SIGHT SCIENCES

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

PROTOCOL ID #:	05474
CURRENT REVISION:	[redacted]
REVISION DATE:	March 16, 2018
SPONSOR:	Sight Sciences, Inc. 3000 Sand Hill Road Building 3, Suite 105 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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[redacted]	[redacted]	[redacted]

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1 PROTOCOL SYNOPSIS

Protocol Title	Randomized, Controlled Trial to Evaluate the Safety and Effectiveness of the TearCare® System in the Treatment of the Signs and Symptoms of Dry Eye Disease (OLYMPIA)
Protocol ID Number	05474
Study Device	TearCare® System
Control Group	Warm compress and lid massage
Primary Objective	To demonstrate the safety and effectiveness of a single TearCare® treatment compared to a daily regimen of combined warm compress therapy and lid massage to treat the signs and symptoms of dry eye disease in adult patients.
Study Design	Prospective, randomized, single-masked, multi-center treatment study. This is a post-market study.
Primary Effectiveness Endpoint	Mean Change from baseline to 1 month in Tear Break-Up Time (TBUT)
[redacted]	[redacted]
Safety Endpoints	○ Device-related adverse events ○ Best corrected visual acuity (ETDRS) ○ Intraocular pressure (IOP) ○ Discomfort/pain during treatment

Inclusion Criteria	1. At least 22 years of age 2. Reports dry eye symptoms [redacted] 3. Reports having to use artificial tears or lubricants regularly [redacted] 4. OSDI Score [redacted] 5. TBUT [redacted] 6. Meibomian gland obstruction in both eyes [redacted]. 7. Best corrected visual acuity of 20/100 or better in both eyes. 8. Willing and able to comply with the study procedures and follow-up 9. Willing and able to provide informed consent 10. English-speaking

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

	14. Ocular trauma [redacted]. 15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis. 16. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation 17. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and ectatic disease of the cornea 18. Punctal occlusion or punctal plug placement [redacted] 19. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.) 20. Allergies to silicone tissue adhesives 21. [redacted] 22. Use of antihistamines (oral or topical) [redacted] 23. Subject is currently on a systemic medication(s) (other than anti-histamines) that is known to cause ocular dryness[1] and whose dose of this medication(s) has not been stable [redacted] 24. Subject has taken or is currently taking Accutane. 25. Subject requires chronic use (i.e. for any portion of the study) of topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications or who has been on any of these medications [redacted]. 26. Subject is currently using Retin A or Latisse. 27. Participation in another ophthalmic clinical trial within 30 days prior to enrollment. [redacted] 28. Co-existing conditions that could interfere with the

	assessment of safety or effectiveness of treatment (e.g. macular disease, pregnancy, nursing, etc.).
Number of Subjects Enrolled and Randomized	200
Randomization	1:1
Number of Centers	Up to 15
Study Duration for Each Subject	12 months
Total Study Duration	Approximately 18 months
Schedule of Visits	Baseline, Day 1, Week 1, 1 Month, 3 Month, 6 Month, 7 month, 9 Month, 12 Month
Treatments	TearCare Group: TearCare procedure at Baseline and re-treatment at 6 months Warm Compress & Lid Massage: [redacted]

[redacted]

2 STUDY OBJECTIVE

The objective of this study is to demonstrate the safety and effectiveness of a single TearCare® treatment compared to a daily regimen of combined warm compress therapy and lid massage to treat the signs and symptoms of dry eye disease in adult patients.

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

3 BACKGROUND AND JUSTIFICATION FOR THE STUDY

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

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.[5] 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.[5] Essentially, not only do dry eye patients directly suffer, but there is also a burden to healthcare, employers, and society.

[redacted]

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.[6] 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.[7] In fact, AAO guidelines state that these conditions coexist in the majority of the patients with the disease.[8]

In terms of the mechanism of action for dry eye disease, the International Dry Eye Workshop (DEWS)[2] explained that tear hyperosmolarity and the symptoms of dry eye result from water evaporation caused by low aqueous tear flow and/or excessive evaporation. This reduced, concentrated tear volume, in turn results in further inflammation and tear film instability creating a vicious cycle. The DEWS report concluded the following: "Since both aqueous tear deficiency and increased evaporative tear loss occur in most cases of dry eye disease and are linked by common pathogenetic mechanisms, expert clinicians are increasingly basing treatment decisions on an assessment of severity rather than discrete deficiencies."[9]

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:

[redacted]

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.[10,11,12,13] The DEWS II report states that meibomian gland disease is considered the leading cause of dry eye in clinic and population based studies.[14] 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.[15] When this occurs, it can result in ocular discomfort and, in many cases, ocular surface disorders that can affect vision.

To address this, use of warm compresses and lid massage are recommended for the treatment of dry eye by the AOA, AAO, and the International Workshop on Meibomian Gland Dysfunction.[16,17,18] It is believed that the heat helps melt the oily obstructions in the meibomian glands and helps reduce gland inflammation, thereby helping to restore the ability of the meibomian glands to effectively secrete oil onto the tear film and prevent rapid tear evaporation.

[redacted]

It has been shown that warm compress therapy can lead to improved lipid production and flow on to the tear film.[19,20,21] 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.[22,23,24] The tear film is demonstrably thicker and more stable with an increased contribution of lipid to its surface.[25,26,27]

In addition to warm compresses, various alternative approaches to heating the eyelids have been proposed.[28,29,30,31,32] Widespread adoption of these approaches has been limited due to a variety of factors including questions about duration of effectiveness, issues related to ease of use, lack of reimbursement, and the out-of-pocket cost of the treatment to the patients.

Sight Sciences has developed the TearCare™ System to provide a safe and effective treatment for the signs and symptoms of dry eye disease. The System is designed to conform to the eyelids to deliver controlled, precise heat to the tarsal plates and underlying meibomian glands of the eyelids for 15 minutes in the monitored setting of an ophthalmologist or optometrist office. In addition to blinking during TearCare™

[redacted]

treatment to naturally express melted meibum, the physician then uses the Express™ Forceps to further express the meibomian glands manually immediately following the eyelid heat treatment.

In this study, the TearCare System will be compared with standard-of-care warm compress treatment and lid massage in patients with dry eye disease. The objective is to demonstrate that the TearCare System is safe and effective in relieving the signs and symptoms of dry eye disease and that it is superior to a commonly prescribed, standard treatment of warm compress and lid massage.

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

4 DESCRIPTION OF DEVICE

4.1 CURRENT INDICATION FOR USE

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

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

4.2 PROPOSED INDICATION FOR USE

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

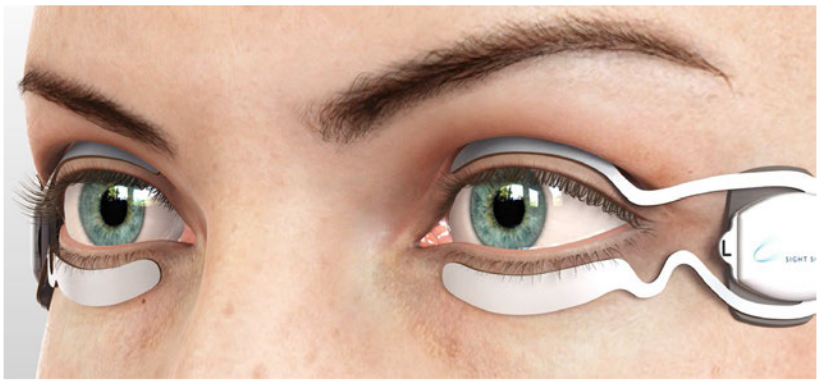
> "The TearCare® System is indicated for the treatment of the signs and symptoms of dry eye disease (DED)."

