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

PROTOCOL ID #:	07093
CURRENT VERSION:	H
REVISION DATE:	August 26, 2022
SPONSOR:	Sight Sciences, Inc. 4040 Campbell Avenue, Suite 100 Menlo Park, CA 94025 877-266-1144

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	10-09-2020	3308
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1 PROTOCOL SYNOPSIS

Protocol Title	Prospective, Randomized, Masked, Controlled Trial to Evaluate the Safety and Effectiveness of the TearCare® System in the Treatment of the Signs and Symptoms of Dry Eye Disease (SAHARA)
Protocol ID Number	07093
Study Device	TearCare® System
Control Group	Restasis® (0.05% Cyclosporine ophthalmic emulsion)
Primary Objective	To demonstrate the safety and effectiveness of TearCare® procedures compared to Restasis® to treat the signs and symptoms of dry eye disease in adult patients.
Study Design	Prospective, randomized, masked, multi-center, superiority, non-significant risk study.
Primary Effectiveness Endpoint	Mean Change from baseline in: o Tear Break-Up Time (TBUT) o Ocular Surface Disease Index (OSDI) score Superiority will be assessed at 6 month
Secondary Effectiveness Endpoints	Mean Change from baseline in: o Total Meibomian Gland Secretion Score o Corneal staining scores o Conjunctival staining scores o Number of Meibomian Glands Yielding any liquid o Number of Meibomian Glands Yielding clear liquid o Symptom Assessment in Dry Eye (SANDE) scores o Eye Dryness Score o Schirmer score o Ocular protection index (OPI): Interblink interval (IBI)/TBUT
Primary Safety Endpoint	o Procedure (TearCare)/Treatment (Restasis)-related adverse events
Secondary Safety Endpoints	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 to 6 months 3. Reports having to use artificial tears or lubricants regularly over the past month to relieve dry eye symptoms. 4. Schirmer tear test (with anesthesia) ≥5 to ≤15 mm in 5 minutes 5. OSDI Score of 23-79 6. TBUT of ≥1 to ≤7 seconds in both eyes 7. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤12 in each eye. 8. At least 15 glands in each lower eyelid should be expressible, with a sterile cotton swab, at the slit lamp. 9. Best corrected visual acuity of 20/100 or better in both eyes. 10. Willing and able to comply with the study procedures and follow-up 11. Willing and able to provide informed consent 12. English-speaking

Exclusion Criteria	1. Use of any of the following medications: a) Cyclosporine (Restasis, Cequa etc.) or Xiidra and serum tears within 60 days prior to baseline; b) Antihistamines (oral or topical) within 7 days prior to baseline. c) Systemic medication(s) that is known to cause ocular dryness (e.g., diuretics, anti- hypertensives, anti-depressants, antihistamines, hormone therapy) and whosedose of this medication(s) has not been stable within 30 days prior to baseline. There must be no anticipated adjustments to the dose of these medications for the durationof the trial. d) Accutane (at any time); e) Oral tetracyclines or azithromycin within 30 days prior to baseline; or f) Topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications within 30 days prior to baseline. 2. Any of the following dry eye treatments: a) Office-based dry eye treatment (e.g. IPL, TearCare, thermal pulsation [LipiFlow], iLux etc.) within 12 months prior to baseline either as part of routine care or clinical investigation; b) Planned or recent surgical procedures to the eye or eyelid (90 days prior to baseline) c) Meibomian gland expression within 6 months prior to baseline; d) Blephex or debridement within 3 months prior to baseline is an exclusion; e) Punctal occlusion or punctal plugs. Investigators can choose to remove the punctal plugs 15 days prior to baseline; f) Use of tear neurostimulators (i.e., True Tear, iTear100, Tyrvaya) within 2 weeks of the baseline visit. (Subjects must refrain from using tear neurostimulators for the durationof the study.); or g) Any history of meibomian gland probing 3. History of eyelid, conjunctiva, or corneal surgery (including refractive surgery) within the past year prior to baseline. 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 2 weeks of the baseline visit. 5. Active hordeolum, stye, or chalazion at the time of the baseline visit. 6. History of Herpes Simplex or Herpes Zoster of the eye or eyelid. 7. Any active, clinically significant ocular or peri-ocular infection, inflammation, or irritation.

	8. Recurrent clinically significant eye inflammation, other than dry eye, within 3 months prior to baseline. 9. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded. 10. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, distichiasis, trichiasis). 11. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area. 12. 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. 13. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g., pterygium, anterior membrane dystrophy, Salzmann's nodules, etc.) 14. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea 15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis. 16. Ocular trauma within 3 months prior to baseline. 17. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation 18. Systemic diseases resulting in dry eye (e.g. autoimmune diseasessuch as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.) 19. Subject is currently using Retin A /Retin A derivatives. 20. Subject has permanent eyeliner/lid tattoos, eyelash extensions or wears false eyelashes. 21. Subject is currently using Latisse, Lash Boost or any other type of eyelash growth serum. 22. Allergies to silicone tissue adhesives, acrylates and/or copper. 23. Subject has a pacemaker or implantable cardiac defibrillators (ICD). 24. Participation in another ophthalmic clinical trial 30 days prior to baseline. Subject must also be willing to refrain from another ophthalmic study for the duration of the study. 25. 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 theprotocol. For example, subjects who are pregnant or nursing or have active, wet macular degeneration are excluded.

Number of Subjects Enrolled	Approximately 412 enrolled
Randomization	1:1
Number of Centers	Up to 25
Study Duration for Each Subject	Up to 24 months
Total Study Duration	Approximately 40 to 50 months
Schedule of Visits	TearCare group (Study Device): Baseline, Procedure Day 0, Day 1, Week 1, Month 1, Month 3, Month 5, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24 TearCare procedure will be given within 7 days of Baseline and at 5 Months. Beginning at 9 Months, subjects will receive an additional TearCare procedure when TBUT drops lower than Baseline or within 2 seconds of baseline AND if OSDI worsens by at least 15 points compared to the previous visit*. *(*Based on the recommended cutoffs for OSDI Total score, the severity of the subject's dry eye symptoms is categorized as; Normal – 0-1, Mild – 13-22, Moderate – 23-32, Severe – 33 or higher)* Restasis group (Control): Baseline, Restasis Day 0, Day 1, Week 1, Month 1, Month 3, Month 6 Subjects will be required to self-administer 1 drop twice a day from baseline through the Month 6 visit. At Month 6, subjects from the Restasis group will be crossed over to the TearCare group and will receive one (1) TearCare procedure and will be followed as below: Day 1, Week 1, Month 1, Month 9, Month 12

2 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of TearCare® procedures when compared Restasis® to treat the signs and symptoms of dry eye disease in adult patients.

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 sufferfrom dry eye. The prevalence of dry eye disease increases with age, especially in postmenopausal women. It is estimated that dry eye disease affects more than 7 million Americans older 40 years of age[1], and approximately 1 million to 4 million Americans between 65 to 84 years of age.3

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

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

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

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

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

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

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

[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.

concluded the following: "Since both aqueous tear deficiency and increased evaporative tear loss occur in most cases of dry eye disease and are linked by common pathogenetic mechanisms, expert clinicians are increasingly basing treatment decisions on an assessment of severity rather than discrete deficiencies."8

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

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

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

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

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

[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

[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.

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.

Current treatment for MGD includes lid hygiene, oral tetracycline, doxycycline or minocycline, topical erythromycin or bacitracin ointments, homogenized castor oil eye drops, topical corticosteroids and 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 has been shown that warm compress therapy can lead to improved lipid production and flow on to the tear film.[18,19,]
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]

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

[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
[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.

compliance. As a result, various alternative approaches to heating the eyelids have been proposed. [24,25,26,27,28]

Cyclosporine 0.05% (Restasis®) is a highly specific immunomodulator that primarily affects T-lymphocytes, and it does not inhibit the phagocytic system as much as corticosteroids. To date, topical cyclosporine has been clinically shown to increase production of a patient's own natural tears in chronic dry eye, MGD, ocular rosacea, and contact lens intolerance. [29,30] In the treatment of MGD, after three months post-treatment, multiple objective clinical findings were reduced. Lid margin vascular injection and tarsal telangiectasis improved, the mean fluorescein staining score was decreased, and the tear break-up time was improved after cyclosporine use for 3 months.[31] It is believed that the cyclosporine ameliorates MGD by addressing underlying pathophysiology. The abnormal meibum has a melting point above the ocular surface temperature that solidifies and obstructs the ducts, leading to further inflammation and perpetuating the vicious cycle. As topical cyclosporine is a highly specific immunomodulator that affects primarily T-lymphocytes, it may decrease the inflammation of the meibomian glands and reduce their plugging and dysfunction.

In this study, the safety and effectiveness of the TearCare System in patients with dry eye disease will be evaluated. The objective is to evaluate whether the TearCare System is safe and effective in relieving the signs and symptoms of dry eye disease and if it is superior to Cyclosporine 0.05% (Restasis®).

[24] 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.

[25] 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.

[26] Mori A, Oguchi Y, Goto E, et al. Efficacy and safety of infrared warming of the eyelids. Cornea. 1999;18:188–193.

[27] 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.

[28] 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.

[29] Perry HD, Doshi-Carnevale S, Donnenfeld ED, Kornstein HS. Topical cyclosporine A 0.5% as a possible new treatment for superior limbic keratoconjunctivitis. Ophthalmology. 2003;110(8):1578-1581. doi:10.1016/S0161-6420(03)00538-4

[30] Stonecipher K, Perry HD, Gross RH, Kerney DL. The impact of topical cyclosporine A emulsion 0.05% on the outcomes of patients with keratoconjunctivitis sicca. Curr Med Res Opin. 2005;21(7):1057-1063. doi:10.1185/030079905X50615

[31] Perry HD, Doshi-Carnevale S, Donnenfeld ED, et al., Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea (2006);25:pp. 171–175.

