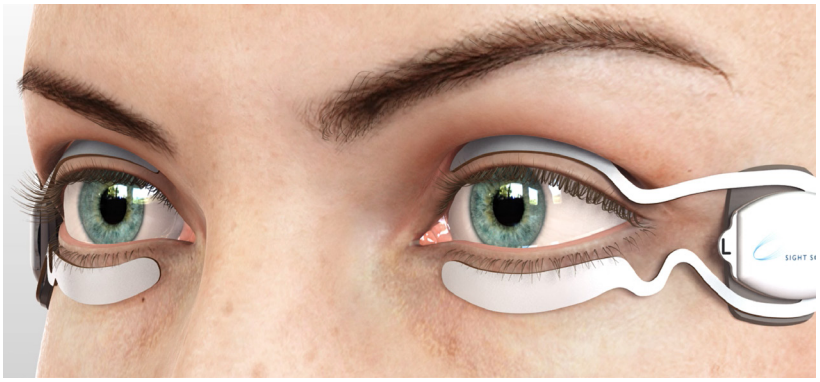


Figure 2: TearCare SmartHub

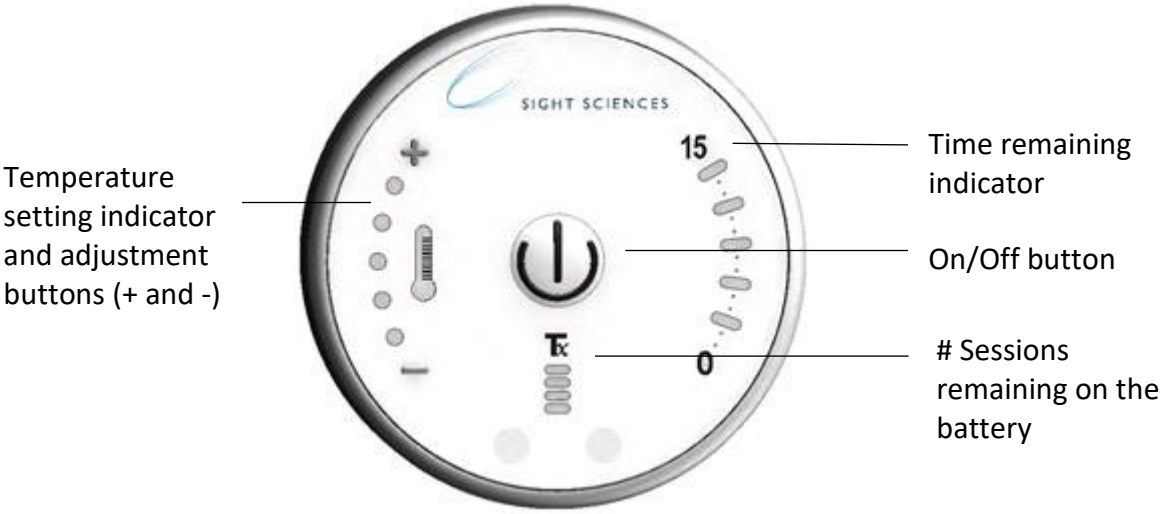
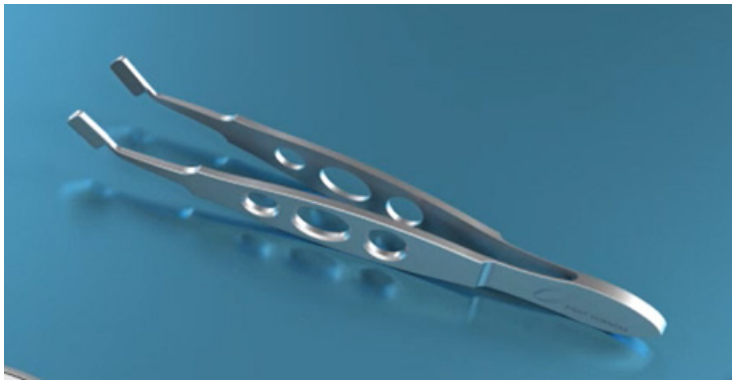


Figure 3: Clearance Assistant Device



To use the System, the flexible SmartLid devices are applied to the external surface of the upper and lower eyelids of the patient (Figure 1). The SmartLids 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 are able to 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.[32,33,34] 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.[35,36,37]

Immediately following the TearCare session, the clinician uses the Clearance Assistant device to manually express the meibomian glands in all four eyelids.

4.4 DEVICE MODIFICATION

At the beginning of August 2019, while the study was ongoing, Sight Sciences modified the SmartLid device to allow the clinician to gently bend the flexible elements to achieve better conformance and adherence of the SmartLids to the eyelids. Since it is possible that this design change could impact the clinical outcomes in the study, additional subjects were added to the study to ensure a full sample size of 138 subjects with the modified SmartLid design. We anticipate a final enrollment of approximately 238 subjects, approximately 100 prior to the modification (Cohort 1 subjects), and 138 after the modification was introduced (Cohort 2 subjects).

[32] Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf. 2004;2:149-165.
[33] 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.
[34] Jones et al. TFOS DEWS II Management and Therapy Report. The Ocular Surface 2017;15:575-628.
[35] 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.
[36] 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.
[37] Medical electrical equipment Part 1: General requirements for basic safety and essential performance (IEC 60601-1).

4.5 INSTRUCTIONS FOR USE

Instructions for Use are provided with each TearCare System.

4.6 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. While most investigators should have experience in performing manual expression of the meibomian glands, which is a standard procedure for dry eye patients, investigators will be trained in the protocol method for performing meibomian gland expression using the Clearance Assistant device. 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 41-45°C). Clinical validation testing was also performed 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 SmartLid 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 SmartLid devices have a minimum shelf life of 6 months.

5.2 PREVIOUS CLINICAL EXPERIENCE

The TearCare System has been studied in two pilot studies. The first study was conducted in 2013 as an Investigator-sponsored study with a prototype version of the TearCare System. The second study was initiated in 2017 with a commercial version of the TearCare System (Sight Sciences protocol #05429). These two studies are summarized below.

5.2.1 CLINICAL STUDY OF THE PROTOTYPE TEARCARE SYSTEM (2013)

A prototype version of the TearCare System was tested in a single center, prospective, randomized study. The study enrolled 18 subjects who were randomized to two treatment arms: (a) Prototype TearCare System, or (b) warm compress treatment. Subjects randomized to the TearCare arm (n=10 subjects) received one, 10-minute session with the prototype device followed by manual expression of the meibomian glands. Subjects randomized to the warm compress arm (n=8 subjects) received standard warm compress therapy (Fire & Ice Mask, Rhein Medical, Inc.) for 5 minutes per day for 2 weeks. Subjects were followed for 4 weeks, with follow-up visits at 1 day, 2 weeks, and 4 weeks.

No adverse events were reported in this study. Table 1 presents the effectiveness outcomes from this study.

This study demonstrated the safety of the TearCare System and provided evidence that TearCare System provides statistically significant improvement in meibomian gland secretion, tear break-up time, and dry eye symptoms. Results from this study informed the decision to continue development on the TearCare System.

Table 1: Prototype TearCare System - Study Results (2013)

	TearCare (n=10 subjects, 20 eyes)			Warm Compress control (n=8 subjects, 16 eyes)		
	Baseline	**4 weeks**	**Change BL to 4 wks – p value**	**Baseline**	**4 weeks**	**Change BL to 4 wks – p value**
Tear Break-up Time (sec) – Mean (SD)	4.6 (0.8)	16.8 (3.1)	<0.0001	4.1 (1.1)	4.6 (1.8)	0.27
Dry Eye Symptom Questionnaires						
Total **OSDI** Score (0 to 100)	37.0 (17.5)	19.6 (9.9)	0.01	27.8 (23.3)	34.3 (22.6)	0.21
Total **SPEED** Score (0 to 28)	13.8 (2.7)	7.4 (4.0)	0.001	13.6 (6.0)	10.1 (6.7)	0.19
Meibomian Gland Assessment						
Total Meibomian Gland Score (0 to 45)	13.4 (7.4)	43.2 (1.4)	<0.0001	7.6 (4.5)	15.4 (7.7)	0.03
# Glands Secreting Any Liquid (0 to 15)	3.6 (3.6)	14.9 (0.3)	<0.0001	1.1 (1.1)	4.4 (3.8)	0.04
# Glands Yield Clear Liquid (0 to 15)	0.3 (0.7)	12.9 (1.8)	<0.0001	0 (0)	1.25 (1.8)	0.08

5.2.2 CLINICAL STUDY OF THE TEARCARE SYSTEM (2017)

Following completion of the design and development of the commercial version of the TearCare System, a single center pilot study was initiated to collect additional clinical data. The results from this study were published in Clinical Ophthalmology.[38]

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.

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

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

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 2 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 2: 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.

5.2.3 SUMMARY

The two prior clinical studies provided preliminary clinical data with the TearCare System. Both of these studies were small, single-center pilot studies.

This current trial is being undertaken to evaluate the safety and efficacy of the TearCare system versus treatment with the LipiFlow System in a prospective, multi-center, hypothesis-driven, randomized, controlled trial. The study is intended to demonstrate that the TearCare System is indicated in the treatment of signs and symptoms of dry eye disease.