4.3 DEVICE DESCRIPTION

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

[redacted]

[redacted]



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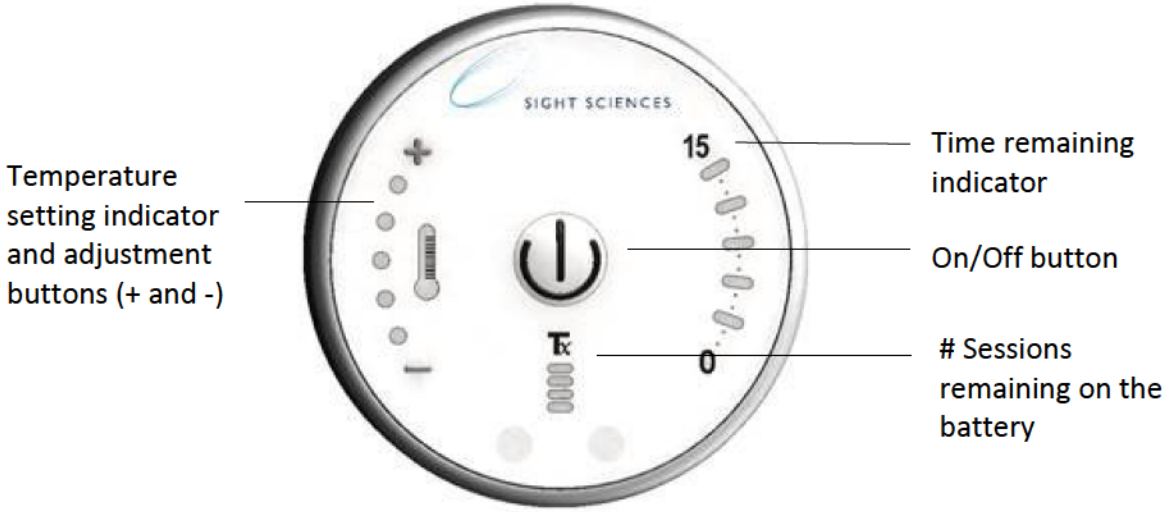

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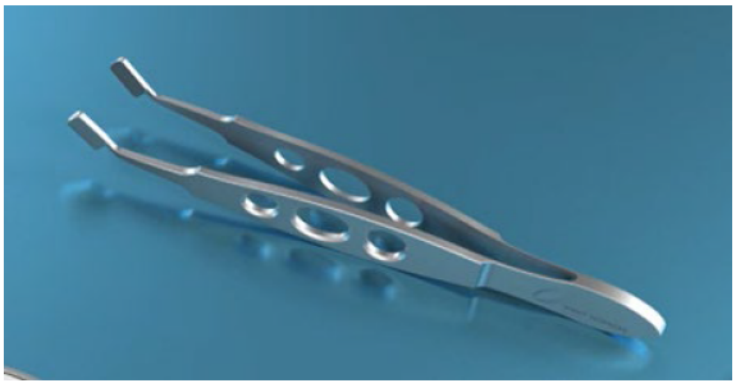


To use the System, the flexible iLid devices are applied to the external surface of the upper and lower eyelids of the patient (Figure 1). The iLid devices are then connected to the TearCare SmartHub. When the SmartHub is turned on and the physician initiates the procedure, the TearCare System begins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

Immediately following the TearCare session, the clinician uses the Express Forceps to manually express the meibomian glands in all four eyelids.

4.4 INSTRUCTIONS FOR USE

Instructions for Use are provided with each TearCare System.

4.5 TRAINING

Prior to the start of the study, investigators and study staff who have not been previously trained in the proper use of the TearCare System will be trained in its use. While most investigators should have experience in performing manual expression of

[redacted]

the meibomian glands, which is a standard procedure for dry eye patients, investigators will be trained in the protocol method for performing meibomian gland expression using the Express Expression Forceps. 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

[redacted]

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

5.2 PREVIOUS CLINICAL EXPERIENCE

The TearCare System has been studied in two pilot studies. The first study was conducted in 2013 as an Investigator-sponsored study with a prototype version of the

TearCare System. The second study was initiated in 2017 with a commercial version of the TearCare System (Sight Sciences protocol #05429). These two studies are summarized below.

5.2.1 CLINICAL STUDY OF THE PROTOTYPE TEARCARE SYSTEM (2013)

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

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

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

[redacted]

5.2.2 CLINICAL STUDY OF THE TEARCARE SYSTEM (2017)

Following completion of the design and development of the commercial version of the TearCare System, a single center pilot study was initiated to collect additional clinical data.

Objectives

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

Subjects

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

Methods

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

Results

Twenty-four subjects were enrolled and completed 6 months follow-up. Data are summarized in Table 2 below.

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

in the TearCare group also showed significantly greater improvement in dry eye symptoms as measured by the three questionnaires.

No adverse events were reported in either group.

[redacted]

Conclusions

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

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

5.2.3 SUMMARY

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

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

6 STUDY ENDPOINTS

6.1 EFFECTIVENESS ENDPOINTS

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

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

- **Primary effectiveness endpoint**
  - Mean Change from baseline in Tear Break-Up Time (TBUT)
- **Secondary effectiveness endpoints**
  - Mean Change from baseline in OSDI score[39]
  - Mean Change from baseline 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 SANDE scores [41,42]
  - Eye Dryness Score
- **Treatment Duration Endpoints**
  - Mean 3- and 6-month Change from baseline for successful primary and secondary endpoints
- **Additional Exploratory Endpoints**

[redacted]

- Number of meibomian glands yielding clear liquid secretions
- Number of meibomian glands secreting any liquid (clear or cloudy)
- Use of dry eye lubricants
- Assessment of all effectiveness endpoints at 7, 9 and 12 months.

6.2 SAFETY ENDPOINTS

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

- Device-related adverse events (all adverse events will be recorded)
- Best corrected visual acuity (ETDRS)
- Intraocular pressure (IOP)
- Discomfort/pain during treatment

7 STUDY DESIGN

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

7.1 STUDY DEVICE AND CONTROL ARM

In this study, TearCare treatment will be compared with standard-of-care warm compress treatment plus lid massage. Warm compress treatment plus lid massage, once a day, was chosen for the control arm since it is one of the most commonly prescribed treatments for dry eye disease.[43,44]

TearCare treatment includes an in-office 15 minute treatment session with the TearCare System immediately followed by manual expression of the meibomian glands using the Express Expression Forceps. Subjects randomized to TearCare will receive one in-office treatment session at the baseline visit and one re-treatment at 6 months.

[redacted]

Subjects randomized to the Warm Compress and Lid Massage Group will be instructed to use a moist warm compress for 5 minutes and then perform lid massage. They will be instructed to perform this at home once per day during the follow-up period. This regimen is consistent with the recommendations of the International Workshop on Meibomian Gland Dysfunction.[45] Subjects in the warm compress and lid massage group will perform their first daily session in the investigator's office so that the clinician can insure the subject is performing the treatment properly.

[redacted]

7.3 STUDY CENTERS

This study will be conducted at up to 15 centers in the United States. No center will have more than 20% of the target enrollment.

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 [redacted]
3. Reports having to use artificial tears or lubricants regularly [redacted]
4. OSDI Score [redacted]
5. TBUT [redacted]
6. Meibomian gland obstruction in both eyes [redacted]
7. Best corrected visual acuity of 20/100 or better in both eyes.
8. Willing and able to comply with the study procedures and follow-up
9. Willing and able to provide informed consent

[redacted]

10. English-speaking

8.2 EXCLUSION CRITERIA

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

1. Any active, clinically significant ocular or peri-ocular infection or inflammation
2. Recurrent clinically significant eye inflammation, other than dry eye, [redacted] t
3. History of eyelid, conjunctiva or corneal surgery (including refractive surgery) within the past year. In addition, subjects with any history of the following are excluded: chalazion surgery, surgery on the tarsal conjunctiva, radial keratotomy (RK), complicated blepharoplasty, lid reconstruction, or significant complications post-refractive surgery.
4. [redacted]
5. Meibomian gland expression within 6 months prior to enrollment. [redacted].
6. In the clinical judgement of the investigator, meibomian glands have significant capping, atrophy, or are unable to be digitally expressed.
7. Contact lens use within the past 2 weeks. ([redacted]
8. [redacted]
9. History of Ocular Herpes Simplex or Ocular Herpes Zoster
10. Clinically significant ocular surface abnormalities that may affect tear film distribution or treatment (e.g. pterygium, anterior membrane dystrophy, etc.)
11. Clinically significant eyelid abnormalities in either eye (e.g. entropion/ectropion, blepharospasm, aponeurotic ptosis, lagophthalmos, notching of lid margin, distichiasis, trichiasis).
12. Clinically significant anterior blepharitis. In addition, collarettes or flakes of more than one quarter of the eyelid are excluded.
13. Clinically significant dermatologic or cutaneous disease of the eyelid or periocular area.
14. Ocular trauma [redacted]
15. Any active, clinically significant allergic, vernal, or giant papillary conjunctivitis.
16. Known history of diminished or abnormal facial, periocular, ocular or corneal sensation
17. Corneal surface abnormalities such as corneal epithelial defects (other than punctate staining), ulcers, corneal epithelial dystrophies, keratoconus, and

