A RANDOMIZED, MASKED (EVALUATOR), CONTROLLED, PROSPECTIVE PILOT STUDY OF THE EFFECTIVENESS AND SAFETY OF THE TIXEL®, VERSUS LIPIFLOW® IN THE TREATMENT OF MEIBOMIAN GLAND DYSFUNCTION

Study Protocol No: **CLN 0798**

Version: **2.0**

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Investigational Product: **Tixel Fractional System**

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1 INTRODUCTION

1.1 Background

Dry Eye Disease (DED) is often caused by a chronic lack of sufficient lubrication and moisture on the surface of the eye. Consequences of dry eyes range from subtle to constant eye irritation, significant inflammation and even scarring of the front surface of the eye.

Meibomian glands are located in the tarsal plate of the upper and lower eyelids, where they terminate along the interior rim (or margin) of the eyelids. These glands secrete meibum, which is a lipid-rich essential component of a healthy tear film. When sufficient meibum is not present in the tear film, the aqueous layer of the tear film is disrupted and readily evaporates causing irritation, redness, and inflammation of the lid margin and surrounding tissues. Meibomian Gland Dysfunction (MGD) is associated with a failure of these glands to produce adequate quantities of meibum due to atrophy, inflammation, or obstruction and is thought to be the most common cause of evaporative Dry Eye Disease [1; Schaumberg DK 2011].

Initial treatments for the signs and symptoms related to MGD and DED are the use of oil-based artificial tears to supplement the lack of lipid in the tear layer and oral Omega and anti-inflammatory prescriptions to decrease inflammation in the soft tissue in the eyelids. Another common treatment is the use of warm compresses applied over the eyelid for extended periods of time, followed by digital massage of the glands by the patient to try and express oil from the meibomian glands. The results of these treatments are often limited and temporary if not continued on a regular basis.

1.2 Study Rationale

Thermal pulsation has been used in clinical settings to provide heat and mechanical stimulation to the eyelids to unblock plugged meibomian glands and reduce symptoms of MGD. Currently there are two FDA cleared thermal pulsation devices; LipiFlow by Johnson and Johnson (K112704) and iLux by Tear Film Innovations, Inc. (K172645). The LipiFlow and iLux systems place a heated plate (40 to 43°C) against the eyelids (Lipiflow on the eyelid conjunctiva) and apply gentle pressure on the lid surfaces. Warming the eyelid tissue softens or melts the meibum, which is known to facilitate gland expression using pressure.

The Tixel device uses heat delivered by a small hot element called the Tip. The device tip is heated during treatment and contacts the skin for a very short period each time it is applied. The Tixel device has been used on the skin area around the eyes to reduce wrinkles, but it has been reported by patients treated with the Tixel that after treatment their eyes feel less dry. The Tixel

system, although applying higher temperature compared with the two predicate devices, is considered to mimic the combination of pressure and temperature effect in a similar manner.

The aim of the current randomized, controlled study is to examine the effect of the Tixel device on the relief of the signs and symptoms of Meibomian Gland Dysfunction (MGD) compared to the FDA approved device, LipiFlow.

1.3 Primary efficacy endpoint rationale

The primary objective of the study is to determine the efficiency of the therapy, in improving TBUT in eyes with DED due to MGD. This objective was chosen because a reduced TBUT is one of the most common signs of DED due to MGD. TBUT is considered abnormal when shorter than 10 seconds. The reason for choosing the margin of 1.5 second as a success criterion is following the recent IPL study performed by Lumenis and received an FDA approval. In the study the difference between the IPL arm and the control arm was 1.24 second. The IPL arm was 1.99 second in combination with MGX, and the sham +MGX was 0.75 meaning that the IPL alone was responsible to 1.24 second from baseline to 4 weeks follow-up (Effectiveness of Intense Pulsed Light for Improving Dry Eye Syndrome - Study Results - ClinicalTrials.gov).

2 THE INVESTIGATIONAL DEVICE

2.1 Device description

Tixel C (Novoxel®, Israel) is a thermomechanical system developed for fractional treatment. The system is designed for the treatment of soft tissue by direct conduction of heat, enabling tissue coagulation combined with micro ablation with low thermal damage to the surrounding tissue.

Figure 1 - The Tixel C Console and Handpiece Configuration

The system consists of a handpiece connected to a console (Figure 1). The handpiece applies a therapeutic element, the "tip", fixated on the distal section. The tip is comprised of a gold-plated copper base and a thin-walled titanium alloy cover (Figure 2)