6 STUDY ENDPOINTS

6.1 EFFECTIVENESS ENDPOINTS

This study will collect data to assess the impact of each treatment on the signs and symptoms of dry eye disease. Tear Break-Up Time and meibomian gland secretion scores, which measure the treatment effect of the device on the signs of dry eye disease, are the primary endpoints. The Ocular Surface Disease Index (OSDI) questionnaire, which is a validated instrument for measuring the severity of symptoms of dry eye disease, is the key secondary endpoint. The following other secondary endpoints have been chosen to collect additional data regarding changes in the signs and symptoms of dry eye disease in study subjects: Corneal and Conjunctival Staining, the Symptom Assessment iN Dry Eye (SANDE) questionnaire, the Eye Dryness Score, and Meibomian Gland Secretion Score (number of glands yielding clear liquid or any liquid at all).

For each outcome measure, results from the TearCare subjects will be compared with results from the LipiFlow subjects. All the primary and secondary endpoints will be at 1 month.

- **Primary effectiveness endpoints**
  - Mean Change from baseline in Tear Break-Up Time (TBUT)
  - Mean Change in the total Meibomian Gland Secretion Score[39]

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

- **Secondary effectiveness endpoints**
  - Mean Change from baseline in OSDI score[40]
  - Mean Change from baseline in corneal staining scores
  - Mean Change from baseline in conjunctival staining scores
  - Mean Change from baseline in SANDE scores [41,42]
  - Eye Dryness Score
  - Mean Change from baseline in the number of meibomian glands yielding clear liquid secretions
  - Mean Change from baseline in the number of meibomian glands secreting any liquid (clear or cloudy)
- **Additional Exploratory Endpoints**
  - Use of dry eye lubricants

6.2 SAFETY ENDPOINTS

- **Primary Safety Endpoint**
  - Device-related adverse events (all adverse events will be recorded)
- **Secondary Safety Endpoints**
  - Discomfort/pain during treatment
  - Change in best corrected visual acuity (ETDRS)
  - Change in intraocular pressure (IOP)

7 STUDY DESIGN

This is a prospective, randomized, controlled, single-masked, multi-center treatment study. This is a post-market study intended to collect data to update the indication for use for the TearCare System. To reduce potential bias in the study, study staff performing the endpoint assessments will be masked as to the subject's treatment arm. Subjects cannot be masked as it will be obvious to them which treatment they are receiving.

[40] 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.

[41] Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, Foulks GN, Dana R. Development and Validation of a Short Global Dry Eye Symptom Index. Ocular Surface. 2007;5(1):50-57.

[42] Amparo F, Schaumberg DA, Dana R. Comparison of Two Questionnaires for Dry Eye Symptom Assessment: The Ocular Surface Disease Index and the Symptom Assessment iN Dry Eye. *Ophthalmology*. 2015;122(7):1498-1503.

7.1 STUDY DEVICE AND CONTROL ARM

In this study, treatment with the TearCare System (study device) will be compared with treatment with the LipiFlow System (control arm).

TearCare treatment includes an in-office 15 minute bilateral treatment session with the TearCare System immediately followed by manual expression of the meibomian glands using the Clearance Assistant device. Subjects randomized to TearCare will receive one in-office TearCare treatment on study Day 0.

The LipiFlow System is indicated for use as follows:

> The LipiFlow System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including Meibomian Gland Dysfunction (MGD), also known as Evaporative Dry Eye or Lipid Deficiency Dry Eye.

Subjects randomized to LipiFlow will receive the LipiFlow procedure bilaterally conducted per the device instructions for use. The LipiFlow procedure will be performed in-office on study Day 0.

7.2 STUDY CENTERS

This study will be conducted at up to 15 centers in the United States. No center will have more than 20% of the target enrollment (i.e. ≤28 subjects per site in Cohort 2).

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 23-79
5. TBUT of ≤7 seconds in both eyes
6. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤12 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 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. Use of any of the following medications:
    a) Restasis or Xiidra within 60 days prior to enrollment;
    b) Antihistamines (oral or topical) within 10 days prior to enrollment;
    c) 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;
    d) Accutane (at any time);
    e) Oral tetracyclines or azithromycin within 30 days prior to enrollment; or
    f) Topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications within 30 days prior to enrollment.

    NOTE: Use of any of the above medications (with the exception of 1c) is not permitted during the 1 month follow-up period.
2. Any of the following dry eye treatments:
    a) Office-based dry eye treatment (e.g. IPL, thermal pulsation [Lipiflow], etc.) within 12 months prior to enrollment;
    b) Meibomian gland expression within 6 months prior to enrollment;
    c) Blephex or debridement within 3 months prior to enrollment is an exclusion;
    d) Punctal occlusion or punctal plug placement within 30 days prior to enrollment;
    e) Use of TrueTear device within the past 2 weeks. (Subjects must refrain from using the TrueTear device for the duration of the study.); or
    f) Any history of meibomian gland probing
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. Contact lens use within the past 2 weeks. (Subjects must refrain from wearing

contact lenses during the 1 month follow-up.)
5. History of Ocular Herpes Simplex or Ocular Herpes Zoster
6. Any active, clinically significant ocular or peri-ocular infection or inflammation
7. Recurrent clinically significant eye inflammation, other than dry eye, within 3 months prior to enrollment
8. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded.
9. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, distichiasis, trichiasis).
10. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area.
11. 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.
12. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy, Salzmann's nodules, etc.)
13. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea
14. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis.
15. Ocular trauma within 3 months prior to enrollment.
16. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation
17. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.)
18. Subject is currently using Retin A or Latisse.
19. Subject has permanent eyeliner/lid tattoos, eyelash extensions or wears false eyelashes.
20. Subject is currently using Lash Boost.
21. Allergies to silicone tissue adhesives
22. 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.
23. 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. For example, subjects who are pregnant or nursing or have active, wet macular degeneration are excluded.

9 STUDY PROCEDURES

9.1 STUDY SCHEDULE

Table 3: Study Visit Schedule

Visit (Visit Window)	**Baseline** (Day -7 to 0)	**Treatment**[b] (Day 0)	**Day 1** (Day 1)	**Week 2** (Day 12-16)	**1 Mo** (Day 21 – 35)
Informed Consent	X[a]				
Demographics, Ocular & Medical History	X				
Medication use	X			X	X
Questionnaires: OSDI, SANDE, Eye Dryness Score	X				X
Manifest Refraction and Best-corrected visual acuity (ETDRS)	X		X[c]	X[c]	X
Slit Lamp Exam	X		X	X	X
Tear Breakup Time	X			X	X
Corneal Staining	X			X	X
Conjunctival Staining	X			X	X
Schirmer 1 Test (without anesthesia)	X				
Meibomian Gland Secretion Scoring	X			X	X
IOP [d]	X		X	X	X
Subject Eligibility	X				
Randomization	X				
TearCare or LipiFlow Treatment		X			
AE Assessment	X	X	X	X	X
Discomfort/Pain Questionnaire		X	X		
Collect Eye Drop/Lubricant Log					X

[a] Subjects may sign the informed consent up to 30 days in advance of the baseline visit.

[b] The TearCare or LipiFlow treatment must be performed within 7 calendar days of the Baseline visit. If scheduling permits, it may be performed on the same day as the Baseline visit following Randomization. Refer to Section 9.5.1 for details.

[c] On Day 1 and Week 2, Best Corrected Spectacle Visual Acuity (BCSVA using EDTRS) is measured without manifest refraction (MR). If the VA has worsened by ≥10 letters (per ETDRS) from baseline, then MR should be performed, the ETDRS measurement should be repeated, and the VA post-MR should be recorded.

[d] IOP measured via applanation tonometry should be measured at baseline using standard of practice at each site with the same method to be used for all consecutive visits in the study.

9.2 NUMBER OF SUBJECTS, DURATION OF FOLLOW-UP AND STUDY DURATION

A total of up to 238 subjects will be enrolled and randomized in the study. Assuming a 15% screen failure rate, approximately 278 subjects will be enrolled and screened to obtain up to 100 randomized subjects using the initial SmartLid design (Cohort 1) and

138 randomized subjects using the modified SmartLid design (Cohort 2). All subjects will be followed for 1 month.

It is anticipated that enrollment in the study will take 8-11 months. Including the 1-month follow-up period, the study is expected to last 9-12 months.

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 SmartLid Devices and Clearance Assistant Devices
- LipiFlow System and Activators
- ETDRS Visual Acuity System
- Slit lamp
- Wratten filter (yellow) (for corneal staining)
- Goldmann Tonometer or other applanation tonometer
- Meibomian Gland Evaluator (TearScience, Inc.)
- Fluorescein sodium strips (for TBUT and corneal staining)
- Lissamine green strips (for conjunctival staining)
- Filter strips (for the Schirmer test)
- 2-20µL & 20-200 µL 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
- Ruler
- 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 baseline visit should be performed within 30 days

of the subject signing the informed consent. 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 AND TREATMENT VISIT(S)

9.5.1 SCHEDULING THE BASELINE AND TREATMENT VISIT(S)

To facilitate scheduling, the Baseline and Treatment Visits may be performed in the same day or on two separate days. If these visits are performed over two days, the Treatment Visit must be within 7 calendar days of the Baseline Visit. For follow-up scheduling purposes, the date of the Treatment Visit is Day 0.

Refer to Table 3 for which tests and exams are to be performed in each visit. Endpoint assessments performed during the Baseline visit must be performed by a Masked Assessor (See Section 9.7).

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, TESTS 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 3 should be performed. Refer to Appendix A for instructions for performing the exams and administering the questionnaires.

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. Items with an asterisk (*) must be performed by a Masked Assessor (Refer to Section 9.7 for more information on the Masked Assessor).