4. DESCRIPTION OF DEVICE

4.1. DEVICE DESCRIPTION

The Sight Sciences' TearCare System being studied in this study is comprised of the following components:

- SmartLid™ devices
- SmartHub™ Kit, including SmartHub, SmartHub Nest, and Charging Adapter
- Clearance Assistant Plus™ devices with debridement edge

The SmartLid devices are custom designed to conform to the tarsal plate of each respective eyelid allowing subjects to blink normally throughout the procedure and naturally express melted meibum with every blink. Immediately following the thermal procedure, the physician uses the Clearance Assistant device to further express the meibomian glands manually to maximize the evacuation of melted meibum. The Clearance Assistant also provides a tool for debridement to thoroughly remove any blockages at the meibomian gland orifices to facilitate and enhance natural and manual meibum evacuation.

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 subject 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 Plus device (shown in Figure 3 below) is single-use, sterile device that is designed to facilitate debriding the eyelid margin. It also allows for manual expression of the meibomian glands after the application of heat by the TearCare SmartLid devices.

Figure 1: SmartLid Devices applied to the Eyelids

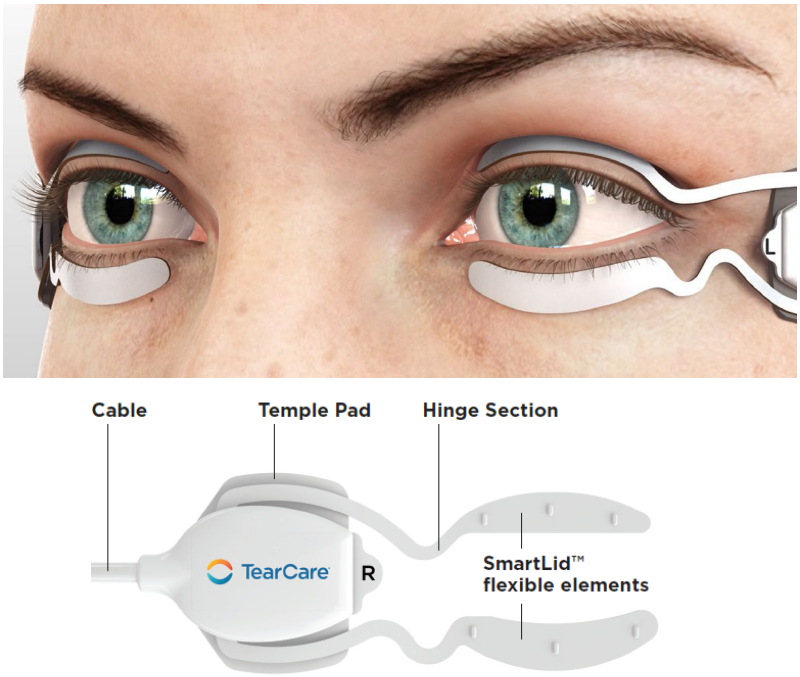


Figure 2: TearCare SmartHub

No.	Function
1	Power button
2	Warmth setting increase button
3	Warmth setting indicator #4 (of 5)
4	Active therapy indicator
5	Warmth setting decrease button
6a	SmartLid Port - left
6b	SmartLid Port - right
7	Charging Port
8a	SmartLid error indicator - left
8b	SmartLid error indicator - right
9	Remaining Procedures (battery indicator)
10	Timer complete indicator
11	Timer indicators

Figure 3: Clearance Assistant Plus Device

In this study, the investigator will use the Clearance Assistant device to debride all four eyelid margins by sweeping (very gently scraping) the debridement edge across the lid margin and line of Marx's back and forth going over meibomian gland orifices. Then the flexible SmartLid device will be applied to the external surface of the upper and lower eyelids of the subject (Figure 1). The SmartLids will then be connected to the TearCare SmartHub. When the SmartHub is turned on the investigator will initiate the procedure and the TearCare System will begin delivering heat to the eyelids. The system should automatically and gradually increase the temperature over 2-3 minutes until it reaches the maximum set point temperature of 45°C. A complete TearCare procedure under this study is anticipated to last 15 minutes.

The SmartHub has 5 temperature set points (ranging from 41 to 45°C), which are intended to allow the investigator 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 procedure. Subjects are able to blink naturally during the session.

The temperature range for the TearCare System used in this study 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 procedure duration for this study were also chosen because they are below the time-temperature threshold at which heat contacting the skin will first show signs of

[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.

cutaneous damage and edema and are within the safety limits specified for medical electrical equipment.[35,36,37]

Immediately following the TearCare procedure, the investigator will use the Clearance Assistant device to manually express the meibomian glands in all four eyelids under direct visualization.

4.2. DEVICE RECALL

In March 2022, Sight Sciences, Inc issued a voluntary recall of the SmartHubs. This recall was initiated in response to recent feedback received from the FDA wherein they believed the SmartHub devices did not appropriately fall within a 510(k)-exemption due to technological variances. The information received from the FDA indicated that the SmartHub was incorrectly categorized and consequently outside the 510(k)-exemption due to its technological differences from other devices within that product code.

There was no elevated safety concern. As a result, all clinical sites and the IRB were notified of the recall and return material authorizations (RMAs) were issued. Sight Sciences decided to replace all existing SmartLids and SmartHubs with a newer version of SmartLids and SmartHubs which resulted from the insignificant modifications to the current study devices as described below in section 4.3.

4.3. DEVICE MODIFICATION

- The SmartLid device was modified to include pre-curved lids with removeable liners on the adhesive elements (temple pad and lids). The pre-curved lids conform to the shape of the eyelids with less manipulation by the clinician, potentially eliminating the manual bending step.

- Artwork changes were made to the SmartHub membrane switch to improve visualization of the current functions such as (1) Clearly identifiable power button, (2) Left/right SmartLid port use indicators, (3) timer indications (0, 3, 15 minutes), and (4) remaining battery/procedure counter. All user interactions remain the same. No changes were made to the thermal functionality and intended use of the system.

- The intended use for the new 510(k)-cleared TearCare system was updated to the following: “The TearCare® System is intended for the application of localized heat therapy in adult patients with evaporative dry eye disease due to meibomian gland dysfunction (MGD), when used in conjunction with manual expression of the meibomian glands”. Additionally, during the 510(k) review, the TearCare system software was updated by modifying the temperature regulation algorithm. This algorithm receives feedback regarding the temperatures being sensed at the thermistors in the SmartLids and runs continuously in the

background during each therapy session. The TearCare system therapeutic temperature settings and timing have not changed.

4.4. INSTRUCTIONS FOR USE

Instructions for Use for the TearCare System and Clearance Assistant device for this study will be provided to each investigator.

4.5. TRAINING

Prior to the start of the study, investigators and study staff will be trained on the proper use of the TearCare System, as needed. Investigators will also be trained in the method of lid debridement and manual expression described in this protocol. 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 following testing and analyses were 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 procedure. 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.

[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).

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 meet its performance specifications 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

5.2.1. CLINICAL STUDY OF THE PROTOTYPE TEARCARE SYSTEM (2013)

The TearCare System has been evaluated in four 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). The third study was conducted in 2018 wherein subjects received a single TearCare® treatment. The fourth and most recent study was initiated in 2019 to study the safety and effectiveness of a single treatment with the TearCare® System compared to a single treatment with LipiFlow® (Johnson & Johnson). All four studies are summarized below.

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.

Results from this study informed the decision to continue development on the TearCareSystem.

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)

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 for the treatment of signs and symptoms of dry eye disease.

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.

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)

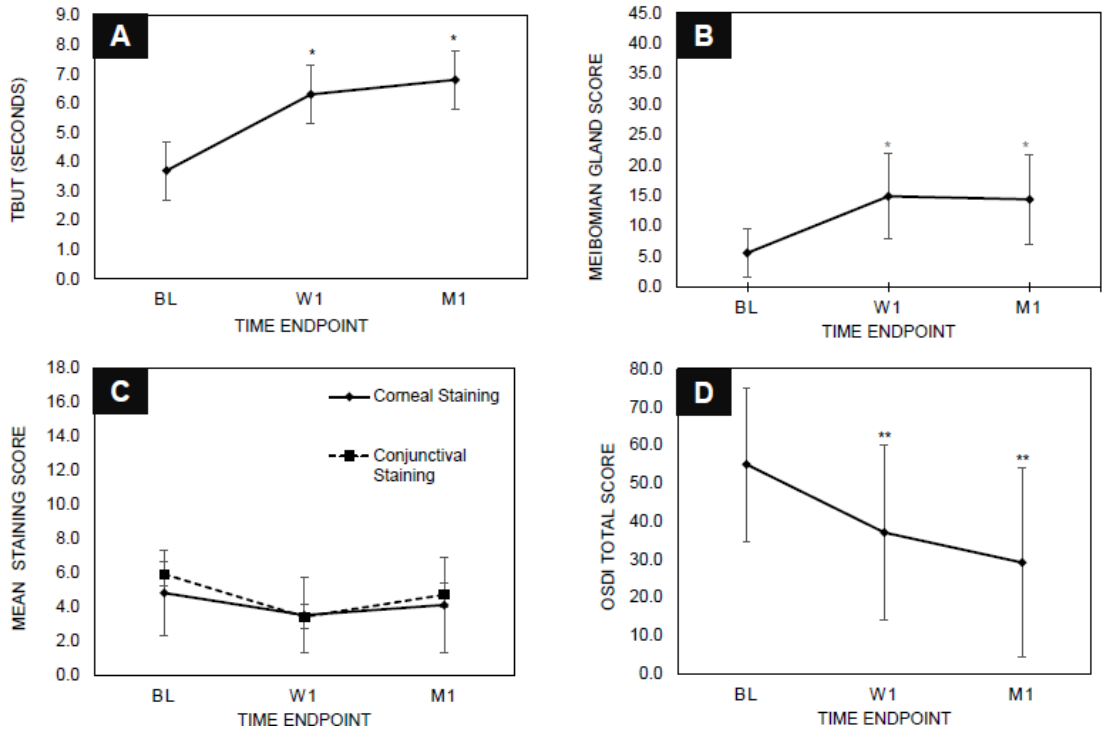
5.2.3. CLINICAL STUDY OF THE TEARCARE SYSTEM-CHEETAH (2018)

The CHEETAH study was a multicenter, prospective, exploratory, interventional trial, involving 58 eyes (29 subjects) that received a single TearCare® treatment and were assessed at baseline, post-procedure one week and one month. The primary success endpoint was assessed as the mean change from baseline in TBUT, Ocular Surface Disease Index (OSDI), total Meibomian Gland Secretion Score (MGSS) and corneal/conjunctival staining. Adverse events and changes in visual acuity were measured to assess safety.

