Meibomian Gland Dysfunction Treatment:

Study Protocol

NCT Number: NCT04229888

Document Date: January 27, 2020

TITLE: Subject Masked Clinical Evaluation of Thermopulsation Treatment (Lipiflow) for Meibomian Gland Dysfunction

INVESTIGATORS: Anna A. Tichenor, Denise Howard, Jennifer Pence, Ping Situ, Carolyn Begley

INVESTIGATION SITE: Indiana University

STUDY OVERVIEW

Dry eye is a multifactorial chronic condition reducing quality of life by vision limitations and discomfort. LipiFlow, an FDA approved thermal pulsation treatment device, was designed to treat MGD related lipid deficiency evaporative dry eye. In previous studies, Lipiflow has been proven efficacious over standard dry eye therapies. However, many studies were limited in that the subject receiving treatment was aware of the difference and could potentially introduce bias for the newer technology. The current study aims to investigate the efficacy of Lipiflow when compared to a simulated placebo treatment. The impact on ocular health and perceived symptoms will also be evaluated.

RATIONALE AND SIGNIFICANCE: Meibomian gland dysfunction is a common condition in clinical practice coinciding with reduced tear film stability and patient complaints of dryness and irritation. The number of therapeutic devices and clinical trials focused on this complex issue are growing. Although many clinical trials show the increased efficacy of thermal pulsation treatment options compared to traditional therapy, subjects in all of these studies were aware of the treatment they were undergoing; thus, the possibility for subject bias was high.

STUDY AIM: The current study aims to systematically investigate the efficacy of Lipiflow treatment in patients with Meibomian gland dysfunction. This study will compare a single Lipiflow treatment to a single simulated placebo treatment in the same patient to mask subjects from any potential bias for newer technology.

STUDY DESIGN

The study is a prospective, clinical trial, comparing the difference in results between Lipiflow and a placebo control (subject masked to treatment), and also comparing treatment versus no treatment between eyes (subject not masked to treatment).

There will be 4 study visits in this investigation, an initial screening visit, a placebo treatment visit, a Lipiflow treatment visit and an exit/assessment visit (in that order). Potential subjects will be called and administered a telephone screener for dry eye symptoms, medical and ocular history to exclude those with previous ocular surgery, etc., before being scheduled for Visit 1. If eligible based on the telephone screener, time and day of visit schedule will be discussed with subject to make an effort to keep appointments at the same time of day, and all visits will be tentatively scheduled for the subject. Visit 1 will check remaining eligibility criteria including presence of meibomian gland dysfunction and review criteria from telephone screener to confirm eligibility.

SUBJECT POPULATION

Up to 16 adults with meibomian gland dysfunction and symptoms of dry eye disease will be enrolled in this study. The minimum sample size requirement based on sample size calculations is 14 subjects.

SUBJECTS

Inclusion Criteria:

1. Evidence of Meibomian gland obstruction in both eyes
    a. Number of functional meibomian glands < 6 in the lower eyelids of both eyes (that is, number of meibomian glands yielding liquid secretion with MGE less than 6) (ref: Korb DR, Blackie CA: Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea 2008, 27(10):1142-1147.)
    b. At least 10% dropout total in both eyes for both eyelids as seen on meibography images
2. Remaining Meibomian glands not severely truncated.
3. Reported dry eye symptoms by DEQ-5 score > 6

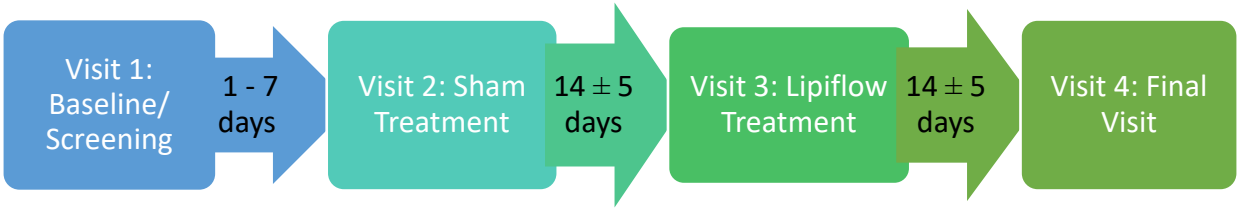
4. Willingness and ability to adhere to the instructions set forth in this clinical protocol.
5. At least 18 years of age

