Femtosecond laser-assisted arcuate incisions versus manual arcuate incisions outcomes

An investigator initiated clinical trial

1. TITLE PAGE

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IRB / ERC

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(funding only, this is an investigator-initiated study IIT # 50130883)
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Test Articles: LenSx laser arcuate relaxing incisions
Manual (blade) arcuate relaxing incisions

Investigators: Clayton Blehm, MD, Gainesville, GA

2. GENERAL INFORMATION

Objective	To compare the effectiveness of LenSx laser arcuate relaxing incisions vs. manual (blade) arcuate relaxing incisions in patients with low, but significant, levels of astigmatism.
Test Article(s)	LenSx laser arcuate relaxing incisions
Control Article(s)	Manual (blade) arcuate relaxing incisions
Sample size	41 patients, 82 eyes
Study Population	Subjects ≥40 years of age presenting for astigmatism reduction at the time of cataract surgery or refractive lens exchange who are considered appropriate candidates for arcuate incisions.
Number of sites	One site (Gainesville, GA)
Study Design	A prospective, randomized, contralateral eye comparative study
Masking	None
Variables	Primary Endpoint: Residual refractive astigmatism Secondary Endpoint: Percentage of eyes with refractive astigmatism ≤ 0.50 D Uncorrected monocular distance visual acuity Corneal astigmatism at 3 months Manifest refraction at 3 months Exploratory Endpoints: Topographic changes
Duration / Follow-up	Pre-operative to 3 months post-operative

Study will be registered with clinicaltrials.gov.

3. TABLE OF CONTENTS

4. INTRODUCTION

Multiple options exist for the treatment of astigmatism at the time of cataract surgery. Many clinicians believe the residual refractive cylinder following cataract surgery should remain at 0.5D or less to achieve the most desirable visual outcomes. Patients with low levels of preoperative corneal astigmatism can opt for arcuate relaxing incisions. Manual (blade) arcuate relaxing incisions are in common use. More recently, laser arcuate incisions have been introduced with a promise of more predictable outcomes when compared to the manual technique.

5. OBJECTIVE(S)

The objective of this study is to compare the effectiveness of LenSx laser arcuate relaxing incisions vs. manual (blade) arcuate relaxing incisions in patients with low, but significant, levels of astigmatism.

The primary outcome measure will be the residual refractive astigmatism. Secondary outcome measures will be the percentage of eyes with refractive astigmatism ≤ 0.50 D, uncorrected monocular distance visual acuity, corneal astigmatism and manifest refraction at 3 months. Exploratory endpoint will be the topographic changes.

6. SUBJECTS

6.1. Subject Population

Eligible test subjects will be patients presenting for astigmatism reduction at the time of cataract surgery or refractive lens exchange surgery who are interested and eligible for arcuate incisions.

A total of 41 subjects at one site will be enrolled. Subjects must meet the inclusion criteria. Prior to enrollment, subjects will be provided information on the study and asked to sign a patient information and consent form to participate. The patient information and consent form will be approved by an appropriate ethics committee.

6.2. Inclusion Criteria

Subjects are eligible for the study if they meet the following criteria:

Note: Ocular criteria must be met in both eyes.

- are willing and able to understand and sign an informed consent;
- are willing and able to attend all study visits;
- are more than 40 years of age, of either gender and any race;
- are presenting for cataract surgery or refractive lens exchange with a desire to reduce astigmatism and will be implanted with a non-toric lens

- have good ocular health, with no pathology that compromises visual acuity (outside of residual refractive error and cataract)
- have 0.50D to 1.75D of regular corneal astigmatism
- have potential acuity of 20/25 or better
- Are scheduled to have a non-toric monofocal IOL (SN60WF) lens implanted in both eyes

6.3. Exclusion Criteria

If any of the following exclusion criteria are applicable to the subject or either eye, the subject should not be enrolled in the study.