The baseline TBUT of 3.7±1.1 seconds was improved by 2.6±1.6 (70%) seconds at one week and by 3.1±2.2 (84%) seconds at one month. Mean baseline OSDI of 54.9±20.2 improved by 17.9±20.9 at one week and 25.8±24.3 at one month. The baseline MGSS of 5.6±4.0 improved by 9.3±4.0 at one week and 8.8±5.8 at one month. Corneal and conjunctival staining improved by 1.4±2.8 and 1.2±2.9 from a mean baseline of 4.8±2.5

and 5.9±3.2, respectively. No device-related adverse events or significant changes in visual acuity were observed. Results are shown in Figure 4 below:

Figure 4: MGSS, TBUT, OSDI and Corneal-Conjunctival Staining by Visit



5.2.4. CLINICAL STUDY OF THE TEARCARE SYSTEM-OLYMPIA (2019)

The OLYMPIA study was a prospective, masked, multi-center RCT conducted at ten U.S. sites designed to study the safety and effectiveness of a single treatment with the TearCare® System in treating the signs and symptoms of DED associated with MGD in comparison with a single treatment with LipiFlow® (Johnson & Johnson).
Subjects with signs and symptoms of DED and MGD (N=136) were randomized 1:1 to a single treatment of either TearCare® or LipiFlow®. Key inclusion criteria were regular use of lubricating drops, Ocular Surface Disease Index (OSDI score between 23 to 79 (moderate to severe), Meibomian gland secretion score (MGSS ≤ 12, TBUT of ≤ 7 seconds, and at least 15 expressible glands in each lower eyelid. TBUT and MGSS were measured as primary endpoints. Secondary endpoints included Corneal conjunctival staining, number of meibomian glands yielding clear and any liquid recorded. To reduce potential bias in subjective endpoint assessments, the clinician performing the treatments did not perform the endpoint assessments and the clinician performing the endpoint assessment was blinded to which treatment the patient had received.
Symptoms were recorded in the form of OSDI, Symptom Assessment in Dry Eye (SANDE) and Eye Dryness Severity (EDS) questionnaires. Non-inferiority of TearCare® compared

to LipiFlow® in improving TBUT and MGSS was evaluated at one month. Any adverse events, either patient reported, or observed by the investigators, were recorded for safety.

Both groups demonstrated improvements in mean TBUT and MGSS, 3.0 ± 4.4 and 11.2 ± 11.1 in the TearCare® group and 2.6 ± 3.3 and 11.09 ± 10.4 in the LipiFlow® group. In the TearCare® group, mean corneal and conjunctival staining were reduced respectively by 0.3 ± 1.2 and 0.7 ± 2.2; the mean number of expressible glands and glands expressing clear liquid increased respectively by 4.3 ± 3.6 and 1.8 ± 3.7 (Figure 5). The TearCare® group showed an improvement in mean SANDE, EDS and OSDI scores respectively by 38.2 ± 31.0, 35.4 ± 34.1 and 27.9 ± 20.6 (Figure 6).

Device related ocular adverse events were reported in two subjects (loss of visual acuity) for the TearCare® group and three subjects (loss of visual acuity, corneal abrasion and foreign body sensation) for the LipiFlow® group.

Figure 5: TBUT, MGSS, Corneal and Conjunctival staining per follow up time point. Bluelegends, line and bars represent TearCare group and red legends, line and bars represent LipiFlow group.

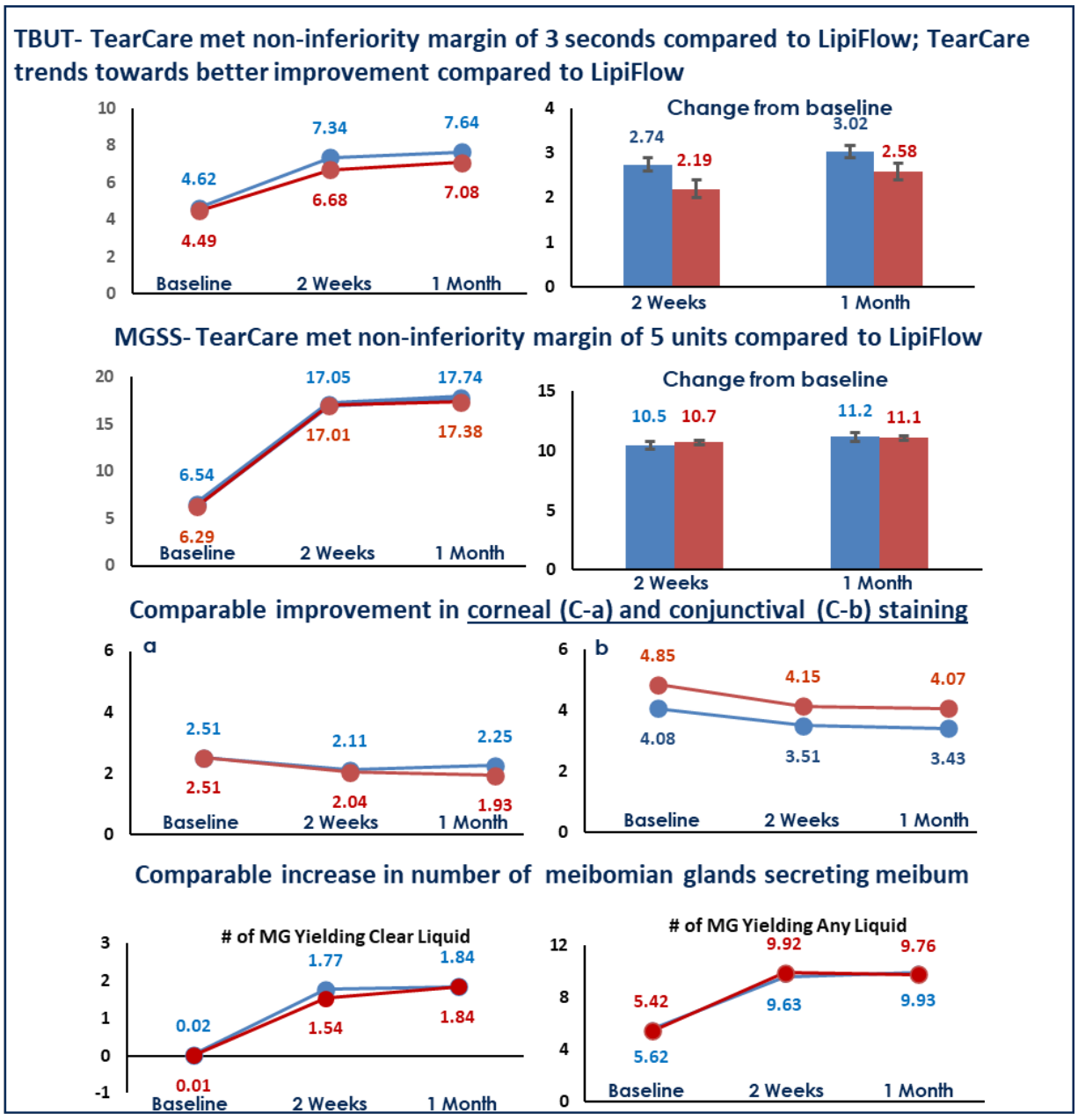
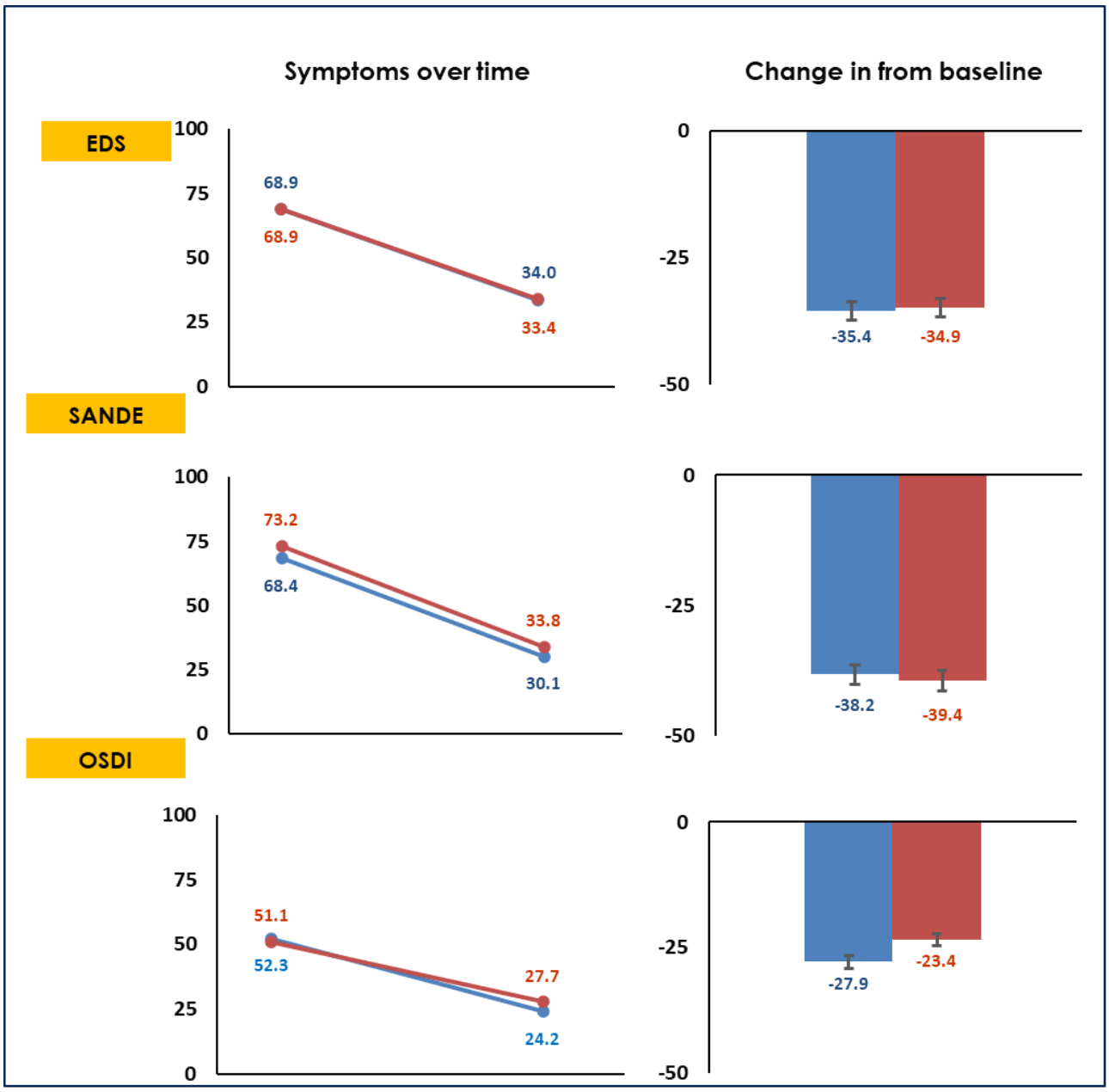