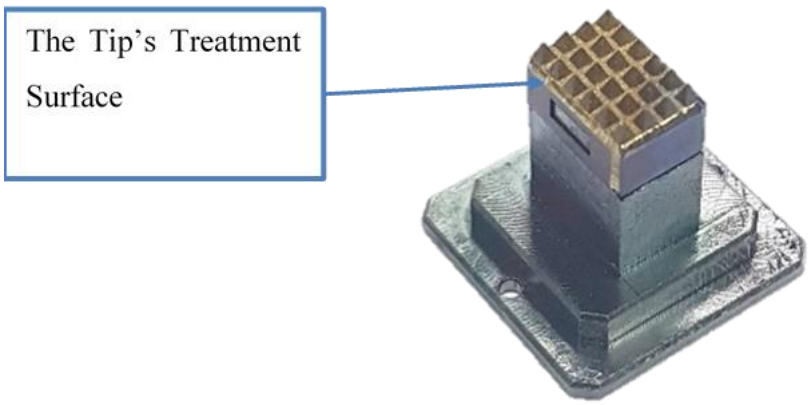

Figure 2 - The Tixel Small Tip

The handpiece is equipped with a precise motion system based on a linear motor and a digital signal processing (DSP) motion controller. The system design enables precise pre-set periods of skin contact duration. The active surface of the Tixel small Tip consists of an array of 24 (6x4) square-based pyramids evenly spaced within a boundary area of 0.30cm^2. The pyramids are 1.25mm tall with a flat rectangular apex of approximately 0.01mm^2. The blunt apex of the pyramid allows effective heat transfer and prevents mechanical puncturing of the skin. The backplane of the tip attaches to a ceramic heater that maintains a Tip base temperature of 400°C during the treatment. The heating enables effective self-sterilization before and during treatment, significantly reducing the risk of cross-contamination from the tip. When the handpiece is not activated, the tip is safely retracted to its home position. When the user activates the handpiece, the linear motor rapidly advances the tip which comes in brief contact with the tissue, and then pulls it back. Thermal energy is transferred to the skin, creating tissue micro ablation and tissue coagulation. The tip recedes within a precisely controlled distance and time to its home position. The duration of the pulse, defined as the time of contact between tip and skin, ranges from 5ms to 16ms.

A second system parameter is the travel or “protrusion” of the tip. Protrusion is defined as the distance that the tip travels from the distal edge of the handpiece (which also functions as a distance gauge). The protrusion adjustment, measured in micrometres (µm), is designed to ensure good thermal coupling between the tip and the tissue. Adequate combined settings of the two parameters, pulse duration and protrusion, contribute to the desired thermal effect followed by the clinical outcome.

2.2 Safety Features of the Tixel C

-The device tip base temperature is maintained at 400°C, but the dermal thermal lesion under the specified operation parameters is limited to 250µm (for eyelid treatment parameters), while eyelid thickness varies between 500-1500 µm. Therefore, there is no risk related to the Tip temperature to the eyelid muscles or meibomian gland or to the eye (sclera or cornea) as shown in pre-clinical and human body histology.

-When the device is contacting the skin for extremely short periods of time, the maximal tissue temperature creating micro ablation is lower than 150°C. The pressure applied by the tip during contact is limited to gently “compress” the eyelid surface resulting in negligible pressure on the eye as shown in laboratory tests.

-The device is IEC-60601 certified (both safety and EMC tests).

-Tixel is approved for use as a medical device by the FDA (The previous version of the Tixel C equipped with the same handpiece and Tip assembly) European Union, Australia, Brazil, South Africa, South Korea, Taiwan Thailand, Israel, among other countries.

-Two clinical studies of the Tixel treatment of peri-orbital wrinkles have received IRB approvals (3 clinical sites in the US and 3 clinical sites in Israel). One study was completed without any related AEs and only 2 patients with AEs in total (5.9%) in the Tixel group. A second study is under process.

-The Tixel device is designed with core safety, which is ensured via several aspects of its components:

-The device has an over-temperature automatic thermal shutdown in case of undesired temperature rise. This component is strictly hardware based.

-In case of a power fail, the tip will always be retracted backwards to its home position.

-The system is always in a rested (home) position and activated only when the trigger is pressed.

-An air-cooled system which does not contain any type of cooling liquid such as water.

-Mechanical BIT (Built-In Test). Before commencing operational mode, the system verifies free motion of the mechanical system.

3 LIPIFLOW® SYSTEM

The LipiFlow System is a medical device intended for use by Eye Care Professionals (ECP) to apply localized heat and pressure therapy to a patient's eyelids. It is cleared to be marketed by the United States Food and Drug Administration and will be used as the control device in this study.

3.1 LipiFlow Indications for Use

The LipiFlow System is indicated for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye.

3.2 LipiFlow Components

The LipiFlow Console provides the user interface and control elements of the system, including software, algorithms and control elements (Figure 3).

Figure 3 - The LipiFlow Console and Activator disposable

The Activator, a single-use sterile device, delivers automated therapeutic energies to each meibomian gland. Its contoured design vaults the cornea and protects the eye allowing a maximum therapeutic temperature of 43 degrees Celsius to reach glands from the inner eyelid, without damaging the eyelid or delicate structures of the globe. Insulation protects the cornea from exceeding a safe 39.5 degrees Celsius, while a pressure feedback loop sends pulsed

sequences to expel blockages. Force equalization protects the globe from pressure transmission by focusing energy only on the eyelid. Delivered through the LipiFlow Activator, Vectored Thermal Pulse™ (VTP) technology applies a combination of heat and pressure to the inner eyelid to safely remove gland obstructions and stagnant gland content. Vectored heat and adaptive force equalization targets the pulse, heat, and pressure on the meibomian glands to maximize effectiveness. Therapeutic motion provides proximal-to-distal parastalsis to clear gland contents.