1. Questionnaires: OSDI, SANDE and Eye Dryness VAS
2. Demographics, medical and ocular history
3. Medication use: ocular and systemic

4. Manifest refraction and ETDRS Best-corrected visual acuity*
5. Slit Lamp Exam*
6. Tear Breakup Time*
7. Corneal Staining*
8. Conjunctival Staining*
9. Schirmer 1 Test
10. Meibomian Gland Secretion Scoring*
11. Intraocular pressure*

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.

Subjects who fail screening may be re-screened for the study after 60 days. If they are re-enrolled, they should be assigned a new subject ID.

NOTE: Questionnaires 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 be Randomized.

9.5.3 RANDOMIZATION

Subjects will be randomized to either the TearCare (i.e. “treatment group”) or LipiFlow (i.e. “control group”) using a pseudo-random number generator with subjects enrolled according to a predetermined list. Randomization will use permuted blocks with random block sizes of 2 or 4. The investigational site will be provided a set of envelopes with randomization assignments. Following randomization, the subject should undergo the applicable procedures described in the sections below.

9.5.4 TREATMENT FOR TEARCARE GROUP

Subjects randomized to the TearCare Group will undergo the following procedure bilaterally. Refer to the TearCare Instructions for Use for detailed instructions for operating the TearCare System.

1. Obtain a new set of SmartLid 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 SmartLid 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 SmartLid devices to the SmartHub.
5. Inform the subject that the SmartLid 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 SmartLid 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.
10. Using the Clearance Assistant Device, 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. Additional passes of expression may be performed to ensure complete expression.
    g. Should the subject experience discomfort, it is reasonable to apply additional topical anesthetic (i.e. proparacaine or tetracaine). Alternatively, Akten® (lidocaine hydrochloride ophthalmic gel) 3.5% or equivalent may be applied into the lower eyelid fornices.
    h. The goal is to express each zone until the meibum coming out is clear. Typically, complete expression takes approximately 5 minutes/eye.
11. Immediately following the treatment, ask the subject to complete the Pain/Discomfort Questionnaires.

9.5.5 TREATMENT FOR LIPIFLOW GROUP

Subjects randomized to the LipiFlow Group will undergo the following procedure bilaterally. Refer to the LipiFlow Instructions for Use for detailed instructions for performing the LipiFlow procedure.

1. Seat the subject in a reclining chair.
2. Place an anesthetic drop in each eye.

3. Put a lubricating drop on the surface of the sterile, disposable Activator.
4. With a finger placed on the lid between the lid margin and the orbital bone, roll the finger to lift the lid margin of that particular lid off the globe.
5. Have the subject look down at their feet and slip the Activator below the upper lid of the first eye.
6. Have the subject then look up and place the Activator behind the lower lid. Have the subject close their eyes.
7. Align the handle of the Activator so that it is parallel to the bridge of the subject's nose. Place a piece of tape to secure the handle to the bridge of the subject's nose.
8. Assure that the outer surface so the bladder comes in full contact with the external side of the lids.
9. Loop the tubing over the subject's ear.
10. Repeat for the fellow eye.
11. Plug the tubing into the LipiFlow console.
12. Initiate the procedure by pressing start button on the console.
13. The procedure will last 12 minutes.
14. Once the procedure is complete, remove the tape from one Activator. Slightly depressed the sclera to release any suction between the disposable and the eye.
15. Have the subject look up and slip the Activator from under the lower lid, and then look down and remove from the upper lid.
16. Repeat for the fellow eye.
17. Place a lipid based drop in each eye.
18. Immediately following the treatment, ask the subject to complete the Pain/Discomfort Questionnaires.

9.5.6 FOLLOW-UP INSTRUCTIONS FOR SUBJECTS

Review the following instructions with subjects at the completion of the visit.

During the 1 month follow-up:

1. Dry Eye Lubricants/Drops: Subjects should make every effort to refrain from using any dry eye drops, lubricants, or other type of dry eye treatment (e.g. warm compresses, prescription medication, etc.). If they require "rescue therapy" to relieve their symptoms, they should use the same type of drops or lubricants they were using prior to the study.
2. Dry Eye Lubricant/Drop Log: Provide subjects with the Lubricant/Drop log and instruct them to record any use of drops or lubricants during the follow-up period.
3. Other Dry Eye Medications: Subjects should not use any other medications for dry eye disease (e.g. Restasis, Xiidra, etc.)
4. Other Treatments for Dry Eyes: Subject should not have any other treatments for dry eyes. For example, they should not use warm compresses or perform lid

massage. They should not use the True Tear device or have any other in-office dry eye treatments.

5. Anti-histamines: Subjects should not use any anti-histamines.

9.6 FOLLOW-UP VISITS

Prior to the Visit: Reminder Call

A few days before the follow-up visit, it is recommended that the coordinator contact the subject to remind them not to use dry eye drops or lubricants on the day of the follow-up visit since these products can affect the endpoint assessments.

At the Beginning of the Follow-up Visit: Maintaining Masking of Study Personnel

Endpoint assessments performed during the Follow-up visit must be performed by the Masked Assessor (See Section 9.7).

At the beginning of the follow-up visit, the coordinator should remind the subject to not reveal their randomization group to the study personnel who will be performing the follow-up exams.

Order of Procedures During the Follow-Up Visit

Follow-up procedures will be performed per the Study Schedule provided in Table 3 (page 30) 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. Questionnaires
2. Manifest refraction, if required per this protocol, and ETDRS Best-corrected visual acuity
3. Slit Lamp Exam
4. Tear Breakup Time
5. Corneal staining
6. Conjunctival staining
7. Meibomian Gland Secretion Scoring
8. IOP
9. Assessment of adverse events

The following activities can be performed in any order:

- Medication Use
- Collection of Lubricant/Drop Log (for the 1 Month visit only)

9.7 PHOTOGRAPHY DURING EXAMS AND TEARCARE PROCEDURE

Photographs or videos may be made during the baseline or follow-up exams or during the TearCare procedure. These images may be used for educational, training or marketing purposes. Subject consent must be obtained prior to taking any photographs or videos. Subjects do not have to agree to consent to being filmed in order to participate in the study.

9.8 MASKED ASSESSOR

To reduce potential bias in the study, study staff performing endpoint assessments will be masked as to the subject's treatment arm. In addition, to ensure consistency in performing the endpoint assessments the study staff member who performs the baseline assessments should also perform the follow-up assessments. An alternate Masked Assessor may be appointed to handle scheduling conflicts, but every effort should be made to have the same person performing all endpoint assessments throughout the study. Masked Assessors may not perform the randomization, the TearCare procedure, or the Lipiflow procedure

The following assessments must be performed by a Masked Assessor:

- Manifest refraction and BCVA
- Slit lamp exam
- Tear Break-up Time
- Corneal staining
- Conjunctival staining
- Meibomian gland secretion scoring
- IOP
- AE assessment

9.9 MANAGEMENT OF DRY EYE SYMPTOMS DURING FOLLOW-UP

During follow-up, subjects should refrain from using any dry eye treatments, including drops, lubricants, warm compresses, etc. If they require "rescue therapy" to relieve their symptoms, they should use the same type of drops or lubricants they were using prior to the study. They should document use of drops or lubricants on the Lubricant/Drop Log.

Subjects should not use Restasis or Xiidra during the study. Use of these drugs will result in the subject being excluded from the "Per Protocol" analysis from the time of initiation of these drugs forward.

Subject should not be treated with other dry eye treatments (e.g. IPL, TrueTear, punctal plugs, etc.) during the course of the study. Administration of these treatments will result in the subject being excluded from the "Per Protocol" analysis from the time of initiation of these treatments forward.

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

9.10 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.

If a subject withdraws from the study post-randomization but prior to receiving the TearCare or Warm Compress treatment, then that subject may be replaced in the study by a newly enrolled subject.

9.11 SUBJECTS LOST TO FOLLOW-UP

Subjects who do not show up for a follow-up must be contacted to attempt to have them come for the follow-up. For those subjects who cannot be reached, at least 3 phone call attempts should be made and documented. If still no response, a registered letter shall be sent to the address on file for the subject in an attempt to make contact. If a subject misses two consecutive follow-up visits without any contact with the study staff, the subject will be considered lost-to-follow-up unless there is a further communication by the subject.

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. Non-ocular adverse events do not need to be recorded as adverse events unless they meet the definition of serious adverse event or are believed to be related to the study device or a study procedure. 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) or study testing methods.

- Eyelid/eye pain requiring discontinuation of the procedure
- Eyelid/eye pain ≥1 day after the procedure
- Burn, erythema, or swelling of the eyelids
- Thermal injury to the eye, including conjunctiva, cornea or lens
- Physical pressure-induced injury to the eyelid

- Corneal deformation
- Foreign body sensation
- Formation of a chalazion or stye
- Infection of the eyelid or ocular surface
- Ocular surface irritation or inflammation (e.g. Conjunctival injection, conjunctival or corneal abrasion, chemosis)
- Allergic or inflammatory reaction to the SmartLid or LipiFlow activator
- Loss in BCVA (ETDRS) of ≥10 letters

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.[43,44,45,46] 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 SmartLid devices and has been designed to not exceed the maximum allowable temperature.

2. Corneal abrasion: If the SmartLid 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.

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 SmartLid devices, and operate the TearCare System.
- The clinician will be trained in how to perform meibomian gland expression using the TearCare Clearance Assistant
- The study staff will be trained to perform procedures required in this protocol

[43] 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

[44] 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.

[45] 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.

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

12 STATISTICAL CONSIDERATIONS

12.1 EVALUABILITY

All subjects on whom the TearCare or LipiFlow 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.