Figure 6: SANDE, EDS and OSDI scores per follow up time point Blue legends, line andbars represent TearCare group and red legends, line and bars represent LipiFlow group.



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 which measure the treatment effect on the sign of dry eye disease is the primary endpoint. The secondary endpoints have been chosen to collect additional data regarding changes in the signs and symptoms of dry eye disease in study subjects.

For each outcome measure, results from the TearCare group will be compared with results from the Restasis group. Study success will be assessed at 6 months for superiority of the TearCare system in treating dry eye disease compared with Restasis as measured by Tear Break-Up Time.

- **Primary effectiveness endpoints**
  - Mean Change from baseline in Tear Break-Up Time (TBUT)
  - Mean Change from baseline in OSDI score[39]

- **Secondary effectiveness endpoints**
  - Mean Change in the total Meibomian Gland Secretion Score[40]
  - Mean Change from baseline in corneal staining scores
  - Mean Change from baseline in conjunctival staining scores
  - Mean Change from baseline in the number of meibomian glands yieldingclear liquid secretions
  - Mean Change from baseline in the number of meibomian glandssecreting any liquid (clear or cloudy)
  - Mean Change from baseline in SANDE scores [41,42]
  - Eye Dryness Score
  - Ocular protection index (OPI): Interblink interval (IBI)/TBUT Schirmerscore
  - Use of dry eye lubricants

[39] 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.

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

[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.

6.2 SAFETY ENDPOINTS

- **Primary Safety Endpoint**
  - Procedure (TearCare)/Treatment (Restasis)-related adverse events (all adverse events will be recorded)

- **Secondary Safety Endpoints**
  - Change in best corrected visual acuity (ETDRS)
  - Change in intraocular pressure (IOP)

7 STUDY DESIGN

This is a prospective, randomized, masked, multi-center, superiority, non-significant risk study. To reduce potential bias in the study, study staff performing the endpoint assessments will be masked as to the subject's treatment allocation. Subjects cannot be masked as it will be obvious to them which treatment they are receiving.

7.1 STUDY DEVICE AND CONTROL GROUP

In this study, TearCare procedures using the TearCare System (study device) will be compared with Restasis (control group).

TearCare procedures in this study will include an in-office eyelid debridement, 15-minute bilateral thermal session with the TearCare System, immediately followed by manual expression of the meibomian glands using the Clearance Assistant Plus device. Subjects randomized to TearCare will receive one in-office TearCare procedure within 7 days of the Baseline visit and at 5 Months. Beginning at 9 Months, subjects will receive an additional TearCare procedure when TBUT drops lower than Baseline or within 2 seconds of baseline AND if OSDI worsens by at least 15 points compared to the previous visit.

Subjects randomized to Restasis group will be required to self-administer 1 drop twice a day from baseline through the Month 6 visit. At Month 6, subjects will be crossed over to the TearCare group and will receive one (1) TearCare procedure.

7.2 STUDY CENTERS

This study will be conducted at up to 25 centers in the United States. No center will have more than 20% of the target enrolled and treated (i.e., 70 subjects per site) without priorapproval from the sponsor.

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 to 6 months
3. Reports having to use artificial tears or lubricants regularly over the past month to relieve dry eye symptoms.
4. Schirmer tear test (with anesthesia) ≥5 to ≤15 mm in 5 minutes
5. OSDI Score of 23-79
6. TBUT of ≥1 to ≤7 seconds in both eyes
7. Meibomian gland obstruction in both eyes based on a total Meibomian Gland Secretion Score ≤12 in each eye.
8. At least 15 glands in each lower eyelid should be expressible, with a sterile cotton swab, at the slit lamp.
9. Best corrected visual acuity of 20/100 or better in both eyes.
10. Willing and able to comply with the study procedures and follow-up
11. Willing and able to provide informed consent
12. 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) Cyclosporine (Restasis, Cequa etc.) or Xiidra and serum tears within 60 days prior tobaseline;
    b) Antihistamines (oral or topical) within 7 days prior to baseline;
    c) Systemic medication(s) that is known to cause ocular dryness (e.g. diuretics, anti-hypertensives, anti-depressants,antihistamines, hormone therapy) and whose dose of this medication(s) has not been stable within 30 days prior to baseline. 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 baseline; or
    f) Topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications within 30 days prior to baseline.

2. Any of the following dry eye treatments:
    a) Office-based dry eye treatment (e.g. IPL, TearCare, thermal pulsation [LipiFlow], iLux etc.) within 12 months prior to baseline either as partof routine care or clinical investigation;
    b) Planned or recent surgical procedures to the eye or eyelid (90 days prior to baseline)
    c) Meibomian gland expression within 6 months prior to baseline;
    d) Blephex or debridement within 3 months prior to baseline is anexclusion;
    e) Punctal occlusion or punctal plug Punctal occlusion or punctal plugs. Investigators can choose to remove the punctal plugs 15 days prior to baseline;
    f) Use of tear neurostimulators (i.e., True Tear, iTear100, Tyrvaya) within 2 weeks of the baseline visit. (Subjects must refrain from using tear neurostimulators for the duration of the study.); or
    g) Any history of meibomian gland probing
3. History of eyelid, conjunctiva, or corneal surgery (including refractive surgery) within the past year prior to baseline. 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 complicationspost-refractive surgery.
4. Contact lens use within 2 weeks of the baseline visit.
5. Active hordeolum, stye, or chalazion at the time of the baseline visit.
6. History of Herpes Simplex or Herpes Zoster of the eye or eyelid.
7. Any active, clinically significant ocular or peri-ocular infection, inflammation, or irritation
8. Recurrent clinically significant eye inflammation, other than dry eye, within 3months prior to baseline
9. Clinically significant anterior blepharitis. In addition, collarettes or flakes of morethan one quarter of the eyelid are excluded.
10. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion,blepharospasm, aponeurotic ptosis, lagophthalmos, distichiasis, trichiasis).
11. Clinically significant dermatologic or cutaneous disease of the eyelid orperiocular area.
12. In the clinical judgement of the investigator, meibomian glands have significant capping, atrophy, or are unable to be expressed, digitally or with a sterile cottonswab.
13. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy,Salzmann's nodules, etc.)

14. Corneal surface abnormalities such as corneal epithelial defects (other thanpunctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea
15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis.
16. Ocular trauma within 3 months prior to baseline.
17. Known history of diminished or abnormal facial, periocular, ocular, or cornealsensation
18. Systemic diseases resulting in dry eye (e.g., autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis,etc.)
19. Subject is currently using Retin A/Retin A derivatives.
20. Subject has permanent eyeliner/lid tattoos, eyelash extensions or wears falseeyelashes.
21. Subject is currently using Latisse, Lash Boost or any other type of eyelash growth serum.
22. Allergies to silicone tissue adhesives, acrylates and/or coppers.
23. Subject has a pacemaker or implantable cardiac defibrillators (ICD). Participation in another ophthalmic clinical trial 30 days prior to baseline. Subject must also be willing to refrain from another ophthalmic study for the duration of the study.
24. Co-existing condition, either ocular or non-ocular that, in the judgement of theinvestigator 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 TABLE 3: TEARCARE STUDY VISIT SCHEDULE

Visit	Baseline	Day 0 [b]	Day 1	Wk 1	1 M	3 M	5 M	6 M	9 M	12 M	15 M	18 M	24M
Window days	**-7 to 0**	**0**	**1**	**5-9**	**21-35**	**70-100**	**120-155**	**170-210**	**250-300**	**330-390**	**420-480**	**510-570**	**691-780**
Informed Consent	X [a]												
Demographics, Ocular & Medical History	X												
Medication use	X			X	X	X		X	X	X	X	X	X
Questionnaires (OSDI, SANDE, Eye Dryness Score)	X			X	X	X		X	X	X	X	X	X
BCVA [d]	X		X [e]	X [e]	X	X		X	X	X	X	X	X
Blink rate	X			X				X		X			X
Slit Lamp Exam	X		X	X	X	X		X	X	X	X	X	X
TBUT	X			X	X	X		X	X	X	X	X	X
Corneal Staining	X			X	X	X		X	X	X	X	X	X
Conjunctival Staining	X			X	X	X		X	X	X	X	X	X
Schirmer Test	X			X	X			X		X			X
MGSS	X			X	X	X		X	X	X	X	X	X
IOP [f]	X		X	X	X	X		X	X	X	X	X	X
Subject Eligibility	X												
Randomization	X												
TearCare Procedure		X					X						
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Eye Lubricant/Drop Log					X	X	X	X	X	X	X	X	X

[a] Subjects may sign the informed consent up to 60 days in advance of the baseline visit.

