Study Protocol

EVALUATION OF THE LIPIFLOW SYSTEM WITH A NEW ACTIVATOR (MODEL LFD-2100)

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Evaluation of the LipiFlow System with a New Activator (Model LFD-2100)

PROTOCOL NUMBER: DRYE-105-ACTS

SPONSOR: Johnson & Johnson Surgical Vision Inc.
1700 East Saint Andrew Place
Santa Ana, California 92705
(714) 247-8200

Investigator Agreement:

As an Investigator, I agree to:

- Implement and conduct this study diligently and in strict compliance with this agreement; the protocol; Good Clinical Practices; 21CFR812, ISO 14155 and all other applicable FDA regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB), FDA; and all other applicable laws and regulations.
- Supervise all testing of the device where human subjects are involved.
- Ensure that the requirements for obtaining informed consent are met.
- Obtain authorization for use/disclosure of health information (e.g., HIPAA authorization or equivalent).
- Maintain all information supplied by Johnson & Johnson Surgical Vision in confidence and, when this information is submitted to an independent IRB/IEC or any other group, it will be submitted with a designation that the material is confidential.

I have read this Protocol in its entirety, and I agree to all aspects.

Investigator Printed Name	Signature	Date
Subinvestigator Printed Name	Signature	Date
Subinvestigator Printed Name	Signature	Date
Subinvestigator Printed Name	Signature	Date

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PERSONNEL AND FACILITIES

SPONSOR: Johnson & Johnson Surgical Vision, Inc. ("JJSV")
1700 East Saint Andrew Place
Santa Ana, CA 92705

SPONSOR PERSONNEL:

Medical Monitor:

Medical Safety Officer:

Sr. Manager, Clinical Operations:

Study Manager:

Clinical Research Scientist:

Biostatisticians:

EMERGENCY TELEPHONE NUMBERS:

PROTOCOL CHANGE HISTORY

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original.	N/A.
2.0	1, 4, 10	1, 2, 5, and 9	Update the sample size.	To allow more patients to be treated with Activator LFD-2100 in the study.
	10.3	14-15	Update the LipiFlow treatment procedures.	To align with the latest LipiFlow Thermal Pulsation System Instructions for Use.
	11	17	Add the list of "Study-Specific Anticipated Adverse Events".	To clarify the study-specific anticipated AEs.
	Appendix A	25-30	Update the investigator questionnaire.	To collect more feedback from investigators.
	Appendix G	44	Add "Adverse Event and Complaint Reporting Instructions" as Appendix G.	To provide instructions on Adverse Event and Complaint reporting.
	Personnel and Facilities, and Appendix G	iv, 44	Update information of the study manager.	To list the new study manager and his contact information.
3.0	1, 20.3	4, 28	Update the sample size calculation, meanwhile the overall sample size is not changed and will not impact the date collection.	To update sample size calculation

1. SYNOPSIS

PROTOCOL:	Evaluation of the LipiFlow System with a New Activator (Model LFD-2100) Protocol Number: DRYE-105-ACTS
STUDY TREATMENTS:	Investigational Product: The new Activator (Model LFD-2100).
STUDY OBJECTIVE:	The purpose of this study is to confirm the clinical use of the LipiFlow system with Activator LFD-2100 to successfully complete LipiFlow treatment procedure in human subjects. Additionally, the investigator rating of the ease of use of the LipiFlow system with Activator LFD-2100 will be obtained.
CLINICAL HYPOTHESIS:	The Activator Model LFD-2100 will provide successful LipiFlow treatments in 95% or more cases.

OVERALL STUDY DESIGN:

Structure:	Prospective, open-label clinical study.
Number of sites:	Three (3) to 5 investigators in up to 4 sites in the USA.
Duration:	A pre-treatment visit and a treatment visit (may happen on the same day)
Administration:	Minimum 50 eyes and up to 100 eyes will be treated in this study. The investigators or designees will perform LipiFlow treatment with the Activators LFD-2100 on both eyes. The Investigator or designee will complete a questionnaire regarding the clinical use of Activator LFD-2100. The treatment reports automatically generated by LipiFlow Console after completion of each treatment will be collected.
Visit Schedule:	Each subject will have 1-2 visits which include informed consent, screening for study participation, and receiving the LipiFlow treatment. A questionnaire will be completed by the investigator or designee. A typical pre-treatment visit will be approximately 30-60 minutes long, and a typical treatment visit will take another 30-60 minutes.

STUDY POPULATION CHARACTERISTICS:

Condition: Adults with bilateral meibomian gland dysfunction (MGD) (refer to inclusion/exclusion criteria for requirements).

Number of Subjects/Eyes: Minimum 50 eyes and up to 100 eyes to be treated.

Each research subject must meet the following inclusion/exclusion criteria in order to participate in this study:

Inclusion Criteria (all criteria apply to each study eye):

To be able to participate in this study, subjects must:

- Be at least 22 years old.
- Has been diagnosed as bilateral MGD prior to the study visit, or has evidence of MGD in both eyes. NOTE: MGD diagnosis can be based on prior medical records, investigator opinion or based on assessment of meibomian glands of the lower eyelid (see Appendix E).
- Availability, willingness, ability and sufficient cognitive awareness to comply with study protocol, examination procedures and visit.
- Be willing to provide informed consent and authorization to disclose protected health information or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical procedures.
- Ability to understand and respond in English.

Exclusion Criteria (all criteria apply to each study eye):

Subject will not be able to be in the study, if the subject:

- Has a history of certain medical conditions that have been identified as contraindications and precautions of the LipiFlow System (refer to the *LipiFlow Thermal Pulsation System Instructions for Use* for details)
- Has a history of prior eye surgery or trauma, active eye disease, or other eye abnormality in the study eye(s), which in the opinion of the investigator would confound the study results.
- Is pregnant, or is breast feeding.
- Concurrent participation or expected participation in an interventional (i.e., surgical or pharmaceutical interventional) clinical trial within 14 days prior to study screening.

STUDY ENDPOINTS:

Primary Endpoint:

- Successful completion of LipiFlow treatment with Activator LFD-2100 in 95% or more cases.

Other Endpoints:

- Questionnaire rating of each step in the LipiFlow treatment procedure with Activator LFD-2100.
- Rate of adverse events and complications.

STUDY VISITS AND PROCEDURES:

Inclusion and exclusion qualifications will be assessed at the enrollment visit according to the inclusion/exclusion criteria.

The Informed Consent Document and Authorization for Use/Disclosure of Health Information form to comply with US Health Information Portability and Accountability Act (HIPAA) must be signed by any subjects who agree to participate in the study prior to undergoing any study-specific procedures.

After determination that all inclusion/exclusion criteria have been met, enrolled subjects will receive the LipiFlow system treatment on both eyes. The investigator or designee will complete a questionnaire regarding the clinical use of Activators LFD-2100 for each subject (see **Appendix A**).

VISIT PROCEDURES:

1) Informed consent.
2) Screening and enrollment.
3) Perform a pre-treatment slit lamp evaluation, non-dilated fundus exam, ocular surface staining for all the subjects, and optional meibomian gland assessment at the investigator's discretion.
4) Complete a bilateral LipiFlow treatment with Activators LFD-2100 on both eyes of a subject, and collect the treatment reports automatically generated by LipiFlow console after completion of each treatment
5) Perform a post-treatment slit lamp evaluation and ocular surface staining.
6) Questionnaire: The Investigator or designee will complete a questionnaire regarding the clinical use of Activator LFD-2100 (see **Appendix A**).

DATA ANALYSIS:

The investigator or designee will complete a questionnaire on each step of the LipiFlow procedure with Activators LFD-2100 (see **Appendix A**) for each subject. The treatment reports automatically generated by LipiFlow console after the completion of each treatment will be analyzed and used to evaluate successful completion of the procedure.

SAMPLE SIZE CALCULATION:

The confidence interval approach is used to estimate precision around the true proportion of successful completion of LipiFlow treatment with Activator LFD-2100. Assuming the proportion of successful completion of LipiFlow treatment is 95%, with n= 50 eyes, a two-sided 95% confidence interval will be (89%, 100%), i.e., a precision of 6.0%.

2. BACKGROUND/INTRODUCTION

As defined by the Tear Film and Ocular Surface Society (TFOS) International Workshop on meibomian gland dysfunction (MGD) involving more than 50 clinical and research experts, “Meibomian gland dysfunction is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.”[1]

The LipiFlow® Thermal Pulsation System is designed to apply localized heat and pressure therapy to the eyelids, in subjects with chronic cystic conditions of the eyelids, including MGD. The LipiFlow provides controlled, localized heat and pressure application to the eyelids as a prescription device used in a 12-minute in-office procedure by a licensed physician or technician (by the order of a licensed physician). The LipiFlow uses an efficient method of melting the meibomian gland obstructions by applying heat to the inner eyelid surface, in closest proximity to the meibomian glands. Additionally, the LipiFlow improves upon the physician practice of manual eyelid expression by expressing the glands at a level of force far below that required to manually express the glands without heat. The use of LipiFlow has been reported in several publications and presentations to date. Prior clinical studies demonstrate safety, effectiveness and clinical utility of the LipiFlow system with Activator LFD-2000.

[1] Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: Executive summary. Invest Ophthalmol Vis Sci 2011;52(4):1922-29.

JJSV has developed a new model of Activator (Model LFD-2100). The purpose of this study is to evaluate the clinical use of the LipiFlow System with the Activator LFD-2100 to complete a LipiFlow treatment procedure in human subjects.

3. CLINICAL HYPOTHESIS

The Activator Model LFD-2100 will provide successful LipiFlow treatments in 95% or more cases.