12.2 ANALYSIS POPULATIONS

The per-protocol analysis population includes all subjects who have at least one follow-up visit and have no major protocol deviations, including specifically no use of dry-eye medications (Xiidra, Restasis). The primary and secondary endpoint analysis will be performed based on the Cohort 2 per-protocol population.

The intent-to-treat (ITT) analysis population includes all subjects who are randomized to either arm, regardless of treatment received. As a sensitivity analysis, the primary and secondary endpoint analyses will also be carried out on the Cohort 2 ITT population as well.

The effectiveness outcomes for Cohort 1 subjects will be summarized descriptively based on the available data of the per-protocol population. The effectiveness data listings will be Cohort 1 subjects that are excluded from in the per-protocol population will be provided separately.

12.3 SUBJECT ACCOUNTABILITY

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

12.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic variables gender, race, ethnicity, and age will be summarized for all enrolled subjects, along with medical history, by Cohort and combined. Descriptive statistical summaries of pre-treatment parameters (min, max, median, mean, standard deviation) will also be provided for each treatment arm. This includes baseline measurements for each of the study endpoints: TBUT, Total Meibomian Gland Secretion Score, Number of Meibomian glands with any/clear liquid, Corneal Staining, Conjunctival Staining, OSDI Score, SANDE Score, and Eye Dryness Score.

All baseline measurements will be evaluated for adequate balance between the two treatment arms.

12.5 EFFECTIVENESS ENDPOINTS AND ANALYSIS METHODS

All primary and secondary endpoints will be evaluated at 1 month. Outcomes measured on a per-eye basis will be analyzed using data from both eyes, with linear mixed effect models to account for within-person correlation (correlation between right and left eyes).

12.5.1 DESCRIPTIVE ANALYSES

All outcome measures, IOP outcomes, and Use of dry eye lubricants, will be tabulated by visit and treatment group.

12.5.2 PRIMARY EFFECTIVENESS ENDPOINTS

The primary effectiveness endpoints are

- the change from baseline in Tear Break-Up Time (TBUT), and
- the change from baseline in overall Meibomian gland score (MEIB)

Both endpoints will be evaluated at the 1 month visit.

Each of the primary endpoints will be analyzed using a linear mixed effects (LME) ANCOVA model. This will allow for the proper incorporation of within-person correlation into the statistical model, and will also allow for adjustment for baseline measurements. It should be noted that, as described in Section 12.2, the primary analysis on these two primary effectiveness endpoints will be based on the Cohort 2 per-protocol population.

Details of the LME models are provided in the Statistical Analysis Plan (SAP) provided in Appendix B. Hypotheses regarding the primary and secondary effectiveness outcomes are described below.

12.5.3 PRIMARY EFFECTIVENESS HYPOTHESES

The primary study hypotheses will demonstrate non-inferiority of the TearCare treatment as compared to LipiFlow, for both Tear Break-Up Time (TBUT) and overall Meibomian gland score (MEIB) in the Cohort 2 subjects (after SmartLid modification). The full statistical model for the analyses is described in the SAP (Appendix B).

To demonstrate non-inferiority of the TearCare treatment to the LipiFlow control for TBUT we will test the null hypothesis that $\beta_{1,TBUT}$ is less than the non-inferiority margin of 3 seconds:

$$H_0: \beta_{1,TBUT} \leq -3.0$$
$$H_A: \beta_{1,TBUT} > -3.0$$

Where $\beta_{1,TBUT}$ represents the difference in change from baseline (1 month – baseline, so positive is better) between the TearCare treatment and the LipiFlow control. The hypothesis will be tested by constructing a confidence interval (least squares mean interval) for $\beta_{1,TBUT}$ as described in the SAP.

To demonstrate non-inferiority of the TearCare treatment to the LipiFlow control for MEIB we will test the null hypothesis that $\beta_{1,MEIB}$ is less than the non-inferiority margin of 5 units:

$$H_0: \beta_{1,MEIB} \leq -5.0$$
$$H_A: \beta_{1,MEIB} > -5.0$$

Where $\beta_{1,MEIB}$ represents the difference in change from baseline (1 month – baseline, so positive is better) between the TearCare treatment and the LipiFlow control for the overall Meibomian gland score. The hypothesis will be tested by constructing a confidence interval (least squares mean interval) for $\beta_{1,MEIB}$ as described in the SAP.

Both hypotheses will be tested at a one-sided α = 0.05. As both hypotheses will need to be rejected for study success there is no multiplicity adjustment necessary.

If non-inferiority of the TearCare device is established as described above, then we will proceed to test for superiority for each of the two primary endpoints, that is, we will repeat the two hypothesis tests with non-inferiority margins set to 0. If either of the two superiority tests is rejected then the TearCare device will be declared superior for that endpoint.
The primary effectiveness outcomes of the Cohort 1 per-protocol population will be summarized separately by descriptive statistics for continuous variables such as mean, median, standard deviation, minimum, and maximum.

12.5.4 POOLABILITY

Using a linear mixed effects modeling approach described in Appendix B, poolability of the effectiveness outcomes for Cohort 2 per-protocol population will be evaluated across centers by testing a Treatment-by-Center interaction (TxC). If the TxC interaction is significant at α=0.15 a Center effect will be included in the final model and results will be reported separately by Center. For this analysis, Centers with less than 5 enrolled subjects will be combined into a single virtual center.

12.5.5 MISSING DATA

As a sensitivity analysis, multiple imputations for the primary outcome at the 1 month time point will be carried out using baseline characteristics and 2-week outcomes as predictors. Details are provided in the SAP.

12.5.6 SECONDARY EFFECTIVENESS ENDPOINTS

The secondary effectiveness endpoints include change from baseline for the following outcomes:

1. Ocular Surface Disease Index (OSDI) score
2. Corneal staining scores
3. Conjunctival staining scores
4. Symptom Assessment iN Dry Eye (SANDE) scores
5. Eye Dryness Score
6. Number of Meibomian Glands Yielding any liquid
7. Number of Meibomian Glands Yielding clear liquid

If both primary effectiveness hypotheses are both met for the Cohort 2 per-protocol population, then we will sequentially test each of the secondary effectiveness endpoints based on the Cohort 2 per-protocol population to determine whether there is a significant change between baseline and 1 month. In each case we will test the null hypothesis that the change is 0 against the appropriate alternative (depending on the favorable direction). All testing of the secondary endpoints will be done using a two-sided alpha of 0.05. We will test the secondary endpoints in the order listed, stopping at the point where a test fails to reject. This sequential procedure controls the overall type I error rate for the secondary endpoints.

The secondary endpoints can be divided into two groups, those which are measured on a per-eye basis (Corneal Staining, Conjunctival Staining, Meibomian gland scores) and those measured on a per-subject basis (OSDI Score, SANDE Scores, Eye Dryness Score).

The per-eye secondary endpoints (Corneal Staining, Conjunctival Staining, Meibomian gland counts) will be tested using a similar linear mixed effects modeling approach as for the primary endpoint, with treatment as a fixed effect, and including a random intercept per subject to account for correlation.

The per-subject secondary endpoints (OSDI score, SANDE scores, Eye Dryness Score) are measured at the subject level so there is only one measurement per subject. For these endpoints a paired t-test will be used to evaluate change from baseline to 1 month.

The secondary effectiveness outcomes of the Cohort 1 per-protocol population will be summarized separately by descriptive statistics (mean, median, standard deviation,

minimum, and maximum for the continuous variables; count and percent for the categorical outcomes).

12.5.7 Additional Exploratory Analyses

The use of dry eye lubricants will be summarized by Treatment group at one month.

12.6 Safety Endpoints and Analysis

12.6.1 Descriptive Analyses

All adverse events, measures of pain and discomfort, changes in IOP, and changes in BCVA (EDTRS) will be tabulated by visit and treatment group.

12.6.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of ocular adverse events.

12.6.3 Primary Safety Analysis

All adverse events will be reported by treatment group and AE category. Any serious adverse events will be completely described in the study report. The primary safety endpoint will be summarized for each treatment group.

We will compute the incidence of ocular events in two ways: first as a simple proportion, counting the number of subjects with any event (that is, counting the first event per person in either eye), then as an incidence rate, counting all events including repeated events per subject.

12.6.4 Secondary Safety Endpoints

The secondary safety endpoints include:

- Discomfort/pain during treatment
- Change in best corrected visual acuity (ETDRS)
- Change in intraocular pressure (IOP)

These endpoints will be summarized by treatment group and visit.

12.7 Sample Size Calculation

Up to 100 Cohort 1 subjects and 138 Cohort 2 subjects, approximately 119 in the TearCare group and 119 in the LipiFlow group, will be enrolled and randomized in the study. Sample size was calculated to provide more than 90% power to meet both the TBUT and MEIB effectiveness endpoints in Cohort 2 and sufficient precision around the

adverse event estimates. The sample size also takes into account an estimated 10% dropout rate. Details of the sample size calculation can be found in Appendix B.

12.8 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: 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
  - Randomization procedures
  - Instruction in how to use the TearCare System
  - Instruction in how to perform study procedures
  - Guidance in how to administer questionnaires to subjects
  - Procedures for maintaining masking of study personnel
  - Records and reports
- Interim Monitoring: Sight Sciences or CRO personnel will visit the clinical site routinely 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. Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.
- 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

14.1 DATABASE MANAGEMENT

The study database will be designed using an electric data capture (EDC) system that is compliant with 21 CFR Part 11 and relevant guidance documents. The EDC will be developed and maintained by an independent, qualified data management firm.

The database will incorporate time-stamped audit trails, protection of human subjects, restricted access, and data security at the component level. Each database module, including each individual eCRF, will be validated by conducting a series of standard tests that demonstrate usability and correctness of the database system. The database will be maintained on an ongoing basis and will be routinely backed up.