ectatic disease of the cornea
18. Punctal occlusion or punctal plug placement [redacted]
19. Systemic diseases resulting in dry eye (e.g. autoimmune diseases such as Sjogren's syndrome, rheumatoid arthritis, lupus, Graves' disease, sarcoidosis, etc.)
20. Allergies to silicone tissue adhesives
21. [redacted]
22. Use of antihistamines (oral or topical) within 10 days prior to enrollment. [redacted]
23. Subject is currently on a systemic medication(s) (other than anti-histamines) that is known to cause ocular dryness[46] and whose dose of this medication(s) has not been stable within 30 days prior to enrollment. [redacted]
24. Subject has taken or is currently taking Accutane.
25. Subject requires chronic use (i.e. for any portion of the study) of topical ophthalmic antibiotics, anti-glaucoma medications, steroids, non-steroidal anti-inflammatory medications [redacted]
26. Subject is currently using Retin A or Latisse.
27. Participation in another ophthalmic clinical trial within 30 days prior to enrollment. Subject must also be willing to refrain from another ophthalmic study for the duration of the study.
28. Co-existing conditions that could interfere with the assessment of safety or effectiveness of treatment (e.g. macular disease, pregnancy, nursing, etc.).

9 STUDY PROCEDURES

9.1 STUDY SCHEDULE

The Study Schedule is shown below in Table 3.

[redacted]

[redacted]

9.2 Number of Subjects, Duration of Follow-up and Study Duration

A total of 200 subjects will be enrolled and randomized in the study. Assuming a 15% screen failure rate, approximately 230 subjects will be enrolled and screened to obtain 200 randomized subjects. All subjects will be followed for 12 months.

It is anticipated that enrollment in the study will take 3-6 months. Including the 12-month follow-up period, the study is expected to last 15-18 months.

Analysis of the primary outcome will occur when the last subject has reached the 1 month follow up. In order to evaluate long-term results of the TearCare treatment, data will be re-analyzed after the last subject reaches the 6 month follow-up and then again after the last subject reaches the 12 month follow up.

[redacted]

[redacted]

9.4 INFORMED CONSENT AND POINT OF ENROLLMENT

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

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

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

9.5 BASELINE VISIT

9.5.1 SCHEDULING THE BASELINE VISIT

The baseline visit may be performed over two separate visits. If the visit is performed over two visits, then all baseline exams and questionnaires (Section 9.5.2) and randomization (Section 9.5.3) should be performed in the first visit. If the subject is randomized to the warm compress and lid massage group, the treatment for warm compress and lid massage (Section 9.5.5), and the associated discomfort/pain questionnaire and AE assessment should be performed at the first visit. If the subject is randomized to TearCare, then the TearCare procedure (Section 9.5.4) and the associated Discomfort/pain questionnaire and AE assessment may be performed on a separate visit, as long as it is performed within 7 days of the first visit. If the TearCare procedure is performed on a second visit, then the date of the second visit will be Day 0 of the study for scheduling purposes.

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

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

[redacted]

9.5.3 RANDOMIZATION

Subjects will be randomized to either the TearCare (i.e. "treatment group") or Warm Compress and Lid Massage (i.e. "control group") using a pseudo-random number generator with subjects enrolled according to a predetermined list. Randomization will

use permuted blocks with random block sizes of 2 or 4. The investigational site will be provided a set of envelopes with randomization assignments. Following randomization, the subject should immediately undergo the applicable procedures described in the sections below.

9.5.4 TREATMENT FOR TEARCARE GROUP

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

[redacted]

[redacted]

9.5.5 TREATMENT FOR WARM COMPRESS AND LID MASSAGE GROUP

1. Subjects randomized to the Warm Compress and Lid Massage Group should be provided with the written instructions for how to perform the daily warm compress and lid massage (per the method described by Finis, et al[47]) at home. These instructions are provided in Appendix B.
2. Go over the instructions provided in Appendix B and have the subject perform each step in the presence of study staff. This is to ensure the subject properly understands the instructions.
3. Immediately following the warm compress treatment, ask the subject to assess whether s/he experienced any ocular discomfort or pain during or immediately after the treatment using the scales provided on the case report form.
4. Instruct the subject to perform the warm compress/lid massage once every day.
5. Provide the subject with a copy of the Warm Compress Use Log and instruct them to record each time they perform the warm compress/lid massage treatment.
6. Instruct the subject that if they require lubricant drops to relieve dry eye symptoms during the follow-up period, they should only use Refresh Plus® drops which will be supplied to them in single-use vials by the investigator. Provide the

[redacted]

subject with a supply of these single-use vials. Record on the Refresh Plus Vials worksheet how much is provided to the subject.

7. Instruct the subject that they should not reuse the vial. Once opened, they should discard the vial. Instruct the subject to bring the unused vials back at the next follow-up visit so that they can be counted.

9.6 FOLLOW-UP VISITS

9.6.1 FOLLOW-UP VISIT ROUTINE PROCEDURES

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 to bring their unused Refresh Plus vials and, if they are in the warm compress group, their Warm Compress Log.

Also, since dry eye drops and lubricants can affect the endpoint assessments, it is important to remind subjects, on the day of the Follow-up visit, not to use any of these products before the Follow-up 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 9.7).

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

Order of Procedures During the Follow-Up Visit

Follow-up procedures will be performed per the Study Schedule provided in Table 3 (page 28) 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 and ETDRS Best-corrected visual acuity
3. Slit Lamp Exam
4. Tear Breakup Time
5. Corneal and conjunctival staining score
6. Meibomian Gland Secretion Scoring

7. IOP
8. Assessment of adverse events

The following activities can be performed in any order:

- Medication Use
- Collection of Warm Compress Log
- Count unused Refresh Plus Vials

At the End of the Follow-Up Visit

At the end of the follow-up visit, provide subjects with a new supply of Refresh Plus vials, if needed. Record how many vials are provided to the subject.

For subjects in the Warm Compress and Lid Massage group, provide them with a new Warm Compress Log for use in the next follow-up period.

9.6.2 6 MONTH FOLLOW-UP VISIT: RE-TREATMENT [redacted]

Scheduling the 6 Month Visit

Like the Baseline visit, the 6 month visit may be performed over two separate visits. If the visit is performed over two visits, then all required visit elements except the TearCare procedure and Discomfort questionnaire should be performed in the first visit. The TearCare procedure and the associated Discomfort/pain questionnaire may be performed on a separate visit, as long as it is performed within 7 days of the first visit. If the TearCare procedure is performed on a second visit, then the date of the second visit will be considered the date of the 6 Month visit for subsequent visit scheduling purposes.

At the 6 month follow-up visit, all subjects will undergo the tests and exams listed in Table 3 (page 28).

TearCare Group: Re-Treatment

After completion of the follow-up tests and exams, subjects in the TearCare group will undergo re-treatment with the TearCare System, following the instructions provided in Section 9.5.4.

[redacted]

[redacted]

[redacted]

9.7 MASKED ASSESSOR

To reduce potential bias in the study, study staff performing endpoint assessments will be masked as to the subject's treatment arm. In addition, to ensure consistency in performing the endpoint assessments the study staff member who performs the baseline assessments should also perform the follow-up assessments. An alternate Masked Assessor may be appointed to handle scheduling conflicts, but every effort should be made to have the same person performing all endpoint assessments throughout the study. The Masked Assessor should not perform the randomization, in-office TearCare Treatment, gland expression or the in-office warm compress treatment prior to home use. Masking will be maintained until all subjects at the site have passed the 6-month follow up time.

The following assessments must be performed by Masked Assessor:

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

The study coordinator should collect the Warm Compress Log from the subject.

9.8 MANAGEMENT OF DRY EYE SYMPTOMS DURING FOLLOW-UP

During follow-up, if subjects require drops to relieve their dry eye symptoms, they may use Refresh® Plus lubricant vials which have been supplied by the investigator. Other types of over-the-counter lubricants should not be used. Subjects should bring the unused vials to each follow-up visit so that they can be counted.

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

Subject should not be treated with other dry eye treatments (e.g. LipiFlow, punctal plugs, etc.) during the course of the study. Administration of these treatments will

result in the subject being excluded from the "Per Protocol" analysis from the time of initiation of these treatments forward.

