Study Protocol

A Post-Market Evaluation of LipiFlow Treatment in Cataract Surgery Practice

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A Post-Market Evaluation of LipiFlow Treatment in Cataract Surgery Practice

PROTOCOL NUMBER: DRYE-102-SELF

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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; ISO 14155 and all other applicable regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB) 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 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
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TABLE OF CONTENTS

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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	Personnel and Facilities	v	Study personnel update	Change in study manager
	1.0 Synopsis, 8.1 Inclusion Criteria and 8.2 Exclusion Criteria	3-4 and 16-18	Updated exclusion criteria	Clarify dry eye treatment information (medication and home remedies), definition of keratitis, and contact lens restrictions.
	10.3 Preoperative Visit # 1 Procedures: Screening and baseline; Appendix B	26 53	Clarified the number of measurements required for keratometry and biometry	Some keratometers only measure 3 sets of measurement per test, instead of the 5 sets per test. This change allows either, as long as 3 tests are done.
	10.3 Randomization and Enrollment	27	Wording has been updated to reflect the electronic randomization method used for the study	Randomization will be done electrically rather than manually.
	10.4 Preoperative Visit # 2 Procedures	29	Clarified the number of measurements required for keratometry and biometry	Some keratometers only measure 3 sets of measurement per test, instead of the 5 sets per test. This change allows either, as long as 3 tests are done.
	10.6 Postoperative procedures	30	Note 2 was clarified for contact lens wearers and a note was added to address subject follow-up should only one eye be implanted with a TECNIS Symfony IOL	To clarify contact lens wear restrictions and subject follow-up if both eyes are not implanted with a study lens.
	10.6 Postoperative procedures	31-32	Wording for near visual acuity testing was changed to be specific for the M&S system	The M&S System was validated for near visual acuity testing, so this System will be used for continuity across all test distances, rather than using a light box for near only.
	Appendix C	54	Removed equipment that is not being used in this study and expanded the ancillary supplies to allow the clinical sites to use any commercially-available standard fluorescein strip to replace the Amcon DET fluorescein strips	To clarify equipment being used in the study and to address shortages in the world-wide supply of Amcon DET fluorescein strips
	Appendix F	63-64	Clarified the number of times the blinking exercises had to be performed	The instructions are not standardized and the medical monitor felt we needed to reduce the number of times per day
	Appendix R	82	Near visual acuity changed to be specific to M&S System	The M&S System was validated for near visual acuity testing, so this System will be used for continuity across all test distances, rather than using a light box for near only.

1. SYNOPSIS

PROTOCOL TITLE: A Post-Market Evaluation of LipiFlow Treatment in Cataract Surgery Practice

PROTOCOL NUMBER: DRYE-102-SELF

STUDY TREATMENTS: LipiFlow® Thermal Pulsation System ("LipiFlow")

TECNIS Symfony® Extended Range of Vision IOLs, Model ZXR00, and TECNIS Symfony® Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300 and ZXT375 ("Symfony"), (Johnson & Johnson Surgical Vision, Santa Ana, CA)

STUDY OBJECTIVE: The study objective is to evaluate the LipiFlow treatment in adult patients with mild to moderate meibomian gland dysfunction (MGD) undergoing bilateral cataract surgery in terms of preoperative surgical planning and postoperative outcomes including refractive outcomes, visual outcomes and ocular comfort.

CLINICAL HYPOTHESIS: LipiFlow treatment will improve the precision of preoperative biometric measurements, improve postoperative refractive predictability, improve postoperative visual outcomes and improve postoperative ocular comfort, due to improved Meibomian gland function.

OVERALL STUDY DESIGN:

Structure: This is a post-market, prospective, randomized, multi-center, bilateral, open-label, cross-over, comparative clinical study.

Study group will undergo preoperative LipiFlow treatment and Control group will not receive preoperative LipiFlow treatment. Three (3) months postoperatively, both groups will be evaluated for clinical outcomes and the Control group will receive LipiFlow treatment as the cross-over group. The Control group will be evaluated at 4 months postoperative for clinical outcomes.

Number of sites: Up to 7 sites in the USA

Duration: 6 months (1 month preoperative to approximately 4 months postoperative)

Administration:

Preoperative: Biometry measurements will be performed in both study and control groups on two measurement visits 2 - 4 weeks apart. Only the study group will receive a LipiFlow treatment preoperatively.

Operative: Study and control groups will undergo bilateral cataract surgery with Symfony non-toric or Symfony toric IOL implantation.

Postoperative: Postoperative evaluations at 1-day and 1-week will be performed per investigators standard of care. Study specific visits include 1-month and 3-month postoperative evaluations in both study and control groups. The control group will receive a cross-over LipiFlow treatment at the end of the 3-month visit and return for 4-month postoperative evaluations.

Visit Schedule:

Study group (pre-operative LipiFlow treatment) subjects will undergo a minimum of 4 visits for both eyes: one baseline preoperative visit (per site standard of care), which includes the LipiFlow treatment (can occur on the same day after biometric measurement has been performed, or within 1 week of Visit #1), a second preoperative visit 2 – 4 weeks after the LipiFlow treatment visit, and two postoperative visits at 1 month and 3 months.

Control group (post-operative LipiFlow treatment) subjects will undergo a minimum of 5 visits for both eyes: one preoperative visit at baseline (per site standard of care), a second preoperative visit (2 - 4 weeks after first preoperative visit), and Postoperative Visits at 1 month, 3 months including crossover LipiFlow treatment, and 4 months.

See **Appendix A** for a diagram of the study visit flow.

STUDY POPULATION CHARACTERISTICS:

Condition:

Bilateral mild to moderate MGD with none to moderate dry eye symptoms, scheduled for bilateral cataract surgeries with Symfony IOL implantation.

Number of Subjects:

Approximately 140 subjects will be randomized and bilaterally implanted, to achieve approximately 110 evaluable subjects (55 in the study arm and 55 in the control arm).

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

- Minimum 22 years of age.
- Bilateral cataracts for which phacoemulsification extraction and implantation with Symfony IOLs have been planned.
- Evidence of MGD in both eyes based on assessment of meibomian glands of the lower eyelid with a total meibomian gland secretion score of ≤ 15 (on a scale of 0 to 45) for each eye.
- None to moderate dry eye symptoms with questionnaire total scores between 0 and 15 on the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire.

  Note: In each site, there should be no more than 30% enrolled subjects with none dry eye symptoms.
- Clear intraocular media other than cataract in each eye.
- Availability, willingness, ability and sufficient cognitive awareness to comply with the study protocol including: randomization; examination procedures; completion of planned bilateral cataract surgeries; compliance with no use of other MGD or dry eye treatments (except over-the-counter artificial tears, ocular lubricants, ointments, emollients or ω-3 dietary supplements) during the study; and attendance of all study visits.
- Ability to understand, read and write English to consent to study participation and complete study questionnaires.
- Willingness to sign informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing country.

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

- Any medical finding that would predictably result in a postoperative best corrected distance visual acuity worse than 20/30 in either eye.
- Use of systemic or ocular medications that, in the opinion of the investigator, may affect vision or impact pupil dilation or iris structure.
- Irregular corneal astigmatism.
- Any clinically-significant corneal pathology / abnormality other than regular corneal astigmatism.
- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils).

- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration, including pseudoexfoliation, trauma, or posterior capsule defects.
- Unwillingness or inability to stop wearing contact lens at least two weeks prior to the baseline visit.
- Known ocular disease or pathology that, in the opinion of the investigator, may affect visual acuity or require surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.).
- Systemic disease condition that causes dry eye (e.g., Stevens-Johnson syndrome, vitamin A deficiency, rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, leukemia, Riley-Day syndrome, systemic lupus erythematosus, Sjögren's syndrome).
- Unwillingness or inability to abstain from the use of systemic medications known to cause dryness (e.g., isotretinoin (Accutane®)) for the study duration. Subjects must have discontinued these medications for at least 1 month prior to the baseline Preoperative Visit #1 measurements.
- Unwillingness or inability to abstain from the use of systemic antihistamines:
    - at least two weeks prior to the baseline Preoperative Visit #1 measurements through Preoperative Visit #2, or per site standard of care for cataract surgery, whichever is longer; and
    - at least 2 weeks prior to the Month 3 measurements; and
    - at least 2 weeks prior to the Month 4 measurements (Control group only)
- Unwillingness or inability to abstain from use of prescription medications for treatment of MGD or dry eye. Subjects must have discontinued using prescription medications (e.g., lifitegrast (Xiidra) for MGD or dry eye at least 1 month prior to the baseline Preoperative Visit #1 measurements.
- Any of the following ocular (eye or eyelid) conditions in <u>either</u> eye within 3 months prior to the LipiFlow treatment visit:
    - Prior intraocular, oculoplastic, corneal or refractive surgery procedure (LASIK, LASEK, RK, PRK, etc.).
    - Ocular trauma.
    - Ocular Herpes simplex or Herpes zoster (eye or eyelid) infection.
    - History of recurrent ocular inflammation (e.g., retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis).
    - Punctal plug insertion or punctal occlusion.

- Any of the following active ocular (eye or eyelid) conditions in either eye at the baseline Preoperative Visit #1 measurements:
    - Active ocular infection (e.g., viral, bacterial, mycobacterial, protozoan or fungal infection of the cornea, conjunctiva, lacrimal gland, lacrimal sac or eyelids including hordeolum/stye).
    - Active ocular inflammation (e.g., retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis).
    - Moderate to severe (Grade 2-4) allergic, vernal or giant papillary conjunctivitis
    - Severe (Grade 3 or 4) inflammation of the eyelid (e.g., blepharochalasis, staphylococcal blepharitis or seborrheic blepharitis).
    - Eyelid abnormalities that affect lid function (e.g., entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis).
    - 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).
- Concurrent participation or participation within 30 days prior to study visit in any other clinical trial.
- Planned monovision correction.
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes.

STUDY ENDPOINTS:

Key Study Endpoints:

- Mean monocular UCDVA at 3 months postoperative in the Study and Control groups.
- Precision (standard deviation) of preoperative axial length (AL), anterior chamber depth (ACD), and keratometric measurements (K) for the study and the Control group.
- Rate of refractive predictability (i.e., within 0.50 D of target refraction, and within 1.00 D of target refraction) at 3 months postoperative for the Study and Control groups.
- Rate of bothersome ocular symptoms (halos, night glare, starbursts, and night vision difficulties) at 3 months postoperative for the Study and the Control groups.
- Mean change in total meibomian gland score in the Study group compared to the Control group from Baseline to the 1-month postoperative visit.

Other Endpoints:

- 1-Month Postoperative Visit:
    - Mean change in Number of Meibomian Glands Yielding Liquid Secretion (MGYLS) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in ocular surface stain grade from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in Tear Break-up Time (TBUT) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in Eyelid Margin Evaluation from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
- 3-Months Postoperative Visit:
    - Mean monocular BCDVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean binocular UCDVA and BCDVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean binocular UCIVA in the Study group at 3 months postoperative compared to the control.
    - Mean binocular UCNVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean manifest refraction spherical equivalent (MRSE) at 3 months postoperative compared to target MRSE in the Study group compared to the Control group.
    - Contrast acuity in the Study group at 3 months postoperative compared to the Control group.
    - Mean change in total Standard Patient Evaluation of Eye Dryness (SPEED) score from Baseline visit to 3 months postoperative in the Study group compared to the Control group.
    - Mean change in total meibomian gland score in the Study group compared to the Control group from Baseline to 3 months postoperative.
- Control Group 4-Months Postoperative Visit:
    - Mean change in monocular UCDVA and BCDVA from 3 months to 4 months postoperative.
    - Mean change in binocular UCDVA and BCDVA from 3 months to 4 months postoperative
    - Mean change in binocular UCIVA from 3 months to 4 months postoperative
    - Mean change in binocular UCNVA from 3 months to 4 months postoperative

  - Mean MRSE at 4 months postoperative compared to target MRSE
  - Percent of eyes with MRSE within 0.50 D and within 1.00 D of target MRSE at 4 months postoperative
  - Contrast acuity at 4 months postoperative compared to 3-month.
  - Mean change in total meibomian gland score from 3 months to 4 months postoperative.
  - Mean change in total SPEED score from 3 months to 4 months postoperative.
- Rates of adverse events in the Study and Control groups.
- Rates of medical and/or lens findings in the Study and Control groups.

STUDY VISITS AND PROCEDURES:

Inclusion and exclusion qualifications will be assessed at the start of Preoperative Visit #1 according to the protocol criteria. The Informed Consent Document and Authorization for Use/Disclosure of Health Information form (HIPAA authorization) 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 be randomized to either Study group or Control group in a 1:1 ratio.

Study visit schedule, procedures and key data collected at each visit are shown in **Appendix A, Appendix B, and Section 10.2, Visit Schedule, Table 1**.

DATA ANALYSIS:

Key study endpoints are the comparisons between study group and control group for precision of biometric measurements preoperatively, mean change in total Meibomian gland score at 1 month postoperatively, mean monocular UCDVA at 3 months postoperatively, rate of refractive predictability at 3 months postoperatively and rate of directed reported ocular symptoms at 3 months postoperatively. Additional endpoints will be evaluated at 1 and 3 months postoperatively for the both groups and 4 months postoperatively for crossover Control group.

Visual acuity data will be converted to LogMAR values prior to analysis. Comparisons between study group and control group for the mean monocular UCDVA at 3 months postoperatively will be performed using one-sided two-sample t-tests with alpha set at 0.05. Precision of preoperative biometric measurements is defined as the average of the three computed standard deviations from each preoperative visit. The Study group is expected to have better total Meibomian gland score at 1 month postoperatively compared to the Control group, and to have better

precision of preoperative biometric measurements, lower rate of refractive outliers, and lower rate of bothersome ocular symptoms at 3 months postoperatively compared to the Control group.

ANALYSIS POPULATION:

The primary study population will be all eyes that are randomized and implanted with study IOLs, except for the precision of biometric measurements, which will be evaluated at the preoperative visits. Mean change in total Meibomian gland score will be compared between the study group eyes and the control group eyes at 1 month postoperatively. All other key study endpoints will be evaluated at 3 months postoperatively. Additional endpoints will be evaluated at 1 month and 3 months postoperatively for the study group and the control group, and 4 months postoperatively for crossover control group only.

ADDITIONAL ANALYSES:

Descriptive statistics for all continuous data such as visual acuity, manifest refraction and meibomian gland score will include mean, standard deviation, minimum and maximum values. Mean LogMAR BCDVA, UCIVA, UCNVA and contrast acuity will be reported and compared between the Study group and Control groups at 3 months postoperatively. Mean MRSE at 3 months postoperatively will be reported and compared to target MRSE between the Study group and Control groups. The frequency and proportion of eyes with MRSE within 0.50 D and within 1.00 D of target MRSE will be reported. Mean change from preoperative visit to 1 month postoperatively in number of Meibomian Glands Yielding Liquid Secretion (MGYLS), assessment of eyelid margin evaluation, ocular surface stain grade and TBUT will be compared between the Study group and the Control group. Mean change from preoperative visit to 3 months postoperatively in total SPEED score will be compared between the Study group and the Control group. Mean change in monocular and binocular UCDVA and BCDCA, binocular UCIVA and UCNVA, contrast acuity, total Meibomian gland score, and total SPEED score from 3 months to 4 months postoperatively in the cross-over Control group will be reported. The frequency and proportion of eyes with optical/visual, medical and lens complications will also be reported over time. Rates of adverse events will be reported.

SAMPLE SIZE DETERMINATION:

The sample size determination is based on the primary endpoint of uncorrected distance visual acuity (UCDVA). There is 90% power to detect a 1-line or greater difference in mean UCDVA between the treatment and control groups with 55 subjects in each group. This assumes one-sided two-sample t-test with an alpha of 0.05 and standard deviation of 1.6 lines. Adding 20% screen failure/drop-out rate will require enrolling 69 subjects per group.

Interim database locks will be allowed; for example, one may be performed for after completion of the second preoperative visit.