4 CLINICAL STUDY DESIGN

4.1 Objective

The objective of this study is to evaluate the safety and effectiveness of the Tixel device in adults with meibomian gland dysfunction (MGD).

4.2 Description of the Study

This study is a randomized, open-label, pilot clinical study comparing the Tixel device to an active control, which will be the LipiFlow System. The goal of this study is to compare between the Tixel device and the LipiFlow System and estimate the magnitude of the differences, if they exist, in terms of safety and effectiveness. A total of up to 30 patients (60 eyes) will be randomized for bilateral treatment and will be assigned in a 1:1 ratio into the Tixel treatment group or the control group at up to 2 study sites in Israel and/or Europe. The evaluator will be masked as to the randomization assignments. Both eyes will receive the same randomized assignment and both eyes of each patient will be evaluated at all time points. One eye will be selected as the designated “study eye” for statistical purposes: The study eye is the eye with the lower baseline TBUT. If both eyes have the same TBUT, the right eye will be the study eye.
Outcome Measures

4.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the change from baseline to the 4-weeks follow up exam in Tear Break-Up Time (TBUT). TBUT must be assessed by a masked rater. The changes from baseline will be evaluated.

4.2.2 Secondary Effectiveness Endpoints

- Change from baseline in patient symptoms using the Ocular Surface Disease Index (OSDI) at the 4-weeks and 12 weeks follow-up exam. OSDI is a scoring that evaluates patient symptoms based on a validated questionnaire [4].
- Changes from baseline to 4-weeks and the 12-weeks follow-up exam in Meibomian Gland Score (MGS). MGS must be assessed by a masked rater.

  The MGS is determined for the lower eyelids using a device that applies a standardized pressure to an area including 5 glands (Meibomian Gland Evaluator, Johnson & Johnson Vision) while viewing the eyelid margin using a slit lamp microscope to determine the presence and quality of the gland secretions. A total of 15 glands in three lower eyelid zones (nasal, medial, temporal) will be evaluated. Each gland is graded from 0 to 3 (0 = no secretion, 1 = inspissated, 2 = cloudy, 3 = clear liquid). The maximum MGS score is 45 in each eye. The clinician performing the MGS must not be involved in the study procedure and must be blinded to which arm of the study the patient is randomized.
- Change from baseline to the 12-weeks follow-up exam in Tear Break Up Times (TBUT), as assessed by a masked rater.

4.2.3 Primary Safety Endpoint

The primary safety endpoint will be a comparison of the incidence of device-related adverse events (e.g., increase in the lid margin such as development of floppy eyelids, entropion or ectropion; and lash integrity) for the two-treatment arms.

4.2.4 Secondary Safety Endpoints

Secondary safety endpoints will be the following assessments:

- The evaluation of discomfort and pain during treatment
- Changes from baseline following treatment for the test and control devices for the following assessments:
  - o Ocular Surface Staining
  - o Intraocular Pressure
  - o Cornea OCT evaluation to detect changes (cornea thickness, cornea deamination) following treatment- will be performed on a subset of 10 patients, who first enrolled, only in the Tixel arm (since LP has a protective cup on the cornea).

5 PATIENT POPULATION

The study will include adult patients with symptoms of MGD/evaporative dry eye.

5.1 Inclusion Criteria

1. Age 18 years and older of any gender or race.
2. Provision of written informed consent prior to study participation.
3. Willingness and ability to return for all study visits.
4. A positive history of self-reported dry eye symptoms for three months prior to the study using the Ocular Surface Disease Index (OSDI) questionnaire, and a score of ≥ 23 at the baseline visit.
5. Evidence of meibomian gland (MG) obstruction, based on a total Meibomian Gland Score (MGS) of ≤12 in the lower eyelids for each eye. The rater of MGS must not be involved in the study procedure.
6. Non-invasive tear break-up time (TBUT) <10 seconds in both eyes. The rater of TBUT must not be involved in the study procedure.
7. Agreement/ability to abstain from dry eye/MGD medications for the time between the treatment visit and the final study visit. Ocular lubricants are allowed if no changes are made during the study.
8. Fitzpatrick skin type I-VI.

5.2 Exclusion Criteria

1. History of ocular surgery including intraocular, oculo-plastic, corneal or refractive surgery within 1 year.
2. Patient with giant papillary conjunctivitis.
3. Patient with punctal plugs or who have had punctal cautery.
4. Ocular injury or trauma, chemical burns, or limbal stem cell deficiency within 3 months of the baseline examination.
5. Active ocular herpes zoster or simplex of eye or eyelid or a history of these within the last 3 months.
6. Patient who are aphakic.
7. Cicatricial lid margin disease identified via slit lamp examination, including pemphigoid, symblepharon, etc.
8. Active ocular infection (e.g., viral, bacterial, mycobacterial, protozoan, or fungal infection of the cornea, conjunctiva, lacrimal gland, lacrimal sac, or eyelids including a hordeolum or stye).