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

9.9 WITHDRAWAL AND DISCONTINUATION

All subjects have the right to withdraw at any point during the treatment without prejudice. The investigator can discontinue any subject at any time if continued participation in the study would result in harm to the subject. All efforts should be made by the investigator to retain the subject in the study. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) the subject discontinued the study. The reason must be recorded in the subject's file and on the Study Exit Form.

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

9.10 SUBJECTS LOST TO FOLLOW-UP

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

10 ADVERSE EVENTS (AES)

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

10.1 DEFINITIONS OF AE, SAE, SADE, USADE

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

10.2 LIST OF ANTICIPATED POTENTIAL ADVERSE EVENTS

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

- Burn, erythema, or swelling of the eyelids
- Conjunctival injection (Moderate or severe)
- Conjunctival abrasion
- Corneal abrasion
- Corneal deformation
- Allergic or inflammatory reaction to medical adhesive on the iLid device

- Formation of a chalazion or stye
- Loss in BCVA of 2 lines or greater
- Worsening of dry eye symptom
- Increased discomfort or pain of ocular surface (grittiness, foreign body sensation, etc.)
- Discomfort or pain of eyelids or orbit

10.3 Reporting Adverse Events and Unanticipated Adverse Device Effects

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

Any ocular-related **serious adverse event** (SAE) should be reported to the study sponsor within one working day of learning of the event. Non-ocular-related SAEs should be reported to the study sponsor within two working days of learning of the event. Email the AE CRF to 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, 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. The goal of the procedure is to provide a safe, reproducible, and

effective treatment for dry eye disease, a disease for which there is an unmet need for effective therapies.

11.2 ANTICIPATED ADVERSE DEVICE EFFECTS

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

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

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

11.4 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

All anticipated study risks are listed in Section 10.2.

11.5 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

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

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

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

1. Overheating of the eyelids: All TearCare treatments will be done in the investigator's office under direct supervision of the investigator. The device delivers heat to the eyelids at a temperature ranging from 41-45°C. This temperature range was selected because it is both safe for eyelid heating and

effective for melting obstructions in the meibomian glands.[48,49,50,51] The user can adjust the temperature up or down to a level that is comfortable, and may also shut off the System at any time if it is too uncomfortable or painful. In addition, the TearCare System continuously monitors and regulates the temperature at the tissue-contacting surface of the iLid devices and has been designed to not exceed the maximum allowable temperature.

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

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

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

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

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

[redacted]

12 STATISTICAL CONSIDERATIONS

12.1 EVALUABILITY

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

12.2 ANALYSIS POPULATIONS

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

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

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 treatment arm. This includes baseline measurements for each of the study endpoints: TBUT, Meibomian Gland Secretion Score, Corneal Staining, Conjunctival Staining, OSDI Score, SANDE Score, and Eye Dryness Score.

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

12.5 ENDPOINTS AND ANALYSIS METHODS

All primary and secondary endpoints will be evaluated at 1 month for submission for regulatory approval. Outcomes measured on a per-eye basis will be analyzed using linear mixed effect models to account for within-person correlation (correlation

between right and left eyes). If the primary endpoint is successful at 1 month, and for all successful secondary endpoints, treatment duration will be further evaluated at 3 and 6 months.

12.5.1 DESCRIPTIVE ANALYSES

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

12.5.2 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness outcome is the change from baseline in Tear Break-Up Time (TBUT) at the 1 month follow up. TBUT will be analyzed using a linear mixed effects (LME) model. This will allow for the proper incorporation of within-person correlation into the statistical model, and will also allow for adjustment for baseline measurements.

Details of the LME model are provided in the Statistical Analysis Plan (SAP) provided in Appendix C. Hypotheses regarding the primary and secondary effectiveness outcomes are described below in Section 12.6.

12.5.3 POOLABILITY

Using the LME modeling approach outlined above, poolability 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.

12.5.4 MISSING DATA

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

12.5.5 SECONDARY EFFECTIVENESS ENDPOINTS

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

1. Ocular Surface Disease Index (OSDI) score,
2. Total Meibomian Gland Secretion Score,
3. Corneal staining score,
4. Conjunctival staining score,

5. Symptom Assessment iN Dry Eye (SANDE) Frequency score, Severity Score and Total score.
6. Eye Dryness Score (EDS)

[redacted]

12.5.6 EVALUATION OF TREATMENT DURATION

If the primary endpoint is successful at the one month primary time point, then treatment duration will be evaluated using a hierarchical testing procedure. Using data that are obtained at the 3- and 6-month follow-up visits we will again test the primary hypothesis comparing change from baseline Tear Break-Up Time (TBUT) between the treatment and control. We will use the same linear mixed effects (LME) model as in the primary analysis, evaluating each time point separately. The two time points will be tested sequentially, stopping at 3 months if the test fails at that point. Treatment duration will be the maximum time point at which this treatment duration testing succeeds, either 1, 3, or 6 months.

This analysis will not be carried out if the primary 1-month endpoint fails, it is not intended to establish primary effectiveness in the event of study failure at one month.

Note that this analysis will be carried out using data that will be at least partially obtained after the primary database lock. However every effort will be made to maintain the masking of assessors through the 6-month follow-up as described in section 9.7.

This analysis does not affect the type I error for the primary endpoint. The 1- 3- and 6-month TBUT outcomes will likely be highly correlated, however the sequential testing will appropriately control the time-wise type I error rate.

For each secondary endpoint that is successful at the one month time point using the hierarchical testing procedure described in 12.5.5, treatment duration will be evaluated at the 3- and 6-month follow up. Evaluation of treatment duration for the secondary endpoints will be based on sequential testing of 3- and 6-month follow up times separately, in the same manner as for the primary endpoint. Secondary endpoints that fail at the 1-month time point will not be evaluated for treatment duration.

12.5.7 Additional Exploratory Analyses

The following additional effectiveness analyses will be provided at the time of regulatory submission:

- Number of meibomian glands yielding clear liquid secretions
- Number of meibomian glands secreting any liquid (clear or cloudy)
- Use of dry eye lubricants, collected through counting unused vials of Refresh Plus

The meibomian gland-related measurements will be analyzed in the same manner as the per-eye secondary endpoints.

Lubricant use will be summarized by Treatment group at each follow-up visit.

12.5.8 Modeling of Extended Follow-up Results

After the initial 1 month primary analysis, subjects will be followed up to 12 months to evaluate durability of the treatment effect. After the 6 month visit, subjects in the Warm Compress group will cross over into the TearCare arm. Treatment duration will be evaluated primarily via comparisons of treatment versus control change in TBUT at each of the 3- and 6-month time points separately as described in 12.5.6.

After 6- and 12-month follow-up is complete the longitudinal study data will be re-analyzed, again using LME modeling methods. These models will allow us to evaluate the following:

- Maintenance of the Treatment effect using the full longitudinal data on each subject,
- A more detailed evaluation of the baseline effects, if any.

At the 12 month follow-up the Warm Compress subjects will have received TearCare treatment at 6 months, thus we will lose a comparison to randomized control subjects at this point. However for those subjects who receive TearCare at 6 months we will be able to carry out a before- versus after- TearCare comparison, which may provide useful supplementary information.

12.5.9 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.

[redacted]

[redacted]

12.7 Sample Size Calculation

A total of 200 subjects, 100 in the TearCare group and 100 in the Warm Compress group, will be enrolled and randomized in the study. Sample size was calculated to provide more than 90% power for the TBUT and OSDI effectiveness endpoints and sufficient precision around the adverse event estimates. The sample size also takes into account an estimated 10% dropout rate. Details of the sample size calculation can be found in Appendix C.

12.8 Interim Analysis

The primary analysis for this study will occur after the final subject reaches their 1 month follow-up. The results of this analysis will be used for regulatory submission. Further analyses after all subjects have reached their 6- and 12-month follow up will be used to investigate duration of the TearCare treatment effect as outlined above.

There will be no interim analyses.