- Irregular astigmatism (e.g. keratoconus)
- Corneal pathology (e.g. scar, dystrophy, pterygium, moderate-to-severe dry eye)
- Monocular status (e.g. amblyopia)
- Previous radial keratotomy, corneal refractive surgery or other corneal surgery (e.g. corneal transplant, DSAEK, lamellar keratoplasty)
- Previous anterior or posterior chamber surgery (e.g., vitrectomy, laser iridotomy)
- Diabetic retinopathy
- Macular pathology (e.g. ARMD, ERM)
- History of retinal detachment
- Subjects who have an acute or chronic disease or illness that would confound the results of this investigation (*e.g.*, immunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, and any other such disease or illness), that are known to affect post-operative visual acuity.

Pregnancy has a known effect on the stability of refractions and visual acuity. As such, subjects who become pregnant during the study will not be discontinued but their data may be excluded from analyses of effectiveness.

6.4. Exclusion Criteria during surgery

If any of the following exclusion criteria are applicable to the study eye, the subject should not continue in the study.

- If the laser arcuate procedure cannot be completed due to physiological or other considerations.
- If there are complications related to completion of the arcuate incisions.
- Other procedure, such as pupil stretch, expanders, iris hooks during surgery.

Note: Any subject in which surgery has been aborted for either eye should immediately be discontinued from the study and an exit form completed for that subject. These subjects will be followed up as per the clinic standard of care, monitored for safety, and their data will be excluded from the study efficacy analysis (obtained from FDA database Research Results Feb, 05, 2009). All adverse events will be appropriately documented and reported.

Participants who are considered to be a vulnerable subject population will not be enrolled into the study. Vulnerable populations include, but are not limited to, the following:

- Prisoners
- Nursing home residents /institutionalized individuals
- Mentally disabled /cognitively impaired individuals
- Sponsor employees and their family members
- Site employees and their family members that are directly and indirectly involved with the study
- Economically and/or educationally disadvantaged individuals
- Comatose individuals / traumatized individuals
- Adults who do not read and/or write
- Patients with deafness or severe hearing disability
- Terminally ill individuals / individuals with life-threatening conditions

7. STUDY DESIGN

7.1. Study Design

This study is a comparative, prospective, randomized contralateral eye study of visual outcomes after LenSx laser arcuate relaxing incisions utilizing the Woodcock nomogram at 90% thickness vs. manual (blade) fixed keratome diamond knife at 600 microns for arcuate relaxing incisions utilizing the Donnenfeld nomogram. Subjects will be assessed pre-operatively and at 1 day, 1 month and 3 months post-operatively. Clinical evaluations will include measurement of visual acuity, manifest refraction and corneal astigmatism measurement with the Lenstar and slit lamp exam.

The primary outcome measure will be the residual refractive astigmatism. Secondary outcome measures will be the percentage of eyes with refractive astigmatism ≤ 0.50 D, uncorrected monocular distance visual acuity, corneal astigmatism and manifest refraction at 3 months. Exploratory endpoint will be the topographic changes.

7.2. Methods Used to Minimize Bias

This is a contralateral eye study where one eye will be randomized to either the laser group or the manual group. This is expected to minimize patient bias.

The measurement of visual acuity will be conducted in a systematic fashion to minimize bias. Individuals conducting visual acuity measures will be instructed to perform the same testing in the same fashion for all subjects, with the same level of encouragement to subjects.

All data collection will be completed through provided Case Report Forms (CRFs). All site personnel involved in the study will be trained in regard to conducting study-specific procedures.

8. STUDY PROCEDURE

8.1. Visits and Examinations

Subjects will participate in six study visits. Visits will include an uptake visit, one operative visits, and 3 postoperative visits (Visit numbers 3-5 below). The visit schedule, complete with window and associated CRF forms, are displayed in Table 8.1-1. Details of each study visit, including testing to be conducted, are provided below.

Table 8.1-1. Visit Schedule

Visit Number	Visit Name	Visit Window	CRF Number
1	Preoperative	-30 to 0 days from surgery	1
2, 2A	Operative	0 from surgery	2, 2A
3, 3A	1 Day Postoperative	1-2 days postoperative	3, 3A
4	1 Month Postoperative	30 (±12) days postoperative*	4
5	3 Months Postoperative	90 (±20) days postoperative*	5

*From second eye surgery

8.1.1. Preoperative

At the preoperative exam, subjects will be consented, qualified for the study (compared with inclusion/exclusion criteria), and assigned a study ID/subject number. Subject numbers will be assigned sequentially in the order of enrollment. Pre-operative qualification should take place no more than 30 days prior to surgery.