[b] TearCare procedure 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. Beginning at 9 Months, subjects will receive an additional TearCare procedure when TBUT drops lower than Baseline or within 2 seconds of baseline AND ifOSDI worsens by at least 15 points compared to the previous visit.

[d] BCVA should be collected after manifest refraction using ETDRS visual acuity chart

[e] On Day 1 and Week 1, Best Corrected Spectacle Visual Acuity (BCSVA using ETDRS) 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.

[f] 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 TABLE 4: RESTASIS STUDY VISIT SCHEDULE

Restasis *1 drop of Restasis ophthalmic emulsion should be instilled in both eyes, approximately 12 hours apart from each other. Example: 1st drop should be instilled between 7 to 8 AM and 2nd drop between 7 to 8 PM. In contact lens wearers, drops should be administered at least 15 minutes after contact lens removal.*							***Restasis CROSSOVER to TearCare***					
Visit	**Baseline**	**Day 0**	**Day 1**	**Wk 1**	**1 M**	**3 M**	**6 M/TearCare**	**Post Procedure**			**9 M**	**12 M**
Window days	**-7 to 0**	**0**	**1**	**5-9**	**21-35**	**70-90**	**150-180**	**Day 1**	**Wk 1**	**1 M**	**220-280**	**320-390**
								1	**5-9**	**21-35**		
Informed Consent [a]	X											
Demographics, Ocular & Medical Hx	X											
Medication use	X			X	X	X	X		X	X	X	X
Questionnaires (OSDI, SANDE, Eye Dryness Score)	X			X	X	X	X		X	X	X	X
BCVA [b]	X		X [c]	X [c]	X	X	X	X [c]	X [c]	X	X	X
Blink rate	X			X			X		X			X
Slit Lamp Exam	X		X	X	X	X	X	X	X	X	X	X
TBUT	X			X	X	X	X		X	X	X	X
Corneal Staining	X			X	X	X	X		X	X	X	X
Conjunctival Staining	X			X	X	X	X		X	X	X	X
Schirmer Test	X			X	X		X		X	X		X
MGSS	X			X	X	X	X		X	X	X	X
IOP [d]	X		X	X	X	X	X	X	X	X	X	X
Subject Eligibility	X											
Randomization	X											
Restasis (1gtt BID)		X	X	X	X	X						
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Crossover and TearCare Procedure							X					
Treatment preference questionnaire												X
Eye Lubricant/Drop Log					X	X	X			X	X	X

[a] Subjects may sign the informed consent up to 60 days in advance of the baseline visit.

[b] Restasis must be dispensed within 7 calendar days of the Baseline visit. If scheduling permits, it may be dispensed on the same day as the Baseline visit following Randomization.

[c] BCVA should be collected after manifest refraction using ETDRS visual acuity chart

[d] On Day 1 and Week 1, Best Corrected Spectacle Visual Acuity (BCSVA using ETDRS) 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.

[e] 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.

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

A sample size of 200 subjects is estimated to provide sufficient power (90%) for this study. Nonetheless, given the 24 months follow up period, and in an attempt to collect additional data regarding changes in the signs and symptoms of dry eye disease, a total of up to 350 subjects will be enrolled and randomized in the study. Assuming a 15% screen failure rate, approximately 412 subjects will be enrolled to obtain up to 175 randomized subjects in each study group. All subjects will be followed for up to 24 months.

It is anticipated that enrollment in the study will take 16-26 months. Including the 24 months follow-up period, the study is expected to last 40-50 months.

9.4 MATERIAL AND EQUIPMENT

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

a. TearCare SmartHub Kit (includes a SmartHub, charging nest and charging adapter)
b. TearCare SmartLid Devices and Clearance Assistant Plus Devices
c. TearCare wipes
d. Restasis (Cyclosporine 0.05%) Ophthalmic Emulsion
e. ETDRS Visual Acuity System
f. Slit lamp
g. Wratten filter (yellow) (for corneal staining)
h. Goldmann Tonometer or other applanation tonometer
i. Meibomian Gland Evaluator (TearScience, Inc.)
j. Fluorescein sodium strips (for TBUT and corneal staining)
k. Lissamine green strips (for conjunctival staining)
l. Filter strips (for the Schirmer test)
m. Preservative-free sterile saline
n. Proparacaine 0.5% or tetracaine 0.5% ophthalmic drops
o. Akten® (lidocaine hydrochloride ophthalmic gel) 3.5% or equivalent
p. Stopwatch
q. Ruler
r. Sterile scissors
s. Thermometer
t. Webcam and/or laptop

9.5 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 60 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.

9.6 BASELINE AND STUDY GROUP VISIT(S)

9.6.1 SCHEDULING THE BASELINE AND DAY 0 VISIT(S)

To facilitate scheduling, the Baseline and Day 0 Visits may be performed on the same day or on two separate days and following randomization. If these visits are performed over two days, Day 0 must be within 7 calendar days of the Baseline Visit.

Refer to Table 3 for which tests and exams are to be performed at each visit for both groups. Endpoint assessments performed during the Baseline visit must be performed by a Masked Assessor (See Section 9.9).

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.

9.6.2 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 9.9 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. Blink Rate*
6. Slit Lamp Exam*
7. Tear Breakup Time*
8. Corneal Staining*
9. Conjunctival Staining*
10. Schirmer Test*
11. Meibomian Gland Secretion Scoring*
12. Intraocular pressure*
13. Adverse Event Assessment

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 30 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 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.

9.6.3 RANDOMIZATION

Subjects will be randomized to either the TearCare (i.e., “device group”) or Restasis (i.e.,“control group”). Randomization will be performed using a 1:1 ratio and will be stratified by site. Computer-generated randomization will be administered through the electronic data capture (EDC) system.

Following randomization, the subject should undergo the applicable procedures described in the sections below.

9.6.4 PROCEDURE FOR TEARCARE (STUDY DEVICE GROUP)

Subjects randomized to the study device group (TearCare) 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. Position the subject at the slit lamp to perform debridement of the eyelid margin followed by expression of the meibomian glands such that expression takes place within 3 minutes of completion of the thermal portion of the procedure.
3. Apply 1 drop of proparacaine or tetracaine into each eye.
4. Visualize the lid margin and line of Marx's (LOM) and debride eyelid margins by sweeping (very gently scraping) the debridement edge across the LOM back and forth going over meibomian gland orifices. Start nasally and work laterally multiple times using gentle pressure until the eyelid margins appear free of debris, keratin, and gland capping. Often the gland orifices become visible at this point.
5. Wipe the subject's eyelids and temple with the TearCare wipes to remove any make-up, oil, dirt, or lotion. Allow the skin to dry or pat dry with a tissue. Use care not to allow any of the wipe to get into the eye.
    a. ***Caution:*** *Eyelid cleansing may lead to skin irritation, which would put a patient at increased risk for thermal injury. If the patient is observed to have skin irritation, or if the patient complains of skin irritation after eyelid cleaning, do not proceed with the TearCare treatment.*
6. Remove the liner from the upper SmartLid to reveal adhesive. Continue to prebend the SmartLid, if needed. Peel from temporal tab towards nasal and discard the liner. (For each eye)
7. 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.
8. Connect the SmartLid devices to the SmartHub.
9. Inform the subject that the SmartLid devices will heat up very quickly once the TearCare procedure is started.
10. Start TearCare procedure. Subjects should be encouraged keep their eyes open and blink naturally during the TearCare procedure.
11. If the subject indicates the temperature is too hot, decrease the temperature set point to a setting that is comfortable for the subject.
12. Following the thermal portion of the TearCare procedure, remove the SmartLid devices from the subject, position the subject at the slit lamp biomicroscope, repeat debridement if deemed necessary and using the Clearance Assistant Plus 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.

9.6.5 RESTASIS DISTRIBUTION (CONTROL GROUP)

Subjects randomized to the control group (Restasis) will be provided with Restasis® (Cyclosporine 0.05% ophthalmic emulsion) for use in both eyes. Subjects should be instructed to follow steps below while administering Restasis:

<u>Preparing the bottle for first-time use:</u>

a. Pull off shipping cover by pulling straight up. Remove the pull tab on the olive green colored protective cap by pulling the end of the pull tab away from the bottle then winding it counterclockwise.
b. Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap. Prime the bottle for first time use by squeezing 2 drops onto a tissue. Do not let the bottle tip touch the tissue.
c. After use, recap the bottle with the olive green colored protective cap by pushing straight down onto the bottle.
d. Turn the bottle upside down a few times before putting drops in eyes to make sure the medicine is mixed well.
e. Instill one drop in both eyes approximately 12 hours apart from each other. The first drop should be instilled between 7 to 8 AM and second drop between 7 to 8 PM.
f. Do not discontinue use of medication unless instructed by the site staff.

The site staff should give intermittent calls to the subjects to check if they have enough supply of the drops that last until their next visit. Please instruct subjects to inform the site staff before they run out of the medication. Each subject will receive the first bottle on Day 0 (treatment day). All additional bottles of Restasis will be provided at the protocol defined follow-up visits (Week 1, Month 1, and Month 3). To avoid shortage of medication, please try to bring the subject in at the early part of the visit window. If this requires scheduling an additional visit in between the protocol defined visits, it will be

considered an unscheduled visit.