14.2 SUBJECT IDENTIFICATION

The subjects will be identified by a five digit subject number composed of a one-digit study identification number, a two digit center identification number followed by a two digit sequential subject number. The subject identification will be assigned when informed consent is obtained. In this way, information contained in the study records will be kept as confidential as possible.

14.3 SUBJECT ACCOUNTABILITY

All subjects randomized and treated in this clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation have reached the final reporting period, excluding subjects who were withdrawn.

14.4 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.

14.5 SOURCE DATA AND CASE REPORT FORMS

Source data will be entered into a validated electronic system at each site by trained personnel in accordance with 21 CFR Part 11 requirements. Electronic entries will be 100% verified against corresponding source data at the sites and queried/corrected if needed to the extent possible. Medical site records serve as source data. In addition, data that are collected exclusively for the purpose of this study and not normally recorded in the subjects' medical records can 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.

14.6 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 or LipiFlow 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 D).

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 treated with the device
- Insufficient enrollment in the study
- 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 or if significant protocol/deviations are observed at the site.

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 14.6:

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.

19 PUBLICATION POLICY

Sight Sciences recognizes the value of disseminating research results. It is understood that the Study is part of the Multi-Center Clinical Trial and publication of results is expected. This publications policy applies to journal articles, conference abstracts, and conference presentations (posters and slides) covering Sight Sciences-sponsored clinical studies. This policy is in addition to any arrangement contained in the Clinical Trial Agreement between Sight Sciences and the investigator.

Multi-Site Data

Clinical site investigators are encouraged to propose publications and abstracts that include clinical or research data from multiple clinical sites; such projects will be coordinated by Sight Sciences. Authorship of papers and abstracts resulting from these projects will be determined collaboratively according to the following guidelines:

- The first author on such publications will be the person who primarily wrote the paper and took the lead on the research. In the case of clinical trial papers where all authors contributed equally, authorship order may be based on site enrollment or other criteria at Sight Sciences' discretion.
- Other authors include those who significantly contributed to the specific work.
- At least one person from each clinical site whose study subjects appear in the work will be acknowledged in the manuscript/presentation in some way, either as an author group member, a non-author contributor, or listed in the acknowledgements, depending on the particular policies of the journal or conference.

Single Site Data

After publication of the multi-center study results in a peer-reviewed journal, or if Sponsor has not submitted a manuscript for publication in a peer-reviewed journal within twelve (12) months after the study has been completed, whichever occurs first, Investigators may publish the results of the Study generated by the Investigator, subject to the obligations of the Clinical Trial Agreement between Sight Sciences and the Investigator, and the prior approval of Sponsor in writing.

Publications Review Policy

Investigators must submit all presentations, posters, abstracts and manuscripts pertaining to this study to Sight Sciences for review in advance of their submission. Sight Sciences conducts this review to protect its proprietary rights to information, inventions, or products developed under the Study. Please use the following guideline to determine the absolute minimum advance time for submitting an item to Sight Sciences for review:

- Presentations/Posters: 5 business days in advance of presentation
- Abstracts: 5 business days in advance of submission
- Manuscripts: 30 calendar days in advance of submission for publication

In accordance with the Clinical Trial Agreement, these items must receive written approval from Sight Sciences in order for them to be submitted or presented. If an item is not received in the timeframe listed above, approval may not be granted due to insufficient time for considered review. In addition, since most of our Clinical Trial Agreements require that Sight Sciences has 60 days to review publications, Sight Sciences reserves the rights granted in those Agreements if circumstances require a longer review.

20 BIBLIOGRAPHY

1. American Academy of Ophthalmology's Dry Eye Syndrome Preferred Practice Pattern 2013.
2. American Optometric Association's Clinical Practice Guidelines for Ocular Surface Disorders, updated 2010.
3. Amparo F, Schaumberg DA, Dana R. Comparison of Two Questionnaires for Dry Eye Symptom Assessment: The Ocular Surface Disease Index and the Symptom Assessment iN Dry Eye. *Ophthalmology*. 2015;122(7):1498-1503.
4. Badawi D. A novel system, TearCare®, for the treatment of the signs and symptoms of dry eye disease. Clinical Ophthalmology 2018;12: 683-694.
5. 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.
6. Blackie CA, Korb DR, Knop E, et al. Nonobvious obstructive meibomian gland dysfunction. Cornea. 2010;29:1333–1345.
7. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye 1991;5: 395–411.
8. Bron AJ, Tiffany JM. The contribution of meibomian disease to dry eye. Ocul Surf. 2004;2:149–165.
9. 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.

10. Craig JP, Blades K, Patel S. Tear lipid layer structure and stability following expression of the meibomian glands. Ophthalmic Physiol Opt. 1995;15:569–574.
11. 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.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.
12. 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.
13. Finis D, Hayajneh J, Konig C et al. (2014a) Evaluation of an automated thermodynamic treatment (LipiFlow) system for meibomian gland dysfunction: a prospective, randomized, observer-masked trial. The Ocular Surface 12(2):146–154
14. Fiscella RG. Understanding dry eye disease: a managed care perspective. Am J Manag Care 2011; 17 Suppl 16:S432-9.
15. Foulks G, Bron AJ. Meibomian gland dysfunction: A clinical scheme for description, diagnosis, classification, and grading. Ocular Surface. 2003;1:107-126.
16. Friedland BR, Fleming CP, Blackie CA, et al. A novel thermodynamic treatment for meibomian gland dysfunction. Curr Eye Res. 2011;36: 79–87.
17. 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
18. Goto E, Monden Y, Takano Y, et al. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. Br J Ophthalmol. 2002;86:1403–1407.
19. Gyau DA, Begley CF, Nelson JD. A simple cost effective method for preparing FL and LG solutions. Ocular Surface. 2018;16:139-145.
20. Jones et al. TFOS DEWS II Management and Therapy Report. The Ocular Surface 2017;15:575-628.
21. Knop N, Knop E, Millar T. The international workshop on meibomian gland dysfunction: Report of the subcommittee on anatomy, physiology and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci. 2011 Mar; 52(4): 1938–78.
22. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea. 2008;27: 1142–1147.
23. Korb DR, Blackie CA. Restoration of meibomian gland functionality with novel thermodynamic treatment device–a case report. Cornea. 2010;29:930–933.
24. Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment of meibomian gland dysfunction. Adv Exp Med Biol. 1994;350:293–298.

25. Korb DR, Henriquez AS. Meibomian gland dysfunction and contact lens intolerance. J Am Optom Assoc. 1980;51:243–251.
26. Lane SS, DuBiner H, Epstein RJ, et al; A A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. Cornea. 2012: 31 : 396-404
27. 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
28. Lemp MA, Bardfield L, Blackie CA, et al. Evaluation of a novel method of treatment of dry eye. Invest Ophthalmol Vis Sci. 2008; 127/A154.
29. 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.
30. Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. CLAO J. 1995;21:221–232.
31. Majmudar PA. LipiFlow Study Group. A novel thermal pulsation treatment for obstructive meibomian gland dysfunction: applying heat to the inner eyelid surfaces. Invest Ophthalmol Vis Sci. 2010; 6281/D909.
32. Maskin SL. Intraductal meibomian gland probing relieves symptoms of obstructive meibomian gland dysfunction. Cornea. 2010;29: 1145–1152.
33. Matsumoto Y, Dogru M, Goto E, et al. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. Cornea. 2006;25:644–650.
34. McMonnies CW. Measurement of Symptoms Pre- and Post-treatment of Dry Eye Syndromes. Optom Vis Sci. 2016;93: 1431-1437.
35. Miller K, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, Asbell PA, Pflugfelder SC. Minimally Clinically Important Difference for the Ocular Surface Disease Index. *Arch Ophthalmol*. 2010;128(1):94-101.
36. Mitra M, Menon GJ, Casini A, et al. Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects. Eye (Lond). 2005;19:657–660.
37. Mori A, Oguchi Y, Goto E, et al. Efficacy and safety of infrared warming of the eyelids. Cornea. 1999;18:188–193.
38. 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.
39. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci. 2011;52:1922–1929.
40. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. Eye Contact Lens. 2003;29:96–99.

41. Schaumberg DA, Gulati A, Mathers WD, Clinch T, Lemp MA, Nelson JD, Foulks GN, Dana R. Development and Validation of a Short Global Dry Eye Symptom Index. Ocular Surface. 2007;5(1):50-57.
42. 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.
43. Smith GT, Dart J. External eye disease. In: Jackson TL, ed. Moorfields Manual of Ophthalmology. Philadelphia: Mosby Elsevier; Chap 4:2008.
44. 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.

21 APPENDIX A – METHODS FOR EXAMS, TESTS AND QUESTIONNAIRES

21.1 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. Multivitamins and general health supplements do not need to be recorded.

21.2 MANIFEST REFRACTION AND VISUAL ACUITY

Masked assessment: This assessment should be performed by the masked assessor.

Best-corrected visual acuity will be measured using the ETDRS method. Subjects should undergo manifest refraction prior to the ETDRS test, with the exception of the Day 1 and week 2 follow-up visit. On Day 1 and week 2, the subject's best spectacle corrected visual acuity (BSCVA) (i.e., without manifest refraction) will be measured using the ETDRS method. If the subject's visual acuity has worsened by ≥ 10 letters from baseline, then manifest refraction should be performed and the ETDRS measurement should be repeated.

Manifest Refraction

Refraction will be performed by the Investigator or staff using standard clinical practice.