9. Active ocular inflammation or history of chronic, recurrent ocular inflammation within prior 3 months (e.g. retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis).
10. Ocular surface abnormality that may compromise corneal integrity (e.g., prior chemical burn, recurrent corneal erosion, corneal epithelial defect, Grade 3 corneal fluorescein staining, or map dot fingerprint dystrophy).
11. Lid surface abnormalities (e.g., entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis) that affect lid function in either eye.
12. Anterior blepharitis (staphylococcal, demodex or seborrheic grade 3 or 4).
13. Systemic disease conditions that cause dry eye (e.g., Stevens- Johnson syndrome, vitamin A deficiency, rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, leukemia, Riley-Day syndrome, systemic lupus erythematosus, Sjogren's syndrome).
14. Unwillingness to abstain from systemic medications known to cause dryness for the study duration.
15. Women in child baring age who are pregnant, nursing, or not utilizing adequate birth control measures.
16. Individuals who have either changed the dosing of systemic or non-dry eye/MGD ophthalmic medication within the past 30 days prior to screening.
17. Individuals who are unable or unwilling to remain on a stable dosing regimen for the duration of the study.
18. Individuals using isotretinoin (Accutane) within 1 year, cyclosporine-A (Restasis) or lifitegrast ophthalmic solution (Xiidra) within 3 months, or any other dry eye or MGD medications (antibiotics, non-steroidal anti-inflammatory drugs, corticosteroids) for at least 2 weeks and to maintain abstinence throughout the duration of the study (ocular lubricants are allowed if no changes are made during the study).
19. Individuals wearing contact lenses at any time during the prior three months and at any point during the study.
20. Current skin cancer, malignant sites and/or advanced premalignant lesions or moles in the treatment area.
21. An impaired immune system condition or use of immunosuppressive medication.
22. Collagen disorders, keloid formation and/or abnormal wound healing.
23. Previous invasive/ablative procedures in the areas to be treated within 3 months prior to initial treatment or plans for such treatment during the course treatment, or before complete healing of such treatments has occurred.

24. Any patient who takes or has taken any oral or topical medications, herbal treatments, food supplements, or vitamins which may cause fragile skin or impaired skin healing during the last 3 months.
25. Any patient who has a history of bleeding coagulopathies.
26. Any patient who has tattoos or permanent makeup in the treated area.
27. Any patient who has burned, blistered, irritated, or sensitive skin in any of the areas to be treated.
28. Individuals using another ophthalmic investigational device or agent within 30 days of study participation.
29. Individuals that were treated with LipiFlow in the last 24 months, or Tixel at any point in the past.
30. Treatment in either eye with IPL in the last year.
31. Expression of the meibomian glands within 6 months prior to screening.
32. Use of at home warm compresses or lid hygiene products while participating in study.

6 STUDY PROCEDURES

6.1 Patient Screening and Enrolment

Patients will be screened, assessed, treated and followed according to the schedule of events in Appendix A. Patients must have the study explained to them by the Investigator/Sub-investigator (or other delegated study team if allowed by local regulations), they must be provided sufficient time to consider their participation in the study and provided an opportunity to ask questions of the study team. Patients must sign the most current version of an informed consent form (ICF) approved by an Institutional Review Board (IRB)/Ethics committee. All patients who sign an ICF and meet the entire protocol criteria are considered enrolled patients in the study; if not, they will be considered as screen-failures. Therefore, patients should be pre-screened to the extent possible prior to signing an ICF, but patients should not undergo any study-specific assessments until they have signed the ICF.

6.1.1 Informed Consent

During the informed consent (IC) process with the patient, the study investigator or designee will explain the purpose of the study, the possible risks and benefits, and the schedule of visits required for participation. The study investigator or designee will explain to the patient that,

after signing the IC form, the patient may not be found eligible to participate in the study if he/she doesn't meet all inclusion/exclusion criteria.

The patient may take the IC form and consult with their family, friends or doctor. After reading and understanding the IC, if the patient decides that he/she wishes to participate in the study, he/she should return, with a signed IC form at which time he/she will undergo specific tests as specified in Appendix A. These tests will be done only after the patient signed the ICF, clearly indicating his/her understanding of the requirements and risks involved with study participation and other applicable treatment options.

6.1.2 Patient Identification

At the screening, the patient will receive a unique identifying Patient ID number that will be composed of the site number (2 digits) and a three-digit consecutive patient number. This unique Patient ID will be used throughout the entire study and will be entered in the patient's eCRFs for the screening visit, baseline visit, each treatment visit and the follow-up visits.

8.1.3 General Examination

A general clinical examination is required to assess eligibility. This examination will include demographics information, past medical and ocular history, known allergies, use of Concomitant Systemic and Ophthalmic Medications and patient's report of the daily usage (frequency and dose) of eye lubricants.