The subjects should be instructed to:

a. Store Restasis® between 15-25 °C (59-77 °F)
b. For contact lens wearers, drops should be instilled at least 15 minutes after the removal of the contact lenses.
c. Restasis® can be used with lubricant eye drops, but you should wait at least 15 minutes between using each product. The lubricant eye drops/rescue drops used should be recorded on the Eye Lubricant/Drop log. Sites should make sure to review the log at each visit as described in Section 9.6.6.

9.6.6 FOLLOW-UP INSTRUCTIONS FOR SUBJECTS

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

During study follow-up:

1. Dry Eye Lubricants/Tear Drops: Subjects should make every effort to refrain from using any dry eye drops or lubricants. If they require "rescue therapy" to relieve their symptoms, they should use the same type of tear drops or lubricants they were using prior to the study.
2. Dry Eye Lubricant/Tear 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., Doxycycline, 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/scrub. They should not use the True Tear device or have any other in-office dry eye treatments. If the investigator feels the need for an alternative procedural intervention, 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.
5. Other Ocular Procedures: Subjects should be recommended not to opt for an elective ocular procedure such as cataract surgery, refractive surgery etc. unless medically warranted during the study duration. In case such a surgery/procedure is needed, the subjects should be exited from the study prior to the procedure unless the procedure is performed to treat an adverse event.
6. Antihistamines: Subjects should be advised not to use any antihistamines during the study duration. In case antihistamines are needed during the study duration, topical antihistamines should be tried prior to using oral antihistamines. In case oral or systemic antihistamines are required, subjects should be instructed to discontinue use of antihistamines at least 7 days prior to scheduled study visits. Subjects who are on preexisting stable dose of antihistamines prior to baseline should be instructed to discontinue use of antihistamines at least 7 days prior to scheduled study visits.

7. Use of Contact lens: Subjects should be advised not to use contact lenses at least 72 hours prior to the scheduled study visits.

9.7 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. For the subjects assigned to Restasis group, subjects can use Restasis on day of follow up visits. Since Restasis drops can affect the endpoint assessments, instruct subjects not to use Restasis within 2 hours of the study visit.

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 9.9).

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 and Table 4 (pages 32, 33) 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. Blink Rate
4. Slit Lamp Exam
5. Tear Breakup Time
6. Corneal staining
7. Conjunctival staining
8. Schirmer Test
9. Meibomian Gland Secretion Scoring
10. IOP
11. Assessment of adverse events

The following activities can be performed in any order:

- Medication Use
- Collection of Eye Lubricant/Drop Log (for all visits starting at 1 month)

9.8 PHOTOGRAPHY DURING EXAMS AND TEARCARE PROCEDURE

Photographs or videos will be made during the baseline or follow-up exams or during the TearCare procedure. These images may be used for educational or training 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.

9.9 MASKED ASSESSOR

To reduce potential bias in the study, study staff performing endpoint assessments will be masked as to the subject's study group. 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 group procedure, or the distribution of Restasis medication to subjects randomized to the Restasis group.

The following assessments must be performed by a Masked Assessor:

- Manifest refraction and ETDRS Best-corrected visual acuity
- Blink Rate
- Slit Lamp Exam
- Tear Breakup Time
- Corneal Staining
- Conjunctival Staining
- Schirmer Test
- Meibomian Gland Secretion Scoring
- Intraocular pressure

9.10 MANAGEMENT OF DRY EYE SYMPTOMS DURING FOLLOW-UP

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

Lubricant/Tear Drop Log.

Subjects should not use other medications for dry eye disease (e.g., Doxycycline, Xiidra, etc.) 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 in office or at home dry eye treatments (e.g., IPL, TrueTear, iLux, punctal plugs, warm compresses, lid scrubs 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.

9.11 WITHDRAWAL AND DISCONTINUATION

All subjects have the right to withdraw at any point during the study 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 Procedure or Restasis®, then that subject may be replaced in the study by a newly enrolled subject.

9.12 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 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 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 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 will be considered pre-existing conditions and 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 OCULAR 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 or study testing methods. Please refer to Restasis label for potential AEs related to Restasis use.

- Eyelid/eye pain requiring discontinuation of the study procedure
- Eyelid/eye pain requiring treatment ≥1 day after the study procedure
- Eyelid irritation, or inflammation
- Discomfort or pain of eyelids or orbit
- Ocular symptoms (such as burning, redness, tearing, visual disturbance, redness)
- Burn, erythema, or swelling of the eyelids
- Thermal injury to the eye, including conjunctiva, cornea or lens
- Allergic or inflammatory reaction to medical adhesive on the SmartLid device

- 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
- Worsening of dry eye symptoms
- 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 or designated 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. Record all applicable information in the source document, enter into the EDC system and email the AE CRF to TCsafety@sightsciences.com.

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, record all applicable information in the source document, enter into the EDC system and e-mail the AE CRF to TCsafety@sightsciences.com; 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.

11.2 ANTICIPATED ADVERSE DEVICE EFFECTS

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

11.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

All anticipated study risks are listed in Section 10.2.

11.4 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

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

11.5 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 procedures will be done in the investigator's office under direct supervision of the investigator. During TearCare procedures in this study heat will be applied to the eyelids at a temperature ranging from 41-45°C. This temperature range was selected based on research.[43,44,45,46] The investigator can adjust the temperature up or down to a level that is comfortable for the subject, and may also shut off the System at any time if it is too uncomfortable or painful. In addition, the TearCare System is designed to monitor and regulate the temperature at the tissue-contacting

[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).

surface of the SmartLid devices and not to exceed the maximum allowable temperature.

2. Corneal abrasion: If the SmartLid devices are not positioned properly or come loose during the procedure, there is the potential for a corneal abrasion. To mitigate this, the investigator will apply the strips to the subject and will monitor their position during the procedure 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 investigators will be trained on how to perform expression according to this protocol.

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 on how to use TearCare in this study will be provided to each investigator.
- Investigators will be trained in how to correctly apply and remove the SmartLid devices and operate the TearCare System.
- Investigators will be trained in how to perform lid debridement and meibomian gland expression using the TearCare Clearance Assistant as described in this protocol.
- The study staff will be trained to perform procedures required in this protocol.

12 STATISTICAL CONSIDERATIONS

12.1 EVALUABILITY

All subjects on whom the TearCare or Restasis 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

- Intent-to-Treat Population - The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed on the ITT population. Subjects will be analyzed as randomized.

- Per Protocol Population – The per protocol (PP) 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 (Doxycycline, Xiidra). Subjects will be analyzed as treated.
- Safety Population – The safety population will include all subjects on whom the TearCare or Restasis is attempted. The safety population will be analyzed for all safety assessments. Subjects will be analyzed as treated.

12.3 SUBJECT ACCOUNTABILITY

A complete accounting of subjects by 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. Descriptive statistical summaries of pre-treatment parameters (min, max, median, mean, standard deviation) will also be provided for each group. 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, Blink Rate, Schirmer Score, OSDI Score, SANDE Score, and Eye Dryness Score.

12.5 EFFECTIVENESS ENDPOINTS AND ANALYSIS METHODS

All primary and secondary endpoints will be evaluated at 6 months. 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) as described in Appendix B.

12.5.1 DESCRIPTIVE ANALYSES

The quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative variables will be summarized using counts and percentages.

Summaries of all endpoints will be presented by treatment group and visit. Summaries will also be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

12.5.2 PRIMARY EFFECTIVENESS ENDPOINTS

The primary effectiveness endpoints are:

- the change from baseline in Tear Break-Up Time (TBUT) at 6 months
- the change from baseline in total OSDI at 6 months

The primary endpoint of the change from baseline in Tear Break-Up Time (TBUT) at 6 months will be analyzed using linear mixed effects (LME) models adjusting for baseline and site, and with a random subject effect. These will allow for the proper incorporation of within-person correlation into the statistical models and will also allow for adjustment for baseline measurements.

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.

The primary endpoint of the change from baseline in total OSDI at 6 months will be analyzed using ANCOVA models adjusting for baseline and site.

12.5.3 PRIMARY EFFECTIVENESS HYPOTHESES

The primary study hypotheses regard the superiority of the TearCare treatment as compared to Restasis, for Tear Break-Up Time (TBUT) and total OSDI. The primary endpoints will be tested for TearCare in a hierarchical fixed sequence. The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided.

To demonstrate superiority of the TearCare treatment to the Restasis control for TBUT we will test the following hypotheses:

H_{01}: There is no difference between TearCare and Restasis in the mean change from baseline in TBUT at 6 Months.

H_{11}: The mean change from baseline in TBUT at 6 Months is greater with TearCare than with Restasis.

If H_{01} is rejected, then the study will be considered a success and we will test the following hypotheses to further evaluate superiority of the TearCare treatment to the Restasis control for total OSDI:

H_{02}: There is no difference between TearCare and Restasis in the mean change from baseline in total OSDI at 6 Months.

H_{12}: The mean change from baseline in total OSDI at 6 Months is less with TearCare than with Restasis.

12.5.4 POOLABILITY

Using a linear mixed effects modeling approach described in Appendix B, poolability of the effectiveness outcomes 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

No missing data imputation will be carried out beyond what is built-in to the mixed-effects modeling approach to be used in the primary effectiveness analysis.

No secondary effectiveness endpoints or safety endpoints will be imputed.

12.5.6 SECONDARY EFFECTIVENESS ENDPOINTS

The secondary effectiveness endpoints include change from baseline at 6 Months for the following outcomes:

1. Meibomian Gland Secretion Score
2. Symptom Assessment iN Dry Eye (SANDE) scores
3. Eye Dryness Score
4. Number of Meibomian Glands Yielding any liquid
5. Number of Meibomian Glands Yielding clear liquid
6. Corneal staining scores
7. Conjunctival staining scores
8. Schirmer Score
9. Ocular protection index (OPI): Interblink interval (IBI)/TBUT

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 family-wise 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, Number of Meibomian Glands Yielding any liquid, Number of Meibomian Glands

Yielding clear liquid, OPI, Schirmer Score) and those measured on a per-subject basis (OSDI Score, SANDE Scores, Eye Dryness Score).