Exclusion Criteria:

1. Systemic Conditions
    a. Ocular or systemic conditions that could potentially the limit effectiveness of the study treatment
    b. Beginning new oral or other systemic medications or nutritional supplements or changing dosages within the past 3 months
2. Ocular
    a. Remaining Meibomian glands severely truncated/> 90% total meibomian gland dropout on meibography on upper + lower eyelids in each eye
    b. Previous Lipiflow treatment
    c. Beginning new ocular medications or changing dosages within the past 3 months
    d. Altering dry eye treatment, including, but not limited to, artificial tears, Bruder mask, ophthalmic or allergy drops and lid hygiene within the past 3 months
    e. Previous ocular surgery, trauma, herpes, recurrent inflammation, punctal plugs or occlusion within 3 months of the baseline examination
    f. Ocular surface abnormality potentially compromising corneal integrity in either eye
    g. Active ocular infection in either eye or evidence of latent infections, such as Herpes simplex or zoster
    h. Ocular surface or eyelid abnormalities that preclude use of Lipiflow device
    i. Participating in another ophthalmic clinical trial involving a therapeutic drug or device within the past 30 days
    j. Habitual contact lens wear within 3 months
3. Pregnant or nursing by self report

STUDY VISITS AND PROCEDURES

There will be 4 study visits: Baseline/Screening, Sham treatment, Lipiflow treatment, Final visit.



Visit 1 (screening)

1. Subjects will complete these symptom questionnaires in the following order, for each eye individually using iPAD in Qualtrics:
    a. DQ
    b. CSQ

    c. DEQ-5 (score must be >6 to continue in study) (1 month recall)
2. Medical and Eye Health History
3. Visual Acuities at Distance (best corrected, LogMar)
4. Slit lamp examination of ocular surface and lids (minimally invasive)
    a. Subjects must show Meibomian gland obstruction
    b. No evidence of ocular infection, surgery or trauma or any other abnormalities that would preclude Lipiflow treatment (subject excluded)
5. LipiView
    a. Lipid layer thickness
    b. Meibography (upper and lower eyelids)
6. Study Procedures
    a. FBUT (video recorded, 3x)
    b. Corneal Staining (photo)
    c. Conjunctival Staining (photo)
7. Determine eligibility and tell subject
    a. Both eyes need to qualify
8. Eye to be tested chosen by random number chart (Jenn)
    a. Investigator is masked

<u>Visit 2: Sham Treatment (1 – 7 days after Visit 1, same time of day if possible)</u>

1. Subjects will complete these symptom questionnaires in the following order using iPAD.
    a. CSQ: Each eye separately
    b. DEQ-5 (score must be >6 to continue in study): each eye (1 month recall)
2. Visual Acuities (BCVA, LogMar)
3. LipiView
    a. Lipid layer thickness
4. Slit lamp examination of ocular surface and lids
    a. Overall health: grading scales and measures
    b. FBUT (video), corneal and conjunctival staining
5. Study Procedures: before treatment
    a. Video gland expression with slit lamp biomicroscope, using meibomian gland expressor
6. Sham treatment to tested eye
    a. Sham treatment on tested eye
    b. Tape and patch other eye
    c. Anesthetic in both eyes
7. CSQ for each eye. Questionnaire about treatment comfort
8. Study Procedures: after treatment
    a. Lipiview: lipid layer thickness OU
    b. Slit lamp ocular health examination OU
    c. Video tear breakup 3x
    d. Video gland expression with slit lamp biomicroscope, using meibomian gland expressor
9. Make sure subject is scheduled for next appointment (14 ± 5 days)

<u>Visit 3: Lipiflow Treatment (14 ± 5 days later, same time of day if possible)</u>

1. Subjects will complete these symptom questionnaires in the following order.
    a. CSQ: Each eye separately
    b. DEQ-5: each eye (since the last visit)
2. Visual Acuities (BCVA, LogMar)
3. LipiView
    a. Lipid layer thickness
4. Slit lamp examination of ocular surface and lids
    a. Overall health: grading scales and measures
    b. FBUT (video), corneal and conjunctival staining
5. Study Procedures: before treatment
    a. Video gland expression with slit lamp biomicroscope, using meibomian gland expressor
6. Placebo treatment to tested eye
    a. Lipiflow on tested eye
    b. Tape and patch other eye
    c. Anesthetic both eyes
7. CSQ for each eye. Questionnaire about treatment comfort.
8. Study Procedures: after treatment
    a. Lipiview: lipid layer thickness OU
    b. Slit lamp ocular health examination OU
    c. Video gland expression with slit lamp biomicroscope, using meibomian gland expressor
9. Make sure subject is scheduled for next appointment (14 ± 5 days)