4. STUDY DESIGN

Minimum 50 eyes and up to 100 eyes will be treated in this prospective, open-label clinical study. The investigator or designee will perform LipiFlow treatment with the Activators LFD-2100 on both eyes of a subject. The data from the treatment reports generated by the LipiFlow console and from the questionnaire will be used to assess the clinical utilization of the Activator LFD-2100.

5. ACRONYMS

- FDA: Food and Drug Administration
- IEC: Independent Ethics Committee
- IRB: Institutional Review Board
- MGD: Meibomian Gland Dysfunction
- MGE: Meibomian Gland Evaluator
- JJSV: Johnson & Johnson Surgical Vision

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to confirm the clinical use of the LipiFlow system with Activator LFD-2100 to successfully complete a LipiFlow treatment procedure in human subjects. Additionally, the investigator rating of the ease of use of the LipiFlow system with Activator LFD-2100 will be obtained.

7. STUDY PRODUCTS

The LipiFlow® Thermal Pulsation System is a prescription device with an indication for use for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction, also known as evaporative dry eye or lipid deficiency dry eye. The LipiFlow is used by a

physician or technician in an in-office procedure to provide controlled heat to the inner eyelid surface and intermittent pressure to the outer eyelid to facilitate release of lipid from the cystic glands.

The LipiFlow has been most-recently cleared under pre-market notification (K192623) to market the device in the U.S (Class II device). The LipiFlow with the existing Activator Model LFD-2000 is in commercial distribution based upon a determination by the FDA that the device is substantially equivalent to a legally marketed device. The new Activator Model LFD-2100 is a modification of LFD-2000. The risk assessment supports that the use of the LipiFlow with LFD-2100 in this study is non-significant risk because the system is designed to control the application of heat and pressure within a safe range and time. The use of the newly designed LFD-2100 does not change the overall residual risk of the device or introduce new risks to the patient and/or user as compared to the Activator Model LFD-2000. No new potential hazards and harms to the patient or user were identified for the device modifications relative to the existing risk assessment for the Activator Model LFD-2000. The risk assessment was conducted to confirm that the change from LFD-2000 to LFD-2100 does not trigger any new risks, as the design specifications of the activator between the iterations remained unchanged, and that the main clinical efficacy intended use of regulated heat and pressure delivery to the eyelid remained unchanged.

8. STUDY POPULATION

Each research subject must meet the following inclusion/exclusion criteria in order to participate in this study:

Inclusion Criteria (all criteria apply to each study eye):

To be able to participate in this study, subjects must:

- Be at least 22 years old.
- Has been diagnosed as bilateral MGD prior to the study visit, or has evidence of MGD in both eyes. NOTE: MGD diagnosis can be based on prior medical records, investigator opinion or based on assessment of meibomian glands of the lower eyelid (see Appendix E).
- Availability, willingness, ability and sufficient cognitive awareness to comply with study protocol, examination procedures and visit.
- Be willing to provide informed consent and authorization to disclose protected health information or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical procedures.
- Ability to understand and respond in English.

Exclusion Criteria (all criteria apply to each study eye):

Subject will not be able to be in the study, if the subject:

- Has a history of certain medical conditions that have been identified as contraindications and precautions of the LipiFlow System (refer to the *LipiFlow Thermal Pulsation System Instructions for Use* for details).
- Has a history of prior eye surgery or trauma, active eye disease, or other eye abnormality in the study eye(s), which in the opinion of the investigator would confound the study results.
- Is pregnant, or is breast feeding.
- Concurrent participation or expected participation in an interventional (i.e., surgical or pharmaceutical interventional) clinical trial within 14 days prior to study screening.

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select the existing LipiFlow users who are licensed to practice medicine and are experienced in performing the LipiFlow treatment at the investigative site. Investigators will be selected from either ophthalmologists, optometrists, or technicians who are experienced in LipiFlow treatment with Activator LFD-2000. Licensed ophthalmologists, optometrists and/or study coordinators with Good Clinical Practice (GCP) training, and experienced in conducting clinical trials in the fields of optometry and ophthalmology will consent subjects and perform screening as well as pre-, and post-treatment testing.

The sites where this trial will be conducted are required to have adequate staff support, as well as the necessary instrumentation to conduct study testing.

9.2 INVESTIGATOR OBLIGATIONS

Investigators are required to fulfill the following obligations:

- Conduct the study in accordance with the relevant and current protocol. Investigator will only make changes to a protocol after notifying and obtaining approval from the IRB except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct and supervise the study.
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- Be responsible for protecting the rights, safety and welfare of subjects under the investigator's care, with particular focus on assuring subjects are not improperly influenced or coerced toward participation.
- Be responsible for the control and documentation of the devices under investigation.

- Inform subjects that the device(s) are being used for investigational purposes and that requirements relating to obtaining informed consent and IRB approval are met according to 21CFR50, 21CFR56, 21CFR812 and all other applicable laws and regulations.
- Maintain confidentiality as required by HIPAA or similar laws and regulations.
- Shall not obtain written informed consent from any subject to participate or allow any subject to participate before obtaining IRB approval.
- Document in each subject's case history that informed consent was obtained prior to participation in the study as required by 21CFR812.
- Report to JJSV and the reviewing IRB any adverse experiences that occur during the course of the study in accordance with applicable laws and regulations.
- Maintain adequate and accurate records in accordance with applicable laws and regulations and make available all study documents and subject medical records for inspection by either JJSV, duly authorized regulatory agencies (e.g., FDA) and/or the IRB.
- Submit progress reports on the investigation to JJSV and the reviewing IRB at regular intervals, but no less often than yearly as required by 21CFR812.150.
- Report all changes in research activity and all unanticipated problems involving risks to subjects to the IRB.
- Supervise and permit investigational device use and disposition in accordance with applicable regulations and protocol requirements. Upon completion of enrollment or termination of the study or the investigator's part of the study, or at JJSV's request, return to JJSV any remaining supply of the investigational device.
- Provide sufficient accurate financial information to JJSV to allow JJSV to submit complete and accurate certification or disclosure statements as required by 21CFR54. Promptly update this information if any relevant changes occur during the course of the investigation or for up to one year following completion of the study
- Comply with all other obligations of clinical investigators and requirements according to all applicable FDA regulations (e.g., 21CFR812), all other applicable laws and regulations, and all conditions of approval imposed by the reviewing IRB, the FDA and the regulatory agency of the country in which the study is being conducted.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately informed about the protocol, the investigational device, their study-related duties and functions and agree to fulfill their obligations in meeting the above commitments.

Investigators shall provide adequate time and resources to conduct and report on the study. The Investigator, or delegate, shall notify JJSV of any change in the conduct of the study including changes in study personnel assigned to the study project, location of the investigational device(s), or maintenance of study records, etc.

9.3 INVESTIGATOR APPROVAL

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant

documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Study Files/Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV. Study sites will obtain IRB approvals and fulfill any other site-specific and/or region-specific regulatory requirements. The investigator is required to report to JJSV within five working days any withdrawal of approval by the reviewing IRB for his/her participation in the investigation.

Prior to the start of subject enrollment, the following documents must be approved:

- Confidentiality Agreement
- Clinical Trial Agreement
- Investigator Agreement/Protocol Signature page
- Financial Disclosure form
- Signed and dated copy of investigator's current curriculum vitae
- Copy of the investigator's current medical license

By signing the study documents, the investigator agrees to conduct this study according to the obligations above and all other applicable regulatory and legal requirements.

10. EXPERIMENTAL PLAN

10.1 OVERVIEW

The study will be conducted in accordance with the principles of the Declaration of Helsinki and in accordance with U.S. Code of Federal Regulations, ISO 14155 and all other applicable laws and regulations. The study will not begin until IRB approvals have been obtained.

Study activities may be delegated to qualified study staff, but the Principle Investigator is responsible for all study activities. Delegation must be documented before study activities commence. Individuals involved in the conduct of this study will have documented training applicable to their respective roles.

All tests in this protocol are to be performed by the investigators or designees who are representative of the end-user community for the LipiFlow system (e.g., ophthalmologists, optometrists and technicians). All tests will be performed in a clinic, an office or laboratory setting and may be observed by JJSV personnel. Three to five investigators or designees will perform the LipiFlow treatments per this protocol on approximately 25 – 50 subjects per investigator or designee, resulting in treatments in minimum 50 eyes and up to 100 eyes in total.

Informed consent will be obtained for each subject prior to any study-specific activities. The subjects may refuse participation or exit the study at any time. If new information

becomes available that may impact a subject's willingness or ability to continue participation in the study, the informed consent form will be revised, and each subject will be re-consented.

After screening and enrolment, if a subject meets all inclusion / exclusion criteria, the investigator or designee will perform a complete LipiFlow treatment with Activator LFD-2100 on both eyes of a subject.

The investigator or designee will complete a questionnaire regarding the clinical use of the Activator LFD-2100 (see **Appendix A**). The treatment reports automatically generated by LipiFlow Console after completion of each treatment will be printed out and collected. The reports will present confirmation of treatment completion together with treatment information such as the changes in pressure and temperature during the treatment.

Typical duration of study exams and treatment will last approximately 1-2 hours. All data will be de-identified or encoded to protect the privacy of the subject and confidentiality of the data. Although the study is not masked, to maintain consistency, it is recommended that a single individual (study technician or coordinator designated by the investigator) conduct all study-related eye testing, although a back-up person should also be designated and trained.