2. BACKGROUND/INTRODUCTION

As defined by the Tear Film and Ocular Surface Society (TFOS) International Workshop on 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.”[i]

Clinical signs of MGD may include rounding, thickening and irregularity of the eyelid margin; changes in the lid vascularity and presence of telangiectasia; pouting, plugging and narrowing of the gland orifices; reduction in volume and number of glands secreting liquid; and changes in gland secretion quality, clarity and viscosity with greater pressure required to express secretions.[ii] The clinical cascade of obstructive MGD involves reduced lipid secretions, which leads to hyperosmolarity and instability of the tear film, increased opportunity for bacterial growth, evaporative dry eye and ocular surface inflammation and irritation.[i]

MGD is one of the most common ophthalmic conditions found in clinical practice.[ii] Yet MGD is often underdiagnosed because it requires diagnostic expression of the meibomian glands, particularly in patients without obvious signs of MGD.[iii] Population-based studies have reported a prevalence of MGD ranging from 3.5% to 69.3% with differences among studies by race/ethnicity and parameters used to define presence of MGD.[iv] According to the International Workshop on MGD Report published in 2011, “MGD may well be the leading cause of dry eye disease throughout the world”. [i]

Patients undergoing cataract surgery frequently have MGD because of the increased prevalence of the chronic disease with age.[v] Several studies have observed significant increases in the frequency of lid margin changes, meibomian gland abnormalities and lipid profile alterations with older age, particularly in patients older than 50 years.[vi,vii,viii] Not surprisingly, patients undergoing cataract surgery often present with MGD-related dry eye symptoms, which also increase in prevalence with older age.[ix]

The limited studies in the literature indicate that the treatment of patients with MGD prior to cataract surgery may be beneficial but further study is needed.[x] Since a healthy tear film is important in maintaining consistent visual quality and ocular

comfort after cataract surgery, treating MGD before surgery may help promote better post-surgical meibomian gland function, which is essential for tear film stability, visual quality and ocular comfort.

Building upon the concept of eyelid warming and massage/expression, the LipiFlow® Thermal Pulsation System is designed to remove the meibomian gland obstruction, thus alleviating a cause of the resultant evaporative dry eye. 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 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.[xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx,xxi] Prior clinical studies demonstrate safety, effectiveness and clinical utility of treatment with the LipiFlow in patients with MGD and dry eye symptoms.

In addition, JJSV designed the Symfony IOL series in response to a patient need for lenses that can provide good distance vision, improved intermediate and near vision compared to standard monofocal IOLs, and less dysphotopsia compared to a multifocal IOL. The Symfony IOL utilizes diffractive technology to elongate the range of focus while keeping halos to a minimum and also to reduce chromatic aberration to maintain contrast sensitivity. The purpose of the current study is to evaluate if the LipiFlow treatment prior to cataract surgery with Symfony IOL implantation improves IOL power planning and postoperative visual outcomes and ocular comfort.

3. CLINICAL HYPOTHESIS

This study will demonstrate that the LipiFlow treatment will improve the precision of preoperative biometric measurements, improve postoperative refractive predictability, improve postoperative visual outcomes and improve postoperative ocular comfort, due to improved Meibomian gland function.

4. STUDY DESIGN

This study is a 6-month, post-market, prospective, randomized, multicenter, bilateral, open-label, cross-over, comparative clinical investigation.

The study will be conducted at up to 7 sites in the U.S.A. Approximately 140 subjects will be randomized and bilaterally implanted, to achieve approximately 110 evaluable subjects (55 in the study arm and 55 in the control arm). Subjects are to be treated on both eyes by LipiFlow and to be implanted bilaterally with the Symfony IOLs.

JUSTIFICATION OF STUDY DESIGN

The study is to be conducted in USA as a post-market study. The study is designed to evaluate improvements in biometry reliability, visual outcomes and refractive outcomes after LipiFlow treatment versus an active control group and, through a cross-over design, to evaluate visual and refractive outcomes after postoperative LipiFlow treatment. The study design allows evaluation of preoperative and postoperative LipiFlow treatments on cataract surgery outcomes.

5. ACRONYMS

The following acronyms are used throughout the document:

- ACD: Anterior Chamber Depth
- AL: Axial Length
- BCDVA: Best Corrected Distance Visual Acuity
- D: Diopters
- IOL: Intraocular Lens
- MGD: Meibomian Gland Dysfunction
- MGE: Meibomian Gland Evaluator
- MGYLS: Meibomian Glands Yielding Liquid Secretion
- MR: Manifest Refraction
- MRC: Manifest Refractive Cylinder
- MRS: Manifest Refractive Sphere
- MRSE: Manifest Refraction Spherical Equivalent
- SPEED: Standard Patient Evaluation of Eye Dryness
- TBUT: Tear Break-up Time
- UCDVA: Uncorrected Distance Visual Acuity
- UCIVA: Uncorrected Intermediate Visual Acuity
- UCNVA: Uncorrected Near Visual Acuity

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the LipiFlow treatment in adult patients with mild to moderate meibomian gland dysfunction (MGD) undergoing bilateral cataract surgery in terms of preoperative surgical planning and postoperative outcomes including refractive outcomes, visual outcomes and ocular comfort.

6.1 KEY STUDY ENDPOINTS

- MEAN MONOCULAR UCDVA AT 3 MONTHS POSTOPERATIVE IN THE STUDY AND CONTROL GROUPS
    - Success criteria: Statistically significantly lower mean LogMAR UCDVA is expected in the study group eyes compared to control group eyes at 3 months postoperative.

- PRECISION (STANDARD DEVIATION) OF PREOPERATIVE AL, ACD, AND KERATOMETRIC MEASUREMENTS (K) FOR THE STUDY AND THE CONTROL GROUP
    - AL, ACD and K values will have three sets of measurements at the Preoperative Visit #1 and again at the Preoperative Visit #2. For AL, ACD and keratometry, the standard deviation of each set of measurements will be computed at both preoperative visits, and the average of the three computed standard deviations from each preoperative visit is defined as the precision. The difference in precision between the two preoperative visits will be calculated for AL, ACD and K values. The precisions of the AL, ACD and keratometry measurements are expected to be better (smaller standard deviation) for study group eyes than the ones for control group eyes.

- RATE OF REFARACTIVE PREDICTABILITY AT 3 MONTHS POSTOPERATIVE FOR THE STUDY AND CONTROL GROUPS
    - The frequency, proportion and 95% confidence intervals of eyes with achieved MRSE within 0.50 D and 1.00 D of targeted MRSE will be summarized at 3 months postoperatively. The proportion of study group eyes with achieved MRSE within 0.50 D and within 1.00 D of targeted MRSE is expected to be greater compared to control group eyes.

- RATE OF BOTHERSOME OCULAR SYMPTOMS AT 3 MONTHS POSTOPERATIVE FOR THE STUDY AND CONTROL GROUPS
    - The rate of directed reports of bothersome ocular symptoms (halos, night glare, starburst, and night vision difficulties) at 3 months postoperatively is expected to be lower for study group eyes than that for control group eyes.

- MEAN CHANGE IN TOTAL MEIBOMIAN GLAND SCORE IN THE STUDY GROUP COMPARED TO THE CONTROL GROUP FROM BASELINE TO 1 MONTH POSTOPERATIVE
    - Change in total Meibomian gland score is defined as total Meibomian gland score at 1 month postoperative minus the score at Baseline (before LipiFlow treatment). Greater mean change in total Meibomian gland score is expected for study group eyes than that for control group eyes.

6.2 OTHER ENDPOINTS

- 1-Month Postoperative Visit:
    - Mean change in Number of Meibomian Glands Yielding Liquid Secretion (MGYLS) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in ocular surface stain grade from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in Tear Break-up Time (TBUT) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.
    - Mean change in Eyelid Margin Evaluation from Baseline visit to 1 month postoperative in the Study group compared to the Control group.

- 3-Month Postoperative Visit:
    - Mean monocular BCDVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean binocular UCDVA and BCDVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean binocular UCIVA in the Study group at 3 months postoperative compared to the control.
    - Mean binocular UCNVA in the Study group at 3 months postoperative compared to the Control group.
    - Mean manifest refraction spherical equivalent (MRSE) at 3 months postoperative compared to target MRSE in the Study group compared to the Control group.
    - Contrast acuity in the Study group at 3 months postoperative compared to the Control group.
    - Mean change in total Standard Patient Evaluation of Eye Dryness (SPEED) score from Baseline visit to 3 months postoperative in the Study group compared to the Control group.
    - Mean change in total meibomian gland score in the Study group compared to the Control group from Baseline to 3 months postoperative.

- Control Group 4-Months Postoperative Visit:
  - Mean change in monocular UCDVA and BCDVA from 3 months to 4 months postoperative.
  - Mean change in binocular UCDVA and BCDVA from 3 months to 4 months postoperative
  - Mean change in binocular UCIVA from 3 months to 4 months postoperative
  - Mean change in binocular UCNVA from 3 months to 4 months postoperative
  - Mean MRSE at 4 months postoperative compared to target MRSE
  - Percent of eyes with MRSE within 0.50 D and within 1.00 D of target MRSE at 4 months postoperative
  - Contrast acuity at 4 months postoperative compared to 3-month.
  - Mean change in total meibomian gland score from 3 months to 4 months postoperative.
  - Mean change in total SPEED score from 3 months to 4 months postoperative.
- Rate of adverse events in the Study and Control groups.
- Rates of medical and/or lens findings in the Study and Control groups.

7. STUDY PRODUCTS

7.1 LIPIFLOW THERMAL PULSATION SYSTEM

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 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 cleared under pre-market notification (K161357) to market the device in the U.S (Class II device). The LipiFlow is in commercial distribution based upon a determination by the FDA that the device is substantially equivalent to a legally marketed device. In addition, the use of the device in this study is in accordance with the cleared indication for use in the commercial product labeling. The risk assessment supports that the use of the LipiFlow in this post-market study is non-significant risk because the device is designed to control the application of heat and pressure within a safe range and time. Thus, this post-market study is an exempted investigation under 21 CFR 812.2(c)(2).

7.2 INTRAOCULAR LENSES

The lens models to be used in this study are the commercially-available Symfony IOLs. The TECNIS Symfony Extended Range of Vision Intraocular Lenses (IOLs), lens model ZXR00 and toric lens models ZXT150, ZXT225, ZXT300, and ZXT375, are ultraviolet light-absorbing posterior chamber IOLs which are intended to mitigate the effects of presbyopia and provide a continuous range of high-quality vision by extending the depth of focus.

The TECNIS Symfony® Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of preexisting corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only.

The TECNIS Symfony® Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model Series ZXT IOLs are intended for capsular bag placement only.

8. STUDY POPULATION

All study subjects will be enrolled from the normal surgical cataract population with bilateral mild to moderate MGD, scheduled for bilateral cataract surgeries with Symfony IOL implantation, at up to 7 sites in the U.S.A. Approximately 140 subjects will be randomized and bilaterally implanted, to achieve approximately 110 evaluable subjects (55 in the study arm and 55 in the control arm).

This study will include mild to moderate MGD subjects scheduled for bilateral primary phacoemulsification cataract extraction and Symfony IOL implantation and who meet all the study inclusion and exclusion criteria in both eyes. All subjects who meet the inclusion/exclusion criteria will be offered enrollment in the study. Eligibility criteria may not be waived by the investigator. Any questions regarding patient eligibility are to be discussed with JJSV prior to subject enrollment. Those subjects who meet the inclusion/exclusion criteria and agree to participate will be randomized to either the Study group or the Control group and will be bilaterally treated with the LipiFlow

system. The subjects will be enrolled at each site sequentially until the recruitment goals are met or the site limit is reached. To minimize bias, each investigator will manage subject enrollment at his/her site to the extent possible to achieve an even distribution with respect to age among the study groups.

8.1 INCLUSION CRITERIA

Note: All criteria apply to each study eye.

- Minimum 22 years of age.
- Bilateral cataracts for which phacoemulsification extraction and implantation with Symfony IOLs have been planned.
- Evidence of MGD in both eyes based on assessment of meibomian glands of the lower eyelid with a total meibomian gland secretion score of ≤ 15 (on a scale of 0 to 45) for each eye.
- None to moderate dry eye symptoms with questionnaire total scores between 0 and 15 on the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire[xxii].

  Note: In each site, there should be no more than 30% enrolled subjects with none dry eye symptoms.
- Clear intraocular media other than cataract in each eye.
- Availability, willingness, ability and sufficient cognitive awareness to comply with the study protocol including: randomization; examination procedures; completion of planned bilateral cataract surgeries; compliance with no use of other MGD or dry eye treatments (except over-the-counter artificial tears, ocular lubricants, ointments, emollients or ω-3 dietary supplements) during the study; and attendance of all study visits.
- Ability to understand, read and write English to consent to study participation and complete study questionnaires.
- Willingness to sign informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing country.

8.2 EXCLUSION CRITERIA

Note: All criteria apply to each study eye.

- Any medical finding that would predictably result in a postoperative best corrected distance visual acuity worse than 20/30 in either eye.
- Use of systemic or ocular medications that, in the opinion of the investigator, may affect vision or impact pupil dilation or iris structure.
- Irregular corneal astigmatism.

- Any clinically-significant corneal pathology / abnormality other than regular corneal astigmatism.
- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils).
- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration, including pseudoexfoliation, trauma, or posterior capsule defects.
- Unwillingness or inability to stop wearing contact lens at least two weeks prior to the baseline visit.
- Known ocular disease or pathology that, in the opinion of the investigator, may affect visual acuity or require surgical intervention during the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.).
- Systemic disease condition that causes dry eye (e.g., Stevens-Johnson syndrome, vitamin A deficiency, rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, leukemia, Riley-Day syndrome, systemic lupus erythematosus, Sjögren's syndrome).
- Unwillingness or inability to abstain from the use of systemic medications known to cause dryness (e.g., isotretinoin (Accutane®)) for the study duration. Subjects must have discontinued these medications for at least 1 month prior to the Baseline Visit measurements.
- Unwillingness or inability to abstain from the use of systemic antihistamines:
  - at least two weeks prior to the baseline Preoperative Visit #1 measurements through Preoperative Visit #2, or per site standard of care for cataract surgery, whichever is longer; and
  - at least 2 weeks prior to the Month 3 measurements; and
  - at least 2 weeks prior to the Month 4 measurements (Control group only)
- Unwillingness or inability to abstain from use of prescription medications (e.g., lifitegrast (Xiidra) for treatment of MGD or dry eye. Subjects must have discontinued using prescription medications for MGD or dry eye at least 1 month prior to the baseline Preoperative Visit #1 measurements.
- Any of the following ocular (eye or eyelid) conditions in <u>either</u> eye within 3 months prior to the LipiFlow treatment visit:
  - Prior intraocular, oculoplastic, corneal or refractive surgery procedure (LASIK, LASEK, RK, PRK, etc.).
  - Ocular trauma.
  - Ocular Herpes simplex or Herpes zoster (eye or eyelid) infection.

  - History of recurrent ocular inflammation (e.g., retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis).
  - Punctal plug insertion or punctal occlusion.
- Any of the following active ocular (eye or eyelid) conditions in either eye at the baseline Preoperative Visit #1 measurements:
  - Active ocular infection (e.g., viral, bacterial, mycobacterial, protozoan or fungal infection of the cornea, conjunctiva, lacrimal gland, lacrimal sac or eyelids including hordeolum/stye).
  - Active ocular inflammation (e.g., retinitis, macular inflammation, choroiditis, uveitis, iritis, scleritis, episcleritis, keratitis).
  - Moderate to severe (Grade 2-4) allergic, vernal or giant papillary conjunctivitis
  - Severe (Grade 3 or 4) inflammation of the eyelid (e.g., blepharochalasis, staphylococcal blepharitis or seborrheic blepharitis).
  - Eyelid abnormalities that affect lid function (e.g., entropion, ectropion, tumor, edema, blepharospasm, lagophthalmos, severe trichiasis, severe ptosis).
  - 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).
- Concurrent participation or participation within 30 days prior to study visit in any other clinical trial.
- Planned monovision correction.
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes.

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select ophthalmic surgeons who have completed a residency in ophthalmology (or its documented equivalent) and are licensed to practice medicine and perform surgery at his/her investigative site. Each site will have one designated principal investigator; some sites may have additional implanting sub-investigators/surgeons.