Endpoints assessed at the eye level will be analyzed with linear mixed effects models adjusting for baseline and site, and with a random subject effect. Two-sample t-tests and Wilcoxon rank sum tests will be conducted on the average of the two eyes as supportive analyses. Endpoints assessed at the subject level will be analyzed using ANCOVA models adjusting for baseline and site, with two-sample t-tests and Wilcoxon rank sum tests as supportive analyses. No imputation will be performed for secondary efficacy variables.

All secondary effectiveness variables collected will be summarized descriptively (n, mean, standard deviation, median, min and max) by treatment group and visit.

12.5.7 Additional Exploratory Analyses

The use of dry eye lubricants will be summarized by study group.

12.6 Safety Endpoints and Analysis

12.6.1 Descriptive Analyses

All adverse events, changes in IOP, and changes in BCVA (EDTRS) will be tabulated by visit and study group.

12.6.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of procedure (TearCare)/treatment (Restasis)-related adverse events.

12.6.3 Secondary Safety Endpoints

The secondary safety endpoints include:

- Change in best corrected visual acuity (ETDRS)
- Change in intraocular pressure (IOP)

These endpoints will be summarized by treatment group and visit.

12.6.4 Safety Analysis

All adverse events will be reported by study 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 study 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.

12.7 SAMPLE SIZE CALCULATION

A sample size of 200 subjects is estimated to provide sufficient power (90%) for this study. Nonetheless, given the 24 months follow up period and in an attempt to collect additional data regarding changes in the signs and symptoms of dry eye disease, up to 300 subjects, approximately 150 in the TearCare group and 150 in the Restasis group, will be enrolled and randomized in the study. This will provide more than 90% power to meet the TBUT effectiveness endpoint and sufficient precision around the adverse event estimates. The sample size also takes into account an estimated 10% dropout rate per 6 months. Details of the sample size calculation can be found in Appendix B.

In May of 2021, the study protocol was revised to update the appropriate Schirmer test parameters for inclusion. Since the study treated some subjects that did not meet these parameters at baseline, the planned sample size of the study was increased to approximately 310 subjects, approximately 155 in the TearCare group and 155 in the Restasis group.

In August of 2022, the sample size was increased to 350 subjects, with up to 175 in the TearCare group and up to 175 in the Restasis group in order to account for additional subjects (an estimated 10) not meeting all eligibility criteria and a possible slightly higher dropout rate per 6 months (~11%).

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 consist of on-site and remote monitoring visits. 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 six-digit subject number composed of a two-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 who are 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 a 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 tcsafety@sightsciences.com.

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

17 ETHICAL CONSIDERATIONS

17.1 DECLARATION OF HELSINKI

This study shall be conducted in accordance with the Declaration of Helsinki (Appendix 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 AND DRUG ACCOUNTABILITY

With each shipment of study devices and drug (Restasis®), 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 and Drug 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. The drug (Restasis®) should be stored as per the storage recommendation between 15-25 °C (59-77 °F). When study devices or drug are used, returned or disposed of, their disposition (including the disposition and date of disposition) must be recorded on the Device and Drug Accountability log.

Device and Drug 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 and drug 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

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.

<u>Multi-Site Data</u>
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. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop. Ocul Surf. 2007;5:75–92.
2. Lemp MA, Crews LA, et al. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study. Cornea. 2012: 31: 472-478.
3. Fiscella RG. Understanding dry eye disease: a managed care perspective. Am J Manag Care 2011; 17 Suppl 16:S432-9.
4. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. Cornea 2011;30(4):379-87.
5. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tusbota K, Stapleton F. TFOS DEWS II Definition and Classification Report. The Ocular Surface 2017;15:276-283.
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
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
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. 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.
25. 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.
26. Mori A, Oguchi Y, Goto E, et al. Efficacy and safety of infrared warming of the eyelids. Cornea. 1999;18:188–193.
27. 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.

28. 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.
29. Perry HD, Doshi-Carnevale S, Donnenfeld ED, Kornstein HS. Topical cyclosporine A 0.5% as a possible new treatment for superior limbic keratoconjunctivitis. Ophthalmology. 2003;110(8):1578-1581. doi:10.1016/S0161-6420(03)00538-4
30. Stonecipher K, Perry HD, Gross RH, Kerney DL. The impact of topical cyclosporine A emulsion 0.05% on the outcomes of patients with keratoconjunctivitis sicca. Curr Med Res Opin. 2005;21(7):1057-1063. doi:10.1185/030079905X50615
31. Perry HD, Doshi-Carnevale S, Donnenfeld ED, et al., Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea (2006);25:pp. 171–175.
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).
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.
39. Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye 1991;5: 395–411.
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.
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).
47. 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
48. 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.
49. 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.
50. Medical electrical equipment Part 1: General requirements for basic safety and essential performance (IEC 60601-1).
51. DEWS. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. Ocul Surf. 2007;5:133.
52. Lemp MA, Hamill JR. Factors affecting tear film break-up in normal eyes. Arch Ophthalmol. 1973;89:103–105.
53. Norn MS. Desiccantion of the precorneal tear film. I. Corneal wetting time. Acta Ophthalmol (Copenh) 1969;47:865–880.
54. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J 1995;21: 221–232.
55. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea. 2008;27: 1142–1147.

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

21 APPENDIX 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 dryeye 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 andweek 1 follow-up visit. On Day 1 and week 1, 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 ina 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.

Tear film stability is measured by a test of TBUT, defined as the time to initial breakup of the tear film after a blink.

Measuring Tear Break-Up Time

1. The fluorescein-impregnated strip is moistened with sterile saline and applied gently by touching against the superior bulbar conjunctiva.
2. Measure TBUT approximately 30 seconds after instilling the fluorescein. Ask the subject to blink several times and to move the eyes, to mix the fluorescein in the tears.
3. Use the cobalt blue illumination of the slit lamp and a Wratten filter. Use a beam width of approximately 4 mm, and full height. Move the beam slowly from side to side to cover the entire cornea.[47,48,49]
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. The time from upstroke of the last blink to the first tear film break or dry spot formation is recorded as the TBUT measurement.
6. Repeat the test 3 times per eye and take the average of the 3 measurements.

[47] DEWS. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. Ocul Surf. 2007;5:133.
[48] Lemp MA, Hamill JR. Factors affecting tear film break-up in normal eyes. Arch Ophthalmol. 1973;89:103–105.
[49] Norn MS. Desiccantion of the precorneal tear film. I. Corneal wetting time. Acta Ophthalmol (Copenh) 1969;47:865–880.

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 stopwatch

21.5 CORNEAL STAINING

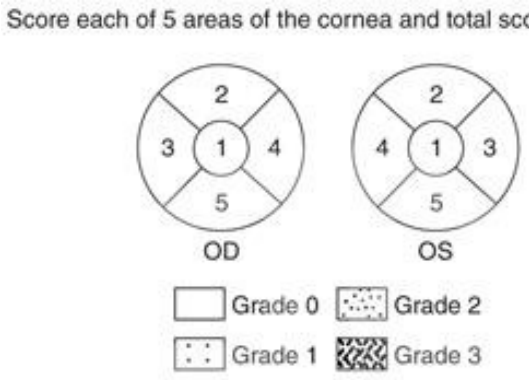
Masked assessment: This assessment should be performed by the masked assessor.

Measuring Corneal staining

1. Measure corneal staining within 3-4 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 7 below. [50]

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

Figure 7: 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

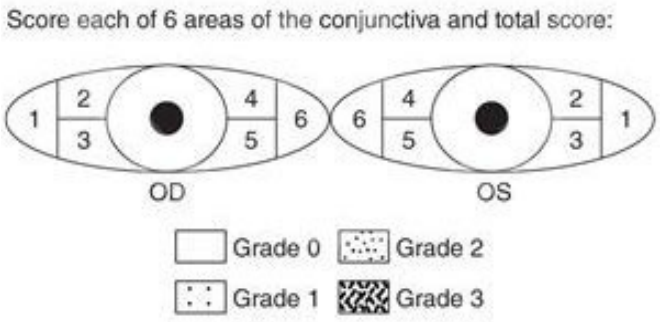
- Ask subjects to blink several times to assure the uniform distribution of dye in cul-de-sac
- Make sure to use moderate illumination to avoid hyper reflection from the spots of fluorescein uptake

21.6 CONJUNCTIVAL STAINING

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

1. The lissamine green-impregnated strip is moistened with sterile saline and applied gently by touching against the superior bulbar conjunctiva.
2. Wait at least 1 minute before grading the conjunctival staining. Perform grading within 4 minutes of instilling the dye.
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 8.

Figure 8: 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 TEST

The Schirmer Test measures aqueous tear quantity and is an indication of aqueous-deficient dry eye.

Procedure

1. The Schirmer test, with anesthesia, should be performed in a dimly lit room.
2. Instill 1 drop of anesthetic into each eye and wait approximately 4 minutes.
3. Gentle blotting of the corners of the eyelids with a facial tissue is allowed to catch the over spill. Any direct, active blotting of the cul-de-sac will not be allowed.
4. Ask the patient to look up and draw the lower lid gently downward and temporally hook the rounded bent end of the sterile strip into the lower cul-de-sac at the temporal one-third of the lower eyelid margin.
5. Start the timer
6. To minimize artifacts from this test, ask subjects to gently close their eyelids until 5 minutes have elapsed. Ask subjects to open their eyes and remove the strips.
7. Because the tear front will continue advancing a few millimeters after it has been removed from the eyes, it is important to mark the tear front with a ball point pen at precisely 5 minutes.