The investigators will be provided with the LipiFlow Consoles (if needed), LipiFlow Activator LFD-2100, Semi-permanent Cable, Lid Stabilizer Tape, and the LipiFlow, Activator, and Cable Instructions for Use (IFU), including the Quick Start Guide. Prior to human use, Activator LFD-2100 will be described in sufficient details in a Clinical Investigator Brochure to adequately describe the theory of operation and compliance to applicable standards in humans.

10.2 VISIT SCHEDULE

Each subject will have a 1-2 study visits which include informed consent, screening for study participation and performing the LipiFlow treatment with Activator LFD-2100 (see **Appendix C**). Unscheduled visits may be conducted as necessary at the discretion of the investigator for clinically-indicated follow-up.

Inclusion and exclusion qualifications will be assessed prior to study treatment. The Informed Consent Document must be signed by any subjects who agree to participate in the study prior to undergoing any study-specific procedures.

Study parameters and methods are listed as below:

1) Informed consent

2) Screening and Enrollment: including but not limited to reviewing medical and ocular history, discussing study eligibility etc.

3) Perform a pre-treatment slit lamp evaluation, non-dilated fundus exam, ocular surface staining for all the subjects, and optional meibomian gland assessment at the investigator's discretion.

4) Complete a bilateral LipiFlow treatment with Activator LFD-2100 on both eyes of a subject, and collect the treatment reports automatically generated by the LipiFlow console after completion of each treatment.

5) Perform a post-treatment slit lamp evaluation and ocular surface staining.

6) Questionnaire: The Investigator or designee will complete a questionnaire regarding the clinical use of the Activator LFD-2100 (**Appendix A**).

10.3 PROCEDURES

The procedures in the Pre-treatment visit include Informed Consent, Screening & Enrollment, and Pre-treatment slit lamp evaluation, non-dilated fundus exam, ocular surface staining, and optional meibomian gland assessment (at the investigator's discretion). The procedures in the Treatment Visit include LipiFlow Treatment, post-treatment slit lamp evaluation, ocular surface staining, and completion of the Questionnaire. These procedures must be done in the order shown as below.

Informed Consent

The Investigator or designee identifies potential study participants by reviewing medical records of subjects. Potential study participants are scheduled for the study visit.

At the visit, the Investigator or designee conducts the informed consent discussion and explains the study purpose, procedures, benefits, risks, discomforts, precautions and subject responsibilities to the potential study participant. The Investigator may provide written delegation of authority to a trained and qualified study staff member (e.g., study coordinator, technician) to conduct the consent discussion; however, the Investigator should be available to answer the potential participant's questions, as needed.

Once the Investigator or designee has answered all the potential participant's questions to his/her satisfaction and the potential study participant has voluntarily agreed to participate in the study, written informed consent is obtained using the IRB/IEC-approved informed consent document. The subject and the person conducting the consent discussion (Investigator or designee) print their names, sign and date the consent. If the subject is unable to read, the consent document can be read to the subject in front of an impartial witness, who also prints his/her name, signs and dates the consent.

All subjects enrolled in the study must sign the current IRB/IEC-approved informed consent document. The informed consent must be signed before any study-specific examinations are performed, and this must be documented in the source documents. An authorization for use/disclosure of health information form (HIPAA authorization) or similar medical measurement privacy law documentation must also be signed.

The Investigator maintains the signed informed consent document and the signed authorization form as a permanent part of the subject's medical records and provides a signed copy of the consent to the subject. The Investigator or designee documents in the medical records that informed consent was obtained prior to any study-specific procedures and a copy of the signed consent was given to the subject.

As the Informed Consent Form is signed prior to any study-specific procedures, some subjects may not qualify after study-specific testing is performed. Subjects will be considered screen-failures if they do not qualify or if they qualify but decide not to proceed with study treatment. These subjects will be exited from the study.

Screening & Enrollment

Following the informed consent process, the Investigator or designee will perform the screening exam procedures and evaluate the subject conditions that affect study eligibility, as listed in **Sections 8**. The screening exam may be ended prior to completion if the Investigator or designee determines that the subject does not meet one or more of the eligibility criteria. The subject must meet all the study inclusion / exclusion criteria based on testing and medical history discussion conducted at the visit.

The screening exam to be performed for each eye includes:

MEDICAL AND OCULAR HISTORY

To determine the presence of any systemic or ophthalmic factors that may affect the subject's eligibility based on the study inclusion and exclusion criteria in **Sections 8**, the Investigator or designee obtain the subject's medical and ophthalmic history at the visit, including assessment of:

1) demographic information (age, gender, race/ethnicity);
2) ophthalmic conditions and medications;
3) history of ocular surgery, ocular injury, ocular infection, ocular inflammation, ocular allergy, eyelid abnormality, or ocular surface abnormality;
4) pregnant and breastfeeding conditions, if applicable;
5) recent participation in another ophthalmic clinical trial;
6) employment or relationship with any employee at the clinical study site.

BIOMICROSCOPIC SLIT-LAMP EXAM

A biomicroscopic slit-lamp exam must be performed at the study visit to determine if the subject meets inclusion/exclusion criteria (see **Appendix D**). The Investigator or designee evaluates the eyelids, palpebral and bulbar conjunctiva, cornea, anterior

chamber, iris and lens using a slit lamp biomicroscope. The Investigator or designee everts the upper eyelid to evaluate the upper palpebral conjunctiva. The Investigator or designee assesses the findings for the presence of any medical findings.

NON-DILATED FUNDUS EXAM

A non-dilated fundus exam shall be performed at the study visit to determine the status of the ocular media, retina and lens and to determine if the subject meets inclusion/exclusion criteria.

Potential participants who are approached with the informed consent document will be documented on the Subject Accountability Log. A subject who does not meet the eligibility criteria or who chooses to discontinue study participation at any time is documented on the Subject Accountability Log as a Screen Failure or Exited Subject along with the reason. All subjects who sign the informed consent document are assigned a subject identifier.

MEIBOMIAN GLAND ASSESSMENT (OPTIONAL)

The MGD diagnosis can be based on prior medical records, investigator opinion, or in conjunction with an assessment of meibomian glands of the lower eyelid (see Appendix E). The need for the meibomian gland assessment is at the investigator's discretion.

If the Investigator or designee decides to conduct the meibomian gland assessment to evaluate the function of the meibomian glands, the Investigator or designee can assess the color and consistency of the secretion characteristics from the gland orifices along the lower eyelid in each eye. The Investigator or designee evaluates the glands using a slit-lamp biomicroscope and a handheld instrument, Meibomian Gland Evaluator (MGE) (as shown in **Appendix E**), to apply gentle pressure along the eyelid margin, which simulates a forceful blink in yielding secretions from the glands. This instrument provides a standardized method to apply the same amount of pressure at each visit and for each subject to ensure measurement consistency. This Class I, 510(k)-exempt device is commercially available, and is being used in this study in accordance with the indications in the commercial product labeling.

There are approximately 20 to 30 meibomian glands along the lower eyelid. The Investigator or designee assesses and grades glands located temporally, centrally and nasally. The central region of the Meibomian Gland Evaluator should be carefully placed in the temporal, central and nasal regions as described in **Appendix E** to avoid overlap in the gland assessment.

OCULAR SURFACE STAINING

Ocular surface staining of the cornea and conjunctiva shall be evaluated. The Investigator or designee assesses the corneal staining after instillation of fluorescein dye

in the eye, and assesses the conjunctival staining after instillation of lissamine green dye in the eye, as defined in **Appendix F**.

LipiFlow Treatment

If a subject meets all inclusion / exclusion criteria, the investigator or designee will perform a complete LipiFlow treatment with the Activator LFD-2100 on both eyes of a subject.

If the Treatment Visit doesn't happen on the same day of the Pre-reatment Visit, a biomicroscopic slit-lamp exam must be performed before LipiFlow treatment performed at the Treatment visit to assess the findings for the presence of any medical findings.

The Investigator or designee cleans the lid margin and then performs treatment with the LipiFlow system per the *LipiFlow Thermal Pulsation System Instructions for Use*. The Investigator or designee documents any problems with the LipiFlow system during treatment. The Sponsor will investigate any reported problem with the LipiFlow system.

TREATMENT PROCEDURES

1. Inspect expiration date on Activator LFD-2100 packaging and place Activators LFD-2100 in subject's eyes.

Inspect the expiration date on the Activator LFD-2100 packaging before using the Activator. Verify the date has not expired.

1.1. Cable setup

Prior to using Activator II (LFD-2000), the Cable (Model CBL-2000) must be attached to the Console and locked into place with the locking clip. Plug the Cable connector into the Console and push the locking clip into the connector.

1.2. Disinfect cable and connect Activator LFD-2100

Disinfect the Cable plug to Activator LFD-2100 and tubing with isopropyl alcohol (70-90% concentration) prior to connection to the Activator LFD-2100.

The investigator or designee will open the Activator LFD-2100 package consisting of the combined lid warmer and eye cup. Before removing the Activator LFD-2100 from its package, connect the Cable to the Activator while inside the package to minimize user handling prior to insertion. Leave the Activator II inside the package until the Activator LFD-2100 self-test is completed.

1.3. Run Activator LFD-2100 self-test:

Once the Activator LFD-2100 is connected, a message indicating that the system is running a Activator self-test is briefly displayed on the Console Treatment screen above the pressure sequence overview graph.

1.4. Inspect and Placement of Activator LFD-2100:

The investigator or designee will inspect the Activators LFD-2100 to ensure that there are no rough or sharp edges and then place the Activators LFD-2100 in subject's eyes.

1.5. Stabilize the Activator LFD-2100:

Position the patient in a reclined or supine position for treatment. Place 2 drops of commercially available anesthetic in the eye(s) to be treated. Once the Activator is placed correctly, secure the Activator with medical-grade adhesive tape (either the Lid Stabilizer or surgical tape).