Investigators will be selected from surgeons who are experienced in LipiFlow treatment in MGD patients, as well as in small-incision, phacoemulsification and multifocal IOL implantation in cataract patients. All sites are required to have adequate staff support for reporting and subject follow-up, 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 JJSV and the Investigational Review Board (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 and be responsible for the control and documentation of the devices under investigation
- 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
- 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 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
- Ensure the IRB that is responsible for initial and continuing review of the study complies with applicable laws and regulations
- Report all changes in research activity and all unanticipated problems involving risks to patients to the IRB and JJSV
- Supervise and permit 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 ancillary supplies
- 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 laws and regulations, and all conditions of approval imposed by the reviewing IRB
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately informed about the protocol, the study 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 signed and returned to JJSV:

- 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
- Hospital/Ambulatory Surgery Center Clinical Study Acknowledgement, if required

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

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

This study will be a post-market, prospective, multicenter, bilateral, randomized, open-label, cross-over, comparative clinical study conducted at up to 7 sites in the U.S. Approximately 140 subjects will be randomized and bilaterally implanted, resulting in approximately 110 evaluable subjects (55 in the study arm and 55 in the control arm).

After signing the informed consent, subjects meeting all inclusion and exclusion criteria will be randomized to either the Study group or the Control group.

The duration of study participation is from the initial Preoperative Visit #1 to a final visit at 3 months or 4 months after the second-eye cataract surgery, depending upon the subject's randomized group assignment. All subjects in both arms are intended to have bilateral cataract surgery. The subjects randomized to Study group will undergo preoperative LipiFlow treatment and the subjects randomized to Control group will not receive preoperative LipiFlow treatment. Three months postoperatively, both groups will be evaluated for clinical outcomes and the Control group will receive LipiFlow treatment as the cross-over group. The Control group will be evaluated at 4 months postoperative for clinical outcomes.

Key data collection for all subjects/eyes includes distance visual acuities, manifest refraction, contrast acuity, keratometry, biometry, corneal topography, visual symptoms, Meibomian gland evaluation, biomicroscopic slit-lamp findings, complications and adverse events. A chart summary of all examination or treatment procedures required at each study visit is provided in **Appendix B**. If needed, specific equipment necessary to perform the required procedures will be supplied for the duration of the study (**Appendix C**). The study visit schedule is described in Section 10.2.

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 vision testing, although a back-up person should also be designated and trained.

10.2 VISIT SCHEDULE

The study visit schedule for all study subjects is outlined in **Table 1**.

Subjects randomized to the **Study Group** will undergo a minimum of the following four study visits (with visit windows shown in parentheses):

1) Preoperative Visit #1, including LipiFlow treatment (may occur on the same day or within 1 week of Visit #1)
2) Preoperative Visit #2 (2 - 4 weeks after LipiFlow treatment)
3) 1 Month Postop (30 - 60 days after cataract surgery on second eye)
4) 3 Months Postop (10 to 14 weeks after cataract surgery on second eye)

Subjects randomized to the **Control group** will undergo a minimum of the following five study visits (with visit windows shown in parentheses):

1) Preoperative Visit #1
2) Preoperative Visit #2 (2 - 4 weeks after Preoperative Visit #1)
3) 1 Month Postop (30-60 days after cataract surgery on second eye)
4) 3 Months Postop (10 to 14 weeks after cataract surgery on second eye), including the crossover LipiFlow treatment, which should occur within 0 - 7 days after the 3 months postoperative visit
5) 4 Months Postop (4 to 6 weeks after receiving crossover LipiFlow treatment)

Unscheduled visits may be conducted as necessary at the discretion of the investigator for medically-indicated follow-up.

Table 1: Visit Schedule

NAME OF VISIT	GROUPS	PROCEDURES	VISIT WINDOW
Preoperative #1	All	Informed Consent, Screening, Baseline, Randomization and Enrollment	Per site practice
LipiFlow Treatment	Study Group	LipiFlow treatment	LipiFlow treatment can occur on the same day or within 1 week of Visit #1
Preoperative #2	All	Preoperative	Study Group: 2-4 weeks after LipiFlow treatment; Control Group: 2-4 weeks after Visit #1
1 Month Postop	All	1 month postoperative	30-60 days after cataract surgery on second eye
3 Months Postop	All	3 months postoperative; The crossover Control group will receive LipiFlow treatment within 0-7 days after the 3 months postoperative visit	10 to 14 weeks after cataract surgery on second eye
4 Months Postop	Crossover Control Group Only	4 months postoperative	4 to 6 weeks after receiving crossover LipiFlow treatment

10.3 PREOPERATIVE VISIT #1 PROCEDURES

The procedures in Preoperative Visit #1 include Informed Consent, Screening & Baseline Exam, Randomization & Enrollment. These procedures must be done in the order shown below.

Informed Consent

The Investigator or designee identifies potential study participants by reviewing medical records of patients who are planning to have bilateral cataract surgery. Potential study participants are scheduled for the initial preoperative visit.

At the initial 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 subject's questions, as needed.

Once the Investigator or designee has answered all the subject's questions to the subject's satisfaction and the potential study participant has voluntarily agreed to participate in the study, written informed consent is obtained using the IRB-approved informed consent document. The subject and the person conducting the consent discussion (Investigator or designee) print their names, sign and date the consent.

All subjects enrolled in the study must sign the current IRB-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 treatment 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 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 at the beginning of the preoperative visit, 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 surgery. These subjects will be exited from the study.

Screening and Baseline

Following the informed consent process, the Investigator or designee will perform the screening and baseline exam procedures and evaluate the subject conditions that affect study eligibility, as listed in Sections 8.1 and 8.2. The screening and baseline 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 and exclusion criteria based on testing conducted at the Visit #1.

Besides Medical and Ocular History, the screening and baseline 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 8.1 and 8.2, 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) systemic conditions and concomitant systemic medications that may cause dry eye;
3) ophthalmic conditions and medications, including last use of medications for MGD or dry eye and dosage and frequency of pre-existing use of OTC products;
4) history of contact lens wear (must be removed prior to examination and treatment);
5) history of ocular surgery, ocular injury, ocular infection, ocular inflammation, ocular allergy, eyelid abnormality, or ocular surface abnormality;
6) recent participation in another ophthalmic clinical trial.

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. 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 adverse events.

MEIBOMIAN GLAND ASSESSMENT

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 diagnostic instrument, Meibomian Gland Evaluator (MGE) (as shown in **Appendix G**), 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, as shown in **Appendix G**. The central region of the Meibomian Gland Evaluator should be carefully placed in the temporal, central and nasal regions as described in **Appendix G** to avoid overlap in the gland assessment.

VISUAL ACUITY TEST

The subject must be predictably capable of achieving Snellen 20/30 (Decimal 0.6) or better best corrected distance vision in each eye after cataract extraction and IOL implantation. The surgeon may use his/her judgment, the Potential Acuity Meter (PAM), or other methods (e.g., pinhole, laser interferometer, etc.) to estimate the subject's potential postoperative acuity.

Preoperative UCDVA and BCDVA tests should be performed per site standard of care.

MANIFEST REFRACTION AND REFRACTION ADJUSTMENTS

Preoperative manifest refraction is required. Preoperative refraction tests would be performed per site standard of care.

CORNEAL TOPOGRAPHY

In each designated preoperative visit, corneal topography measurements will be collected on both eyes. The instrument printouts and anonymized database export from the respective instruments will be collected from the site. No irregular corneal astigmatism should be present preoperatively.

KERATOMETRY AND BIOMETRY,

In each designated preoperative visit, the investigator shall repeat 3 sets of biometry / keratometry measurements with at least 3 measurements in each set (depending on the measuring device).

Predicted postoperative corneal astigmatism, as measured by keratometry, should be less than 1.00 D. No irregular astigmatism should be present preoperatively. If the preoperative keratometric astigmatism is greater than 0.50 D, assess the impact of posterior corneal astigmatism (PCA) on predicted residual astigmatism by using a calculator that accounts for PCA (e.g., J&J TECNIS Toric Calculator, Barrett Toric Calculator, etc.).

IOL POWER AND TARGETED REFRACTION

Axial length and anterior chamber depth (ACD) must be measured to determine the appropriate lens power to implant using an A-Constant. Non-contact biometry is preferred; however, surgeons should use the biometry method with which they have the most experience and which was used in the determination of personalized A-Constants for the Symfony lens.

The lens power should be calculated to achieve emmetropia at distance. Intentional over- or under-correction (outside ± 0.50 D) should NOT be planned for either eye;

however, surgeons may adjust the targeted refraction as necessary to achieve emmetropia based on surgeon factors, study subject experience and/or subject first-eye outcomes.

ADDITIONAL PREOPERATIVE EXAMINATION PROCEDURES AT PREOPERATIVE VISIT #1:

- Informed consent documentation
- Subject demographic information
- Planned surgery dates for each eye
- Cataract type and density for each eye
- Potential visual acuity, targeted refraction, IOL power calculations for each eye
- Fundus exam results for each eye
- Ocular surface staining for each eye
- Eyelid margin evaluation for each eye
- TBUT for each eye
- Meibomian gland imaging through LipiScan / LipiView II for each eye
- Ocular / Visual symptoms assessment (non-directed; spontaneous)
- PRVSQ questionnaire
- Ocular and systemic medications
- SPEED questionnaire
- Adverse events

Note that if the subject had a recent dilated retinal exam performed at the study site within 60 days prior to the Preoperative Visit #1, the prior examination data may be used for the baseline dilated retinal exam with the date of the dilated exam documented.

Randomization and Enrollment

Randomization will take place after the subject has signed the informed consent document and has met all inclusion and exclusion criteria. As part of the informed consent process, the investigator or delegate will explain to the subject the requirements of a randomized study and the differences expected between the two groups.

Randomization ensures subjects are assigned with an equal probability to the Study or Control groups without the subject or Investigator knowing which group the subject will be assigned to until after the subject has completed the baseline exam. Randomization helps to reduce any differences between Study and Control groups in baseline characteristics.

A randomization list has been created by the JJSV biostatistician and uploaded into the electronic data collection (EDC) system. Subjects will be randomized on a 1:1

basis to receive the LipiFlow treatment preoperatively (Study group) or after the 3-month postoperative visit (Control group). The randomization is stratified by site and blocked to reduce the imbalance between the number of subjects in the Study and Control groups. Randomization will take place after the subject has signed the informed consent document and has met all the inclusion/exclusion criteria. Once a subject has met the eligibility criteria, the site will access the EDC system to determine the randomization assignment.

If the subject is randomized to the Study group, the subject is scheduled for the LipiFlow treatment on the same day or within 1 week of the Preoperative Visit #1. If the subject is randomized to the Control group, the subject is scheduled for the second preoperative visit 2 - 4 weeks after Visit #1.

All subjects who sign an informed consent document and have been evaluated as eligible for the study enrollment will be documented on the Screening and Enrollment Log. A subject who does not meet the eligibility criteria or who chooses to discontinue study participation prior to randomization is documented on the Screening and Enrollment Log as “Not Enrolled” along with the reason. All subjects who undergo randomization are documented as “Enrolled” on the Screening and Enrollment Log and are assigned a subject identifier.

LipiFlow Treatment

The preoperative LipiFlow treatment is only applicable and required for the subjects in the Study group. It can be performed on the subjects on the same day or within 1 week of the Preoperative Visit #1.

If the LipiFlow treatment is performed on the same day as Preoperative Visit #1, the medical/ophthalmic history and slit lamp evaluation do not need to be repeated before treatment. In this case, the Investigator must review the baseline history and slit lamp exam information prior to treatment to ensure no contraindication to LipiFlow treatment is present. If the LipiFlow treatment visit is performed on a different day from Preoperative visit #1, the Investigator or designee documents any changes to medical/ophthalmic history and performs a slit lamp evaluation to determine if an ocular adverse event is present prior to treatment. If the subject has an active ocular adverse event, the LipiFlow treatment should not be performed at this visit.

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

The Investigator or designee performs slit-lamp evaluation after LipiFlow treatment to check for any adverse events. At the completion of the exam, the subject is instructed on how to perform blinking exercises (**Appendix F**) for 1 month after treatment to facilitate the flow of oils from the meibomian glands into the tear film. The subject is advised to return for Pre-Operative Visit #2, which must be scheduled 2 - 4 weeks after the LipiFlow treatment.

At the completion of Preoperative Visit #1, the subject is reminded not to use any MGD or dry eye prescription medications or other treatments during the study (except for pre-existing OTC artificial tears, ocular lubricants, ointments, emollients or ω-3 dietary supplements). The dosage and frequency of any pre-existing use of OTC products upon study entry must be documented in the subject's medical record and in the study case report forms. Except for LipiFlow treatment, no other MGD or dry eye treatment is prescribed or administered to subjects throughout the study.

10.4 PREOPERATIVE VISIT # 2 PROCEDURES

Preoperative Visit #2 will be scheduled 2 - 4 weeks after LipiFlow treatment for the subjects in the Study Group, and 2 - 4 weeks after Preoperative Visit #1 for subjects in the Control group.

The following preoperative procedures at the visit are to be performed (see also **Appendix B**). General descriptions and requirements of the various tests are provided in the manual of testing procedures (**Appendix D)**. At each designated preoperative visit, the investigator will repeat 3 sets of biometry / keratometry measurements with at least 3 measurements in each set (depending on the measurement device).

Preoperative Examination Procedures at Preoperative Visit #2:

- Ocular and systemic medications
- Biomicroscopic slit-lam exam
- Potential visual acuity, targeted refraction, IOL power calculations
- Ocular / visual symptom assessment (non-directed; spontaneous)
- PRVSQ questionnaire
- Keratometry (auto or manual)
- Biometry
- Corneal topography
- Ocular surface staining
- TBUT
- Eyelid margin evaluation

- SPEED questionnaire
- Surgical target (emmetropia), treatment planning, and planned surgery dates
- Adverse events

10.5 ACTIVATOR II SUPPLY

For all the study subjects, Activator II will be obtained from the site consignment supplied by JJSV prior to study initiation. One Activator II 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 study enrollment, any remaining Activator II devices will be shipped back to JJSV following the final JJSV monitoring visit. At all times, the storage, access and use of all the consignment Activators must be controlled.

The IOLs for all the study subjects will be obtained from the site's own inventory.

10.6 POSTOPERATIVE PROCEDURES

Postoperatively, subjects will be examined according to the schedule in Section 10.2, Visit Schedule. The most recently operated eye will be evaluated at the 1-day and 1-week visits per site practice standard of care. Both eyes will be evaluated for all the subjects at the 1-month and 3-month visits. For the subjects in Control group, both eyes will receive crossover LipiFlow treatment within 0 - 7 days after the 3-month postoperative visit, and will be evaluated at the 4-month visit.

To maintain consistency throughout the study, it is recommended that a single individual (study technician or coordinator designated by the investigator) conduct all postoperative study-related vision testing. In addition, a back-up person should also be designated and trained.

NOTE 1: No additional refractive procedures are to be performed during the operative or postoperative study period (e.g., Limbal-Relaxing Incisions (LRIs), PRK, LASIK or LASEK).

NOTE 2: If the subject chooses to wear contact lenses after the cataract surgeries, they must be removed prior to any postoperative visits and prior to any LipiFlow treatment. The subject may resume contact lens wear one hour after completion of treatment or per site standard of practice.

NOTE 3: If the subject is implanted with a TECNIS Symfony IOL only in the first eye, the subject will be followed for monocular testing only until study exit for that first eye. The fellow eye will be considered exited as of the second operative date. Both eyes may still receive the LipiFlow treatment if the subject was randomized to the Control group.

POSTOPERATIVE EXAMINATION PROCEDURES

Postoperative examinations will be conducted 1 and 3 months after second-eye cataract surgery for all subjects, and at 4 months for Control group subjects only. General descriptions and requirements of the various tests are provided in **Appendix D**. The postoperative case report form (CRF) will collect the following information, although not all information is required at every visit (see **Appendix B**):

MANIFEST REFRACTION AND REFRACTION ADJUSTMENTS

Postoperative study manifest refractions are to be performed using the M&S System at a distance of 4.0 meters. Manifest refraction (MR) is to be performed using the Maximum Plus refraction method as detailed in **Appendix M**.

Because 4.0 meters is not optical infinity, refraction adjustments are necessary to ensure proper vision testing, taking into account test distance and refraction distance. **Appendix N** lists the refraction adjustments required for the various vision tests using the BCDVA refraction.

DISTANCE VISUAL ACUITY TEST

Monocular and binocular uncorrected and distance corrected visual acuities will be measured postoperatively under photopic lighting conditions (85 cd/m^2, 80–110 cd/m^2 acceptable) using the M&S System at a test distance of 4.0 meters. For eyes unable to achieve a postoperative BCDVA of Snellen 20/40 (i.e., LogMAR 0.3, number of letters correct 70), a reason must be specified. Instructions for using the M&S System are detailed in **Appendix O**, and for distance visual acuity in **Appendix P**.