A medical history will be taken and exams will include the tests described below:

- manifest refraction,
- visual acuity,
- Corneal astigmatism measurements (Verion, Lenstar, topography),
- Slit lamp exam,

In addition, all site-specific, routine preoperative measures should be undertaken.

Measurements should be made as described in section 8.2 below.

8.1.2. Operative (Surgery)

All subjects will receive a Betadine prep in the usual sterile fashion. They will then be taken to the operative room and treated with the assigned method. Each patient would undergo a randomized process of one eye obtaining LenSx laser arcuate(s) and the contralateral eye obtaining manual blade arcuate(s). Accepted nomograms would be utilized to calculate the exact length and positioning of the arcuate incisions.

Outside of the femtosecond laser arcuate incisions, no other femtosecond procedure will be performed on any eyes. The corneal surgical incisions, capsulorhexis and fragmentation will be performed without use of the femtosecond laser system.

All eyes will be implanted with a non-toric monofocal IOL, specifically the SN60WF lens (Alcon, Fort Worth, TX).

Surgical findings will be recorded and any adverse events/serious adverse events (AEs/ SAEs) occurring during surgery will be noted at this visit. Any other problems during surgery and comments regarding surgery will be documented.

Any subject whose surgery is not completed successfully will be documented in the appropriate case report form. These subjects will be monitored for safety but clinical performance data may be excluded from the analysis.

Immediately following the laser treatment, the arcuate incisions will be opened at an operating microscope. All study subjects will be placed on an appropriate antibiotic and steroid drop QID for one week.

For the following three weeks, only the steroid drop will be continued on a tapered dose.

8.1.3. Postoperative 1 Day

All routine postoperative measures should be undertaken. In addition, the subject will undergo VA testing in accordance with the specifications below (Section 8.2). Adverse events will be monitored.

8.1.4 Postoperative 1 Month

All routine postoperative measures should be undertaken. In addition, the subject will undergo manifest refraction and VA testing in accordance with the specifications below (Section 8.2) and have their corneal astigmatism measured using the Lenstar, Verion and topography devices. Adverse events will be monitored.

8.1.5. Postoperative 3 Months

All routine postoperative measures should be undertaken. In addition, the subject will undergo manifest refraction, VA testing, slit-lamp examination and corneal astigmatism measurements with the Lenstar, Verion and topography devices. Adverse events will be monitored.

8.1.6. Exit Procedures

In the event of premature exit from the study, all study related examinations should be completed where possible. The Exit CRF should be completed, noting that the subject did not complete the study and the reason for premature study exit. If no premature exit from the study occurs, the Exit CRF should be completed at the end of Visit 5 (Postoperative 3 Months).

8.2. Study Methods and Measurements

All routine testing and basic eye examinations should be carried out at each study visit. Abnormalities should be recorded in the CRF "Comment" section. Specific study examination procedures are outlined below.

8.2.1. Manifest Refraction

Perform a manifest refraction with a high contrast logMAR chart under photopic lighting conditions (>85 cd/m^2). Document refraction results with sphere, cylinder and axis readings. If uncorrected visual acuity is not improved by manifest refraction, use zero for sphere and cylinder and draw a line through the blank for the axis.

Note: Each subject should be manually refracted to his/her best correction by an ophthalmologist, optometrist, or a skilled technician using a phoropter or trial lenses.

8.2.2. Visual Acuity (VA)

To obtain logMAR VA, ask subjects to begin reading the chart at the smallest row where all letters are easily distinguishable. Have subjects continue to read rows with smaller letters and encourage subjects to guess at all letters in a line if at least one correct response was given on the previous row. Request subjects read rows

until no letters on a row are read correctly or until all letters on a row are too indistinguishable to even be guessed.

While the subject is reading the chart, record the number of letters on each line read incorrectly by the subject. The last line from which the subject read at least one letter correctly is recorded as the baseline logMAR VA. The actual logMAR VA is calculated using the baseline logMAR VA line and the number of letters read incorrectly. This VA should be recorded as the best-corrected monocular visual acuity at distance.