2. Run LipiFlow Treatment with Activator LFD-2100

After securing the Activator LFD-2100, the investigator or designee will run and complete the LipiFlow treatment with the Activators and monitor the Activators position on the eyelids during treatment.

3. Remove Activator LFD-2100

3.1. Disconnect Activator LFD-2100 from subject's eyes

3.2. Disconnect Activator LFD-2100 from the Cables

After completion of each treatment, the treatment reports automatically generated by LipiFlow Console will be printed out and collected. The reports will show completion of the treatment and additionally the changes of pressure and temperature during the treatment.

Following the completion of LipiFlow treatment, the Investigator or designee will perform a slit-lamp evaluation (**Appendix D**) and ocular surface staining (**Appendix F**) in each eye to check for any adverse events.

Questionnaire

A questionnaire will be administered to the investigator or designee to collect information regarding the clinical use of Activator LFD-2100 (**Appendix A**).

10.4 ACTIVATOR SUPPLY

For all the study subjects, the Activators will be obtained from the site study consignment supplied by JJSV prior to the first study treatment. One Activator will be used on each eye of a subject. Unused back-up Activators are to be returned to the site consignment. At the completion of all study treatments, any remaining Activators will be shipped back to JJSV following the final accountability by a JJSV Study Monitor. At all times, the storage, access and use of all the consignment Activators must be controlled.

10.5 EXIT OF SUBJECTS

An Exit Case Report Form will be completed for all subjects, either when they complete the study or if they exit early.

It is the responsibility of the investigator to provide complete follow-up data to JJSV for each subject, and every attempt should be made to gather that complete follow-up data for all subjects enrolled as missing data can have a negative effect on the study results.

A subject will be considered a "screen failure" if he/she does not meet the inclusion/exclusion criteria or if consent is withdrawn prior to LipiFlow treatment.

If a subject is exited early from the study, the investigator or designee will complete an Exit Case Report Form indicating the reason for study exit. In the event of any serious adverse event, the subject may be exited from the study; however, efforts must be made by the investigator to follow the subject until resolution of the adverse event.

Following study completion or early exit, all study subjects are to be instructed to undergo regular eye examinations at least yearly and also to return to their doctor if any eye complications are experienced in the interim.

10.6 UNSCHEDULED VISITS

During the study period or immediately after (within 1-week), if a non-protocol-required visit is done for the purpose of medically-indicated follow-up for a study eye, data from this visit should be reported using the Unscheduled Visit CRF. The need for unscheduled visits is at the investigator's discretion. Specific examinations to be performed at unscheduled visits are also at the discretion of the investigator (based on the reason for the unscheduled visit) and data are to be recorded in the appropriate section of the case report form.

10.7 PROTOCOL DEVIATIONS

Any departure from the protocol procedures represents a protocol deviation. Protocol deviations may be subject-based (e.g., inclusion/exclusion criteria, informed consent deviation, etc.) or procedural-based (e.g., out-of-interval visits, non-compliance with

testing procedures, etc.). All protocol deviations will be captured in the Electronic Data Capture (EDC) system. Any deviation made to protect the life or physical wellbeing of a subject in an emergency as well as any use of the investigational device without obtaining informed consent must be reported to JJSV within 5 working days. Protocol deviations will be monitored by JJSV, and if the non-compliance is persistent or egregious, JJSV may take action, including but not limited to termination of the investigator's participation in the study. The investigator is also responsible for informing the reviewing IRB of instances of protocol non-compliance in accordance with the IRB requirements.

11. ADVERSE EVENTS AND PRODUCT COMPLAINTS

11.1 DEFINITIONS

Adverse Event (AE)

An adverse event is defined (following ISO 14155) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

Serious Adverse Event (SAE)

An adverse event is considered serious (following ISO 14155) if it is an untoward occurrence which may or may not be related to use of the study device that

- is sight- or life-threatening,
- results in death,
- requires inpatient hospitalization or prolongation of hospitalization (a planned hospitalization for a pre-existing condition without a serious deterioration in health is not considered a serious adverse event),
- results in permanent impairment of a body structure or body function,
- necessitates medical or surgical intervention to prevent permanent impairment to a body structure or function, or
- results in fetal distress, fetal death or a congenital abnormality or birth defect

Device-Related Adverse Event/Adverse Device Effect (ADE)

A device-related adverse event is defined as any adverse even that is believed to be definitely, probably or possibly related to the study device. A device-related event is also considered an adverse device effect (ADE; following ISO 14155) resulting from the use of the study device that may result from user error, insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation of any malfunction of the device.

Study-Specific Anticipated Adverse Events

The study specific anticipated AEs are listed below and will be classified as AE or SAE dependent upon its occurrence and severity during the course of the study:

- Eyelid/eye pain requiring discontinuation of the treatment procedure;
- Eyelid irritation or inflammation (e.g. edema, bruising, blood blister, dermatitis, hordeolum or chalazion);
- Ocular surface irritation or inflammation (e.g. corneal abrasion, conjunctival edema or conjunctival injection/hyperemia); and
- Ocular symptoms (e.g. burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

Study-Specific Serious Anticipated Adverse Events

There is no anticipated study-specific serious adverse event for this study.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE)

Any UADE (USA 21CFR 812.3(s)) or USADE (ISO 14155) is defined as any serious adverse effect on health or safety or 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 investigational plan (i.e., this protocol), application (including a supplementary plan or application), or risk assessment, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.2 PRODUCT COMPLAINT/DEVICE DEFICIENCY DEFINITION

A product complaint/device deficiency is defined (21 CFR 820.3(b) and ISO 14155) as any alleged deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device. This may include malfunctions, use error and inadequacies in labeling. Product complaints can pertain to any marketed JJSV device being used in the study. The investigator is to assess whether the deficiency could have led to a serious adverse event without suitable action or intervention or under less fortunate circumstances.

11.3 ADVERSE EVENT AND COMPLAINT REPORTING REQUIREMENTS

All adverse events and any complaint encountered using any JJSV product, regardless of severity and whether or not attributed to the study device(s), are to be reported to JJSV and recorded on the case report form corresponding to the visit during which awareness of the event occurred. Adverse events are also to be reported to the reviewing IRB/IEC as per the IRB/IEC's reporting requirements. If required, adverse

events will be reported to the appropriate regulatory agencies according to all applicable laws and regulations.

Reporting of adverse events shall follow the applicable Regulations. General guidelines are provided below:

Adverse Event Reporting

An adverse event that is not serious or device-related is to be reported to JJSV in a timely manner. Notification of non-serious and non-device related adverse events will occur by recording events on the CRF when noted. Such adverse events are also to be reported to the reviewing IRB/IEC per their reporting requirements.

Complaints/Device Deficiency Reporting

A general product complaint or device deficiency is to be reported to JJSV in a timely manner. Notification of complaints/device deficiencies will occur by either recording complaints on the CRF when the complaint occurred (e.g. operative form) or by a phone call to the Sponsor. Any device deficiency that could have led to a serious adverse event without suitable action or intervention, or under less fortunate circumstances, must be reported to the sponsor immediately (no later than 24 hours after detection). Device deficiencies that could have led to a serious adverse event should also be reported to the investigator's IRB/IEC per their reporting requirements.

Serious and/or Device-Related Adverse Event Reporting

Serious and/or device related events (ADEs) are to be documented using the Serious Adverse Event/Adverse Device Effect (SAE/ADE) CRF. In the event of a serious adverse event (SAE), which may or may not be related to use of the study device, JJSV must be notified immediately (no later than 24 hours after detection). Any SAE is to be reported by phone (and/or email) and by submitting the completed SAE/ADE CRF. Any SAE or device-related AE should also be reported to the investigator's IRB/IEC per their reporting requirements.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE) Reporting

If during the study, a serious adverse event occurs that may reasonably be regarded as device-related and was not previously expected in nature, severity, or degree of incidence, the investigator is to report the UADE/USADE to JJSV within 24 hours, and to the investigator's IRB/IEC as soon as possible (and no later than 10 working days after learning of the event for sites in the USA as required by 21CFR812).

11.4 CAUSAL RELATIONSHIP

The investigator should always be alert to adverse events that may be related to the study device or the use of the study device (i.e., the procedure specific to the initial application of the device). An attempt should be made in every case to determine the causality of the event. The following definitions are to be used as guidelines in determining the relationship between the event and the study device and/or use of the device.

Definitely related:	If the event is associated with the device and/or the use of the device beyond a reasonable doubt, a causal relationship exists between the adverse event and the device and/or the use of the study device.
Probably related:	There is a reasonable possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event cannot be reasonably explained by another cause.
Possibly related:	The adverse event has not been determined to be related to the device or the use of the device, but no other cause has been identified and the device and/or the use of the study device cannot be ruled out as a possible cause.
Unlikely to be related:	The possibility of a potential causal relationship between adverse event and the device and/or the use of the device could exist, but the adverse event can be reasonably explained by another cause.
Not related:	There is no possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event can be attributed to another cause.

If an adverse event is believed to be definitely, probably or possibly related to the study device and/or the use of the device, the event will be considered related to the study device and/or the use of the device.

11.5 ADVERSE EVENT FOLLOW-UP

For every adverse event, appropriate measures should be undertaken to treat and/or monitor the subject until resolution occurs. Obtain and maintain in the subject's files all pertinent medical data relating to the event including the subject's medical records and medical reports and/or judgments from colleagues or outside specialists who assisted in the measurements of the subject. The investigator should keep JJSV closely informed as to the outcome of serious and/or device-related adverse events, thereby allowing JJSV to comply with the appropriate regulatory reporting requirements. A SAE/ADE Follow-up CRF should be completed each time the subject returns to the investigator for follow-up of serious and/or device-related adverse event until resolution of the event. Any subject who is exited from the study due to a serious and/or device-related adverse event or prior to resolution of such an event will be followed until the outcome is determined.