ETDRS Testing Methods

Test Set-up

Best-corrected visual acuity at Baseline and all scheduled follow-up visits will be measured using the ETDRS charts at 1 or 4 meters.

The ETDRS chart must be placed at a distance of 4.00 meters (13 feet and 1.5 inches, or 157.5 inches) from cornea to chart surface, when using a 4-meter chart. For testing at 1 meter, the distance must be 1.00 (39 and 3/8 inches). A measuring tape or meter stick should always be available to verify the chart distance, even if the examining chair is supposed to be immovable or if reference marks are placed on the floor or walls.

The 1-meter distance is measured from the eye of the participant, seated comfortably in a chair with his/her back firmly placed against the chair, to the center of the 2nd or 4th letter of the 3rd line of the chart.

Note: If it is necessary to refract at the 1-meter distance, remember to add +0.75 sphere to the trial frame. Subtract the +0.75 sphere from the final refraction obtained at the 1-meter distance before recording the refraction on the form.

Methods

Starting at 4 meters, the subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. If the subject is unable to read line 1 (20/200) at 4 meters, then visual acuity testing should be performed at 1 meter.

The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, about one letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, the subject should be encouraged to guess. If the subject identified two (2) letters (e.g., A or B), the subject should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessment of visual acuity, all visual acuity assessments for a subject should be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) at each visit.

Recording and Scoring Best-Corrected Visual Acuity

Using the Visual Acuity Worksheet, circle each letter the subject identifies correctly, write total correct for each row in the place provided, and compute the total correct for all rows. Do not mark letters read incorrectly or not read at all. Each letter read correctly is recorded as one. Only move to the next line if 4 or more letters are read correctly. If 3 or more letters are read correctly in the final line, then that line is used for the Snellen equivalent and the visual acuity score. If 2 or fewer letters are read correctly

in the final line, letters read from that line are added to the total visual acuity score and the previous line is used for the Snellen equivalent.

The number of correct letters will be recorded on the study worksheets and entered into the EDC. For the Day 1 Visual Acuity measurement, if two measurements are made, one BSCVA and one with manifest refraction, the latter VA obtained with manifest refraction should be entered into the EDC.

21.3 SLIT LAMP EXAM

Masked assessment: This assessment should be performed by the masked assessor.

A standard slit-lamp examination shall be performed including inspection of the cornea at a magnification of 10X and/or 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.

21.4 TEAR BREAKUP TIME (TBUT)

Masked assessment: This assessment should be performed by the masked assessor.

Preparation of Fluorescein Solution Per the Gyau Method[47]

1. Obtain a tube with the pre-cut Fluorescein strips prepared per the instructions provided in Appendix C. Make sure the pieces of the strips are lying at the bottom part of the tube.
2. 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.

3. Wait 3-15 minutes before using the fluorescein solution.

[47] Gyau DA, Begley CF, Nelson JD. A simple cost effective method for preparing FL and LG solutions. Ocular Surface. 2 018;16:139-145.

Measuring Tear Break-Up Time

1. Using a micropipette, instill 5µL of the fluorescein solution into the lower conjunctival fornix.
2. Measure TBUT quickly after instilling the fluorescein.
3. Use the cobalt blue illumination of the slit lamp and a Wratten filter.
4. Ask the subject to blink 3 times and then hold their eye open (e.g., “Blink, blink, blink, hold”).
5. Using a stopwatch, record the time when the tear film breaks-up.
6. Repeat the test 3 times per eye and take the average of the 3 measurements.
7. Discard the remaining fluorescein solution and microcentrifuge tube.

Tips for Tear Break-up Time

- TBUT is the number of seconds between a blink and the appearance of a first dry spot or negative staining in the tear film.
- TBUT measurements should be done quickly after installation of the dye because, 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.
- Clear instructions should be provided to subjects about the blink and hold sequence
- Clear instructions should be provided to the study staff about when to start the stop watch

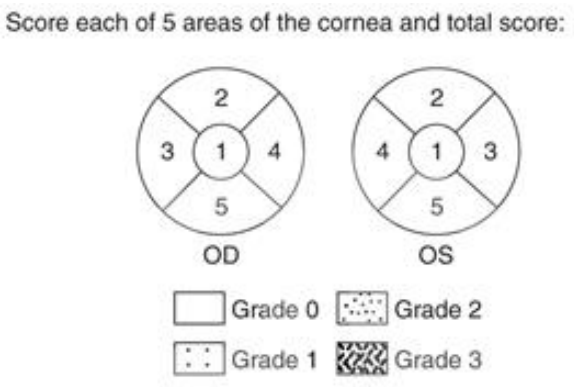
21.5 CORNEAL STAINING

Masked assessment: This assessment should be performed by the masked assessor.

Measuring Corneal staining

1. Measure corneal staining within 1-4 minutes of installation of fluorescein dye to assure the dye does not diffuse into stroma, blurring the discrete margin of any staining defects.
2. Use moderate illumination on the slit-lamp and use cobalt blue filter on with yellow Wratten filter to improve any visualization of corneal staining. Use 3 mm width and 10x magnification for assessing corneal staining. .
3. Grade the corneal staining using the NEI/Industry Grading System provided in Figure 4 below. [48]

Figure 4: NEI/Industry Grading System for Corneal Staining



Grade 0: No staining
Grade 1: Scattered, micropunctate staining
Grade 2: Grouped, micropunctate staining
Grade 3: Diffuse micropunctate or macropunctate staining

Tips for Corneal Staining

- Ask subjects to blink several times to assure the uniform distribution of dye in cul-de-sac
- Make sure to use moderate illumination to avoid hyper reflection from the spots of fluorescein uptake

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

21.6 CONJUNCTIVAL STAINING

Masked assessment: This assessment should be performed by the masked assessor.

Preparation of Lissamine Green Solution Per the Gyau Method[49]

1. Obtain a tube with the pre-cut lissamine green strips prepared per the instructions provided in Appendix C. Make sure the pieces of the strips are lying at the bottom part of the tube.
2. 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.

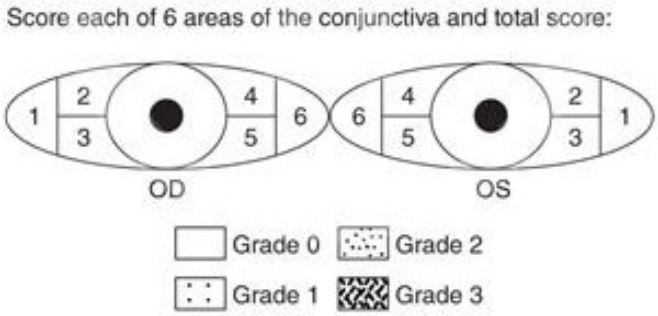
3. Wait 5-15 minutes before using the lissamine green solution.

Grading Conjunctival Staining

1. Instill 5µL of lissamine green solution into the lower conjunctival fornix.
2. Wait at least 1 minute before grading the conjunctival staining. Perform grading within 4 minutes of instilling the solution.
3. Start with a low illumination and increase the level until the lissamine green staining is most visible.
4. Grade the conjunctival staining on moderate illumination per the NEI grading system shown below in Figure 5.
5. After use, discard the remaining solution and microcentrifuge tube.

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

Figure 5: NEI/Industry Grading System for Conjunctival Staining



Grade 0: No staining
Grade 1: Scattered, micropunctate staining
Grade 2: Grouped, micropunctate staining
Grade 3: Diffuse micropunctate or macropunctate staining

Tips for Conjunctival Staining

- Ask subjects to blink several times to assure the uniform distribution of dye in cul-de-sac
- Make sure to identify pooling or a stained mucus strand. Ask subjects to blink a couple of times when in doubt.

21.7 SCHIRMER 1 TEST

The Schirmer 1 Test measures aqueous tear quantity and is an indication of aqueous-deficient dry eye. The Schirmer 1 test, without anesthesia, should be performed by placing the filter strip in the inferior fornix for 5 minutes. Remove the strips and measure wetting in millimeters.

21.8 MEIBOMIAN GLAND SECRETION SCORING

Masked assessment: This assessment should be performed by the masked assessor.

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, [50] 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. Make sure to avoid contact with the ocular surface.

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[51]:

- 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.

21.9 INTRAOCULAR PRESSURE

Masked assessment: This assessment should be performed by the masked assessor.

The same method of measuring intraocular pressure should be used at each visit. Intraocular pressure should be measured with applanation tonometry (e.g. Goldmann tonometer, if available).

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

[51] 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.

21.10 QUESTIONNAIRES

21.10.1 GENERAL INSTRUCTIONS FOR QUESTIONNAIRES

The subject should complete all required questionnaires at the beginning of each visit before conducting other clinical testing. The only exception to this guideline is the Discomfort/Pain Questionnaire administered on Day 0, which is completed by the subject just following the study treatment (refer to instructions provided in Sections 9.5.4 and 9.5.5).

Provide a paper copy of the questionnaires and a blue or black ink pen to the subject. Review the instructions for each 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) without any assistance.

Study staff should review the questionnaires 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.

21.10.2 OSDI QUESTIONNAIRE

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

21.10.3 SANDE QUESTIONNAIRE AND EYE DRYNESS VAS

The SANDE is a simple dry eye instrument containing two items measuring the frequency and severity of symptoms, each is assessed on a 100 mm visual analog scale (VAS) ranging from 'Never/Very comfortable' to 'All the time/Very severe' and scored from 0 to 100. The Eye Dryness Visual Analog Scale measures subject's level of discomfort related to eye dryness ranging from "No discomfort/maximal discomfort."