The following distance visual acuity measurements are to be performed per the visit schedule in **Appendix B**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCDVA	4 m	Photopic (85 cd/m^2)	Monocular, Binocular	+0.25 D adjustment only
BCDVA	4 m	Photopic (85 cd/m^2)	Monocular, Binocular	No adjustment; ETDRS Rx only

INTERMEDIATE VISUAL ACUITY TEST

Binocular uncorrected intermediate visual acuity will be measured under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using the M&S System at a test distance of 66 cm. Instructions for using the M&S System are detailed in **Appendix O** and for intermediate testing in **Appendix Q.**

The following intermediate visual acuity measurements are to be performed per the visit schedule in **Appendix B**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCIVA	66 cm	Photopic (85 cd/m^2)	Binocular	No adjustment

NEAR VISUAL ACUITY TEST

Binocular uncorrected near visual acuity will be measured under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using the M&S System at a test distance of 40 cm.

Instructions for using the M&S System detailed in Appendix) and for near testing in **Appendix R**.

The following near visual acuity measurements are to be performed per the visit schedule in **Appendix B**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCNVA	40 cm	Photopic (85 cd/m^2)	Binocular	No adjustment

CONTRAST ACUITY TESTING

Binocular, photopic,10% low contrast acuity and 20/40 contrast threshold tests will be measured using the M&S System. Detailed instructions for contrast acuity testing are provided in **Appendix S**.

BIOMICROSCOPIC SLIT-LAMP EXAM

A biomicroscopic slit-lamp exam must be performed at each postoperative visit to determine the presence or absence of any medical or lens findings, complications or adverse events. IOL decentration and tilt are to be determined subjectively. The center of the lens relative to the pupil can be used to determine IOL decentration. The diffractive rings of Symfony lens can be used as a guide to locate the center of the IOL. Note that the pupil center may not always be aligned with the visual axis of the eye; therefore, the investigator should consider deviations in pupil center from visual axis when reporting IOL decentration.

ND:YAG CAPSULOTOMY

If an Nd:YAG capsulotomy is necessary, it is recommended that the procedure be performed after study completion.

MEIBOMIAN GLAND ASSESSMENT

Meibomian glands assessment is to be measured at the designated postoperative visits. The method of the assessment is described in **Appendix G**.

FUNDUS EXAM

A dilated fundus exam will be done preoperatively and may be performed postoperatively at the investigator's discretion. Examinations may be done dilated with ophthalmoscopy or undilated with any imaging system that allows for undilated views of peripheral retina (e.g., Optomap). The same fundus exam method that was used for preoperatively should be used postoperatively if the exam is performed.

MEIBOMIAN GLAND IMAGING (LIPISCAN/LIPIVIEW II)

Meibomian gland imaging will be captured through LipiScan or LipiView II at the designated visits, to capture Meibomian gland images of both eyes and grade eyelids, as shown in **Appendix I**. Refer to the LipiView Interferometer and LipiScan Instructions for Use for detailed instructions on the device operation. For subjects in Control group, both eyes will be measured at 4-month visit as well. It is recommended that the same methods be used for all study subjects at the site for the duration of the study.

STANDARD PATIENT EVALUATION OF EYE DRYNESS (SPEED) QUESTIONNAIRE

The SPEED questionnaire will be administered at the beginning of any designated visits, prior to any visual acuity testing.

OCULAR / VISUAL SYMPTOMS ASSESSMENT (NON-DIRECTED; SPONTANEOUS)

The subjective ocular / visual symptoms are to be assessed at the designated visits by asking "Are you having any difficulties with your eyes/vision?" Subjects should not be prompted for specific responses; however, if a subject complains of halos, glare or starbursts, the severity should be determined (mild, moderate or severe).

PRVSQ QUESTIONNAIRE

The PRVSQ questionnaire is to be assessed at the designated visits. Subjects will be prompted for specific responses, including halos, night glare or starbursts.

MEDICATIONS

Postoperative medications should be used as is customary for each investigator and recorded in the source document for each subject. Medications will be recorded on each postoperative case report form as applicable.

ADVERSE EVENTS

Subjects should be assessed at each visit for occurrence of and/or change in status of any adverse events, particularly serious and/or device-related adverse events. See Section 11.0, Adverse Events, for further information.

ADDITIONAL PROCEDURES AT DESIGNATED POSTOPERATIVE VISIT(S):

- Eyelid margin evaluation for each eye
- TBUT for each eye
- Ocular surface staining for each eye
- Ocular and systemic medications

Crossover LipiFlow Treatment (Only for Control Group)

The crossover LipiFlow treatment is only applicable to and required for the subjects in the Control group. It will be performed on the Control group subjects on the same day or within 1 week of the 3-month postoperative visit, after all study examination procedures are completed. If the subject has an active ocular adverse event or other contraindications to LipiFlow treatment, the LipiFlow treatment should not be performed at this visit.

The LipiFlow treatment should be performed per the LipiFlow System Instructions for Use.

10.7 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. Patients who will be traveling, relocating or otherwise unavailable for postoperative follow-up visits should not be chosen for this clinical study.

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 randomization.

A subject will be considered “discontinued prior to treatment” if the subject is randomized but does not undergo bilateral LipiFlow treatment (study group) or receive a Symfony lens for various reasons including: the planned implant being aborted due to surgical complications, the subject withdrawing consent prior to treatment, or the subject died prior to treatment. If a subject receives at least one Symfony lens, he/she is to be followed according to the protocol.

A subject will be “discontinued” from the study if one study lens (if implanted unilaterally) or both study lenses (if implanted bilaterally) are removed or if the subject dies.

Subjects will be considered “lost-to-follow-up” from the study only if irretrievably lost for unavoidable reasons such as: subject moved/unable to locate, subject uncooperative/refuses further study participation, subject ill/unable to travel. In the event of subject relocation, efforts must be made by the investigator to secure follow-up information (i.e., slit-lamp findings and general visual acuity, etc.) from the subject’s new physician.

If a subject is exited early from the study, the investigator will send an Exit Case Report Form to JJSV indicating the reason for study exit. In the event of a lens removal or other 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.

10.8 UNSCHEDULED VISITS

During the study period, 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.

Data to be collected may include:

- UCDVA and BCDVA
- Manifest refraction
- Biomicroscopic slit-lamp examination for medical and/or lens findings
- Fundus exam
- Ocular symptoms
- Adverse events
- Ocular and systemic medications

10.9 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 documented using protocol deviation case report forms. Any deviation made to protect the life or physical well-being 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 ADVERSE EVENT 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 (following the guidelines in Section 11.4, Causal Relationship). 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 Serious Anticipated Adverse Events

The following is a list including, but not limited to, ocular serious adverse events that are anticipated and must be reported to JJSV for this study. Adverse event definitions in accordance with the American Academy of Ophthalmology Task Force Consensus Statement are included in **Appendix U**.

- Endophthalmitis/Intraocular infection
- Hypopyon
- Hyphema
- IOL dislocation
- Cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Persistent corneal edema
- Persistent iritis
- Persistent uveitis
- Persistent raised IOP requiring treatment
- Toxic anterior segment syndrome
- Visual symptoms requiring secondary surgical intervention (e.g., lens removal)
- Tilt and decentration requiring secondary surgical intervention (e.g., repositioning)
- Residual refractive error resulting in a secondary surgical intervention
- Retained lens material resulting in secondary surgical intervention

NOTE 1: Wound burps during the first week postoperatively, suture removal, planned blepharoplasty and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

NOTE 2: Persistent corneal edema, IOP increase, and uveitis/iritis will be considered serious according to the guidelines listed in **Appendix U**. (i.e., persistent IOP increase of 10 mm Hg from baseline to at least 25 mm Hg; corneal edema resulting in BCDVA of 20/40 or worse at 1 month or later; and Grade 1+ uveitis/iritis longer than 3 months.

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 as per the IRB's reporting requirements. If required, adverse events will be reported to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations.

Reporting of adverse events shall follow the USA Code of Federal Regulations for sites in the USA. 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 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 48 hours after detection). Device deficiencies that could have led to a serious adverse event should also be reported to the investigator's IRB 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 48 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 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 48 hours, and to the investigator's IRB as soon as possible (and no later than 10 working days after learning of the event for sites in the USA).

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 treatment and follow-up 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 CRF should be completed each time the subject returns to the investigator or other specialist(s) 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 will be followed until the outcome is determined prior to being exited from the study.

12. 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 by the FDA and all other appropriate regulatory agencies, as well as approval of governing IRBs prior to implementation.

13. ETHICS REVIEW AND PATIENT 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 preoperative case report form that a signed agreement of informed consent has been obtained and is in the investigator's possession for each subject. 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 treatment 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 and surgeries throughout the duration of the study
- Implant serial number identification
- Concurrent medications
- Distance visual acuity (NOTE: M&S electronic data and near visual acuity score sheets are considered source documentation and are to be retained by the site; a paper copy of the M&S results will be printed and certified by the site)
- Manifest refraction
- Occurrence and status of any operative complications, postoperative medical or lens findings and adverse events
- Occurrence and status of any subject complaints, e.g., ocular/visual symptoms
- 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 an electronic data capture system. All study staff responsible for entering data into the system must complete certification prior to using the system. The investigator is responsible for ensuring that data are properly recorded on each subject's case report forms 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 after termination or the completion of the study or the investigator's part of the investigation, as directed by JJSV.

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.

An electronic data capture system (EDC) will be used to transmit case report forms from the investigative site to JJSV. Requests for data clarification will be handled through this same system.

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 in EDC.

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 on-line centralized and/or 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 ancillary study material will be monitored by JJSV personnel.

Site Monitoring Plan

Prior to performing any study treatments, 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 will be conducted for all sites prior to or at the time of the treatment.

Throughout the duration of the study, site visits to monitor compliance to this protocol will be made at each investigative site. During a routine site monitoring visit, 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. In addition to subject files, study logs will be checked and conformance to lighting levels for visual acuity tests will be verified.

Training on study-specific procedures may also be conducted during monitoring visits. For this study in particular, a training/monitoring visit is likely to occur just prior to or during the first of the 3-month visits, wherein the most extensive vision testing occurs.

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 MEDICAL OVERSIGHT

The medical monitor will be available throughout the clinical trial to review study results and to answer any questions from investigators. The medical monitor will review and assess any reports of serious and/or device-related adverse events 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 study reports.

16. PUBLICATIONS

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

17. 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).

GENERAL RISKS OF CATARACT SURGERY AND IOL IMPLANTATION

There are risks and complications associated with cataract surgery and IOL implantation in general. These can include worsening of vision, hemorrhage, loss of corneal clarity, inflammation, infections, retinal detachment, pupil changes, glaucoma, etc. Complications can result in poor vision, loss of vision or loss of the eye.

RISK MANAGEMENT

Subjects will be closely monitored thought 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, JSJV 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

The general clinical benefits of the LipiFlow system in providing heat and pressure therapy in adult patients with MGD is expected to be similar to the other existing study results regarding effectiveness and safety outcomes. The LipiFlow treatment is expected to improve the subjects' number of meibomian glands secreting liquid, the quality of gland secretion characteristics, tear break-up time, and to improve dry eye symptoms, without clinically significant safety concerns.

The TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of preexisting corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity.

The TECNIS Symfony Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity.

CONCLUSION

The hazards/risks associated with the LipiFlow and the Symfony IOLs, are acceptable. The potential clinical benefits of the LipiFlow and the Symfony IOLs, outweigh the residual risks when the devices are used as intended.

18. 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 the distribution and 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 25 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 (i.e., medical records, medical reports and/or judgments from colleagues or outside specialists who assisted in the treatment and follow-up of the subject)
- 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)
- Subject medical chart/clinic notes (Not applicable for transfer of ownership to JJSV)

19. 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. STATISTICAL METHODS

This section highlights the analyses for the key study endpoints and all other study endpoints. The preoperative visit and 1-month as well as 3-month postoperative visit are the critical analysis time point for all the key endpoints and other endpoints.

20.1 ANALYSIS POPULATION

The primary study population will be all eyes that are randomized for precision of biometric measurements, and all eyes that are randomized and implanted for all other analyses. Mean change in total Meibomian gland score will be compared between study group eyes and control group eyes at 1 month postoperatively. All other key study endpoints will be evaluated at 3 months postoperatively. Additional endpoints will be evaluated at 1 month and 3 months postoperatively for the study group and control group and 4 months postoperatively for crossover control group only. Missing data will not be imputed.

Since both eyes of the same subject will be randomized into the same group, eye-specific measurements of same subject are clustered and likely to be positively correlated. As a subset analysis, right and left eyes of subjects will be analyzed for the key eye-specific study endpoints separately to assess for any differences by eye. Demographics/enrollment/accountability data and binocular data will be reported for all randomized subjects with study IOLs successfully implanted..

20.2 KEY STUDY ENDPOINTS

- MEAN MONOCULAR UCDVA AT 3 MONTHS POSTOPERATIVE

  The mean LogMAR monocular UCDVA will be reported for study group eyes and control group eyes. Note that a lower LogMAR value is a better acuity. The success criterion is a statistically significantly lower mean LogMAR monocular UCDVA for study group eyes compared to control group eyes ($p \leq$

0.05) at 3 months postoperative. The right eyes and left eyes data from each group will also be presented.

- PRECISION (STANDARD DEVIATION) OF PREOPERATIVE AL, ACD, AND KERATOMETRIC MEASUREMENTS (K)

  AL, ACD and K values will have three sets of measurements at the Preoperative Visit #1 and three sets of measurements at the Preoperative Visit #2. For AL, ACD and keratometry, the standard deviation of each set of measurements will be computed at both preoperative visits and the average of the three computed standard deviations from each preoperative visit is defined as the precision. The difference in precision between the two preoperative visits will be calculated for AL, ACD and K values. The precisions of the AL, ACD and keratometry measurements are expected to be better (smaller standard deviation) for study group eyes than the ones for control group eyes. The right eyes and left eyes data from each group will also be presented.

- RATE OF REFARACTIVE PREDICTABILITY AT 3 MONTHS POSTOPERATIVE

  The frequency, proportion and 95% confidence intervals of eyes with achieved MRSE within 0.50 D and 1.00 D of targeted MRSE will be summarized at 3 months postoperatively. The proportion of study group eyes with achieved MRSE within 0.50D and within 1.00 D of targeted MRSE is expected to be greater compared to control group eyes. The right eyes and left eyes data from each group will also be presented.

- RATE OF BOTHERSOME OCULAR SYMPTOMS AT 3 MONTHS POSTOPERATIVE

  The frequency and proportion of subjects who experienced moderate or severe ocular symptoms (halos, night glare, starburst, and night vision difficulties) will be reported. The rate of directed report bothersome ocular symptoms at 3 months postoperatively is expected to be lower for study group subjects than that for control group subjects.

- MEAN CHANGE IN TOTAL MEIBOMIAN GLAND SCORE FROM BASELINE TO 1 MONTH POSTOPERATIVE

  Change in total Meibomian gland score is defined as total Meibomian gland score at 1 month postoperative minus the score at Baseline (before the LipiFlow treatment). The total Meibomian gland score is the sum of the grades for all 15 glands with a range of 0 to 45. A higher total Meibomian gland score reflects better Meibomian gland function. Greater mean change in total Meibomian gland score is expected for study group eyes than that for

control group eyes. The right eyes and left eyes data from each group will also be presented.

20.3 OTHER ENDPOINTS

- **1-Month Postoperative Visit:**
  - Mean change in Number of Meibomian Gland Yielding Liquid Secretion (MGYLS) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.

    The number of MGYLS (i.e., cloudy or clear liquid with a grade of 2 or 3) will be counted out of the 15 glands assessed with a range of 0 to 15. Mean number of MGYLS will be reported at Baseline visit and 1 month postoperatively. A higher number of MGYLS indicates better Meibomian gland function. Change in number of MGYLS is defined as number of MGYLS at 1 month visit minus number of MGYLS at Baseline visit. Mean change in number of MGYLS from baseline to 1 month postoperative is expected *to be* greater for study group eyes than that for control group eyes.
  - Mean change in ocular surface stain grade from Baseline visit to 1 month postoperative in the Study group compared to the Control group.