12.0 PROTOCOL CHANGES/AMENDMENTS

If the investigator desires to modify any procedure and/or the design of the study, he or she must contact and obtain consent from JJSV regarding the proposed changes prior to

implementation. Any modifications (including additional data collection) require approval of the governing IRB prior to implementation.

13. ETHICS REVIEW AND SUBJECT WELFARE

13.1 INSTITUTIONAL REVIEW BOARD (IRB)

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV.

The investigator is responsible for notifying the IRB of reportable adverse events as well as any other circumstance in which additional procedures outside the protocol were conducted to eliminate apparent hazards to subjects.

13.2 INFORMED CONSENT

The current version of the IRB-approved study informed consent must be signed by each study subject prior to any study-specific examinations being performed. The IRB-approved informed consent is to be signed and dated by the subject as well as by the person who conducted the informed consent discussion. The signed informed consent will be maintained by the investigator as a permanent part of the subject's medical records. A copy of the signed and dated form is to be provided to the subject. The investigator will provide JJSV written acknowledgement on the case report form that a signed agreement of informed consent has been obtained and is in the investigator's possession for each subject. As required by 21CFR812 Part G, the site shall document in the source documents that informed consent was obtained prior to participation in the study for each subject enrolled.

NOTE: The informed consent process also includes obtaining the subject's signature on an Authorization for Use/Disclosure of Health Information for Research Form or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical measurement in the governing countries.

NOTE: The sponsor will secure appropriate insurance for study subjects prior to study start.

14. DOCUMENTATION

14.1 SOURCE DOCUMENTS

Source documents must be kept for all study subjects. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as results of any diagnostic tests or procedures such as topographies or laboratory tests with photographs or instrument printouts.

Each site is expected to adhere to the clinic's own standard documentation requirements for medical charts/clinic notes. However, for the purposes of this clinical study, the medical charts/clinic notes must also include, at a minimum, the following data that will be considered source data and will be reviewed by JJSV:

- Subject's name and study identification number
- Subject's contact information
- Study protocol number and the Sponsor name (JJSV)
- A statement that informed consent was obtained prior to participation in the study (including the date)
- Dates of all subject visits throughout the duration of the study
- Study measurements
- Description of any adverse events and/or product complaints/device deficiencies and documentation of appropriate reporting
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for early exit.

14.2 SUBJECT CONFIDENTIALITY

Subjects will be assigned a site/subject number to maintain subject confidentiality. Subject names may possibly be disclosed to the JJSV or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to maintain confidentiality of personal information to the extent permitted by applicable laws and regulations.

14.3 CASE REPORT FORM COMPLETION

This study will use the IBM Merge EDC system. The investigator is responsible for ensuring that data are properly recorded on each subject's case report form and related documents. Prior to database lock, the investigator will verify completeness and accuracy of data submitted to JJSV.

14.4 STUDY SUMMARY

A final investigator's summary will be provided to JJSV and the reviewing IRB within 3 months after termination or the completion of the study or the investigator's part of the investigation.

15. MONITORING

JJSV will perform three types of monitoring to ensure compliance with regulations: data monitoring, administrative monitoring, and safety monitoring.

15.1 DATA MONITORING

In order to ensure a well-controlled clinical trial, JJSV will follow specific data monitoring procedures, routinely generate reports and periodically review safety and effectiveness data. To avoid bias, any analyses generated prior to site closures will not be disseminated to any of the investigative sites.

To minimize data omissions and inconsistencies on clinical reports and to ensure that data are accurately transcribed to computer data files, JJSV will follow internal data processing procedures that include automated and manual quality control checks to identify any data discrepancies. Any such items will be resolved and documented as needed on the case report forms at the investigative site and in the data management system at JJSV.

Prevention of Missing Data

Methods used to safeguard against missing data that can have deleterious effects on the study integrity and reliability of its outcomes will include training study staff with centralized and on-site programs. In addition, subjects will be encouraged at the time of informed consent to avoid missing study visits, as missing data may affect the study reliability and diminish the scientific value of their contribution to the study.

15.2 ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that study devices, subjects, and forms can be traced and will allow monitoring of investigator progress and compliance. Accountability and traceability of study devices will be monitored, as needed for compliance with study requirements.

Device Accountability

Complete Activator accountability will be maintained at the investigative site by maintaining records of investigational product received from and returned to JJSV. A site log will be used to track investigational equipment for date of receipt, use and disposition/return to JJSV. This site log and any other investigational product information will be maintained in the study binder and monitored by JJSV personnel.

During periodic investigative site monitoring visits, JJSV personnel will review investigative product inventory records and logs to ensure Activator accountability compliance and complete investigational traceability.

Site Monitoring Plan

Prior to performing site initiation, the requirements of the study and reporting mechanisms will be explained to each investigator. When necessary, a pre-study site qualification visit may be performed to assess the adequacy of the site to perform the study for sites that have not previously worked with JJSV or have undergone significant changes or have not been visited in the past year. A study initiation visit may be conducted prior to the first treatment.

Throughout the duration of the study, the compliance to this protocol will be monitored remotely or at each investigative site. During interim site monitoring visits, JJSV will review informed consent documents and subject eligibility, and the data on study case report forms will be verified against subject charts and other source documents to ensure complete and accurate reporting. The subject files will also be reviewed to assure that all adverse events and any issues encountered with JJSV products have been reported in a timely fashion.

JJSV will also review source documents to verify that all required items have been documented in the subject medical charts. Refer to Section 14.1, Source Documents, for a list of items that are required for source documentation.

Training on study-specific procedures may also be conducted during monitoring visits.

Upon study completion, a final close-out site visit to each site will be made to monitor the last of the subject data records and finalize any outstanding study issues.

A separate Study Monitoring Plan will be established prior to study start that will define the type and frequency of monitoring visits and frequency of record monitoring.

15.3 Safety Monitoring

The medical monitor will review results throughout the clinical trial as necessary to ensure the continued safety of the device and to ensure that no subjects are exposed to unreasonable risk. The medical monitor will be available to answer all questions from investigators. The medical monitor will review and assess any reports of serious and/or device-related adverse events as well as device deficiencies that could have led to a serious adverse event and discuss these with the reporting investigator(s) as necessary. The medical monitor, as well as any other qualified personnel designated by JJSV, shall also review any interim progress reports, as applicable.

16.0 PUBLICATIONS

Refer to the Clinical Trial Agreement for information regarding JJSV publication policies.

17.0 RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

RISKS ASSOCIATED WITH USE OF LIPIFLOW

The use of the LipiFlow System in this study is non-significant risk. No device-related serious adverse events are anticipated with the use of the LipiFlow system. Transient, non-serious adverse events which may result from the use of the LipiFlow system include, but are not limited to, the onset or increase in the following ocular signs or symptoms that are either 1) clinically significant as determined by the Investigator, or 2) require medical treatment for resolution:

- Eyelid/eye pain requiring discontinuation of the treatment procedure;
- Eyelid irritation or inflammation (e.g., edema, bruising, blood blister, dermatitis, hordeolum or chalazion);
- Ocular surface irritation or inflammation (e.g., corneal abrasion, conjunctival edema or conjunctival injection/hyperemia); and
- Ocular symptoms (e.g., burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light).

RISK MANAGEMENT

Subjects will be closely monitored throughout the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to JJSV according to Section 11.0, Adverse Events and Product Complaints. Additionally, JJSV will monitor incoming data following the procedures outlined in Section 15.0, Monitoring. The Medical Monitor will ensure subjects are not exposed to additional risks by monitoring serious adverse events, device-related adverse events, and device-deficiencies that could have led to serious adverse events (Section 15.3, Safety Monitoring).

POTENTIAL BENEFITS

There may not be any direct benefit for the subjects participating in the clinical study. The study will provide data to confirm the clinical use of the LipiFlow system with Activator LFD-2100 to successfully complete a LipiFlow treatment procedure in human subjects.

CONCLUSION

The hazards/risks associated with the LipiFlow system are acceptable. The hazards/risks associated with the Activator Model LFD-2100 were mitigated to as low as possible, and residual risks were addressed via risk-benefits analysis. The conclusion of the risk-benefits analysis was that the benefit gained from testing the Activator LFD-2100 in the study outweighs the relatively low risk of harm after all mitigations are implemented when the devices are used as intended.

18.0 RECORDS RETENTION

All study-related correspondence, subject records, consent forms, Authorization for Use/Disclosure of Health Information Forms or similar medical treatment privacy law documentation, records of use of all study products, and original case report forms should be maintained by the investigator.

The investigator must maintain and have access to the following essential documents until notified by the Sponsor. Note: This may be for a minimum of 15 years after completion of the study unless country-specific requirements are longer. JJSV requires notification if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

- All case report forms
- All adverse event information (detailed adverse event forms, follow-up letters, etc.)
- Investigational supply records/inventory
- IRB approval documentation
- Study correspondence
- Study agreements
- Site visit documentation
- Protocol(s) and the reason for any deviations from the protocol
- Subject log(s)
- Clinical Investigator's Brochure
- Completed subject informed consent forms and medical privacy forms (e.g., Authorization for Use/Disclosure of Health information or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries)
- Subject medical chart/clinic notes (Not applicable for transfer of ownership to JJSV)

19.0 TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event of high levels of complications and/or adverse events that are unexpected in nature and/or severity and evaluated as to causality relative to the study device. The clinical investigation may be suspended if the Medical Monitor or IRB, upon review and evaluation of the clinical data, finds unacceptable clinical performance or the level of single or total complications and/or adverse events unacceptable for continuation of the investigation.