Three scores will be obtained from the SANDE:

- Frequency score (ranging from 0 to 100): The distance (in mm) between the left end of the scale and the subject's response.
- Severity score (ranging from 0 to 100): The distance (in mm) between the left end of the scale and the subject's response.
- A SANDE Total score (also ranging from 0 to 100): This is calculated as the square-root of the product of the Frequency and Severity scores.

The Eye Dryness Score is derived from the Eye Dryness Visual Analog Scale. The Eye Dryness Score (ranging from 0 to 100) is the distance (in mm) between the left end of the scale and the subject's response.

Study staff should instruct subjects to record their response to each question by placing a vertical line (not an "X") across the horizontal line of the visual analog scale.

21.10.4 DISCOMFORT/PAIN QUESTIONNAIRE

The Discomfort/Pain Questionnaire is designed to assess the degree of discomfort or pain that the subject experiences during and immediately after the study treatment on Day 0 and post-treatment (Day 1). Subjects are asked to indicate their level of discomfort and pain using a Visual Analog Scale provided in the case report forms.

22 APPENDIX B – STATISTICAL ANALYSIS PLAN

22.1 EFFECTIVENESS ENDPOINTS AND ANALYSIS METHODS

22.1.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoints are the change from baseline in Tear Break-Up Time (TBUT) and the total Meibomian gland secretion score (MEIB) at the 1 month follow up. Change is calculated as: 1 month – baseline, so a positive change is better. Both endpoints will be analyzed using a linear mixed effects (LME) model. This will allow for the proper incorporation of within-person correlation into the statistical tests, and will also allow for adjustment for baseline measurements. Both of these should increase the power over the simple "t-test using one eye" approach.

Since the SmartLid device was modified during the trial, all effectiveness analyses will be carried out with the Cohort 2 subjects only (i.e. subjects enrolled after the modified device was introduced). The primary effectiveness outcomes of the Cohort 1 subjects will be summarized separately by descriptive statistics (mean, median, standard deviation, minimum, and maximum).

The linear mixed effects model for TBUT can be written as follows:

$$y_{ij} = \beta_0 + \beta_1 T_i + \beta_2 TBUT_{ij,0} + b_{0i} + \epsilon_{ij}$$

Where

- $TBUT_{ij,k}$ is the TBUT value for subject *i*, eye *j*, week *k*.
- y_{ij} is the 1 month change from baseline TBUT for subject *i*, eye *j*.
  $$y_{ij} = TBUT_{ij,4} - TBUT_{ij,0}$$
- T_i is the binary treatment indicator for subject *i* (0 = LipiFlow, 1 = TearCare)
- $\beta_0, \beta_1, and\ \beta_2$ are the fixed effect parameters:
  - β_0 is the mean change from baseline for the LipiFlow arm,
    β_1 is the difference between TearCare and LipiFlow in mean change from baseline,
  - β_2 is the effect of each unit change in baseline TBUT.
- $b_{0i}$is the random effect (random intercept term) for subject *i*
  $$b_{0i} \sim N(0, \sigma_a^2)$$
- ϵ_{ij} is the normally-distributed error term
  $$\epsilon_{ij} \sim N(0, \sigma_e^2)$$
- $\{b_{0i}\}$ and $\{\epsilon_{ij}\}$ are independent

To demonstrate non-inferiority of the TearCare treatment to the LipiFlow control for TBUT we will test the null hypothesis that β_1 is less than the non-inferiority margin of 3 seconds:

$$H_0: \beta_1 \leq -3.0$$
$$H_A: \beta_1 > -3.0$$

That is, we seek to reject the non-inferiority null hypothesis that the TearCare change in TBUT is more than 3 seconds worse than the LipiFlow change in TBUT.
For this model there are several equivalent ways to carry out this test:

- Using our estimates of β_1 and its standard error, carry out a t-test for the hypothesis.
- Form a confidence interval for β_1 and show that the lower bound is above -3.0 seconds,
- Calculate the least squares mean (LSM) at the mean baseline TBUT for the contrast between treatment and control, and its associated confidence interval, and show that the lower bound is above -3.0 seconds.

We will use the third (LSM) method since it provides the most flexibility, also allowing exploratory analyses examining the effects of other covariates, contrasts between groups, etc.

As is standard practice in non-inferiority studies, all tests will be carried out at a one-sided $\alpha = 0.05$ (or equivalently, using two-sided 90% confidence intervals).

The MEIB endpoint will use the same model and the same testing methods. To demonstrate non-inferiority of the TearCare treatment to the LipiFlow control for MEIB we will test the null hypothesis that β_1 is less than the non-inferiority margin of 5 units:

$$H_0: \beta_1 \leq -5.0$$
$$H_A: \beta_1 > -5.0$$

The study will be a success if the non-inferiority null hypothesis is rejected for both TBUT and MEIB. No alpha adjustments for multiplicity are necessary.

If the two non-inferiority nulls are rejected then each will be re-tested for superiority (that is, against 0.0 instead of the non-inferiority margin). If the TearCare device is superior to the LipiFlow control for either endpoint (or both) it will be declared superior for that endpoint (or both).

The linear mixed effects models can be fit in SAS or R as follows:

In SAS:

```
Proc Mixed data=TearCare method=ml;
   class SUBJ TRT;
   model TBUT_DIFF =  TRT TBUT_BL  / solution;
   random intercept / subject=SUBJ;
```

In R:

```
Library(lme4)
fit.tbut <- lmer(TBUT.DIFF ~ TRT + TBUT.BL + (1|SUBJ) ,
REML=FALSE, data=TearCare)
```

Note that since we are interested in testing the fixed effects, ML (maximum likelihood) versus REML (residual maximum likelihood) estimates are being used.

If the estimated between-subject variance $\hat{\sigma}_a^2$ is close to 0 we will repeat the analysis without the random intercept term (that is, as a standard ANCOVA without a random patient effect).

There are different options for calculating the standard errors/confidence intervals. Standard diagnostic tests and plots for outliers, normality of the errors, homogeneity of variances, and homogeneity of slopes will be provided. Based on prior data there is every reason to expect that the TBUT and MEIB errors will be approximately normally distributed. However, if residuals do not appear sufficiently normally distributed, we will calculate the confidence interval for β_1 using bootstrap methods.

If the ANCOVA model is unsatisfactory (e.g. linearity of change with respect to baseline is not supported, or the slopes are different) then we will test the primary hypotheses and compute the confidence interval for the difference in change from baseline between the two treatments based on a LME model without the baseline covariate (i.e. a t-test with adjustment for correlation).

22.1.2 POOLABILITY OF CENTERS

Using the LME modeling approach outlined above, poolability will be evaluated across centers by including fixed effects for Center and Treatment by Center interaction in the model and applying a likelihood ratio test. If the TxC interaction is significant at α=0.15 a Center effect will be included in the final model and the results will be reported separately by Center. For this analysis, Centers with less than 5 enrolled subjects will be combined into a single virtual center.

22.1.3 MISSING DATA

Note that since the primary analysis uses maximum likelihood methods on the complete data then any MAR (missing at random) imputation model should provide essentially equivalent results. That is, the missing data are ignorable if they are MAR and we are using full maximum likelihood estimation. However, as a sensitivity analysis, missing data for the primary TBUT outcome at the 1 month time point will be imputed using baseline characteristics and 2-week outcomes. In this, we follow the advice in sections 2.8 and 2.10 of "Multiple Imputation and its Application"[52] to use an imputation model that is more complex than the final analysis model. In order to carry out the imputations we will fit a linear model that predicts TBUT change at 1 month using TBUT at baseline and 2 weeks, along with other covariates, as predictors. Based on pilot study data, we expect that 1 month outcomes will be strongly predicted by intermediate (2 week) results. Using predicted 4-week means and variances from this model we can create multiple imputations for the missing 4-week TBUT changes. Results from the multiple imputations will be combined using Rubin's method.

Further sensitivity analysis can be carried out by extending the mixed effects model for the primary analysis described above to also include repeated measurements across time for each patient and eye. Under this model we can carry out maximum likelihood estimation that allows for one of the two (Week 2, Week 4) measurements for each person to be missing.

22.1.4 SECONDARY EFFECTIVENESS ENDPOINTS

If the primary endpoint is successful (if the null hypothesis for the primary endpoint is rejected) then the secondary endpoints will be tested using a hierarchical testing procedure as described in 12.5.5 based on the Cohort 2 subjects.

The secondary effectiveness outcomes of the Cohort 1 subjects will be summarized separately by descriptive statistics (mean, median, standard deviation, minimum, and maximum for continuous variables; count and percent for categorical variables).

22.2 SAFETY ENDPOINTS AND ANALYSIS

22.2.1 DESCRIPTIVE ANALYSES

All adverse events, measures of pain and discomfort, changes in ocular surface staining, changes in IOP, and chances in BCVA (EDTRS) will be tabulated by visit and treatment group.

[52] Carpenter, J., and Kenward, M. Multiple Imputation and its Application (2013), Wiley UK.

22.2.2 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the incidence of ocular adverse events.

22.2.3 PRIMARY SAFETY ANALYSIS

The primary safety endpoint will be summarized for each treatment group, for each Cohort and overall.

We will compute the incidence of ocular adverse events as a simple proportion, counting the number of subjects with any event (that is, counting the first event per person).

For the simple proportion, we will calculate the 95% CIs using the Agesti and Coull "ADD2" method[53].