12.9 Deviation from the Statistical Plan

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

13 Monitoring Procedures

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

- Site Qualification: 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
  - Guidance in how to instruct subjects to use the warm compress at home and perform lid massage at home.
  - Guidance in how to administer questionnaires to subjects
  - Procedures for maintaining masking of study personnel
  - Records and reports
- Interim Monitoring: Sight Sciences or CRO personnel will visit the clinical site routinely during the study to review charts and to perform source document verification, to ensure proper adherence to the study protocol, and to review regulatory documents. Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.
- Study Closure: At the conclusion of the trial there will be a study closure visit during which several actions, including but not limited to the following, will be performed:
  - A final inspection of the study binder
  - Accountability and return of all devices and study materials to the sponsor
  - Discussion of record retention requirements with the investigator
  - Close-out notification to the IRB

14 DATA AND QUALITY MANAGEMENT

14.1 DATABASE MANAGEMENT

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

The database will incorporate time-stamped audit trails, protection of human subjects, restricted access, and data security at the component level. Each database module,

including each individual eCRF, will be validated by conducting a series of standard tests that demonstrate usability and correctness of the database system. The database will be maintained on an ongoing basis and will be routinely backed up.

14.2 SUBJECT IDENTIFICATION

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

14.3 SUBJECT ACCOUNTABILITY

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

14.4 CONFIDENTIALITY

All medical records associated with the clinical investigation will be made available for review by Sight Sciences personnel, its contract research organization (CRO) and governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area at the investigator's facility, the CRO, the data management firm and at Sight Sciences, Inc.

14.5 SOURCE DATA AND CASE REPORT FORMS

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

Source data and study worksheets are to be maintained at the site in the subject records or in the medical records. All entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. All

source documents must be completed and signed by the authorized study personnel (e.g., study coordinator). No "white-out" is to be used on the source documents.

14.6 Retention Period

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

15 Protocol Modifications and Deviations

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

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

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

16 Device Failures and Malfunctions

All device failures or malfunctions should be recorded on the Device Deficiency Form and reported to Sight Sciences Customer Service (877-266-1144).

17 Ethical Considerations

17.1 Declaration of Helsinki

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

17.2 INSTITUTIONAL REVIEW BOARDS (IRB)

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

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

17.3 INFORMED CONSENT FORM (ICF)

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

17.4 PUBLIC LISTING OF STUDY

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

18 STUDY ADMINISTRATION

18.1 DEVICE ACCOUNTABILITY

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

study devices are used, returned or disposed of, their disposition (including the disposition and date of disposition) must be recorded on the Device Accountability log.

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

18.2 Early Termination or Suspension of an Investigation

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

- The discovery of an unexpected, significant, or unacceptable risk to the study subjects implanted with the device
- Withdrawal of FDA listing of the TearCare product.

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

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

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

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

18.3 Investigator Responsibilities

18.3.1 General Responsibilities of Investigators

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

18.3.2 SPECIFIC RESPONSIBILITIES OF INVESTIGATORS

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

18.3.3 INVESTIGATOR RECORDS

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for the period specified in Section 14.6:

1. All correspondence with another Investigator, an IRB, the Sponsor, a monitor, or FDA, including required reports.
2. Records of each subject's case history and exposure to the device. Case histories include the study CRF's/worksheets and supporting data including, for example, signed and dated consent forms and medical records. Such records shall include:
    a) Documents evidencing informed consent.
    b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
3. The protocol, with documents showing the dates and reasons for each deviation from the protocol.
4. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

18.3.4 INVESTIGATOR REPORTS

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

1. Unanticipated Adverse Device Effects - An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect

occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

2. Withdrawal of IRB Approval - An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.
3. Progress - An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
4. Deviations from the Investigational Plan - An Investigator shall document and report to the Sponsor any deviation from the investigational plan.
5. Informed Consent - If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.
6. Final Report - An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB.
7. Other - An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

18.4 INVESTIGATOR AGREEMENT

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

19 PUBLICATION POLICY

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

Multi-Site Data

Clinical site investigators are encouraged to propose publications and abstracts that include clinical or research data from multiple clinical sites; such projects will be

coordinated by Sight Sciences. Authorship of papers and abstracts resulting from these projects will be determined collaboratively according to the following guidelines:

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

Single Site Data

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

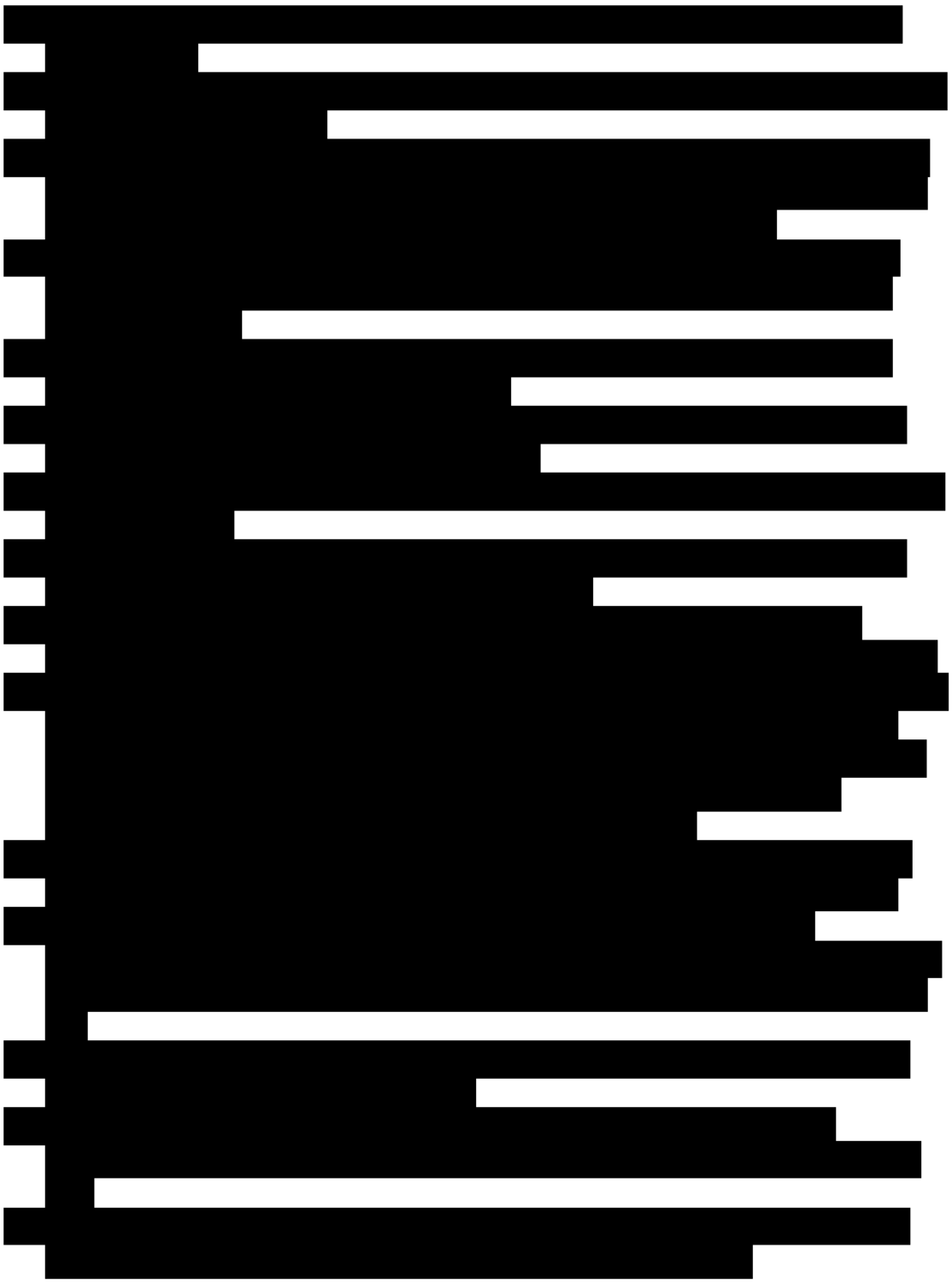
Publications Review Policy

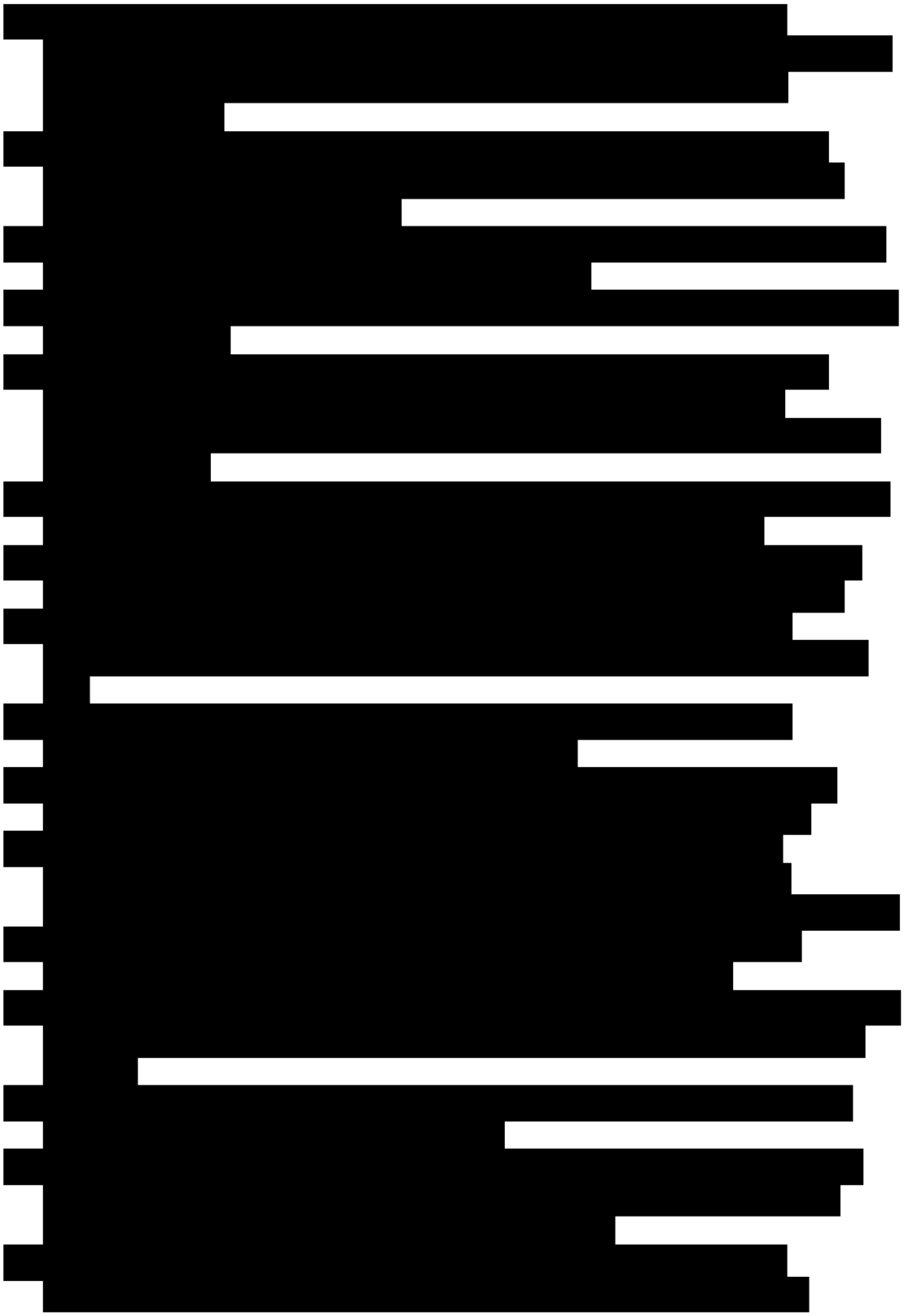
Investigators must submit all presentations, posters, abstracts and manuscripts pertaining to this study to Sight Sciences for review in advance of their submission. Sight Sciences conducts this review to protect its proprietary rights to information, inventions, or products developed under the Study.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

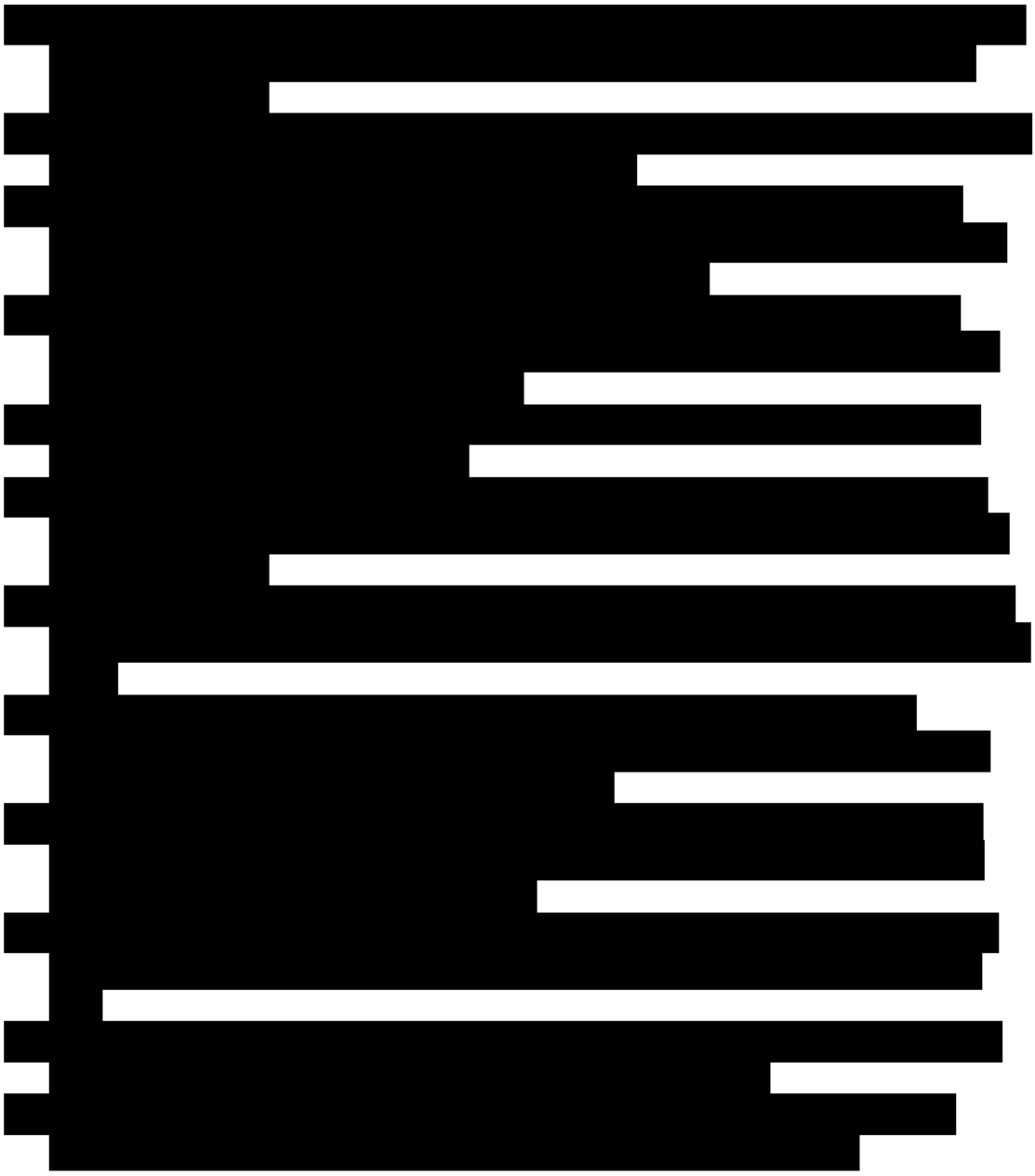
- Presentations/Posters: 5 business days in advance of presentation
- Abstracts: 5 business days in advance of submission
- Manuscripts: 30 calendar days in advance of submission for publication

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

[redacted]







21 APPENDIX A – METHODS FOR EXAMS, TESTS AND QUESTIONNAIRES

21.1 MEDICATIONS

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

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 follow-up visit. On Day 1, subjects' 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 ≥ 2 lines 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.

[redacted]

[redacted]

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 16 x 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.