If causality is shown not to be related to the study device, the study may be resumed in accordance with the IRB and regulations of the FDA. The study will be terminated if causality is shown to be related to the study device.

Additionally, the investigator, or JJSV, may stop a subject's participation at any time. JJSV may also stop the study at any time for reasons it determines appropriate. However, no suspension of the study would be made to disadvantage the study subjects. Following suspension of the study for any reason, all study subjects who have already received treatment would continue to be followed through completion of the study visit schedule.

20.0 STATISTICAL METHODS

20.1 ANALYSIS POPULATION

All treated subjects will be included in the analysis population. All the questionnaire responses and the treatment reports generated by LipiFlow system after completion of treatment will be collected and analyzed to confirm successful completion of the procedure. Questionnaire responses for each item and data from the treatment reports will be summarized for Activator LFD-2100. No imputations for missing values will be used.

20.2 STUDY ENDPOINTS

Primary Endpoint:

- Successful completion of LipiFlow treatment with Activator LFD-2100 in 95% or more cases.

  The treatment reports automatically generated by LipiFlow Console after completion of each treatment will show if the treatment completion is successful. The frequency and proportion of successful completion of treatment will be reported. The expected proportion of successful completion of LipiFlow treatment question will be greater than or equal to 95%.

Other Endpoints:

- Questionnaire rating of each step in the LipiFlow treatment procedure with Activator LFD-2100.

  For questions with a 'Yes' or 'No' response, the frequency and proportion of each question with response 'Yes' will be reported. For questions with five levels of

rating score responses, the frequency and proportion of each level of rating score responses will be tabulated. The mean and median of rating score of each question will also be reported.

- Rate of adverse events and complications.

  The type and rates of adverse events will be summarized.

20.3 SAMPLE SIZE CALCULATIONS

The confidence interval approach is used to estimate precision around the true proportion of successful completion of LipiFlow treatment with Activator LFD-2100. Assuming the proportion of successful completion of LipiFlow treatment is 95%, with n= 50 eyes, a two-sided 95% confidence interval will be (89%, 100%), i.e., a precision of 6.0%.

APPENDIX A. QUESTIONNAIRE - LIPIFLOW TREATMENT WITH ACTIVATOR LFD-2100

The following questions should be completed by the investigators or designees after completion of each of the study cases.

If you rate a score of 1 or 2 on a question, please provide feedback on the corresponding comment space.

Subject Study ID:_____ **Date of LipiFlow Performed on the Subject:_____**

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
1. Inspect and Place Activators LFD-2100 in Subject's Eyes		
1.1 Disinfect cables	Did you disinfect the Cables before connecting to the Activators LFD-2100? If no, please explain	Yes / No
	How would you rate the ease of disinfecting the Cable?	1 Very difficult; 2 Moderately difficult; 3 Neutral; 4 Moderately easy; 5 Very easy
1.2 Connect Activators to Cables	Were you able to connect the Cables to the Activators LFD-2100 while maintaining lidwarmer sterility?	Yes / No
	How would you rate the ease of getting a full connection between the Activators LFD-2100 and the Cables?	1 Very difficult; 2 Moderately difficult; 3 Neutral; 4 Moderately easy; 5 Very easy
	How would you rate the task of connecting the Cables to the Activators LFD-2100 while maintaining lid warmer sterility?	1 Very difficult; 2 Moderately difficult; 3 Neutral; 4 Moderately easy; 5 Very easy

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
1.3 Pass self-test	Did the Activators LFD-2100 automatically start the self-test? If no, please explain.	Yes / No
	Did the Activators LFD-2100 pass the self-test? If no, please explain.	Yes / No
	How would you rate the ease of conducting the Activators LFD-2100 self-test?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy
1.4 Inspect and Place in Subject's Eyes (both)	Were you able to inspect the Activator LFD-2100 and place them in the subject's eyes? If no, please explain.	Yes / No
	How would you rate the ease of handling the Activators LFD-2100 for inspection?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy
	How would you rate the ease of placing the Activators LFD-2100 in the subject's eyes?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy
	How would you rate the ease of determining the correct orientation?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
	How would you rate how well the Activators LFD-2100 bladder fits on the eyelids?	1 Poorly / 2 Somewhat poorly / 3 Neutral / 4 Somewhat well / 5 Very well
1.5 Stabilize the Activators	How well was the Activators LFD-2100 secured into the proper and stable position in the subject's eyes?	1 Poorly / 2 Somewhat poorly / 3 Neutral / 4 Somewhat well / 5 Very well
	How would you rate the task of securing the Activators LFD-2100 with tape?	1 Poorly / 2 Somewhat poorly / 3 Neutral / 4 Somewhat well / 5 Very well
	Please provide comments, if any, on Inspect and Place Activators LFD-2100 in Subject's Eyes step.	
2. Run LipiFlow Treatments with Activators LFD-2100		
	Were the Activators LFD-2100 able to complete a successful treatment? If no, please explain.	Yes / No
	How would you rate the ease of completing a treatment with the Activators LFD-2100?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
	How would you rate how the Activators LFD-2100 remained in position under the eyelids during treatment?	1 Poorly / 2 Somewhat poorly / 3 Neutral / 4 Somewhat well / 5 Very well
	Please provide any comments on running a LipiFlow treatment with Activators LFD-2100.	
3. Remove Activators LFD-2100		
3.1 Disconnect Activators LFD-2100 from subject's eyes	Were you able to remove the Activators LFD-2100 from the subject's eyes? If no, please explain.	Yes / No
	How would you rate the task of removing the Activators LFD-2100 from the subject's eyes?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy
3.2 Disconnect Activators LFD-2100 from the Cables	Were you able to disconnect the Activators LFD-2100 from the Cable? If no, please explain.	Yes / No
	How would you rate the task of disconnecting the Activators LFD-2100 from the Cable?	1 Very difficult / 2 Moderately difficult / 3 Neutral / 4 Moderately easy / 5 Very easy

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
	Please provide comments, if any, on Remove Activators LFD-2100 step.	
4. Feedback on the Activators LFD-2100		
	4.1 Due to the translucent components of the Activator LFD-2100, do you agree it is easy to confirm the Activator is in the right position in the patient's eye?	1 Strongly disagree; 2 Disagree; 3 Neutral; 4 Agree; 5 Strongly Agree Comments: _____
	4.2 Due to the translucent components of the Activator LFD-2100, do you agree you can efficiently position the Activator in the patient's eye?	1 Strongly disagree; 2 Disagree; 3 Neutral; 4 Agree; 5 Strongly Agree Comments: _____

Tests Procedures	*Questions*	*Investigator or Designee Responses (Circle one response per question)*
	4.3 Due to the translucent components of the Activator LFD-2100, do you agree you have confidence in the position of the Activator in the patient's eye during the treatment?	1 Strongly disagree | 2 Disagree | 3 Neutral | 4 Agree | 5 Strongly Agree Comments: _____
	4.4 Due to the translucent components of the Activator LFD-2100, do you agree you can easily assess the position of the Activator in the patient's eye during the treatment?	1 Strongly disagree | 2 Disagree | 3 Neutral | 4 Agree | 5 Strongly Agree Comments: _____
Investigator or Designee Signature:		**Date:**

APPENDIX B EQUIPMENT LIST

The following equipment will be supplied to an investigative site for the duration of the study provided that the site does not already have such equipment available for use. This equipment loan will be documented in the Equipment Use Agreement or Clinical Trial Agreement, which indicates that the equipment is to be returned to JJSV at the completion of the study.

- LipiFlow Activator LFD-2100 (investigational device)
- LipiFlow Instructions for Use (IFU) including the Quick Start Guide (if needed)
- LipiFlow Consoles (if needed)
- Semi-permanent Cable (if needed)
- Meibomian Gland Evaluator (MGE) (if needed)
- Lid Stabilizer Tape (if needed)
- Commercially-available standard fluorescein strips (if needed)
- Commercially-available standard lissamine green dye (if needed)
- Color printer (if needed)

APPENDIX C SUMMARY OF PROCEDRUES REQUIRED AT EACH VISIT

Examination	*Pre-treatment Visit*	*Treatment Visit (may happen on the same day of Pre-treatment visit)*
Informed consent	X	
Screening and Enrollment: including but not limited to reviewing medical and ocular history, discussing study eligibility etc.	X	
Biomicroscopic slit-lamp exam	X[a]	X[a, b]
Meibomian gland assessment (optional, upon investigator's discretion)	X[c]	
Ocular surface staining	X[a]	X[b]
Non-dilated fundus exam	X	
LipiFlow Treatment with Activators LFD-2100		X
Investigator Questionnaire for LipiFlow treatment with Activator LFD-2100		X

[a] Pre-treatment exams. (If the Treatment Visit doesn't happen on the same day of the Pre-reatment Visit, a biomicroscopic slit-lamp exam must be performed before LipiFlow treatment performed at the Treatment visit to assess the findings for the presence of any medical findings.)

[b] Post-treatment exams.

[c] **Note**: MGD diagnosis can be based on prior medical records, investigator opinion. or based on assessment of meibomian glands of the lower eyelid. The need for meibomian gland assessment is at the investigator's discretion.