It is sufficient to record the uncorrected VA at distance for the 1-day visit.

All visual acuity testing is performed monocularly. Postoperatively, conduct testing uncorrected at all visits. In addition, conduct testing with the manifest refraction in place at 1 and 3 months post-operatively.

Distance VA
Measure distance visual acuity using a high contrast logMAR ETDRS chart under photopic lighting (>85 cd/m2) at a distance of 4-6 m.

8.2.3. Corneal astigmatism measurement

This should be performed by an ophthalmologist, optometrist, or a skilled technician. The measurements will include use of the Lenstar device, the Atlas corneal topographer and the Verion imaging system.

8.3 Unscheduled Visits

Unscheduled exams may be conducted at the discretion of the Investigator with all relevant information from the exam recorded in the source documents and on the Unscheduled Visit pages within the CRF booklet.

8.4 Discontinued Subjects

Discontinued subjects are those who do not have an exit visit or who come into the office to be exited prior to the scheduled final study visit. Subjects may be discontinued from the study at any time if, in the opinion of the investigator, their continued participation in the study poses a risk to their health. The reasons for discontinuation include:

a. Adverse event;
b. Lost to follow-up;
c. Subject decision unrelated to an adverse event;
d. Protocol violation;
e. Treatment failure;
f. Other.

To ensure the safety of all subjects who discontinue prior to Visit 5, investigators should assess each subject and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health. Any changes in medical health and/or use of concomitant medications also should be captured.

9. ANALYSIS PLAN

9.1. Analysis Data Sets

All subjects who are enrolled in the study will be evaluated for safety. Efficacy analyses will be performed based on data from those eyes where uncomplicated LenSx or manual arcuate incisions were completed.

9.2. Statistical Methodology

A summary of the data will be prepared for all measurement time points. Summaries of the changes observed between the pre-operative (baseline) and the 3 month post-operative visits will also be summarized. Comparison of the laser and manual groups in terms of post-operative corneal astigmatism, uncorrected visual acuity and residual refractive cylinder and spherical equivalent refraction will be documented.

For variables measured on a continuous scale, these summaries will include the sample size, as well as the mean, standard deviation, median, minimum, and maximum. These summaries will be provided for all eyes completing the study.

9.2.1. Within-treatment Changes

For variables measured on a continuous scale, the statistical significance of within-treatment changes between time points will be investigated using paired t-tests. For variables measured on an ordinal categorical scale, the Wilcoxon signed-rank test will be employed.

9.3. General Statistical Considerations

The statistical analyses will be performed using Statistica, version 12 or higher. Any statistical tests of hypotheses will employ a level of significance of alpha=0.05.

10. SAMPLE SIZE JUSTIFICATION

The sample size [based on a power of 0.8, an alpha of 0.05, an estimated standard deviation of postoperative refractive astigmatism of 0.4D (from the literature) and an expected improvement on average of 0.25D with laser incisions] would be 41 subjects.

11. CONFIDENTIALITY/PUBLICATION OF THE STUDY

The existence of this Study is confidential and should not be discussed with persons outside of the Study. Results will be submitted for publication and presentation at national and/or international meetings. A manuscript will be submitted to peer-review journals for publication but there is no guarantee of acceptance.

12. QUALITY COMPLAINTS AND ADVERSE EVENTS

All subjects will be monitored for adverse events over the course of the study. A place to record any adverse event is included on each case report form.

12.1. General Information

An Adverse Event (AE) is any untoward medical occurrence in a subject who is administered. a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. In clinical studies, an AE can include an untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

12.2. Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking if the patient has any problems.

12.3. Procedures for Recording and Reporting AEs and SAEs

Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on an Adverse Event Form (AEF). A separate AEF must be filled out for each event. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (ie, severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event's relationship to the study treatment.

Nonserious Adverse Events

A nonserious AE is defined as any untoward change in a subject's medical health that does not meet serious criteria noted below (eg, is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.). All adverse events must be reported regardless of whether or not they are related to the study treatment.