Strip Measuring

1. Write the letter "R" on the strip used in the right (OD) eye and the letter "L" on the strip used in the left (OS) eye. Each strip has graduated sections on it that will aid in capturing the appropriate measurement in millimeters.
2. Record only whole numbers, rounding up to the nearest whole number if the tear front is at or greater than the half-millimeter mark.
3. Once marked, each strip will be affixed to the source document (marked side up), in the space provided, and covered completely with transparent tape. The measurement is then to be captured on the source document and transcribed onto the EDC.

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, [51] 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[52]:

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

[52] 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.

- 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).

21.10 BLINK RATE

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

The blink rate of each subject will be measured over a three-minute period using a computer-based algorithm customized to count blinks per minute. Subjects will be instructed to look at a stimulus displayed on computer screen (while seated) and eyelid closure incidences will be collected. Make sure to record the start and stop time of when subject starts and stops viewing the stimulus displayed on the computer screen. Lighting that may cause squinting or minimizes the interpalpebral fissure will be directed away from a subject's field of vision and the monitor brightness will be adjusted to a level which would not cause squinting or minimizes the interpalpebral fissure. Sites will be instructed with the specifications about the brightness, contrast, resolution and ambient light parameters while conducting the test. Blink rate will be utilized to calculate the inter-blink-interval (IBI) and ocular protection index (OPI).

21.11 QUESTIONNAIRES

21.11.1 GENERAL INSTRUCTIONS FOR QUESTIONNAIRES

The subject should complete all required questionnaires at the beginning of each visit before conducting other clinical testing.

Provide a paper copy of the questionnaires and a blue or black ink pen to the subject. Review the instructions for 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.

21.11.2 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

21.11.3 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.

21.11.4 TREATMENT PREFERENCE QUESTIONNAIRE (RESTASIS GROUP ONLY)

Treatment Preference Questionnaire will be administered in subjects randomized to Restasis group at their post TearCare 12M visit. Questionnaire completion guidelines described in Section 21.11.1 should be followed to administer this questionnaire.

22 APPENDIX B – STATISTICAL ANALYSIS PLAN

22.1 ANALYSIS POPULATIONS

- Intent-to-Treat Population - The intent-to-treat (ITT) population includes all randomized subjects. The primary and secondary efficacy analyses will be performed on the ITT population. Subjects will be analyzed as randomized.
- Due to the inclusion criteria revision in May of 2021 for Schirmer's test parameters, the modified ITT (mITT) population includes all ITT except for those subjects that did meet the revised eligibility at the baseline visit.
- Per Protocol Population – The per protocol (PP) population (subset of mITT) includes all subjectswho have at least one follow-up visit and have no major protocol deviations, including specifically no use of dry-eye medications (Doxycycline, Xiidra). Subjects will be analyzed as treated. The primary and secondary efficacy analyses will be performed on the per protocol population.
- Safety Population – The safety population will include all subjects on whom the TearCare or Restasis is attempted. The safety population will be analyzed for all safety assessments. Subjects will be analyzed as treated.

22.2 STATISTICAL HYPOTHESES

The primary study hypotheses regard the superiority of the TearCare procedure as compared to Restasis, for Tear Break-Up Time (TBUT) and total OSDI. The primary endpoints will be tested for TearCare in a hierarchical fixed sequence. The statistical hypotheses are stated in terms of one-sided hypotheses, although statistical testing will be two-sided.

To demonstrate superiority of the TearCare procedure to the Restasis control for TBUT we will test the following hypotheses:

H_{01}: There is no difference between TearCare and Restasis in the mean change from baseline in TBUT at 6 Months.

H_{11}: The mean change from baseline in TBUT at 6 Months is greater with TearCare than with Restasis.

If H_{01} is rejected, then the study will be considered a success and we will test the following hypotheses to further demonstrate superiority of the TearCare procedure to the Restasis control for total OSDI:

H_{02}: There is no difference between TearCare and Restasis in the mean change from baseline in total OSDI at 6 Months.

H_{12}: The mean change from baseline in total OSDI at 6 Months is less with TearCare than with Restasis.

22.3 MULTIPLICITY CONSIDERATIONS

To address the multiple endpoints in this study, the primary and secondary effectiveness endpoints have been ordered in a hierarchical structure. Using this fixed sequence testing strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for testing the two primary effectiveness endpoints and the secondary effectiveness endpoints.

22.4 SAMPLE SIZE CALCULATIONS

22.4.1 TEAR BREAKUP TIME

A minimum of 310 subjects, approximately 155 in the TearCare group and 155 in the Restasis group, will be enrolled and randomized in the study. With an estimated 10% drop out rate at 6 months, a minimum of 139 subjects in each group are expected to be available for the primary efficacy analysis. Assuming a common standard deviation of 2 seconds for the change from baseline in TBUT at 6 months, a sample size of 139 subjects per group will have 98% power to detect a mean difference of 1 second between TearCare and Restasis at a two-sided significance level of 0.05. Assuming an overall 15% drop out rate, a minimum of 100 subjects are expected to be available at 24 months in each group to achieve 90% statistical power. This calculation is conservatively based upon prior TearCare clinical trial data, published data on Restasis, and the use of a two-sample t-test.

22.4.2 SAFETY

With an estimated 10% drop out rate per 6 months, a minimum of 98 subjects are expected to be available for analysis at 24 months in the TearCare group. For an AE that occurs at a rate of 5% within the TearCare group, this sample size would yield a 95% confidence interval with a margin of error of 4.4%; for an AE that occurs at rate 10%, the margin of error would be 6.0% and for an AE that occurs at rate 20%, the margin of error would be 8.1%.

22.4.3 SAMPLE SIZE SUMMARY

With a minimum of 155 in the TearCare group and 155 in the Restasis group, the power for the primary efficacy analysis of TBUT exceeds 90% and provides sufficient precision around the adverse event estimates through 24 months.

22.5 STATISTICAL ANALYSIS

22.5.1 GENERAL CONSIDERATIONS

The quantitative variables will be summarized using number of subjects (n), mean, median, standard deviation, minimum and maximum. The qualitative variables will be summarized using counts and percentages.

Summaries of all endpoints will be presented by treatment group and visit. Summaries will also be provided for demographics, baseline medical history, concurrent therapies, and subject disposition.

For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to MedDRA and WHO Drug dictionaries, as appropriate.

The number of subjects by center will be summarized in a table. Centers with less than 5 enrolled subjects will be combined into a single virtual center for the purpose of statistical analyses.

22.5.2 UNIT OF ANALYSIS

Safety endpoints will be analyzed for both eyes. For subject-level effectiveness endpoints, the unit of analysis will be the subject. For effectiveness endpoints assessed on each eye individually, the unit of analysis will be the eye.

22.5.3 MISSING DATA

No missing data imputation will be carried out beyond what is built-in to the mixed-effects modeling approach to be used in the primary effectiveness analysis.

No secondary effectiveness endpoints or safety endpoints will be imputed.

22.5.4 PRIMARY EFFECTIVENESS ENDPOINTS

22.5.4.1 TEAR BREAKUP TIME

Change from baseline in TBUT will be calculated as visit – baseline such that a positive difference indicates an improvement of dry eye signs. In addition, treatment comparisons between TearCare and Restasis will be calculated as TearCare – Restasis, such that a positive result indicates a better score for TearCare.

Linear mixed effects models will be used to compare the change from baseline in TBUTat the 6 Month visit between TearCare and Restasis. Linear mixed effects models will include fixed terms for baseline TBUT and study site, and a random subject effect to account for within-person correlation (correlation between right and left eyes). The primary analysis will use MCMC imputation to have a full accounting of the ITT population at the 6 Month visit. As supportive analyses, multiple imputation assuming

that data are missing not at random and analyses of observed data only will also be conducted. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted as supportive analyses.

22.5.4.2 TOTAL OSDI

Change from baseline in total OSDI score will be calculated as visit – baseline such that a negative difference indicates an improvement of dry eye symptoms. In addition, treatment comparisons between TearCare and Restasis will be calculated as TearCare – Restasis, such that a negative result indicates a better score for TearCare.

Change from baseline in total OSDI at the 6 Month visit will be analyzed using ANCOVA models adjusting for baseline and site. Two-sample t-tests and Wilcoxon rank sum tests will also be conducted as supportive analyses.

22.5.4.3 POOLABILITY OF CENTERS

Poolability of the effectiveness outcomes across centers will be evaluated by testing a treatment-by-center interaction in a separate model using observed data only. If the 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.

22.5.5 SECONDARY EFFECTIVENESS ENDPOINTS

The secondary effectiveness endpoints include change from baseline at 6 Months for the following outcomes:

1. Meibomian Gland Secretion Score
2. Symptom Assessment iN Dry Eye (SANDE) scores
3. Eye Dryness Score
4. Number of Meibomian Glands Yielding any liquid
5. Number of Meibomian Glands Yielding clear liquid
6. Corneal staining scores
7. Conjunctival staining scores
8. Schirmer Score
9. Ocular protection index (OPI): Interblink interval (IBI)/TBUT

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, Number of Meibomian Glands Yielding any liquid, Number of Meibomian Glands Yielding clear liquid, Blink Rate, Schirmer Score) and those measured on a per-subject basis (OSDI Score, SANDE Scores, Eye Dryness Score).

Endpoints assessed at the eye level will be analyzed with linear mixed effects models adjusting for baseline and site, and with a random subject effect. Two-sample t-tests and Wilcoxon rank sum tests will be conducted on the average of the two eyes as supportive analyses. Endpoints assessed at the subject level will be analyzed using ANCOVA models adjusting for baseline and site, with two-sample t-tests and Wilcoxon rank sum tests as supportive analyses. No imputation will be performed for secondary efficacy variables.

All secondary effectiveness variables collected will be summarized descriptively (n, mean, standard deviation, median, min and max) by treatment group and visit.

22.6 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.

22.6.1 INTERIM ANALYSES

No interim analyses are planned for this study.

23 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.