APPENDIX D SLIT-LAMP EVALUATION

The Investigators or designees shall evaluate the eyelids, palpebral and bulbar conjunctiva, cornea, anterior chamber, iris and lens using a slit lamp biomicroscope. The Investigator or designee everts the upper eyelid to evaluate the upper palpebral conjunctiva. Corneal or conjunctival staining may be conducted as necessary at the discretion of the investigator. The Investigator or designee assesses the findings for the presence of any medical findings.

A) Ratings of Conjunctival Injection

Assess the ocular vascular response via external examination. Specifically, classify the appearance of injected (dilated) blood vessels within the limbus as well as within the bulbar conjunctiva. Observe limbal region and bulbar conjunctiva with the slit lamp at 5X - 12X.

Amount	Grade	Description
None	**0**	No injection present.
Trace	**1**	Slight limbal (mild segmented), bulbar (mild regional), and/or palpebral injection.
Mild	**2**	Mild limbal (mild circumcorneal), bulbar (mild diffuse), and/or palpebral injection.
Moderate	**3**	Significant limbal (marked segmented), bulbar (marked regional or diffuse), or palpebral injection.
Severe	**4**	Severe limbal (marked circumcorneal), bulbar (diffuse episcleral or scleral), or palpebral injection.

B) Ratings of Corneal Edema

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

Amount	Grade	Description
None	**0**	Normal transparency: a. No epithelial or sub-epithelial haziness b. No microcysts c. No stromal cloudiness
Trace	**1**	a. Barely discernable localized epithelial or sub-epithelial haziness, and/or b. 1 to 20 microcysts, and/or c. Barely discernable localized stromal cloudiness
Mild	**2**	a. Faint but definite localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness, and/or b. 21-50 microcysts

Amount	Grade	Description
Moderate	**3**	a. Significant localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness and/or b. 51-100 microcysts
Severe	**4**	a. Definite widespread epithelial or stromal cloudiness, giving dull glass appearance to cornea or numerous coalescent bullae (please note the number and location of bullae), and/or b. >100 microcysts or bullae, and/or c. Numerous striae (please note the number and location of striae or folds)

C) Medical Findings of Other Ocular Surface and Eyelid Irritation or Inflammation

Carry out a full biomicroscopic examination. Corneal or conjunctival staining may be conducted as necessary at the discretion of the investigator. Record and grade by severity the slit lamp findings that cannot be classified as conjunctival injection and corneal edema. Examples include but are not limited to: corneal abrasion, conjunctival edema, eyelid edema, bruising, blood blister, dermatitis, hordeolum or chalazion.

Amount	Grade	Description
None	**0**	No other significant biomicroscopic findings.
Trace	**1**	Minimal findings such as tear film abnormality (debris or low tear break up time), ocular tearing.
Mild	**2**	Mild findings, such as few corneal faint infiltrates, eyelid edema, sensitivity to light.
Moderate	**3**	Significant findings, such as: eyelid inflammation (e.g. blepharochalasis, blepharitis), eyelid dermatitis, chalazion, meibomitis, corneal infiltrates (multiple or dense), conjunctivitis, conjunctival abrasion, epidemic keratoconjunctivitis.
Severe	**4**	Severe findings, such as: iritis with marked cells and/or flare, corneal or conjunctival infection, corneal ulcer, recurrent erosion.

APPENDIX E INSTRUCTIONS FOR MEIBOMIAN GLAND ASSESSSMENT

MGD diagnosis can be based on prior medical records, investigator opinion, or in conjunction with an assessment of meibomian glands of the lower eyelid. The need for the meibomian gland assessment is at the investigator's discretion.

Meibomian gland dysfunction or obstruction may compromise the adequacy of the tear film lipid layer. Meibomian gland obstruction, due to multiple processes including epithelial overgrowth of the orifices and keratotic plugs of the ducts, results in deficient or inadequate meibomian gland secretion. Meibomian gland obstruction frequently occurs without the obvious inflammatory and other characteristic external signs occurring with the frank forms of meibomitis and marginal and seborrheic blepharitis.

To evaluate the function of the meibomian glands, the Investigator or designee assesses the color and consistency of the secretion characteristics from the gland orifices along the lower eyelid. The Investigator or designee evaluates the glands using a slit-lamp biomicroscope and a handheld instrument, Meibomian Gland Evaluator (MGE) (Figure 1), to apply gentle pressure along the eyelid margin, which simulates a forceful blink in yielding secretions from the glands. This instrument provides a standardized method to apply the same amount of pressure at each visit and for each subject to ensure measurement consistency. The pressure applied to the eyelid when using the device is between 0.8 g/mm2 and 1.2 g/mm2. This Class I, 510(k) exempt device is commercially available, and is being used in this study in accordance with the indications in the commercial product labeling. Meibomian Gland Evaluator does not pose a significant risk to patients or users.

Figure 1: Meibomian Gland Evaluator (MGE)

There are approximately 20 to 30 meibomian glands along the lower eyelid. The Investigator or designee assesses 15 glands located temporally, centrally and nasally, as shown in Figure 2. The central region of the Meibomian Gland Evaluator should be carefully placed in the temporal, central and nasal regions as described in this procedure to avoid overlap in the gland assessment.

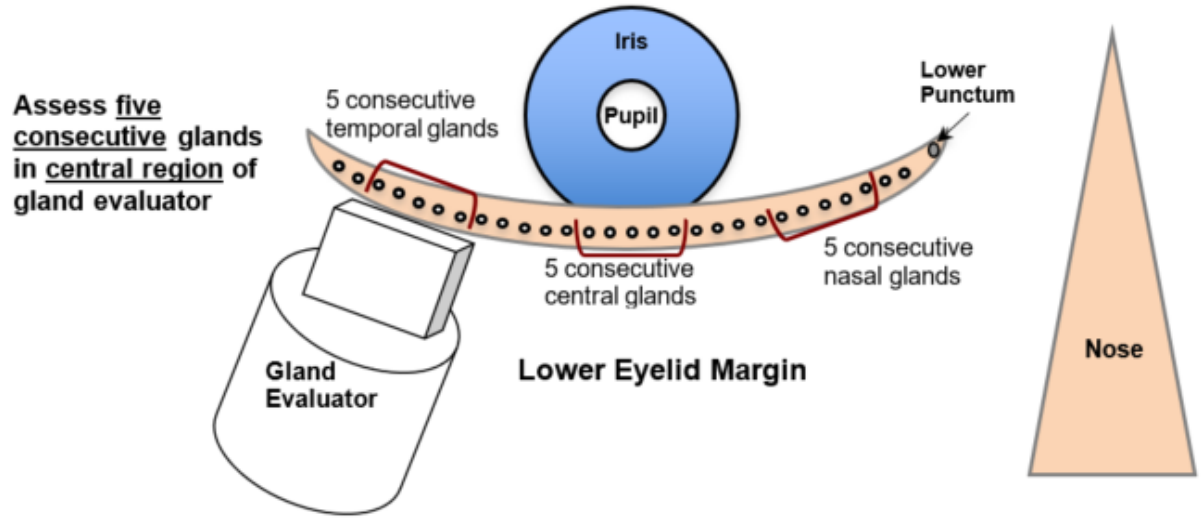
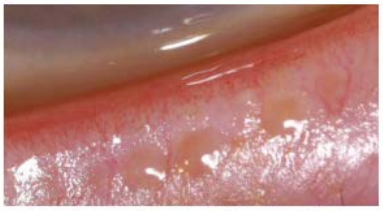


Figure 2: Location of Lower Eyelid Meibomian Glands for Assessment

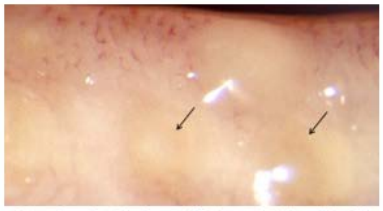
The following procedure is used for examination and grading of meibomian gland function.

1. Under the slit-lamp biomicroscope 10x to 16x magnification, locate the temporal region of the lower eyelid and observe 5 consecutive glands orifices in this region.
2. Holding the Meibomian Gland Evaluator between the forefinger and the thumb, place the instrument contact surface onto the skin immediately below the lash line of the lower eyelid so that the long dimension is parallel to the eyelid margin, and the five glands are in the central region of the Meibomian Gland Evaluator.
3. Once full contact is achieved between the Meibomian Gland Evaluator contact surface and the outer skin of the lower eyelid, rotate the shaft of the Meibomian Gland Evaluator downward approximately 15 to 45 degrees so that it is tangential to the eyeball.
4. Depress the Meibomian Gland Evaluator to exert a constant force over the meibomian glands. Adjust the position of the Meibomian Gland Evaluator to cause the flat surface of the lower eyelid margin to roll slightly outward, facilitating a clear view of the meibomian gland orifices.
5. To facilitate observation of the gland secretions, gently wipe the gland orifices along the eyelid margin clean with a dry cotton swab immediately after applying pressure while maintaining the Meibomian Gland Evaluator in position and maintaining pressure.

6. Hold the Meibomian Gland Evaluator in place over the meibomian glands for a minimum of 10 and a maximum of 15 seconds while evaluating the secretion characteristics from each meibomian gland. The expressed secretion from each gland is graded according to the characteristics displayed in Table 1.