8.1.4 Fitzpatrick Skin Type

The Fitzpatrick skin type will be determined according to genetic disposition, reaction to sun exposure and tanning habits. The Fitzpatrick scale classifies 6 skin types, as summarized below. In this study, all Fitzpatrick skin types I-VI are eligible to participate, consistent with the device labelling.

TYPE I: Highly sensitive, always burns, never tans. Example: Red hair with freckles

TYPE II: Very sun sensitive, burns easily, tans minimally. Example: Fair skinned, fair haired Caucasians

TYPE III: Sun sensitive skin, sometimes burns, slowly tans to light brown. Example: Darker Caucasians.

TYPE IV: Minimally sun sensitive, burns minimally, always tans to moderate brown. Example: Mediterranean type Caucasians, some Hispanics.

TYPE V: Sun insensitive skin, rarely burns, tans well. Example: Some Hispanics, some Blacks

TYPE VI: Sun insensitive, never burns, deeply pigmented. Example: Darker Blacks.

6.2 Pre-Treatment/Baseline Assessments

The following assessments will be performed at the baseline visit, for both treatment arms, prior to treatment (Note: The OSDI must be administered self-assessed prior to clinical evaluations). The detailed instructions can be found in the Testing Methodologies for CLN 0798 study (CLN_0802).

Table 1-Patient Assessments

Assessment	Description
OSDI	Scoring that evaluates patient symptoms based on a validated questionnaire [2 Schiffman RM, 2000]. (OSDI Questionnaire provided in **Appendix B**). OSDI questionnaires include 12 questions in 3 categories. The questionnaire is self- assessed where patients are asked to circle a number next to a description that best represents their answer on a paper form. The numbers for each category are totalled and the total OSDI score is calculated by the formula: sum of scores x 25/# of questions answered. Dry eye severity is then assessed using the chart on the 2nd page of the questionnaire.
Uncorrected Distance Visual Acuity	Patient will be seated with no glasses in front of a Snellen vision chart that is calibrated to measure at 6 meters.
Corrected Distance Visual Acuity	If patient does not regularly wear glasses for distance this test will not be done. The patient will be seated with glasses (if worn) in front of a Snellen vision chart that is calibrated to measure at 6 meters.
Keratometry	Test of corneal curvature conducted using a manual keratometer or simulated keratometry from corneal topography.
Slit Lamp for Anterior Segment Health	Using biomicroscopy to examine anterior segment including lids, adnexa, conjunctiva, sclera, corneal clarity, and surface integrity, anterior chamber, and iris. Grading system:

	• 0=No clinical findings • 1=Non-clinically significant positive findings (including pterygium, pinguecula, corneal scar, conjunctival pigment, corneal arcus, verucca, non-visual significant lens changes) • 2=Abnormal findings
Lid Margin Abnormalities	Scored 0-4 based on the number of the following present in each eye: • irregular lid margin • vascular engorgement • plugged meibomian gland orifices • anterior or posterior replacement of the mucocutaneous junction
Eyelid Margin Assessment	Development of any of the following: • entropion or ectropion • floppy eyelids • loss of lash integrity
Tear Break-Up Time (TBUT)	*Note*: TBUT Assessments must be made by a rater not involved in the study procedure and blinded to the arm to which the patient is randomized • Use one Fluorescein strip per eye • Apply one or two drops of non-preserved saline to the impregnated paper tip. Excess fluid will automatically fall off. Shaking is neither required nor desirable • Ask the patient to look down and in • Gently touch the strip to the superior temporal bulbar conjunctiva for one or two seconds • Ask the patient to blink three times and open eyes naturally • Immediately measure the time between the last blink and the first appearance of a dark spot on the cornea (formation of dry area) • Time shall be recorded in seconds and shall be the average of three consecutive measurements • Repeat with a new strip for the second eye

Corneal Fluorescein Staining Slit Lamp Evaluation	• Use one Fluorescein strip per eye. • Apply 1-2 drops of non-preserved saline to the impregnated paper tip. Excess fluid will automatically fall off. Shaking is neither required nor Desirable. • Ask the patient to look down and in. • Gently touch the strip to the superior temporal bulbar conjunctiva for one or two seconds. • Start with low illumination and gradually increase until staining is visible. • Grade each region according to the National Eye Institute corneal grading below and record the Total Score for each eye. Score will range from 0 to 15. National Eye Institute (NEI) corneal grading scale evaluating five corneal regions: • superior • inferior • central • temporal • nasal Each graded on a 0-3 scale (0=normal-no staining; 1=mild-superficial stippling micropunctate staining; 2=moderate-macropunctate staining with some coalescent areas; 3=severe-numerous coalescent macropunctate areas and/or patches) [3 Lemp MA.1995]
Conjunctival staining Lissamine green	• Use one Lissamine green strip per eye. • Apply 1-2 drops of non-preserved saline to the impregnated paper tip. Excess fluid will automatically fall off. Shaking is neither required nor desirable. • Ask the patient to look down and in. • Gently touch the strip to the superior temporal bulbar conjunctiva for one or two seconds. • Wait at least 1 minute before grading the conjunctival staining. Perform grading within 4 minutes of instilling the dye. • Start with low illumination and gradually increase