    Corneal staining will be evaluated in five corneal regions on a scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The total corneal staining grade will be calculated as the sum of the grades for each of the five corneal regions on a scale from 0 to 15. A lower grade indicates less corneal surface desiccation. Conjunctival staining will be evaluated in six conjunctival regions on a scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe). *The total conjunctival staining grade will be calculated as the sum of the grades for each of the six conjunctival regions on a scale from 0 to 18. A lower grade indicates less conjunctival surface desiccation.* Mean ocular surface stain grade score will be reported at Baseline visit and 1 month postoperatively. Change in ocular surface stain grade score is defined as the score at 1 month visit minus the score at Baseline visit.
  - Mean change in Tear Break-up Time (TBUT) from Baseline visit to 1 month postoperative in the Study group compared to the Control group.

    Three separate measurements of TBUT will be taken on each eye and the average of the three measurements will be calculated for analysis. Mean TBUT will be reported at Baseline visit and 1 month postoperatively. Change in TBUT is defined as TBUT at 1 month visit minus TBUT at Baseline visit. A higher tear break-up time indicates better tear film stability. Mean change in TBUT from baseline to 1 month postoperative is expected greater for study group eyes than that for control group eyes.

- Change in Eyelid Margin Evaluation from Baseline visit to 1 month postoperative in the Study group compared to the Control group.

  The eyelid appearance will be graded as 'Obvious lid changes', 'Minimal lid changes' or 'Normal lid changes'. In addition, the eyelids for the presence of MGD will be graded as either 'Obvious MGD' or 'Non-obvious MGD'. The frequency and percent of eyelid assessment and MGD presence assessment will be presented at Baseline visit and 1 month postoperatively.

- **3-Month Postoperative Visit**:
  - Mean LogMAR monocular BCDVA, mean binocular UCDVA, UCIVA, UCNVA, BCDVA, and contrast acuity will be reported for study group eyes and control group eyes at 3 months postoperative. Better visual acuity outcomes (lower mean LogMAR scores) for study group eyes are expected compared to control group eyes. Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported for MRSE at 3 months postoperative for study group eyes and control group eyes. The difference between MRSE at 3 months postoperative visit and the target MRSE will be calculated. The difference is expected to be smaller (closer to zero) for study group eyes than that for control group eyes. Contrast acuity in the Study group at 3 months postoperative will be compared to the Control group.
  - Mean change in total Standard Patient Evaluation of Eye Dryness (SPEED) score from Baseline visit to 3 months postoperative in the Study group will be compared to the Control group.

    The SPEED score is the sum of frequency and severity scores with a range from 0 to 28. A lower SPEED score represents less frequent and/or less severe symptoms. The mean SPEED score will be reported at Baseline and 3 months postoperative visit. Greater mean change in SPEED score from Baseline to 3 months for study group eyes is expected.
  - Mean change in total meibomian gland score in the Study group will be compared to the Control group from Baseline to 3 months postoperative. Greater mean change in total Meibomian gland score from Baseline to 3 months is expected for study group eyes than that for control group eyes.

- **Control Group 4-Month Postoperative Visit:**
  - Mean change in LogMAR monocular BCDVA and UCDVA and mean change in LogMAR binocular UCDVA, UCIVA, UCNVA, BCDVA, and contrast acuity will be reported for control group eyes from 3 months to 4 months postoperative. Better visual acuity outcomes (lower mean LogMAR scores) at 4 months visit are expected.

  - Mean MRSE at 4 months postoperative will be compared to target MRSE.
  - Frequency and percent of eyes with MRSE within 0.50 D and within 1.00 D of target MRSE at 4 months postoperative will be reported.
  - Mean change in total meibomian gland score and mean change in total SPEED score from 3 months to 4 months postoperative will be reported. An increase in both total Meibomian gland score and total SPEED are expected.
- The frequency and proportion of eyes with optical/visual, medical and lens complications will also be reported over time. Rate of adverse events will be reported in the Study and Control groups.

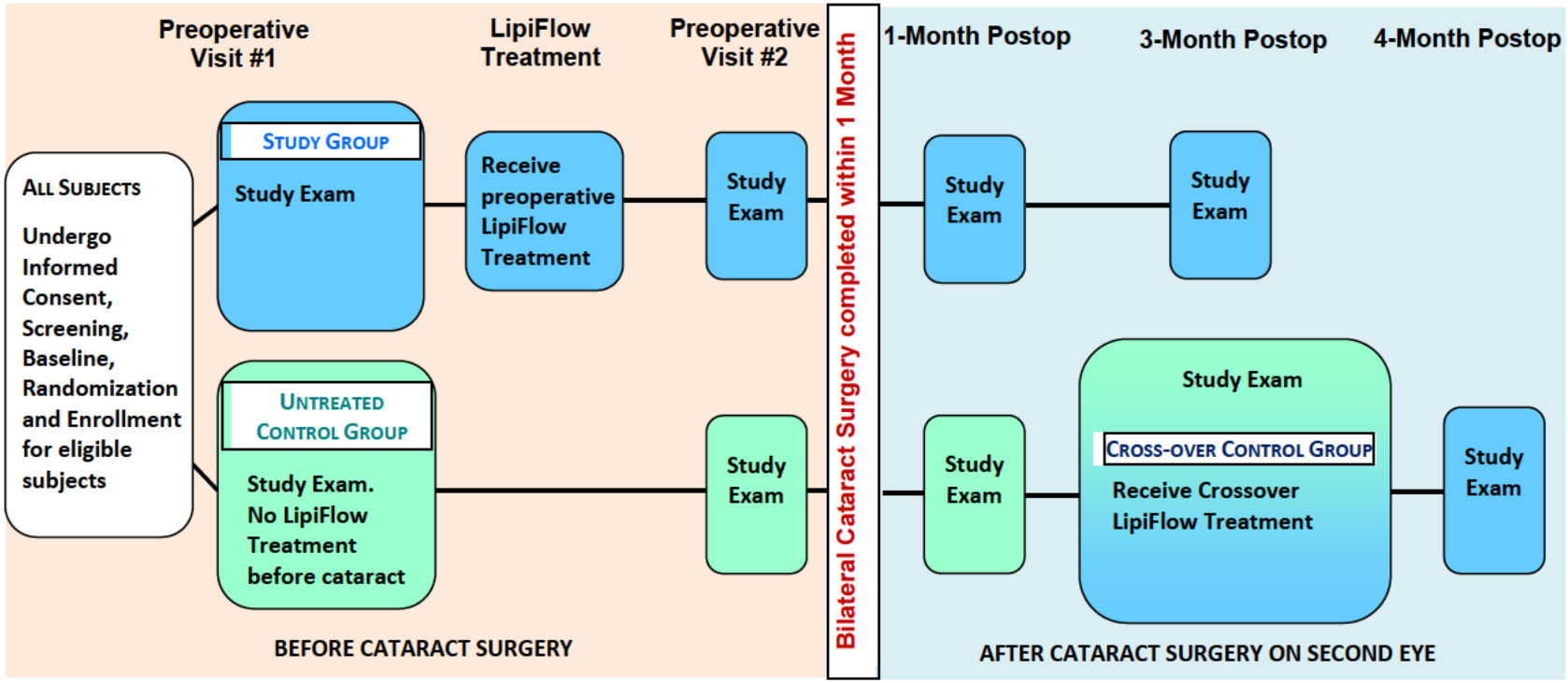
20.4 INTERIM REPORTS

An interim database lock will be performed for preoperative data after completion of the second preoperative visit.

20.5 SAMPLE SIZE CALCULATIONS

The sample size determination is based on the primary endpoint of uncorrected distance visual acuity (UCDVA). There is 90% power to detect a 1-line or greater difference in mean UCDVA between the treatment and control groups with 55 subjects in each group. This assumes one-sided two-sample t-test with an alpha of 0.05 and standard deviation of 1.6 lines. Adding 20% screen failure/drop-out rate will require enrolling 69 subjects per group.

APPENDIX A DIAGRAM OF STUDY FLOW



APPENDIX B SUMMARY OF PROCEDURES REQUIRED AT EACH VISIT

Examination	*Preop Visit #1*	*LF Tx[d] (Study Group Only)*	*Preop Visit #2[e]*	*Operative*	*1-Mo. Post-op*	*3-Mo. Post-op and Crossover LF Tx[f]*	*4-Mo. Post-op (Crossover Group Only)*
Informed consent, medical and ocular history, inclusion/exclusion criteria	X						
Potential visual acuity, targeted refraction, IOL power calculations, corneal topography	X		X				
IOL power/serial number, Toric power/axis (if needed)				X			
Monocular UCDVA, BCDVA	X[c]				X	X	X
Binocular UCDVA, BCDVA					X	X	X
Binocular UCIVA and UCNVA						X	X
Manifest refraction	X[c]				X	X	X
Contrast acuity testing (binocular, 10% contrast acuity and 20/40 contrast threshold)						X	X
Keratometry, biometry (repeat 3 sets of biometry / keratometry measurements)	X		X				
Meibomian gland assessment	X				X	X	X
Ocular surface staining	X		X		X		
TBUT	X		X		X		
Eyelid margin evaluation	X		X		X		
Meibomian gland imaging (LipiScan or LipiView II)	X				X		X
Biomicroscopic slit-lamp exam[a]	X	X	X		X	X	X
Fundus exam[b]	X						
Adverse events	X	X	X		X	X	X
Ocular and systemic medications	X	X	X		X	X	X
Ocular/Visual symptom assessment (non-directed)	X		X		X	X	X
SPEED and PRVSQ questionnaires	X		X			X	X

[a] Includes determination of medical and lens findings/complications, lens orientation. Slit-lamp exam is performed both before and after LipiFlow treatment.
[b] Fundus exam may be performed dilated with ophthalmoscopy or undilated per site practice standard of care.
[c] Preoperative UCDVA, BCDVA and refraction tests will be performed per site practice standard of care.
[d] Preoperative LipiFlow treatment can occur the same day or within 1 week of Preoperative Visit #1.
[e] Preoperative Visit #2 will be 2-4 weeks after LipiFlow treatment for study group and be 2-4 weeks after the Preoperative Visit #1 for control group.
[f] LipiFlow treatment after 3 months postop exams for the Crossover Control group only.

APPENDIX C EQUIPMENT AND ANCILLARY SUPPLIES PROVIDE TO STUDY SITES

The following equipment/supplies will be supplied to an investigative site for the duration of the study provided that the site does not already have such equipment/supplies available for use. This information will be documented in the Clinical Trial Agreement, which indicates that the equipment and any remaining supplies are to be returned to JJSV at the completion of the study.

- M&S Technologies CTS-1000 Smart System© Computerized Vision Testing System, including laptop computer and tablet ("M&S System")
- Commercially-available standard fluorescein strips
- Commercially-available lissamine strips
- Tape measure (meters)
- Activator II

APPENDIX D MANUAL OF TESTING PROCEDURES

Biometry shall be measured with the optical biometry measurement system. The measurement results will be retained by the Investigator.

Biomicroscopic Slit Lamp Examination shall be performed via biomicroscopic slit-lamp exam for determination of medical findings including but not limited to the adnexa, conjunctiva, sclera, cornea, and iris.

Contrast Acuity Test: binocular, best corrected, photopic,10% low contrast acuity and 20/40 contrast threshold test will be measured at the designated postoperative visits. Detailed instructions for contrast sensitivity testing are provided in **Appendix S.**

Corneal Topography shall be measured with a corneal topography system, e.g. the iDesign System (preferred), a Scheimpflug (Pentacam), or Placido (Humphrey) disk-based system. Images will be retained by the Investigator.

Eyelid Margin Evaluation shall be performed preoperatively and postoperatively at designated visits. The Investigator or designee may use 10x to 16x magnification on the slit lamp biomicroscope to evaluate the eyelid appearance, or they may use digital ocular images of the eyelid gained through LipiView II, and grade the eyelid appearance, as defined in **Appendix J**.

Fundus Examination shall be performed with or without pharmacological pupil dilation. If mydriatic agents are used, then installation of mydriatic agents should be used at least 30 minutes prior to determining the status of the ocular media, retina and lens. Based on prior studies, the LipiFlow treatment is not expected to have any effect on the posterior segment and therefore, is not routinely assessed after treatment. However, dilated retinal examination will be performed at scheduled follow-up or unscheduled visits if needed to evaluate an ocular health problem under the physician's discretion.

Keratometry (not simulated K) shall be conducted preoperatively using an auto or manual keratometer. The same keratometry method is to be used at each required visit, e.g., if auto keratometry was recorded at the preoperative exam, all postoperative keratometry readings should be auto K's. Do not use "sim K" from the corneal topography unit.

Lighting levels and lane calibration will be assessed by a representative of the Sponsor to ensure the lane length and lighting conditions are consistent across sites. The site or Sponsor designee will verify the chart background luminance level of 85 cd/m^2 (80-110 cd/m^2 acceptable) prior to use of the measurement device.

Manifest Refraction is to be performed under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using either the phoropter or trials frames and the M&S System. Manifest refraction is to be performed using the Maximum Plus refraction method as detailed in **Appendix M**. Because 4.0 meters is not optical infinity, a refraction adjustment of +0.25 D sphere must be used when performing uncorrected distance visual acuities. **Appendix N** lists the refraction adjustments.

Meibomian Gland Assessment is used to evaluate meibomian gland function. It is used to determine study eligibility based on total meibomian gland secretion score of 15 or less (on a scale of 0 to 45) for each eye at Baseline Visit. The Meibomian Gland Assessment is to be administered preoperatively and at designated postoperative study exams, as defined in **Appendix G**.

Meibomian Gland Imaging through LipiScan or LipiView II will be taken preoperatively and at designated postoperative study visits. LipiScan or LipiView II system will be used to capture, archive, and store the digital images of Meibomian glands of upper and lower eyelids in each eye, as defined in **Appendix I**.

Ocular Surface Staining of the cornea and conjunctiva is evaluated preoperatively and at the designated study visits. 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 H**.

Ocular/Visual Symptom Assessment: The subjective ocular symptoms are to be assessed at the designated visit by asking “Are you having any difficulties with your eyes/vision?” Subjects should not be prompted for specific responses.

PRVSQ questionnaire: Patient-Reported Visual Symptom Questionnaire (PRSVQ) will be used for the assessment. It is a directed questionnaire intended to collect information on visual symptoms. In order to minimize any effect of the doctor-patient relationship may have on a subject’s responses on the questionnaire, the study questionnaires will be self-administered by the subjects. The PRVSQ is to be administered at the start of the preoperative visits and at every follow-up visit, prior to any visual acuity testing.

SPEED Questionnaire is a self-administered, validated assessment tool designed specifically to assess frequency and severity of dry eye symptom. It is used to determine study eligibility based on none to mild dry eye symptoms at Baseline Visit and to evaluate ocular comfort at Baseline and follow-up visits. Dry eye symptoms assessed using the SPEED questionnaire are dryness, grittiness or scratchiness; soreness or irritation; burning or watering; and eye fatigue. The SPEED questionnaire is to be administered preoperatively and at designated postoperative study exams, as defined in **Appendix K**.

Tear Break-Up Time (TBUT) is measured preoperatively and at designated postoperative study exams. Three separate measurements of tear break-up time are taken for each eye using a stopwatch to record the time. For data analysis, the three measurements are averaged to represent the mean tear break-up time for each eye. The Investigator or designee measures tear break-up time under a slit-lamp biomicroscope following instillation of fluorescein dye in the eye using the Dry Eye Test (DET) method, as defined in **Appendix L**.

APPENDIX E INSTRUCTIONS FOR EYELID MARGIN CLEANING

The lower lid margins including the area directly over the meibomian gland orifices are cleaned to remove accumulated devitalized cellular material cell and other products that build up along the lid margin in patients with MGD. Prior research has shown that cleaning the lid margin surface can decrease dry eye symptoms and increase meibomian gland function.[xxiii] Performing lid margin cleaning prior to a LipiFlow treatment may aid in the treatment of MGD because cleaning the meibomian gland orifices and lid margin surface allows for optimal passage of the oil from the gland to the lid margin surface across the mucocutaneous junction and ultimately into the tear film.