For non-serious adverse events, an AEF containing all available information will be collected on a routine basis and submitted to the Medical Monitor at the close of the study.

Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse experience that meets any of the following criteria:

- Results in death.
- Is life-threatening.

NOTE: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.
  All available information on a serious adverse event(s) and any other associated AE, if applicable, must be forwarded to the study coordinator for forwarding to the Medical Monitor immediately (ie, within one working day of the Investigator's or site's knowledge of the event) as follows:
  - In studies utilizing EDC (electronic data capture), all available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.
  - Additional information for any applicable event is to be reported as soon as it becomes available.

In addition to the reporting of serious adverse events to the study Medical Monitor, the SAE must be reported to the IRB / IEC according to their requirements.

The investigator must document all adverse events related to the procedure (serious and non-serious but related) and all serious adverse events (related and unrelated) on the Adverse Procedure Effect and Serious Adverse Event Form. Any procedure-related quality complaints will also be documented.

- **Both the Quality Complaint Form and the Adverse Procedure Effect and Serious Adverse Event Form must be faxed immediately to the study coordinator using the contact information below. Additional relevant information is to be reported as soon as it becomes available.**

Study Coordinator Contact Information for Prospective Laser vs Manual Arcuate Incision Outcome Study

Study Staff	Business Phone	Business email	Home Phone
MaryAnn Thomas	770-532-4444	mthomas@gainesvilleeye.com	770-519-2099

Further, depending upon the nature of the adverse event (serious or non-serious) or quality complaint being reported, the study sponsor may request copies of applicable portions of the subject's medical records. The investigator must also report all adverse events and quality complaints according to the relevant IRB requirements.

12.3.1 Intensity and Causality Assessments

For every adverse event and quality complaint, the investigator must assess the causality as Related or Not Related to the medical procedure under investigation. An assessment of causality will also be performed by the Medical Monitor utilizing the same definitions, as shown below:

Causality

Related — An adverse event or quality complaint classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical procedure has not been demonstrated, but there is a reasonable possibility that the adverse event or quality complaint was caused by the medical procedure.

Not Related — An adverse event or quality complaint classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the adverse event or quality complaint).

Where appropriate, the investigator must assess the intensity (severity) of the adverse event as mild, moderate, or severe based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild — An adverse event is mild if the subject is aware of but can easily tolerate the sign or symptom.

Moderate	An adverse event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An adverse event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

The investigator must document any action taken (i.e., medication, intervention, or treatment plan) and outcome of the adverse event or quality complaint when applicable.

12.4. Follow-Up of Adverse Events and Quality Complaints

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. Any additional data from these follow-up procedures must be documented and available to the study coordinator who, with the Medical Monitor, will determine when the data need to be documented on the CRFs.

13. GCP, ICH and ETHICAL CONSIDERATIONS

This study will be conducted in compliance with Good Clinical Practices (GCPs), including International Harmonization (ICH) Guidelines, and in general, consistent with the 1996 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements will be adhered to.

This study is to be conducted in accordance with Institutional Review Board regulations. The investigator will obtain appropriate IRB/ethics committee approval prior to initiating the study.

13.1 Confidentiality

The data collected will be data typical for the procedure(s) when performed on eyes outside the study. Any data collected will become part of the patient's clinical record. The data will be subject to the same privacy and confidentiality as other data in the clinical record.

Only the principal investigator, research consultant and clinic staff will have access to the data collected. All data shared outside the practice will be de-identified; patients' protected health information will not be available and will not be reported in any analyses or publications. No data will be sold to third parties. De-identified data may be used for future research.

14. STUDY PLAN

Table 14.-1. Study Plan

Activity	Preoperative	Operative	Postoperative		
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
			1 Day	1 Month	3 Month
Informed Consent	X				
Demographics	X				
General Information: Medical History	X				
Surgery		X			
Manifest Refraction	X			X	X
Uncorrected Distance VA	X		X	X	X
Corrected Distance VA	X			X	X
Corneal astigmatism measurement	X			X	X
Monitor for Adverse Events		X	X	X	X
Complete Exit Form[1]					X

[1] Complete Exit Form upon termination of subject participation, or at Visit 5, whichever occurs first.