	until staining is visible. • Record the grade (0-3) of each of the regions (nasal, superior nasal, inferior nasal, temporal, superior temporal, inferior temporal) and record the Total Score for each eye. Score will range from 0 to 18. (0=normal-no staining; 1=mild-superficial stippling micropunctate staining; 2=moderate-macropunctate staining with some coalescent areas; 3=severe-numerous coalescent macropunctate areas and/or patches). • Make sure to identify pooling or a stained mucus strand. Ask patients to blink a couple of times when in doubt.
Meibomian Gland Assessment and Scoring	*Note*: Meibomian Gland Assessments must be made by a rater not involved in the study procedure and blinded to the arm to which the patient is randomized. • Assess lower eyelids using Meibomian Gland Evaluator while viewing the eyelid margin using slit lamp microscope • Evaluate 15 glands in 3 zones (nasal, medial, temporal) • Each gland graded from 0 to 3 • Maximum MGS score=45 in each eye [4 Lane SS. 2012, 5 Blackie CA. 2015]
Intraocular Pressure	Measured by a Goldmann tonometer and recorded in mmHg
Optical Coherence Tomography (OCT) (Will be done only after randomization)	OCT assessment should be performed before any corneal testing. Cornea OCT evaluation will be done to detect changes (cornea thickness, cornea deamination) between baseline and following treatments- will be performed **after randomization**, on a subset of 10 patients (the first 10 enrolled patients), only in the Tixel arm. Images will be coded with site number, patient screening number, visit number and left/right eye and will be uploaded to EDC and/or SharePoint.

6.3 Randomization

Prior to randomization it must be determined that the patient meets all entrance criteria. This includes the completion of all screening tests to determine eligibility. The randomization schedules with patients allocated to the Tixel or control LipiFlow group in a 1:1 ratio will be prepared for each site. Each envelope will have a sequential envelope number on the outside and contain the assigned treatment procedure inside. Before the treatment, the assigned personnel will open the lowest numbered envelope. The envelope number will be documented on the study source documents and in the EDC. Randomization will take place at the treatment visit prior to patient treatment. There are no criteria for crossover in this study, so all patients must be treated according to the arm to which they are randomized.

6.4 Schedule for Study Visits

For the Tixel:

After the randomization to the Tixel arm, each patient will undergo 3 treatment sessions (Day 0, Week 2, Week 4) at 2 weeks intervals (+/-3 days) from the previous treatment, and follow-up sessions at 4-weeks (+/-7 days) and 12-weeks (+/-14 days) after the last treatment session.

For the LipiFlow:

After the randomization to the LipiFlow arm each patient will undergo 1 treatment session (Day 0), and follow-up sessions at 4-weeks (+/-7 days) and 12-weeks (+/- 14 days) after the treatment session.

6.5 Treatments

The study procedure in both study arms shall be performed on both eyes on the same day.

Testing must be done in the following order:

- Concomitant systemic and ophthalmic medications (before treatment 1, only if not done during screening).
- Patient's report of the daily usage (frequency and dose) of eye lubricants. Before treatment 1, only if not done during screening. If data was collected at screening, only changes will be collected.

  Before treatments 2 and 3 in the Tixel arm- patient's report will be collected since the last treatment done.
- Before treatment 1, only for 10 patients randomized to a sub-set of the Tixel arm: Cornea OCT and coded images upload to EDC and/or SharePoint. OCT assessment should be performed before any corneal testing.

The following tests may be done again before treatment #1, only if treatment is being done on a different day than baseline exam, at the discretion of the investigator (these tests will be done prior to treatments 2 and 3 for the Tixel arm):

- Slit Lamp for Anterior Segment
- Lid Margin Abnormalities
- Eyelid Margin Assessment

1. Eye makeup shall be removed.
2. The device shall be prepared for use in accordance with the Instructions for Use (IFU)/User Manual for the device to which the patient is randomized. An IFU/User Manual is packaged with each device that will be used in the study.
3. For the LipiFlow treatment- Anesthetic eye drops shall be applied as per the Testing Methodologies for CLN 0798 study (CLN_0802).
4. For the Tixel treatment-Anesthetic cream/gel may be applied only on the eyelids according to the investigator discretion.
5. Therapy shall be delivered in accordance with the IFU/User Manual for the device to which the patient is randomized. Refer to the Testing Methodologies for CLN 0798 study (CLN_0802) for more information.
6. For Tixel device treatment, the following zones will be treated at the following Parameters: Small tip, 6 milliseconds pulse duration, 400µm protrusion, single pulse in the following order:
    - 5 shots nasal, medial, temporal region directly below/above lid margin next to each other (Figure 4)
    - 5 shots a little lower/higher (Figure 4)