<u>Visit 4: Final/Exit Visit (14 ± 5 days)</u>

1. Subjects will complete these symptom questionnaires in the following order.
    a. CSQ: Each eye separately
    b. DEQ-5: each eye (since the last visit)
2. Visual Acuities
3. LipiView
    a. Lipid layer thickness
    b. Meibography
4. Slit lamp examination of ocular surface and lids
    a. Overall health: grading scales and measures
    b. FBUT (video), corneal and conjunctival staining
5. Study Procedures
    a. Video gland expression with slit lamp biomicroscope, using Meibomian Gland Expressor
6. The subject will be provided information on which eye received treatment at the time of exit.
7. Subject exits study. Can have Lipiflow on other eye, not as part of the study.

<u>Equipment</u>:

1. Slit lamp biomicroscope.
    a. A microscope with a bright light and magnification that can be used to take a close look at the structures of the eye. The binocular aspect provides a stereoscopic view of the eye structures.
2. Lipiview Ocular Surface Interferometer

   a. The Lipiview is a non-invasive device that can capture digital images of interferometric observations of the tear film and of the meibomian glands under near-infrared illumination. It can measure the absolute thickness of the tear film lipid layer. It will also be used to image glands to determine the level of obstructed glands, gland loss, and potential for benefit from thermal pulsation treatment.
3. Lipiflow Thermal Pulsation System
   a. The LipiFlow is a device used for applying localized heat and pressure in adult patients with conditions such as meibomian gland dysfunction. It is an in-office procedure that provides controlled heat to the inner surface of the eyelids and pulsating pressure to the outer eyelid. This heat and pressure facilitates release of lipid, or meibum, from the meibomian glands to liquify and clear clogged glands. The procedure lasts 12 minutes and uses a single– use sterile dome shaped activator that applies heat and pressure to the Meibomian glands to liquefy and clear clogged glands.
4. Describe Placebo treatment.
5. Meibomian Gland Evaluator for expression from meibomian glands

STUDY OUTCOMES

Primary outcome: Change in DEQ-5 score from V3 to V4 for LipiFlow treatment when compared to change in DEQ-5 score from V2 to V3 for sham treatment.

Secondary outcome: Change from V3 to Visit 4 in meibomian gland score (meibomian glands evaluated on the lower eyelid using MGE. 5 glands in 3 regions (nasal, central, temporal) evaluated and scored from 0 to 4 for a max score of 60 in each eye. MGS scale 0 = clear, 1 = cloudy, 2 = granular, 3 = pastelike, 4 = obstruction)

Exploratory outcomes: Change in TBUT, LLT

CLINICAL TRIALS REGISTRATION

This trial will be registered on clinicaltrials.gov. The description of this registration will only describe the primary outcome measures, not any secondary or exploratory measures.

ADVERSE EVENTS

All adverse events that occur during the study will be reported by the investigators.

DATA HANDLING

Data will be collected and recorded using case report forms. The data will then be entered into an electronic system stored on a password protected and encrypted server. Data will be stored for XX years.

STATISTICAL ANALYSES

Sample Size Calculation

The overall sample size estimate for this study is based on the primary outcome measure of change in DEQ-5 score from V3 to V4 for Lipiflow treatment. We hypothesized that the change in DEQ-5 score would be greater for the Lipiflow treatment when compared to the sham treatment. The sample size was calculated with 80% power to detect a mean difference of 3 points, with a standard deviation of 3.5 points on the DEQ-5 questionnaire based on previous studies using a type 1 error of 5%. This power calculation resulted in 14 patients. In order to ensure that the study is powered relative to any loss to follow up, we will recruit a total of 16 patients.

Analysis

A repeated measures analysis of variance (repeat measure ANOVA) will be used for statistical analysis of crossover and treatment effects. Pearson correlation analysis will be performed to evaluate the relationship between Lipiflow treatment and clinical measures. P values< 0.05 will be considered statistically significant.