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

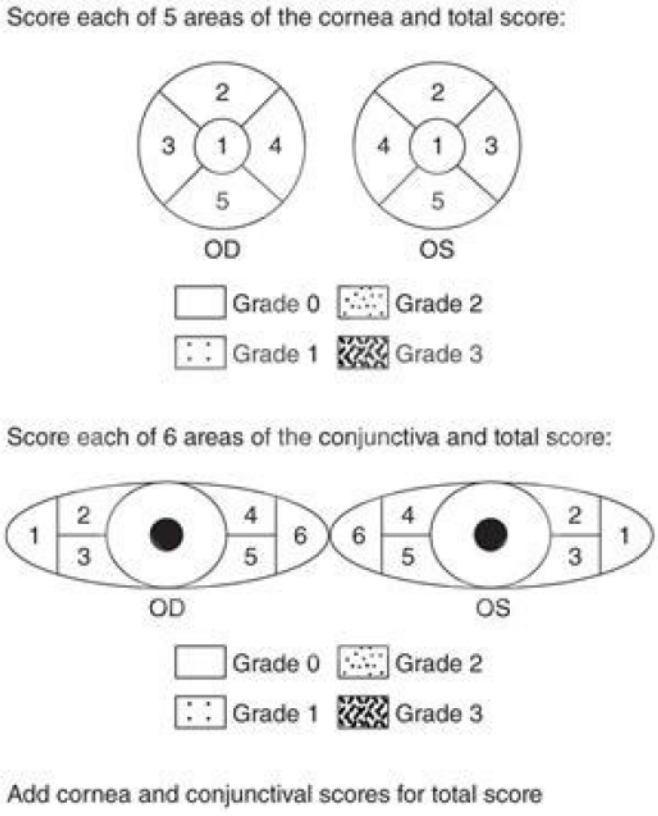
Under the cobalt blue illumination of the slit lamp, tear break-up time should be [redacted]

21.5 CORNEAL STAINING

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

Corneal staining should be assessed immediately following TBUT measurements (i.e. within 1-4 minutes after instillation of fluorescein dye) to assure the dye does not diffuse into stroma, blurring the discrete margin of any staining defects. A yellow Wratten filter should be used to improve any visualization of corneal staining. Grade the corneal staining using the NEI/Industry Grading System provided in Figure 4 below.[52]

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



21.6 CONJUNCTIVAL STAINING

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

[redacted]

[redacted]

[redacted]

21.7 SCHIRMER 1 TEST

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

21.8 MEIBOMIAN GLAND SECRETION SCORING

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

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

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

[redacted]

[redacted]

[redacted]

- 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 a Goldmann tonometer, if available.

21.10 QUESTIONNAIRES

21.10.1 GENERAL INSTRUCTIONS FOR QUESTIONNAIRES

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

Provide a paper copy of the questionnaires and a blue or black ink pen to the subject. Review the instructions for each questionnaire with the subject and answer any questions they have about how to complete them. Then allow the subject to complete the questionnaires on their own (i.e. self-administered).

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

21.10.2 OSDI QUESTIONNAIRE

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

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

21.10.3 SANDE QUESTIONNAIRE AND EYE DRYNESS VAS

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

Three scores will be obtained from the SANDE:

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

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

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

21.10.4 DISCOMFORT/PAIN QUESTIONNAIRE

The Discomfort/Pain Questionnaire is designed to assess the degree of discomfort or pain that the subject experiences during and immediately after the study treatment on

Day 0 and post-treatment (Day 1). Subjects are asked to indicate their level of discomfort and pain using a Visual Analog Scale provided in the case report forms.

22 APPENDIX B – INSTRUCTIONS FOR WARM COMPRESS AND LID MASSAGE

Perform the warm compress and lid massage at home once each day.

Instructions

1. Prepare the warm compress
    a. Using a clean wash cloth, run it under warm, shower temperature tap water to saturate it. It is important that the water be warm, or shower-temperature, but not so hot that it causes pain or injury.
    b. Squeeze the wash cloth to remove excess water.
    c. Fold the washcloth in thirds.

2. Apply the Warm Compresses
    a. Test the washcloth to make sure it is not too hot. If it is too hot, wait about 10 seconds before testing again.
    b. With eyes closed, apply the warm compress over your closed eyelids for 5 minutes.

3. Lid Massage
    a. Lid massage should be performed immediately after completing the 5 minutes with the warm compress.
    b. Do not vigorously rub your eyelids. Avoid contacting or scratching your eye.
    c. To massage the upper eyelids, place one finger at the outer edge of your eyelid to hold it closed and slightly taut. Using the opposite hand, place a finger on the upper eyelid by the nose and, using mild pressure, run the finger along the lower edge of the upper eye lid toward the outside of the eye. Repeat on the opposite eye.
    d. To massage the lower eyelid, place one finger at the outer edge of your eyelid to hold it slightly taut. Look up. Using the opposite hand, please a finger on the lower eyelid by the nose and, using mild pressure, run the finger along the upper edge of the lower lid toward the outside of the eye. Repeat on the opposite side.

4. Warm Compress Log
    a. Use the Warm Compress Log sheet to record the date and time that you perform the warm compress and lid massage. Bring this log with you to each follow-up visit.

23 APPENDIX C – STATISTICAL ANALYSIS PLAN

23.1 ENDPOINTS AND ANALYSIS METHODS

23.1.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness outcome is the change from baseline in Tear Break-Up Time (TBUT) at the 1 month follow up. TBUT will be analyzed using a linear mixed effects (LME) model. This will allow for the proper incorporation of within-person correlation into the statistical tests, and will also allow for adjustment for baseline measurements.

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

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

Where

- $TBUT_{ij,0}$ is the baseline TBUT value for subject *i*, eye *j*, week 0.
- y_{ij} is the 1 month change from baseline TBUT for subject *i*, eye *j*.
  $$y_{ij} = TBUT_{ij,4} - TBUT_{ij,0}$$
- T_i is the 0,1 treatment indicator for subject *i*
- $\beta_0, \beta_1, and\ \beta_2$ are the fixed effect parameters
- $b_{0i}$is the random effect (random intercept term) for subject *i*
  $$b_{0i} \sim N(0, \sigma_a^2)$$
- ϵ_{ij} is the normally-distributed error term
  $$\epsilon_{ij} \sim N(0, \sigma_e^2)$$
- $\{b_{0i}\}$ and $\{\epsilon_{ij}\}$ are independent

[redacted]

[redacted]

23.1.2 POOLABILITY

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

23.1.3 MISSING DATA

Note that since the primary analysis uses maximum likelihood methods on the complete data then any MAR (missing at random) imputation model should provide essentially equivalent results. That is, the missing data are ignorable if they are MAR and we are using full maximum likelihood estimation. However, as a sensitivity analysis, missing data for the primary TBUT outcome at the 1 month time point will be imputed using baseline characteristics and 1-week outcomes. In this, we follow the advice in sections 2.8 and 2.10 of "Multiple Imputation and its Application"[56] to use an imputation model that is more complex than the final analysis model. In order to carry out the imputations we will fit a linear model that predicts TBUT change at 4 weeks using TBUT at baseline and 1 week, along with other covariates, as predictors. Using predicted 4-week means and variances from this model we can create multiple imputations for the missing 4-week TBUT changes. Results from the multiple imputations will be combined using Rubin's method.

Further sensitivity analysis can be carried out by extending the mixed effects model for the primary analysis described above to also include repeated measurements across time for each patient and eye. Under this model we can carry out maximum likelihood estimation that allows for one of the two (Week 1, Week 4) measurements for each person to be missing.

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

23.1.4 SECONDARY EFFECTIVENESS ENDPOINTS

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

23.1.5 EVALUATION OF TREATMENT DURATION

If the primary endpoint is successful at the one month primary time point, then treatment duration will be evaluated via comparisons of treatment versus control change in TBUT at each of the 3- and 6-month time points separately as described in 12.5.6.

For each secondary endpoint that is successful at the one month time point using the hierarchical testing procedure described in 12.5.5, treatment duration will be evaluated at the 3- and 6-month follow up. Evaluation of treatment duration for the secondary endpoints will be based on sequential testing of 3- and 6-month follow up times separately, in the same manner as for the primary endpoint. Secondary endpoints that fail at the 1-month time point will not be evaluated for treatment duration

23.1.6 MODELING OF EXTENDED FOLLOW-UP RESULTS

If the primary endpoint is successful at one month, then as a supplemental analysis we will fit linear mixed effects models to the 1- 3- and 6-month longitudinal results.

[redacted]

The chosen model will allow us to evaluate the following:

- Maintenance of the Treatment effect using the full longitudinal data on each subject, providing some guide as to an appropriate retreatment schedule,
- A more detailed evaluation of the baseline effects, if any.

A summary of any model selection process, as well as more detailed output from the selected model, will be provided in the final report.