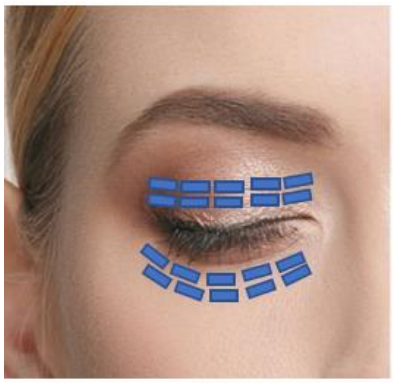

Figure 4-Treatment Zones With Tixel

7. Representatives from the Sponsor may be present during the study visits when required.

8. Throughout the treatment visit, patients will be assessed for any adverse events , including for development of entropion or ectropion, floppy eyelids, and lash integrity assessment.
9. Following treatment, patients will be assessed for the following:
    - Discomfort and Pain from the treatment (Tixel or LP) using the questionnaires in Appendix C. These are visual analogue scale (VAS) questionnaires using a scale from 0-10 to assess eye discomfort and pain. Both questionnaires are to be self-assessed by the patient immediately following treatment.
    - Slit Lamp Evaluation of Anterior Segment Health
    - Corneal Fluorescein Staining Slit Lamp Evaluation
    - Conjunctival staining Lissamine green
    - Intraocular Pressure
    - Assessment of Adverse Events
10. Post Treatment instructions following Tixel treatment:

- Post Treatment instructions sheet will be given to the patient at baseline. The patient will adhere to the instructions following each treatment.
- Patients should be aware that post treatment erythema, edema and some discomfort of the treated areas are possible and should not be a cause for concern.
- It is not recommended to apply moisturizing creams for 24 hours after treatments.
- No makeup, serum, toner or moisturizer with acids or “corrective” ingredients should be applied for at least 48 hours after treatment or until crusts have disappeared. It is preferable to apply non-perfumed makeup.
- The patient should not tan in the treated area for at least 4 weeks after treatment. If sun exposure is necessary for short periods (up to 1 hour), a high SPF (at least 50 SPF) sunscreen must be worn on the lower and upper eyelids and sunglasses and a hat worn. Crusted skin should not be exposed to sun at all.
- Rubbing, scrubbing and scratching the skin in the treated area should be avoided. Any tiny scabs (if present) should not be peeled away.
- Avoid any exposure to chemical substances (such as direct exposure of the skin to cleaning substances) for at least a week after treatment.
- Avoid exposure to dust and airborne dirt for at least a week after treatment.
- Refrain from any sport, especially swimming and/or any other activity involving sweating, for at least a week after treatment.
- Avoid exposure to heat (sauna stay, hot showers, etc.) for at least a week after treatment.

6.6 4-Weeks Follow-Up Visit

Patients will be required to return to the site 4 weeks (+/- 7 days) after the last treatment for the following assessments:

- OSDI (administer first, self-assessed)
- Cornea OCT- (only for the same 10 patients, in the Tixel group who performed the test at baseline). Images will be coded with site number, patient screening number, visit number and left/right eye and will be uploaded to EDC and/or SharePoint. OCT assessment should be performed before any corneal testing
- Concomitant systemic and ophthalmic medications
- Patient's report of the daily usage (frequency and dose) of eye lubricants since the last treatment
- Uncorrected distance visual acuity
- Corrected distance visual acuity
- Keratometry
- Slit Lamp for Anterior Segment Health
- Lid Margin Abnormalities
- Eyelid Margin Assessment
- TBUT (must be performed by a masked rater)
- Corneal Fluorescein Staining Slit Lamp Evaluation
- Conjunctival staining Lissamine green
- Meibomian Gland Assessment and Scoring (must be performed by a masked rater)
- Intraocular Pressure
- Assessment for Adverse Events

6.7 12-Weeks Follow-Up Visit

Patients will be required to return to the site 12 weeks (+/-14 days) after the last treatment for the following assessments:

- OSDI (administer first, self-assessed)
- Concomitant systemic and ophthalmic medications
- patient's report of the daily usage (frequency and dose) of eye lubricants since the last treatment
- Uncorrected distance visual acuity

- Corrected distance visual acuity
- Keratometry
- Slit Lamp for Anterior Segment Health
- Lid Margin Abnormalities
- Eyelid Margin Assessment
- TBUT (must be performed by a masked rater)
- Corneal Fluorescein Staining Slit Lamp Evaluation
- Conjunctival staining Lissamine green
- Meibomian Gland Assessment and Scoring (must be performed by a masked rater)
- Intraocular Pressure
- Assessment for Adverse Events

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Descriptive statistics will be used to summarize continuous variables (number of eyes/patients [N], mean, standard deviation (SD) or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment timepoint. Statistical comparisons within each group will be performed using appropriate statistical methods or models, and the results such as 95% confidence intervals and p values will be reported. All summary tables will be supported with individual patient and eye data listings. Baseline is defined as the last non-missing observation prior to initiation of study intervention. Analyses will be carried out using SAS software or equivalent statistical software.