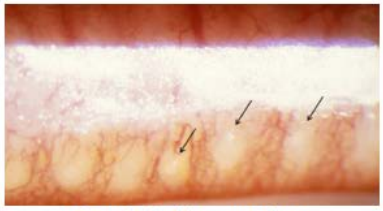


Grade 3: Clear Liquid Oil

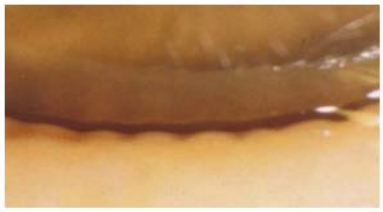


Grade 2: Colored/Cloudy Liquid Oil

Grade 1: Inspissated



Grade 0: No secretion



Grade 0: No secretion

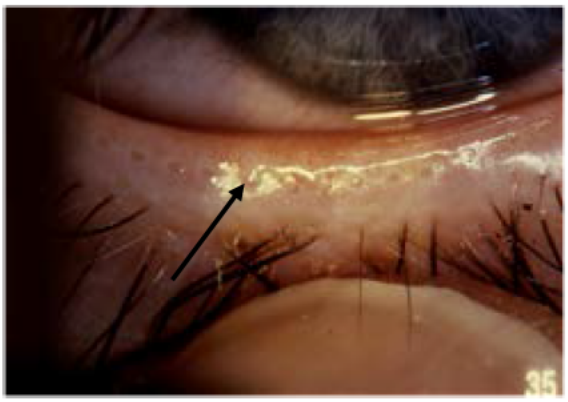
Table 1: Meibomian Gland Assessment Secretion Grading Scale

Grade	Secretion Characteristics
3	Clear liquid oil secretion
2	Colored/cloudy liquid secretion
1	Inspissated (toothpaste-consistency) secretion
0	No secretion (includes capped orifices)

NOTE: *The following conditions are essential to accurately evaluate the meibomian glands:*

1) *The Meibomian Gland Evaluator must be used to standardize the force.* ***Do not apply any additional force after the shaft has been depressed approximately 3 mm.*** *Applying additional force negates the benefit of using an instrument that applies a standard force.*
2) *The Meibomian Gland Evaluator must be held in place for a* ***minimum of 10 and a maximum of 15 seconds.***

7. Move the Meibomian Gland Evaluator over to the nasal region of the lower eyelid and observe 5 consecutive glands orifices in region. Repeat the evaluation of the secretion characteristics in steps 3-6 for each of the 5 nasal meibomian glands.
8. Move the Meibomian Gland Evaluator over to the central region of the lower eyelid (directly below the pupil) and observe 5 consecutive glands orifices in this region. Repeat the evaluation of the secretion characteristics in steps 3-6 for each of the 5 central meibomian glands.
9. Repeat steps 1 to 8 to evaluate the secretion characteristics for the fellow eye. Document the meibomian gland assessment findings.
10. Sum the scores for all 15 glands in the lower eyelid to calculate the total meibomian gland secretion score. Typically, the total meibomian gland secretion score of 18 or less (on a scale of 0 to 45) is indicative of MGD.
11. Disinfect the instrument with alcohol after each use.



Clear liquid secretion at gland orifice

Figure 3: Example of Meibomian Gland Yielding Clear Liquid

APPENDIX F INSTRUCTIONS FOR OCULAR SURFACE STAINING

CORNEAL STAINING

The Investigator or designee assesses the corneal staining after instillation of fluorescein dye in the eye using the following method.

1. Place one drop of commercially available saline on a standard fluorescein strip. Take care to avoid applying the saline to the fluorescein strip holder. Do not shake the strip. Wait ten seconds after application of the saline before proceeding.
2. Instruct the patient to look down and towards the opposite hand from the eye receiving the stain. It may be helpful to ask the subject to fixate on his/her own thumb. Place the subject's thumb to rest on the opposite leg to achieve inferior fixation of approximately 45 degrees down and 20 degrees nasal.
3. Retract the upper eyelid. Introduce the fluorescein strip at an approximate 30-degree angle and touch the superior temporal bulbar conjunctiva, preferably 4 mm or more from the limbus, for 2 seconds, so that 1-2 mm of the flat side makes contact with the ocular surface. Withdraw the strip and release the upper lid.

   NOTE: *If the size of the strip prevents application to the desired position on the superior temporal bulbar conjunctiva, apply the strip to a location on the bulbar conjunctiva as close as possible to the preferred position.*

4. Instruct the subject to close the eyelids completely three times. Wait 1.5 minutes (90 seconds) before evaluating the ocular surface for staining.
5. To observe the fluorescein staining, evaluate the subject's eye under the slit-lamp biomicroscope using a cobalt blue filter transmitting 330 to 400 nm and a beam approximately 4 mm wide and l0 mm high.
6. Examine the entire cornea. Grade the corneal staining observed in the central, inferior, nasal, temporal and superior regions as shown in Figure 4 on a scale of 0 to 3 based on the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye. Document the staining grade.

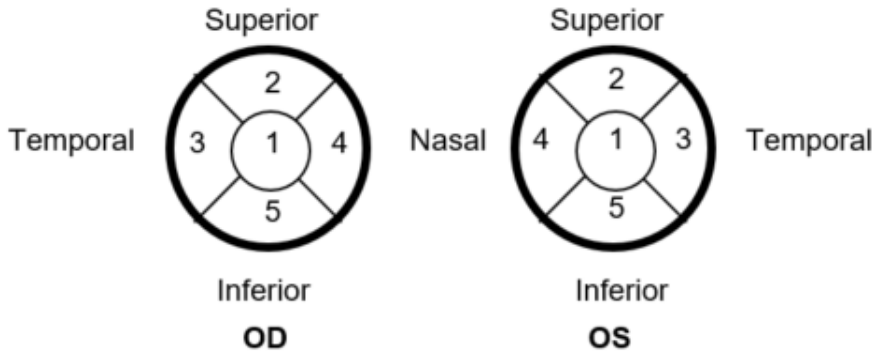


Figure 4: Diagram of Corneal Regions for Fluorescein Staining Grading

CONJUNCTIVAL STAINING

The Investigator or designee assesses the conjunctival staining after instillation of lissamine green dye in the eye using the following method.

1. Place one drop of commercially available saline on a standard lissamine green strip. Take care to avoid applying the saline to the strip holder. Do not shake the strip. Wait ten seconds after application of the saline before proceeding.
2. Instruct the patient to look down and towards the opposite hand from the eye receiving the stain. It may be helpful to ask the subject to fixate on his/her own thumb. Place the subject's thumb to rest on the opposite leg to achieve inferior fixation of approximately 45 degrees down and 20 degrees nasal.
3. Retract the upper eyelid. Introduce the strip at an approximate 30-degree angle and touch the superior temporal bulbar conjunctiva, preferably 4 mm or more from the limbus, for 2 seconds, so that 1-2 mm of the flat side makes contact with the ocular surface. Withdraw the strip and release the upper lid.

   ***NOTE**: If the size of the strip prevents application to the desired position on the superior temporal bulbar conjunctiva, apply the strip to a location on the bulbar conjunctiva as close as possible to the preferred position.*

4. Instruct the subject to close the eyelids completely three times. Wait 1.5 minutes (90 seconds) before evaluating the ocular surface for staining.
5. To observe the lissamine green staining, evaluate the subject's eye under the slit-lamp biomicroscope with a beam approximately 4 mm wide and l0 mm high.
6. Examine the entire bulbar conjunctiva. Grade the conjunctival staining observed in the six regions as shown in Figure 5 on a scale of 0 to 3 based on the Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye. Document the staining grade.

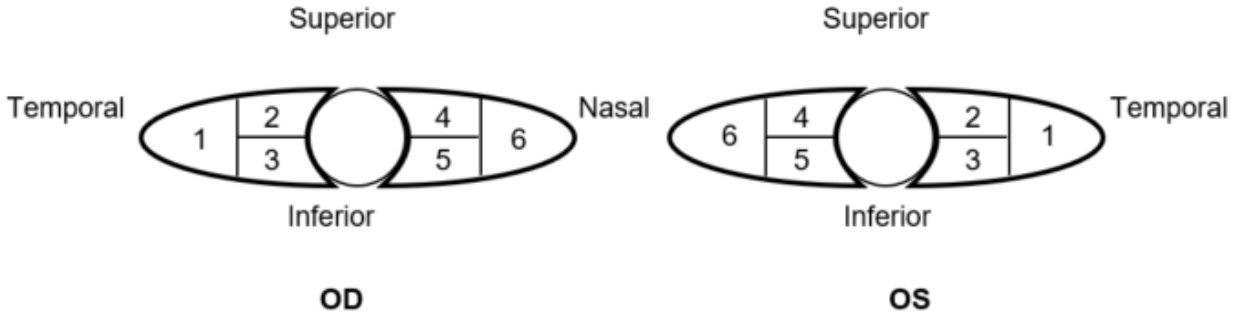


Figure 5: Diagram of Conjunctival Regions for Lissamine Green Staining Grading

APPENDIX G. ADVERSE EVENT AND COMPLAINT REPORTING INSTRUCTIONS

All adverse events and complaints related to using JJSV products must be reported to JJSV.

All adverse events and complaints:

For events that are not considered serious or related to the study device:

1. Record the event and/or complaint on the case report form that corresponds to the visit during which awareness of the event occurred. Additionally, a complaint may be reported via a telephone call to JJSV.
2. Complete the case report form (CRF) in a timely manner.

Serious Adverse Events or device deficiencies that may have led to a serious event

In the event of a serious event (i.e., life- or sight-threatening incident) whether or not related to the device, or a device deficiency that may have led to a serious event, the investigator shall:

1. Notify JJSV immediately (no more than 24 hours after learning of the event) as follows:
   a. Contact the following JJSV personnel by phone and/or email:

   b. Complete an Adverse Event Form and submit to JJSV

Non-serious, device-related Events:

For events that are not considered serious but are believed related to the study device (ADEs):

1. Complete an Adverse Event Form
2. Ensure the data are submitted to JJSV within a timely manner.