The lid margin surface can be divided into three distinct sections: 1) the keratinized surface; 2) the Line of Marx (the stained devitalized surface cells of the mucocutaneous junction denoting the transition between the dry keratinized surface and the wet conjunctival surface); and 3) the conjunctival surface. A healthy keratinized surface has minimal debris, readily visible and uncapped meibomian gland orifices, minimal telangiectasia, and no lid margin irregularities such as lid notching or other findings indicating significant tissue change, as noted on the left in **Figure 1**. Conversely, the majority of MGD patients exhibit tissue changes (e.g. meibomian gland capping) and build-up of material on the keratinized lid margin surface. These changes and accumulated material are readily observed with the slit lamp, as shown on the right in **Figure 1**.

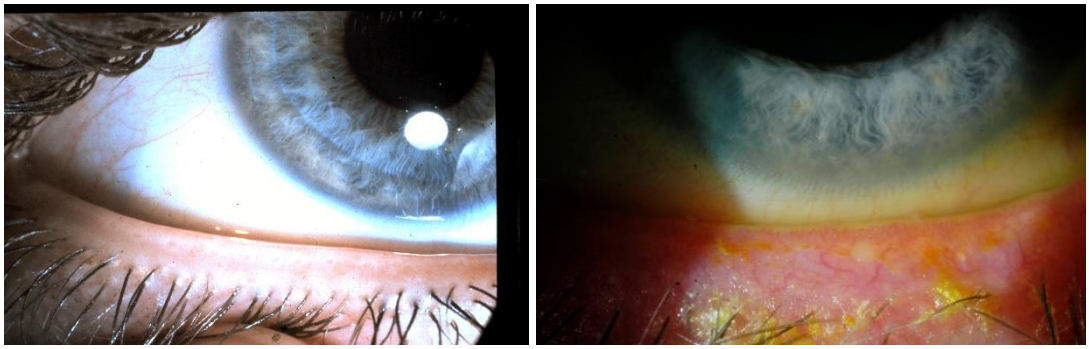


Figure 1: Examples of a healthy lid margin kertanized surface (left) and an abnormal lid margin surface with capped glands and accumulation of debris (right)

The Line of Marx cannot be easily visualized without staining. The accumulated devitalized cells of the Line of Marx are readily observed using lissamine green dye, white light and the slit lamp. A thin staining, slightly elevated Line of Marx that runs parallel to the lid margin and does not undulate is considered normal, as shown on the left in **Figure 2**. As loss of meibomian gland function progresses, the Line of Marx becomes thicker both in height and width, begins to undulate, and finally advances

anteriorly towards the lash line, as shown on the right in **Figure 2**.[xxiv,xxv] Elevation and thickening of the Line of Marx is very common in patients with MGD and occurs in the vast majority of all adults over age 30. With progression of chronic MGD, the Line of Marx advances over the meibomian gland orifices such that the orifices open up onto wet conjunctival surface as opposed to the intended dry keratinized surface. As a result of the changes in the position, thickness and height of the Line of Marx, the delivery of oil from the gland orifices to the tear film is altered.

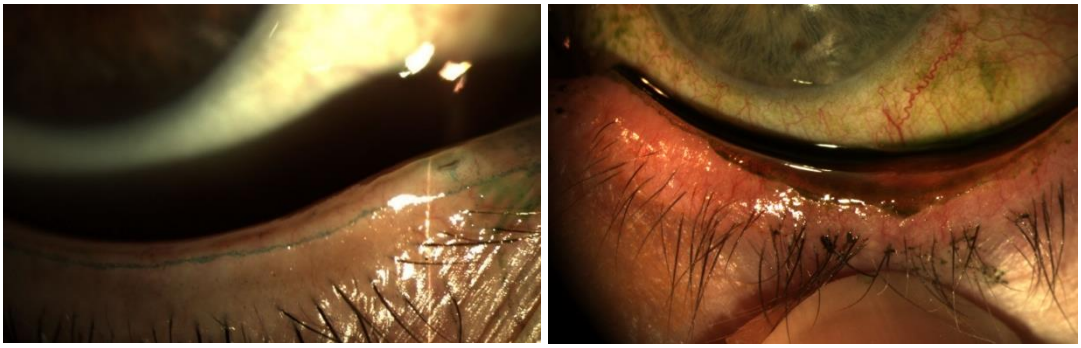


Figure 2: Examples of a healthy stained Line of Marx (left) and an abnormal Line of Marx with thickening, antero-placement and undulation (right)

The Investigator or designee uses the following procedure and a commercially available golf club spud (**Figure 3**) to clean the lid margin surface of the lower eyelids. First, the Line of Marx is cleaned followed by the keratinized lid surface. The wet conjunctival surface is **not** cleaned. In addition, the upper eyelid margins are **not** cleaned.

Figure 3: Golf Club Spud (Hilco Wilson Ophthalmics; Plainville, MA)

NOTE: *The lid margin cleaning procedure is performed without anesthetic and is not intended to remove tissue that cannot be removed with gentle motion and mild pressure of the golf club spud. The patient should not experience discomfort, and there should be no tissue damage evident after the procedure is complete. No post procedure application of topical medications should be necessary.*

Procedure for Cleaning the Line of Marx (the lissamine green stained cells on the surface of the mucocutaneous junction): The goal of the cleaning is to remove the lissamine green stained cells from the Line of Marx.

1. With the patient comfortably seated at the slit lamp (16x magnification with white light), gently evert the lower eyelid.
2. Ask the patient to look up.

3. Stain the conjunctiva and lid margin with lissamine green dye so that the Line of Marx is clearly visible.
4. Place the golf club spud (**Figure 3**) onto the lid margin directly over the Line of Marx.
5. Gently maneuver the golf club spud laterally (nasal to temporal or vice versa) in small wiping motions with mild pressure across the entire length of the Line of Marx, as shown in **Figure 4**.

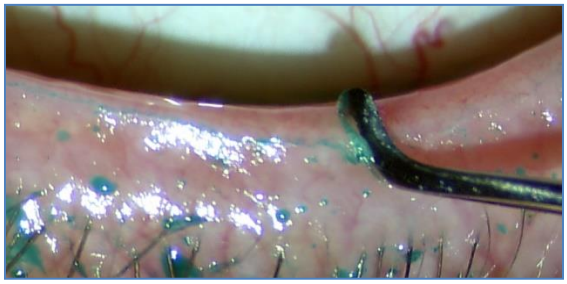


Figure 4: Cleaning the Line of Marx with a Golf Club Spud

6. Adjust the pressure applied to the lid margin as needed based on individual morphology and resistance of the tissue, while monitoring the removal of the lissamine green stained cells. The patient should be comfortable during the procedure. Any discomfort is an indication that the pressure applied needs to be adjusted.
7. After the cleaning of the Line of Marx is complete, verify that few to no stained cells are still visible along the Line of Marx.
8. Repeat steps 1 to 7 for the other eye.

Procedure for Cleaning the Keratinized Lid Surface: The goal of the cleaning is to remove any accumulated debris on the keratinized lid margin and any accumulated material potentially obstructing the meibomian gland orifices.

1. With the patient comfortably seated at the slit lamp (16x magnification with white light), gently evert the lower eyelid.
2. Ask the patient to look up.
3. Place the golf club spud (**Figure 3**) onto the keratinized lid margin with the tip of the spud placed at the edge of the Line of Marx, which was previously cleaned.
4. Gently maneuver the golf club spud laterally (nasal to temporal or vice versa) in small wiping motions with mild pressure across the entire keratinized lid margin surface covering all areas from the edge of the Line of Marx to the base of the lashes at the lash line.
5. Adjust the pressure applied to the lid margin as needed. The patient should be comfortable during the procedure. Any discomfort is an indication that the pressure applied needs to be adjusted.

6. After the cleaning of the keratinized lid margin is complete, verify that little to no sheen is visible on the lid margin surface and any functional meibomian gland orifices are exposed. Narrow furrows or striations, which run perpendicular to the lid margin, may also be observed.
7. Repeat steps 1 to 6 for the other eye.

APPENDIX F INSTRUCTIONS FOR BLINKING EXERCISE

Proper blinking is important to help the flow of oils from the eyelid glands into the tears. Proper blinking occurs when the blinks are complete, so that the upper lid makes full contact with the lower lid, and the frequency of blinking is at least six blinks per minute. Daily activities such as reading and computer use can cause poor blinking habits, including partial blinks where the eyelids do not fully touch and decreased frequency of blinks. Poor blinking worsens the blockage in the eyelid glands. Poor blinking may reduce the effect of the LipiFlow System treatment in improving eyelid gland function. To ensure that poor blinking habits do not interfere with the eyelid gland function, the blinking exercises on the following page must be performed at regular intervals during the day for one month after LipiFlow treatment.

Perform 10 repetitions of the exercises at regular intervals during the day (such as every hour or two) for a minimum of 5 total times per day. Perform the exercises every day of the week until you return for your next study visit. A reminder, such as a watch or phone alarm, can be helpful in prompting the blinking exercises at regular intervals throughout the day.

TIPS

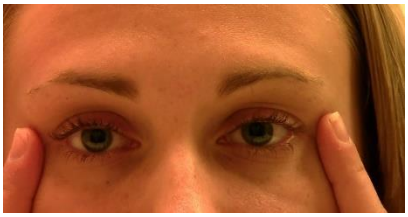
- As a reminder to perform blinking exercises every hour, think about something that you do often in your daily routine, such as answering phone calls or drinking sips of water.

- Remember that blinking quality and frequency are affected by how you use your eyes. If you are reading a book or working on a computer where concentration is required, your frequency of blinking will decrease dramatically. Try remembering to perform one repetition of the blinking exercises whenever you turn a page or every time you save a document.

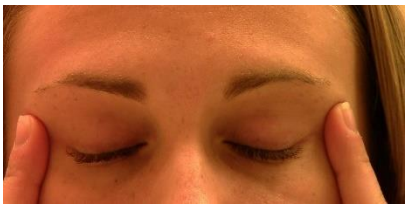
BLINKING EXERCISES:

Perform 10 repetitions every hour for a minimum of 5 times per day every day.

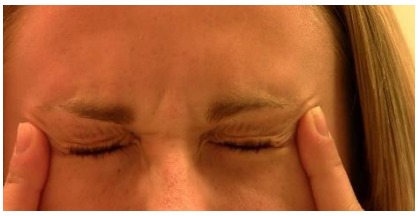
1. Hold your fingers at the corners of your eyes to feel the lid movement.



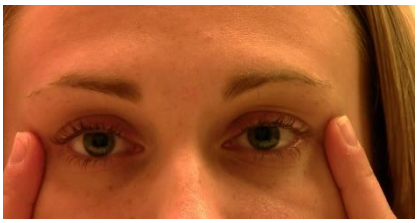
2. **Close your eyelids together with the upper and lower lids completely touching for a count of 2**. *When closing your lids correctly, you will feel no lid movement under your fingers.*



3. **Squeeze your eyelids lightly for a count of 2.** *When squeezing your eyelids lightly, you will feel slight lid movement under your fingers. With a moderate squeeze, you should feel the contraction of the lid muscles under your fingers.*



4. **Open your eyelids to complete the blinking cycle for a count of 2**.



5. **Repeat the following sequence nine more times for a total to 10 repetitions:** CLOSE and count 1 and 2, SQUEEZE and count 1 and 2, OPEN and count 1 and 2

APPENDIX G INSTRUCTIONS FOR MEIBOMIAN GLAND ASSESSSMENT

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 diagnostic 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/mm^2 and 1.2 g/mm^2. 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 9. 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.

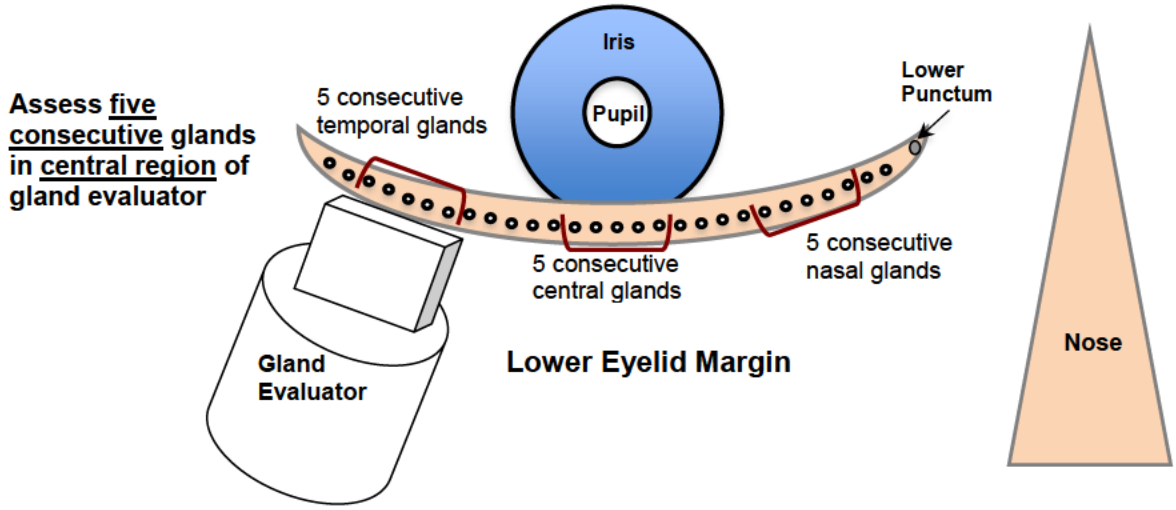


Figure 2: Location of Lower Eyelid Meibomian Glands for Assessment

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.

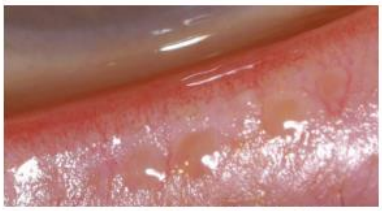
2. Holding the Meibomian Gland Evaluator between the forefinger and the thumb, place the instrument contact surface onto the skin immediately below the lash line of the lower eyelid so that the long dimension is parallel to the eyelid margin, and the five glands are in the central region of the Meibomian 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.

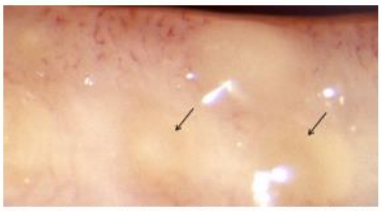
4. Depress the Meibomian Gland Evaluator to exert a constant force over the meibomian glands. Adjust the position of the Meibomian Gland Evaluator to cause the flat surface of the lower eyelid margin to roll slightly outward, facilitating a clear view of the meibomian gland orifices.

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 2**.

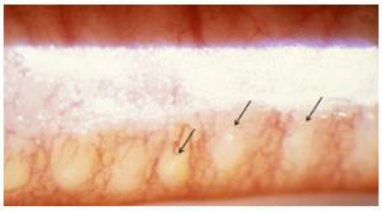


Grade 3: Clear Liquid Oil

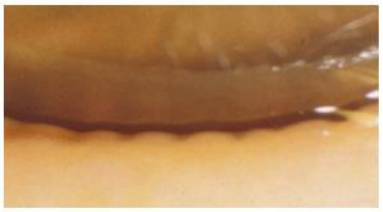


Grade 2: Colored/Cloudy Liquid Oil

Grade 1: Inspissated



Grade 0: No secretion



Grade 0: No secretion

Table 2: 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.***

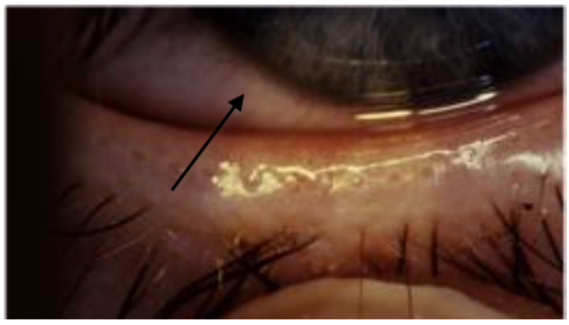
7. Move the Meibomian Gland Evaluator over to the nasal region of the lower eyelid and observe 5 consecutive glands orifices in region. Repeat the evaluation of the secretion characteristics in steps 3-6 for each of the 5 nasal meibomian glands.

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. At the Preoperative Visit #1, sum the scores for all 15 glands in the lower eyelid to calculate the total meibomian gland secretion score. **The Baseline total meibomian gland secretion score must be 15 or less (on a scale of 0 to 45) in each eye to be eligible for the study**.