For the TearCare subjects only, the data from all visits out to 12 months will be used to further investigate the durability of the treatment effect. Similar LME modeling will allow us to evaluate their change from baseline out to 12 months. However since the Warm Compress group will crossover to TearCare at 6 months, there will be no control group to provide an unbiased comparison at the 7, 9 or 12 month points.

For the Warm Compress subjects who cross over, their combined 6 through 12-month data will be analyzed separately (again, using appropriate LME modeling) to evaluate their response to the cross over TearCare treatment. In this analysis their 6-month (pre-crossover) measurements will be used as the new "baseline" that will be used to compare with their 7-, 9- and 12-month outcomes. Again, there will be no control group for comparison.

23.2 SAMPLE SIZE CALCULATIONS

23.2.1 TEAR BREAKUP TIME

The primary Tear Breakup Time (TBUT) endpoint is measured on a per-eye basis. In order to account for the correlation between eyes the sample size is calculated in two steps. The first step is to carry out a standard sample size calculation for the number of eyes based on a two-sample t-test with unequal variances. This test is appropriate for a sample of independent eyes from the two groups, that is, a study in which only one eye per subject is enrolled. The second step is to allow for two eyes per subject by adjusting the independent sample size to account for the correlation between eyes.[57] This is done by multiplying by a "design effect" (DEFF) that can be calculated from the pilot study data (provided in Section 5.2.2). Finally we allow for some loss to follow up and then divide by 2 (eyes per subject) to arrive at a final enrolled sample size in terms of number of subjects.

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

For the sample size calculation, a positive treatment effect for the warm compress control was assumed, reducing the TBUT time per eye by 4 seconds, with a standard deviation of 2. This is somewhat conservative based on the pilot study data (this is on the upper end of what we expect to see for the Warm Compress group).

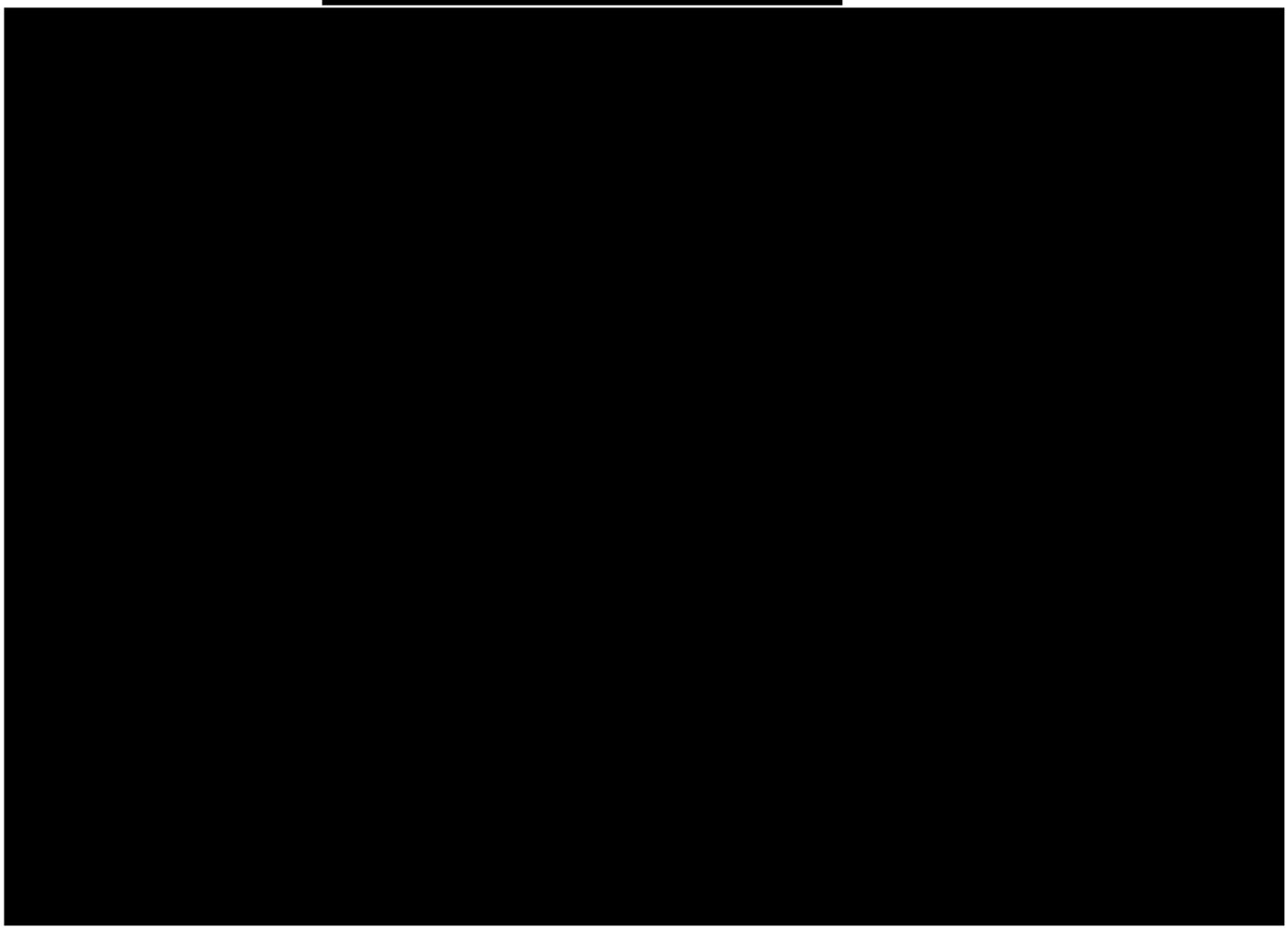
[redacted]

For the TearCare device a treatment effect of 6 seconds, with standard deviation 3 was assumed. This is also somewhat conservative, as it is on the lower end of what we expect to see in the TearCare group based on the pilot study data.

[redacted]

Finally, we will assume that 10% of the enrolled subjects will be lost to follow-up. Based on these assumptions, Table 4 shows sample sizes for powers of 80%, 90%, and 95%.

[redacted]



23.2.2 OSDI

The most important secondary effectiveness endpoint, OSDI, measures subject-reported symptoms. This endpoint is measured on a per-subject basis, so no adjustment for correlation is necessary. For this endpoint a minimum clinically important difference ranges from 7.0 to 9.9 units.[59] Based on data from the TearCare pilot study, we conservatively assumed a 10-point OSDI improvement in the Warm Compress group and an 18.5 point improvement in the TearCare group, and a standard deviation of 18

[redacted]

units. Using these assumptions, the following Table 5 shows the power for a two-sample t-test with unequal variances for a range of sample sizes.

[redacted]

23.2.3 SAFETY

For safety, the following Table 6 shows

- the expected number of events,
- the probability of observing one or more events,
- the upper 95% one-sided CI limit if 0 events are observed, and
- the upper 95% one-sided CI limit if the expected number of events occurs,

for sample sizes of 50,100, and 200 and true proportions of 0.01, 0.02, and 0.05. So if the true rate of an AE is 0.01 then in a sample of 100 individuals we will observe one or more events with probability 0.634. If no events are observed in the sample then the upper 95% one-sided CI limit is 0.026, and if 1 event is observed (the expected number in this case), the upper 95% one-sided CI limit is 0.044.

[redacted]

23.2.4 SAMPLE SIZE SUMMARY

Based on the calculations outlined above, an overall sample of 200 individuals, with 100 in the TearCare group, will provide more than 90% power for the TBUT and OSDI effectiveness endpoints and sufficient precision around the adverse event estimates.

24 APPENDIX D - DECLARATION OF HELSINKI

I. PREAMBLE

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

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

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

II. GENERAL PRINCIPLES

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

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

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

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

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

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

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

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

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

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

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

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

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

III. RISKS, BURDENS AND BENEFITS

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

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

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

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

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

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

IV. VULNERABLE GROUPS AND INDIVIDUALS

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

  All vulnerable groups and individuals should receive specifically considered protection.

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

V. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

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

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

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

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

VI. RESEARCH ETHICS COMMITTEES

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

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

VII. PRIVACY AND CONFIDENTIALITY

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

VIII. INFORMED CONSENT

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

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

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

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

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

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

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

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

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

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

IX. USE OF PLACEBO

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

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

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

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

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

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

X. POST-TRIAL PROVISIONS

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

XI. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

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

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

XII. UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

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

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