22.2.4 SECONDARY SAFETY ENDPOINTS

The secondary safety endpoints include:

- Discomfort/pain during treatment
- Change in best corrected visual acuity (ETDRS)
- Change in intraocular pressure (IOP)

These endpoints will be summarized by treatment group and visit, for each Cohort and overall.

22.3 SAMPLE SIZE CALCULATIONS

Sample size calculations were originally carried out prior to the modification of the SmartLid device. After device modification the trial was "restarted", with Cohort 2 retaining the original sample size of 138 subjects. The subjects initially enrolled in Cohort 1 (up to 100 subjects) will be used in supplemental analyses and to provide additional safety information.

Since the study success criteria is that TearCare will be non-inferior to the control for both TBUT and MEIB, we will calculate the required sample size for Tear Break-Up Time (TBUT) and total Meibomian gland secretion score (MEIB) separately. A power of 95% for each of these two outcomes will produce an overall experiment-wise power between 90.25% (if TBUT and MEIB are uncorrelated), and 95% (if TBUT and MEIB are perfectly correlated).

[53] Agresti, A., and B.A. Coull (1998) Approximate is better than "exact" for interval estimation of binomial proportions. American Statistician 52:119-126.

The primary Tear Breakup Time (TBUT) and total Meibomian gland secretion score (MEIB) endpoints are measured on a per-eye basis. In order to account for the correlation between eyes the sample size is calculated in two steps. The first step is to carry out a standard sample size calculation for the number of eyes based on a two-sample t-test with unequal variances. This test is appropriate for a sample of independent eyes from the two groups, that is, a study in which only one eye per subject is enrolled. The second step is to allow for two eyes per subject by adjusting the independent sample size to account for the correlation between eyes.[54] This is done by multiplying by a "design effect" (DEFF) that can be calculated from the pilot study data (described in Section 5.2.2). Finally we allow for some loss to follow up and then divide by 2 (eyes per subject) to arrive at a final enrolled sample size in terms of number of subjects.

This sample size calculation does not account for the adjustment for baseline in the analysis models. That adjustment should only serve to increase the power of the test, so the simpler calculation is conservative in that sense.

22.3.1 TEAR BREAKUP TIME

For the TBUT sample size calculation, we assume the same positive treatment effect for TearCare and for LipiFlow, reducing the TBUT time per eye by 3 seconds, with a standard deviation of 6.0 seconds. The standard deviation for the change from baseline to 1 month was (conservatively) estimated for TearCare from the pilot data, and for LipiFlow from published results[55].

The sample size is calculated under the following assumptions:

- a one-sided $\alpha = 0.05$ t-test for non-inferiority,
- with a NI margin of 3.0 seconds,
- to obtain 95% power.

The non-inferiority margin was based on published LipiFlow variability[55]. Under these assumptions the required sample size is 176 eyes, 88 eyes per treatment group.

The design effect for a clustered sample when randomization is at the cluster level is calculated as $DEFF = 1 + \delta(m - 1)$ where δ is the intraclass correlation and *m* is the

[54] Campbell M, Walters, S. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley UK, 2014.

[55] Lane, S.S, H.B. DuBiner, R.J. Epstein, P.H. Earnest, J.V. Greiner, D.R. Hardten, E.J. Holland, M.A. Lemp, J.E. McDonald II, D.I. Silbert, C.A. Blackie, C.A. Stevens, and R. Bedi. A New System, the LipiFlow, for the Treatment of Meibomian Gland Dysfunction. Cornea 2012; 31(4): 396-404.

average size of the clusters in the sample[56]. Here *m*=2 so $DEFF = 1 + \delta$. To estimate the intraclass correlation we fit a linear mixed effects model with a random intercept for subjects to obtain estimates of σ_a^2 and σ_e^2. Using these we can estimate the intraclass correlation as $\delta = \sigma_a^2/(\sigma_a^2 + \sigma_e^2)$. From the TearCare pilot data the estimates of the variance components for TBUT are $\hat{\sigma}_a^2 = 1.92$ and $\hat{\sigma}_e^2 = 3.39$, giving a DEFF of 1.36. We will assume that the intraclass correlation for LipiFlow is the same as TearCare. So the sample size calculated using the t-test formulas will be inflated by 1.4 to account for correlation between eyes. Thus the DEFF-adjusted sample size is 246 eyes.

Finally, we will assume that 10% of the enrolled subjects (eyes) will be lost to follow-up. The resulting sample size is 274 enrolled eyes, or 137 enrolled subjects (which we round up to 69 per group).

22.3.2 MEIBOMIAN GLAND SECRETION SCORE

For the MEIB sample size calculation, we assume the same positive treatment effect for TearCare and for LipiFlow, reducing the total Meibomian gland secretion score per eye by 9 units, with a standard deviation of 9.0. The standard deviation for the change from baseline to 1 month was (conservatively) estimated for TearCare from the pilot data, and for LipiFlow from published results[55].

The sample size is calculated under the following assumptions:

- a one-sided $\alpha = 0.05$ t-test for non-inferiority,
- with a NI margin of 5.0 units,
- to obtain 95% power.

The non-inferiority margin was based on published LipiFlow variability[55]. Under these assumptions the required sample size is 142 eyes, 71 eyes per treatment group.

From the TearCare pilot data the estimates of the variance components for MEIB are $\hat{\sigma}_a^2 = 15.93$ and $\hat{\sigma}_e^2 = 20.11$, giving a DEFF of 1.44. We will assume that the intraclass correlation for LipiFlow is the same as TearCare. So the sample size calculated using the t-test formulas will be inflated by 1.5 to account for correlation between eyes. Thus the DEFF-adjusted sample size is 213 eyes.

Finally, we will assume that 10% of the enrolled subjects (eyes) will be lost to follow-up. The resulting sample size is 237 enrolled eyes, or 119 enrolled subjects (which we round up to 60 per group).

[56] Campbell M, Walters, S. How to Design, Analyse and Report Cluster Randomised Trials in Medicine and Health Related Research. Wiley UK, 2014.

22.3.3 SAFETY

For a safety sample of size 238 TearCare eyes (from Cohort 1 and Cohort 2) (since the expected AE rates are quite low there is unlikely to be any meaningful correlation between eyes), if the true incidence rate of ocular adverse events is 2.0% or less then the upper 95% one-sided confidence limit for the AE rate will be less than 6% with probability approximately 0.95. In other words, the power to reject a null of 6% if the true rate is 2.0% is 95%.

22.3.4 SAMPLE SIZE SUMMARY

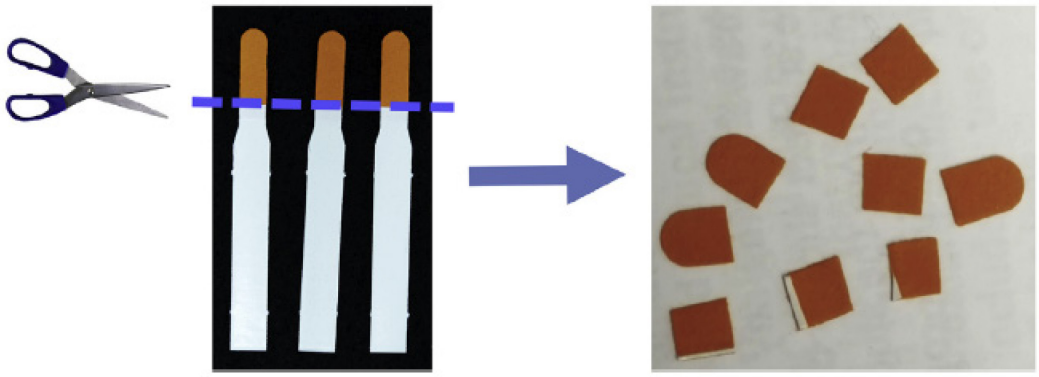
Based on the calculations outlined above, an overall enrolled sample of 138 individuals in Cohort 2, with 69 in each treatment group (total of 276 enrolled eyes) will provide more than 90% power for the combined TBUT and MEIB effectiveness endpoints and sufficient precision around the adverse event estimates. The initial 90-100 subjects enrolled in Cohort 1 will be used for supplemental analyses.

23 APPENDIX C – PREPARING FLUORESCEIN AND LISSAMINE GREEN SOLUTIONS

Use the method described by Gyau et al to prepare the fluorescein and lissamine green solutions.[57]

23.1 PREPARING FLUORESCEIN SOLUTION

1. Put on a pair of sterile gloves.
2. 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.

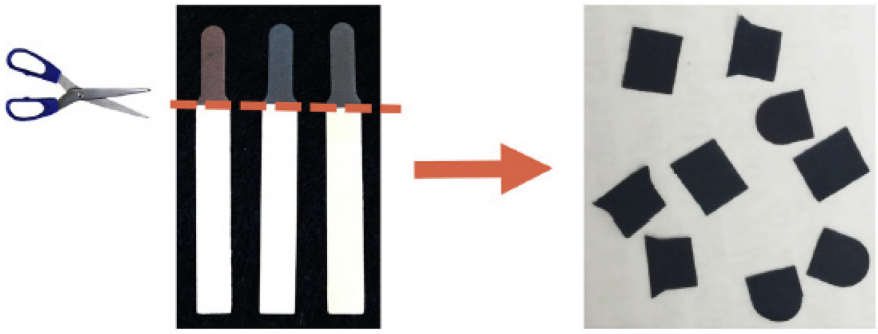


3. Place the 9 pieces into a disposable microcentrifuge tube.

23.2 PREPARING LISSAMINE GREEN SOLUTION

1. Put on a pair of sterile gloves.
2. 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.

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



3. Place the 9 pieces into a disposable microcentrifuge tube.

24 APPENDIX D - 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.