For data analysis, the total meibomian gland secretion score for each eye is calculated based on the sum of the secretion grades for all 15 glands evaluated. In addition, the number of meibomian glands yielding any liquid secretion (i.e., having a secretion score of 2 or 3) is calculated for analysis.



Clear liquid secretion at gland orifice

Figure 23: Example of Meibomian Gland Yielding Clear Liquid

APPENDIX H 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.

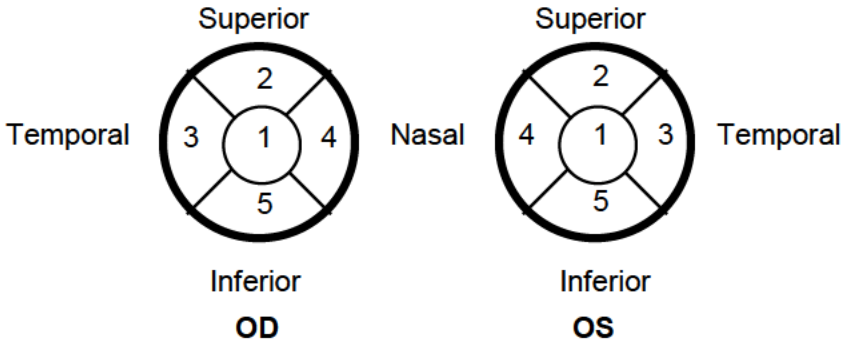


Figure 4: Diagram of Corneal Regions for Fluorescein Staining Grading

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.

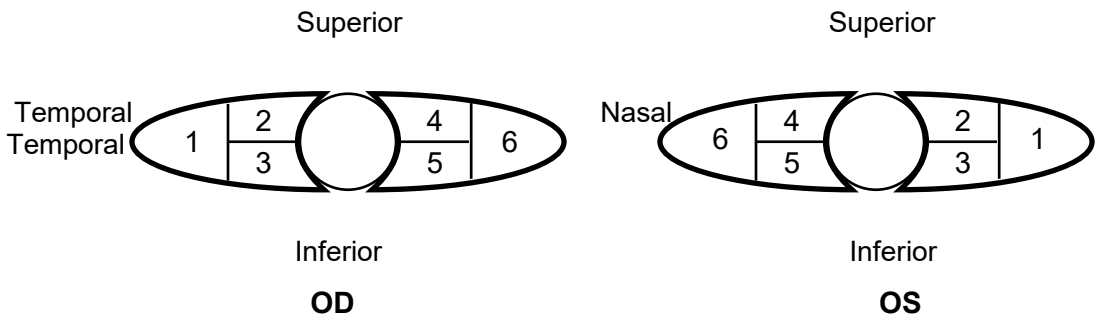


Figure 5: Diagram of Conjunctival Regions for Lissamine Green Staining Grading

APPENDIX I INSTRUCTIONS FOR MEIBOMIAN GLAND IMAGING

The Meibomian gland imaging is used to evaluate the Meibomian gland appearance. It could be performed through LipiView II or LipiScan.

LIPIVIEW II

The LipiView® II Ocular Surface Interferometer is intended for use in adult patients to capture, archive, manipulate and store digital images of specular (interferometric) observations of the tear film, meibomian glands, as well as ocular surface and eyelids. The LipiView II, as shown in **Figure 6**, is a bench-top device and is comprised of a computer system and electronics, chin rest and forehead rest, camera and zoom lens, illuminator and a touchscreen display.

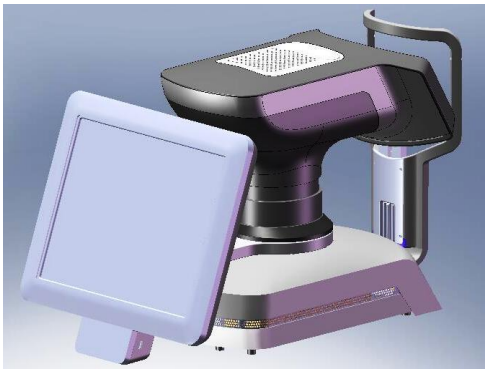


Figure 6: LipiView II Interferometer

Refer to the *LipiView® II Interferometer Instructions for Use* for detailed instructions on the device operation. Failure to follow the instructions may result in improper use of this device. The electronic image data are collected as external data (outside of EDC) by the Sponsor using patient IDs to maintain confidentiality.

LIPISCAN

The LipiScan™ Dynamic Meibomian Imager is intended for use in adult patients to capture, archive, manipulate and store digital images of the meibomian glands. The LipiScan, as shown in Figure 14 is a bench-top device and is comprised of a computer system and electronics, chin rest and forehead rest, camera and zoom lens, illuminator and a touchscreen display.

Figure 7: LipiScan

Refer to the *LipiScan Dynamic Meibomian Imager Instructions for Use* for detailed instructions on the device operation. Failure to follow the instructions may result in improper use of this device. The electronic image data are collected as external data (outside of EDC) by the Sponsor using patient IDs to maintain confidentiality.

APPENDIX J INSTRUCTIONS FOR EYELID MARGIN EVALUATION

At the designated visits, the Investigator or designee uses 10x to 16x magnification on the slit lamp biomicroscope, or use the digital ocular images of the eyelid from LipiView II, and then grades the eyelid appearance, as defined below.

1) **Obvious Lid Changes** – Obvious morphological changes of the lid margins apparent upon first observation including: erythematous lid margins; thickened lid margins; significant telangiectasia; excess vascularization; irregular or serrated lid margins, and acute or chronic inflammation.

2) **Minimal Lid Changes** – Minimal changes, apparent only upon detailed examination of the lid margins.

3) **Normal Lid Appearance** – No significant lid changes.

In addition, the Investigator or designee grades the eyelids as defined below.

1) **Obvious MGD** – Obvious changes of meibomian orifices including: pouting (elevation overlying an orifice); capping (a dome of solidified oil over the orifices); ulceration of epithelialized orifice capping; reduction in number of orifices; and loss of lid area (notching) indicating gland dropout. Lid inflammation not accompanied by the later signs of obvious MGD does not result in a classification of obvious MGD.

2) **Non - Obvious MGD –** No significant meibomian gland signs as described for obvious MGD.

APPENDIX K INSTRUCTIONS FOR STANDARD PATIENT EVALUATION OF EYE DRYNESS (SPEED) QUESTIONNAIRE

The SPEED questionnaire is used to determine study eligibility based on none to mild dry eye symptoms at Baseline Visit and to evaluate ocular comfort at Baseline and follow-up visits. Dry eye symptoms assessed using the SPEED questionnaire are dryness, grittiness or scratchiness, soreness or irritation, burning or watering and eye fatigue.

Symptom frequency is on a scale of:

- 0 (never),
- 1 (sometimes),
- 2 (often), and
- 3 (constant)

Symptom severity is on a scale of:

- 0 (no problems),
- 1 (tolerable–not perfect but not uncomfortable),
- 2 (uncomfortable-irritating but does not interfere with my day),
- 3 (bothersome-irritating and interferes with my day), and
- 4 (intolerable-unable to perform my daily tasks)

The total SPEED score is the sum of frequency and severity scores for all symptoms over a range from 0 to 28. A lower total SPEED score represents less frequent and/or less severe symptoms. **At the Baseline Visit, the total SPEED score must be between 0 and 15 points, reflecting none to moderate dry eye symptoms, to be eligible for the study**.

The Investigator or designee administers the SPEED questionnaire to the subject in the following manner:

1) Explain the questionnaire to the subject to ensure understanding of the instructions without coaching or influencing the subject's responses. Answer the subject's questions as needed to clarify the instructions.

2) Allow the subject to complete the questionnaire and sign/date the last page.

3) After the subject completes the questionnaire, review the forms to ensure all questions have been answered. Ensure the subject makes any corrections that are needed, such as to clarify only one answer for a question.

4) To change or clarify a response, the subject crosses through the incorrect answer with a single line, initials and dates the correction, and writes the correct answer.

5) At the Baseline Visit, score the SPEED questionnaire by totaling the sum of the frequency and severity scores for all symptoms. Determine if the subject's total SPEED score meets the eligibility criterion for none to mild dry eye symptoms.

APPENDIX L INSTRUCTIONS FOR TEAR BREAK-UP TIME TESTING

Tear break-up time is measured at the designated visits. Three separate measurements of tear break-up time are taken for each eye using a stopwatch to record the time. For data analysis, the three measurements are averaged to represent the mean tear break-up time for each eye. The Investigator or designee measures tear break-up time under a slit-lamp biomicroscope following instillation of fluorescein dye in the eye using the Dry Eye Test (DET) method, as described in this section.

1. Place one drop of commercially available saline solution on a commercially-available standard fluorescein strip.
2. Let the excess saline run off by holding the strip vertically with the impregnated end held down. Do not shake the strip after wetting.
3. 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.
4. Retract the upper eyelid. Introduce the DET strip at an approximate 30-degree angle and touch the superior temporal bulbar conjunctiva, preferably 5 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 eyelid.
5. To observe the fluorescein break-up, 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. Use the lowest level of illumination and move the beam from side to side to cover the entire cornea.
6. Ask the subject to blink three times naturally, open, and then refrain from blinking. Tear film break-up is defined as the first observed break-up of the tear film following the third blink. Using a stopwatch to record the time, start the stopwatch as soon as the subject opens his/her eyes after the third blink and stop the stopwatch when the first break-up of the tear film is observed.
7. After the first measurement, instruct the subject to blink naturally three times and take a second measurement as described in step 6. Repeat step 6 for the third measurement. If break-up is not observed within 20 seconds for any measurement, terminate the measurement to prevent possible corneal drying or other effects that might interfere with the subsequent measurements.
8. After a 60-second rest period, instill fluorescein in the fellow eye with a new DET strip and record the tear break-up time following steps 1 through 7.
9. Document the three measurements for each eye.

APPENDIX M MAXIMUM PLUS MANIFEST REFRACTION TECHNIQUE WITH CYLINDER REFINEMENT

Manifest refraction testing will be performed using the M&S System at 4.0 meters with the room lighting set to that required for photopic distance visual acuity testing (85 cd/m^2). NOTE: Objective refraction by either retinoscopy or autorefraction can be used as a starting point for the Manifest Refraction. Always ensure that the endpoint of refraction is maximum plus (or minimum minus) power that yields maximum visual acuity.

1) Occlude the fellow eye.

2) SPHERE: Starting with the objective refraction, refine the sphere to yield best visual acuity. **Important:** Add plus power (or reduce minus) until subject demonstrates at least a 1-line loss from best visual acuity (fogging). Then step down to the most plus (or least minus) sphere power until visual acuity and clarity show no improvement.

3) CYLINDER AXIS: Refine cylinder with a cross-cylinder and the objective cylinder refraction as the starting point. Refine axis first and power second, since the correct axis can be found with an incorrect power, but the correct power cannot be found with an incorrect axis.

    a. Direct the subject's attention to 1 line above (larger letters) the best visual acuity. With the trial cylinder (axis and power) in the phoropter, introduce cross-cylinder for axis refinement. When asking the subject which cross-cylinder axis position is better, "one or two?", remind the subject to look at different letters on the line and report preference based on the overall clarity of the letters.

    b. Refine the axis based on the subject's responses, using small steps (less than five degrees), until the subject reports no difference in the two choices.

    c. Cylinder axis may be further confirmed by bracketing: Slowly rotate the trial cylinder in one direction until the subject reports blurring and note the axis. Rotate the trial cylinder in the opposite direction past the presumed axis until the subject reports blurring, again noting the axis. The average of the two noted axes can be taken as the final astigmatism axis.

4) CYLINDER POWER: Set the cross cylinder to refine cylinder power and present choices to the subject, reminding the subject to look at different letters on the line and report preference based on overall clarity of the letters. Reduce or increase trial cylinder power accordingly.

    a. Maintain the spherical equivalent throughout cylinder power refinement by adjusting the sphere once for every two clicks of cylinder power change.

5) SPHERE CHECK: Introduce fogging lenses again, typically +0.75 D to +1.00 D to ensure that the 20/32 line on the M&S System is blurry. Ask the subject to read the visual acuity chart and move to smaller letters to finalize refraction. Endpoint is when subject achieves best possible acuity and does not show an improvement in acuity with successive one or two clicks of 0.25 D.

APPENDIX N REFRACTION ADJUSTMENTS

Postoperative study manifest refractions are to be performed using the M&S System at a distance of 4.0 meters. Because 4.0 meters is not optical infinity, refraction adjustments are necessary to ensure proper vision testing that accounts for differences between the test distance and refraction distance. The adjustment required (in diopters) is 1/test distance (in meters). To adjust a 4.0-meter refraction to optical infinity, -0.25 D is to be added to the sphere of the refraction to obtain a true distance (infinity) correction. On the other hand, to adjust optical infinity to a 4.0-meter test distance, +0.25 D is to be given. In the case where the refraction distance (4.0 meters) and the vision test distance (4.0 meters) are the same, no adjustment is necessary. The following table lists the refraction adjustments required for the various vision tests in this study:

Refraction Adjustments for Vision Testing

Vision Test	Test Distance	Correction/Adjustment
Uncorrected distance visual acuity (UCDVA)	4.0 m	+0.25 D adjustment only
Best-corrected distance visual acuity (BCDVA)	4.0 m	No adjustment; ETDRS Rx only (phoropter)
Uncorrected intermediate visual acuity (UCIVA)	66 cm	No adjustment
Uncorrected near visual acuity (UCNVA)	40 cm	No adjustment

APPENDIX O INSTRUCTIONS FOR USING THE M&S SYSTEM

Distance, intermediate, low-contrast and near visual acuities will be performed using the M&S System. This system provides descending LogMAR charts with proportionally spaced SLOAN letters at 100% contrast for high contrast visual acuity, 10% contrast for low-contrast distance visual acuity and appropriate contrast levels for letter contrast acuity testing. Each presentation is randomized and is consistent and repeatable. The system is calibrated for both distance to subject and pixels/inch so that optotypes precisely follow ANSI Z80.21-2010 and ISO 8596:2000 with regard to size, spacing between optotypes and spacing between lines.

Figure 4: Example of LogMAR 4.0 meter chart screen

The M&S System background luminance is automatically set to 85 cd/m^2 (range of 80-110 cd/m^2 is acceptable) for photopic testing. Room lighting is to be set to a level lower than the illumination from the laptop screen. Ambient lighting should be dim to dark (less than 50 lux) to maximize pupil size. No surface (including reflective surfaces) within the subject's field of vision should be brighter than the chart background in luminance. The room lighting and screen luminance will be verified each time the computer is turned on using the JJSV-provided, auto-adjusting, monitor-calibration system to ensure light levels are appropriate.

The M&S System will be set up to perform required visual tests in a specific order, with prompts on the screen to allow the technician to set up the subject for monocular or binocular testing, refraction adjustments as needed and uncorrected or best-corrected testing. Letters on all charts will appear randomly, with the technician controlling movement through charts based on subject responses.

As a subject completes a visual acuity line, the technician will select the total number of letters correctly read for that line on the handheld controller, press "Enter" and then confirm the number of letters correct at the next prompt. The M&S System will then advance to the next line of testing and the process will repeat. The system will end the

test when the subject no longer has any correct responses. The number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read. Once a test is completed, follow the prompts on the computer screen to start the next test.

Test results are stored in the M&S computer and a hard copy will be printed and validated as a back-up.

Example of Good-Lite Score Chart

Good-Lite Chart #1							
Line						**Running total number of letters on chart by line**	**Number of letters correct**
1	**H**	**N**	**R**			3	
2	**V**	**Z**	**O**	**S**		7	
3	**O**	**S**	**D**	**V**	**Z**	12	
4	**N**	**O**	**Z**	**C**	**D**	17	
5	**R**	**D**	**N**	**S**	**K**	22	
6	**O**	**K**	**S**	**V**	**Z**	27	
7	**K**	**S**	**N**	**H**	**O**	32	
8	**H**	~~**O**~~	**V**	**S**	**N**	37	
9	**V**	~~**C**~~	~~**S**~~	~~**Z**~~	**H**	42	**38**
10	~~**C**~~	~~**Z**~~	~~**D**~~	~~**R**~~	~~**V**~~	47	
11	~~**S**~~	~~**H**~~	~~**R**~~	~~**Z**~~	~~**C**~~	52	
12	~~**D**~~	~~**N**~~	~~**O**~~	~~**K**~~	~~**R**~~	57	

APPENDIX P INSTRUCTIONS FOR DISTANCE VISUAL ACUITY TESTING

For distance visual acuities, the M&S System laptop should be placed at a test distance of 4.0 meters from the subject for testing distance visual acuities. A laptop setting may be used to reverse charts for rooms that require “folding” via a mirror to reach a distance of 4.0 meters. Whether standard or “folded”, measure and record the test distance accurately. If the room set-up does not allow the computer to be placed at precisely 4.0 meters, the M&S System can be adjusted to account for the actual test distance used.