Further details will be described in the statistical analysis plan, which will be finalized prior to the study database lock.

7.2 Analysis Populations

- Intent-to-Treat Population: The intent-to-treat (ITT) population includes all randomized patients. The primary and secondary efficacy analyses will be performed on the ITT population. Patients will be analysed as randomized.
- Per Protocol Population: The per protocol (PP) population includes all patients who have at least one follow-up visit, complete all the treatments as randomized, and have no major protocol deviations. Patients will be analysed as treated.

- Safety Population: The safety population will include all treated patients. The safety population will be analysed for all safety assessments. Patients will be analysed as treated. A summary table of number (%) of patients in each analysis population/set will be provided.

7.3 Demographic and Baseline Characteristics

Descriptive statistics or frequency tabulation will be provided for demographic and baseline characteristics, such as age, gender, race, and ethnicity.

7.4 Effectiveness Analyses

- Primary endpoint

  The change from baseline at 4 weeks in TBUT in both study arms will be calculated along with 95% confidence interval. The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the change within each study group.

  Ho: $\mu h - \mu c < 1.5$

  HA: $\mu h - \mu c \geq 1.5$

  where $\mu 4w$ and $\mu base$ are the mean at 4 weeks and at baseline, respectively.
- Secondary effectiveness endpoints

- The change from baseline in the TBUT at 4 weeks will be analysed for non-inferiority with a margin of 1.5 using a one-sided two-sample t-test. The non-inferiority hypothesis set will be:

  Ho: $\mu h - \mu c > 1.5$

  HA: $\mu h - \mu c \leq 1.5$

  where μt and μc are the mean changes from baseline for Tixel and control, respectively. Thus, the upper limit of the two one-sided 97.5% CI must be < 1.5 in order to demonstrate Tixel non-inferiority.
- The change from baseline at 12 weeks in TBUT will be calculated along with 95% confidence interval. The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the changes within each study group.
- The change from baseline at 4 weeks and 12 weeks in the Ocular Surface Disease Index (OSDI) will be calculated along with 95% confidence interval. The Paired T-test or

Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the changes within each study group.

- The change from baseline at 4 and 12 weeks in the MGS score will be calculated along with 95% confidence interval. The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the change within each study group.

7.5 Handling of Missing data

Every effort will be made to complete follow-up for all patients and avoid missing data, in particular regarding the primary endpoint variable. However, in the event data is missing, multiple imputation will be used. Missing data in MGS score at 4 weeks will be imputed sequentially using multiple imputation (MI) technique. The imputation model will include age, gender and MGS score at earlier timepoints.

7.6 Interim Analysis

No interim analyses are planned for this study.

7.7 Sample Size Justification

15 patients will be enrolled in each treatment group.

Sample size rationale:

The sample size calculation was based on an expected change from baseline at 4 weeks in TBUT score of 1.5 seconds with a standard deviation of 1.9 seconds within each study group.

Sample size justification:

A sample size of 15 will have 80% power to detect a difference in means of 1.5 assuming a standard deviation of differences of 1.9 (effect size of 0.78), using a paired t-test with a 0.05 two-sided significance level.

Reference:

O'Brien, R.G., Muller, K.E. Applied Analysis of Variance in Behavioral Science Marcel Dekker, New York (1993) Chapter 8 pp. 297-344

7.8 Poolability Analysis

Patient demographic characteristics and background variables shall be summarized. To ensure poolability in case of more than one site, primary effectiveness will be analysed by site.

7.9 Safety Analyses

The incidence rate of device-related adverse events will be calculated along with 95% CI. The reporting period is from baseline through the last study visit.

Secondary safety endpoint:

- The evaluation of discomfort and pain will be summarized in appropriate tables by visit.
- Changes from baseline in ocular surface staining, and intraocular pressure will be calculated along with 95% CI by study group and visit. The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the changes within the study group.
- Cornea OCT evaluation to detect changes (cornea thickness, cornea deamination) following treatment. Changes in Cornea OCT evaluation will be summarized in descriptive tables for the Tixel group.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

AE data will be listed individually and summarized by SOC and by PT within a system organ class.

Treatment-emergent adverse events (TEAEs) are those with onset after initiation of study intervention or if occurring prior to initiation of study intervention, worsened after initiation of study intervention. Only treatment-emergent events will be summarized. All events in the clinical database regardless of when they occurred will be provided in a data listing. Definitions of adverse events, serious adverse events, and categorizations of events can be found in Appendix D.

An overall summary will be presented which gives the number and percentage of patients that experienced any TEAE (overall, ocular, and non-ocular), experienced any treatment related TEAE (overall, ocular, and non-ocular), permanently discontinued treatment due to a TEAE (overall, ocular, and non-ocular), interrupted treatment due to a TEAE (overall, ocular, and non-ocular), experienced a treatment emergent serious TEAEs (overall, ocular, and non-ocular), and that died.

A listing of serious TEAEs will be provided. Continuous safety endpoints shall be summarized using summary statistics such as means, medians, standard deviations, minima, maxima, and relevant percentiles.