The M&S System will be set up to perform the required distance visual acuity tests in a specific order, with prompts on the screen to allow the technician to set up the subject for monocular or binocular testing, refraction adjustment as needed and uncorrected or best-corrected testing. A phoropter may be used for distance acuity and refraction testing.

Subjects should be reminded prior to testing that squinting is not allowed. The technician is to observe the subject to ensure the subject is not squinting during visual acuity testing. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

Distance visual acuity measurements (monocular and binocular UCDVA and BCDVA) are to be performed per the visit schedule in **Appendix B**. To test subjects monocularly, occlude the second eye in the phoropter or with an occluder if trial lenses are used.

Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they must guess. Follow the M&S testing process listed in **Appendix O**. At the end of the test, the number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read in the EDC system.

APPENDIX Q INSTRUCTIONS FOR INTERMEDIATE VISUAL ACUITY TESTING

Intermediate visual acuity will be measured using the M&S System at a test distance of 66 cm using phoropters or trial frames. Subjects should be reminded prior to testing that squinting is not allowed and the testing technician should carefully observe to ensure the subject is not squinting. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

Binocular uncorrected intermediate visual acuity measurements are to be performed per the visit schedule in **Appendix B**. Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they have to guess. Follow the M&S testing process listed in **Appendix O**. At the end of the test, the number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read in the EDC system.

APPENDIX R INSTRUCTIONS FOR NEAR VISUAL ACUITY TESTING

Near visual acuity will be measured using the M&S System as described in **Appendix O**, at a test distance of 40 cm. Subjects should be reminded prior to testing that squinting is not allowed and the testing technician should carefully observe to ensure the subject is not squinting. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

Binocular uncorrected near visual acuity measurements are to be performed per the visit schedule in **Appendix B**. Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they have to guess. Follow the M&S testing process listed in **Appendix O**. At the end of the test, the number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read in the EDC system.

APPENDIX S INSTRUCTIONS FOR CONTRAST ACUITY TESTING

The contrast acuity testing includes photopic 10% low contrast acuity and 20/40 contrast threshold test. The contrast acuity testing is to be performed binocularly per the visit schedule in **Appendix B**, using the M&S system.

The technician is to observe the subject to ensure the subject is not squinting during visual acuity testing. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

Photopic 10% Contrast Acuity Testing

Photopic 10% contrast acuity testing will be performed using the M&S system at a test distance of 4 meters. This system provides a descending LogMAR chart with 10% contrast, proportionally-spaced SLOAN letters.

All subjects will be tested binocularly with best refractive correction. The test will be done under photopic test conditions with the M&S system (see **Appendix O**). Subjects should be instructed to start with the smallest line where they can read all of the letters. If they miss any letters, have them go up a line until they are able to read all the letters on a line easily, then continue to read each subsequently smaller line. The subject should be encouraged to read as many letters possible, even if they have to guess. Testing may be stopped when it is evident that no further readings can be made. Results will be displayed on the laptop screen along with the LogMAR and Snellen acuity. Record the total number of letters read and LogMAR value on the chart.

Photopic 20/40 Contrast Threshold Testing

The photopic 20/40 Contrast Threshold test will be performed using the M&S system at a test distance of 4 meters. The contrast threshold test is a fixed LogMAR Sloan letter chart (20/40) with descending contrast levels. Each line has 5 letters of the same contrast, and subsequent lines have descending letter contrast.

All subjects will be tested binocularly with best refractive correction in place. The test will be done under photopic test conditions with the M&S system (see **Appendix O**). Subjects should be instructed to start at the top-most line and continue reading along the line and down the chart. To test subjects binocularly, encourage subjects to read the lowest line of letters possible even if they have to guess, as results are based on the total number of correctly read letters. Testing may be stopped when it is evident that no further readings can be made. Results will be displayed on the laptop screen along with the contrast threshold value. Record the total number of letters read and contrast threshold on the chart.

APPENDIX T INSTRUCTIONS FOR KERATOMETRY

Keratometry must be performed prior to dilation and any contact with the cornea (e.g., tonometry or pachymetry) as follows:

1. Measure keratometry using the iDesign System and/or an auto or manual keratometer using the same method at each required visit, e.g., if auto keratometry was recorded at the preoperative exam, all keratometry readings postoperatively should be done using the same auto keratometry method.

2. **Do not use "sim K"s from the corneal topography unit.**

3. Always record the flat meridian (smaller number, e.g., 42.25) as K1. Record the steeper meridian (larger number, e.g., 43.00) as K2 along with the corresponding axis (e.g., 42.00 x 65 / 42.25 x 155).

4. Record spherical corneas by placing the corneal curvature values in both K1 and K2 and marking axes 180 attached to K2 (e.g., 44.00 / 44.00 x 180). **Spherical Ks will not be accepted with axes other than 180 (do not use 0).**

APPENDIX U AMERICAN ACADEMY OF OPHTHALMOLOGY TASK FORCE CONSENSUS STATEMENT ON ADVERSE EVENTS FOR INTRAOCULAR LENSES

Tables 1 and 2 in the following document give definitions for adverse events.

CA); Alcon Laboratories, Inc. (Fort Worth, TX); Carl Zeiss, Inc. (Oberkochen, Germany); Oculus, Inc. (Wetzlar, Germany); Consultant and Equity Owner — AcuFocus, Inc. (Irvine, CA); ArcScan (Morrison, CO); Elenza (Roanoke, VA); Visiometrics (Barcelona, Spain).

A.G.: Consultant — Abbott Medical Optics, LensAR (Orlando, FL); Medicem (Cheshire, UK); Refocus Group (Dallas, TX); Tracey Technologies (Houston, TX); Vista Ocular (North Canton, OH); Consultant and Equity Owner — Encore Vision (Fort Worth, TX); LensGen (Irvine, CA); PowerVision (Belmont, CA).

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The American Academy of Ophthalmology Task Force for Developing Novel End Points for Premium Intraocular Lenses members include: Jack T. Holladay, MD, MSEE, Chair; Adrian Glasser, PhD, Co-Chair; Scott MacRae, MD, Co-Chair; Samuel Masket, MD; Walter Stark, MD; and the following U.S. Food and Drug Administration staff members: Malvina Eydelman, MD; Don Calogero, MS; Gene Hilmantel, OD; Eva Rorer, MD; Tieuvi Nguyen, PhD; and Michelle E. Tarver, MD, PhD.

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Special Report: The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses

In 1978, the US Food and Drug Administration approved the first investigational device exemption studies of intraocular lenses (IOLs). Outcomes were initially published in 1983 on pooled, publicly available data from IOL premarket approval studies that were used to support marketing approvals.[1] After publication, this "historical control" information was used as a benchmark for the assessment of the safety and effectiveness of new IOLs. These safety and effectiveness endpoints have been referred to as the "Food and Drug Administration Grid" and "Safety and Performance Endpoints" (SPEs) for IOLs. Although the SPEs were updated on the basis of additional premarket approvals in 1998, they have not been updated to reflect the development of "premium IOLs," including toric, multifocal, accommodative, and phakic IOLs.[2] Premium IOLs may present additional adverse events (AEs) to those already established for monofocal IOLs. Further, most of the AEs in the "Grid" do not have standard definitions, and the definitions used could have changed over time with advances in our understanding of ocular pathology. Considering untoward events associated with premium IOL implantation and that would be appropriate as safety endpoints in clinical studies of new premium IOLs, the American Academy of Ophthalmology's Task Force has developed consensus definitions for premium IOL SPE AEs as shown in Table 1. The AE of secondary IOL intervention has been subcategorized by the type of intervention and IOL exchange, removal, and reposition. These indications are listed and defined in Table 2 and Appendix 1.

At this time, acceptable rates for premium IOL SPE AEs have not been established. However, the definitions proposed may be used during clinical studies of new IOLs going forward to allow for the determination of appropriate SPE rates that can be applied to the assessment of new premium IOLs in the future.

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A.G.: Consultant — Abbott Medical Optics, LensAR (Orlando, FL); Medicem (Cheshire, UK); Refocus Group (Dallas, TX); Tracey Technologies (Houston, TX); Vista Ocular (North Canton, OH); Consultant and Equity Owner — Encore Vision (Fort Worth, TX); LensGen (Irvine, CA); PowerVision (Belmont, CA).

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Table 1. Postoperative Adverse Event Definitions for Intraocular Lenses

Adverse Event	Definition
Chronic anterior uveitis	Persistent anterior segment inflammation characterized by grade 1+ cell or greater using SUN criteria[3]
Clinically significant cystoid macular edema	Macular edema diagnosed by clinical examination and adjunct testing (e.g., OCT, FA) resulting in BCDVA of ≤20/40 at ≥1 mo
Corneal edema	Corneal swelling (stromal or epithelial) resulting in BCDVA of ≤20/40 at ≥1 mo
Endophthalmitis	Intraocular inflammation requiring diagnostic vitreous tap and intraocular antibiotics
Mechanical pupillary block	Shallowing of anterior chamber due to obstruction of aqueous humor flow from the posterior to anterior chamber through the pupil by the crystalline lens, vitreous face, or implanted device
Increased IOP	Elevation of IOP by ≥10 mmHg above baseline to a minimum of 25 mmHg
Rhegmatogenous RD	Partial or complete RD associated with retinal tear
Toxic anterior segment syndrome	Acute, noninfectious inflammation of the anterior segment that starts within 24 hrs after surgery, usually resulting in hypopyon and commonly presenting with corneal edema, that improves with steroid treatment
Secondary IOL intervention	
Exchange	The investigational device is replaced with the same lens model.
Removal	The investigational device is removed and replaced with a noninvestigational lens or no lens is implanted.
Reposition	The existing IOL is surgically moved to another location or rotated.

BCDVA = best-corrected distance visual acuity; FA = fluorescein angiography; IOL = intraocular lens; IOP = intraocular pressure; OCT = optical coherence tomography; RD = retinal detachment; SUN = Standardization of Uveitis Nomenclature.

Table 2. Definitions of Indications for Device Exchange, Removal, or Reposition

Indication	Definition
Capsular block syndrome	Hyper-distention of the lens capsular bag due to the IOL optic blocking egress of fluid through the anterior capsulotomy typically inducing a myopic refractive error
Cataract	Any opacification of the crystalline lens with or without reduced visual acuity
Chronic anterior uveitis	Persistent anterior segment inflammation characterized by grade ≥1+ cell using SUN criteria[3]
Endothelial cell loss	Chronic endothelial cell loss at a rate greater than that due to normal aging
Incorrect IOL power	Postoperative refractive error different from predicted and not due to a calculation or other user error
Iris pigment epithelium loss*	New or worsening iris transillumination defects or increase in pigmented cells in the anterior chamber noted after the 1-wk visit when assessed before instillation of any dilating drops
Lens optic abnormality	Unanticipated visual outcome (e.g., acuity, contrast sensitivity, symptoms) associated with opacification, vacuoles, microvacuoles, or subsurface nanoglistenings and not due to other causes
Malpositioned IOL	Decentration, tilt, or rotation of IOL requiring reoperation May include changes induced by Nd:YAG laser anterior or posterior capsulotomy
Early	If noted before 120 days postoperatively
Late	If noted at ≥120 days postoperatively
Damaged IOL	Crack of lens optic, breakage, or deformity of haptic, or other damage to the IOL May include changes induced by Nd:YAG laser anterior or posterior capsulotomy
Pupil ovalization	Progressive deformation of the pupil with elongation of the pupil in the meridian of the long axis of the IOL Documentation to be made under photopic conditions†
Pain	Graded as ≥4 on the standardized pain numeric rating scale of current pain intensity from 0 (no pain) to 10 (worst possible pain)
Peripheral anterior synechiae	Progressive closure of the anterior chamber angle due to propagation of anterior synechiae in the absence of obvious anterior uveitis
Patient-reported undesirable optical phenomena	Dysphotopsia (positive or negative or both), monocular diplopia, intolerable glare, halos, or other visual symptoms, not due to 1 of the indications listed

IOL = intraocular lens; Nd:YAG = neodymium-doped yttrium aluminium garnet; SUN = Standardization of Uveitis Nomenclature.
*If there is a transillumination defect preoperatively, then a photograph should be taken, and then at each subsequent visit, a photograph should be taken and compared with the preoperative photograph via a standardized photographic method.
†A consensus statement regarding a proposed methodology for standardizing assessment of pupil ovalization is available in Appendix 1.

The American Academy of Ophthalmology Task Force for Developing Novel Endpoints for Premium Intraocular Lenses Members include Jack T. Holladay, MD, MSEE, Chair; Adrian Glasser, PhD, Scott MacRae, MD, Samuel Masket, MD, Walter Stark, MD, and the following Food and Drug Administration staff members: Malvina Eydelman, MD, Don Calogero, MS, Gene Hilmantel, OD, Eva Rorer, MD, Tieuvi Nguyen, PhD, and Michelle E. Tarver, MD, PhD.

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Appendix 1. Oval Pupil Measurement Background and Standard Operating Procedure

Background

The only study of the oval pupil available was by Isotani et al[3] in 1995, who studied the ratio of the major to minor diameter in healthy subjects by using infrared photography. The subjects were dark adapted, so these are scotopic pupil measurements.

Standard Operating Procedure

If the clinician observes an oval or irregularly shaped pupil (dyscoria) at any visit after surgery, photographs should be taken at that visit and each subsequent visit to determine if the ovalization is progressive. The major and minor diameters of the pupil, which may not be orthogonal, are measured on the photograph, which must be taken in photopic conditions (>200 foot-candles or 2153 lux) so the pupil is maximally constricted. The pupil constriction provides the setting for pupil ovalization. For the measurement, the diameters must pass through the center of the least-squares, best-fit ellipse or centroid of the pupil perimeter. The ratio of the major to minor diameter is then calculated and reported. The photograph may be taken with any camera, including but not limited to slit-lamp cameras, topographers, and Scheimpflug devices, but the eye image must be captured under photopic conditions as specified.

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Special Report: American Academy of Ophthalmology Task Force Summary Statement for Measurement of Tilt, Decentration, and Chord Length

Currently, the measurement of tilt and decentration is not commercially available in an instrument or method that has been validated clinically. In lieu of a validated, commercially available instrument or method, the current statuses of 3 different approaches that have been used to measure tilt and decentration are described to help provide the basis for the future development of an instrument or technique.

Definitions

- Decentration of an intraocular lens (IOL) is the lateral horizontal and vertical displacement of an IOL relative to the visual axis as seen by the clinician through the cornea (subject-fixated coaxially sighted corneal light reflex, as described by Chang and Waring[1]).
- Tilt of an IOL is the horizontal and vertical angle from perpendicular of an IOL relative to the visual axis (subject-fixated coaxially sighted corneal light reflex, as described by Chang and Waring[1]).
- Chord length μ is the displacement (distance) between the subject-fixated coaxially sighted corneal light reflex and pupil center.[1] For some diffractive IOLs, the midpoint between pupil center and visual axis may be optimal.

Tilt, Decentration, and Chord Length μ

The goal is to measure tilt, apparent decentration through the cornea, and chord length μ on all subjects with a premium IOL.

Table 1. Ratio of IOL Toricity to Corneal Astigmatism

	Effective Lens Position					
A-constant—>	116.346	117.203	118.059	118.916	119.773	120.630
Surgeon Factor—>	0.287	0.772	1.257	1.742	2.227	2.713
ELP—>	4.000	4.500	5.000	5.500	6.000	6.500
IOL Power	Resulting Ratio of IOL Toricity to 2 D of Corneal Astigmatism					
10	1.359	1.424	1.494	1.571	1.654	1.745
22	1.277	1.330	1.387	1.450	1.519	1.595
34	1.198	1.239	1.284	1.334	1.390	1.452
46	1.121	1.151	1.185	1.223	1.267	1.316

D = diopter; ELP = effective lens position; IOL = intraocular lens.

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