Intrastromal Lenticule Extraction with a New 345nm Ultraviolet Femtosecond Laser: A Six Month Safety Evaluation in Pigmented Rabbits

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Overview and Purpose

This prospective, GLP-regulated safety investigation assessed ocular safety parameters in pigmented rabbits following Intrastromal Lenticule Extraction (ILE) utilizing a novel 345nm ultraviolet (UV) femtosecond laser as compared to LASIK.

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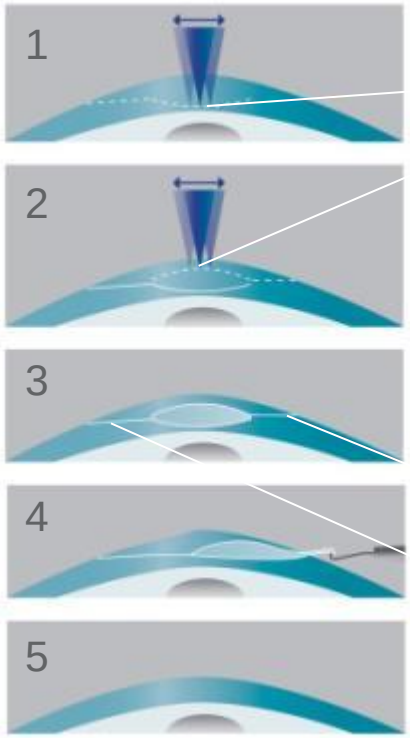
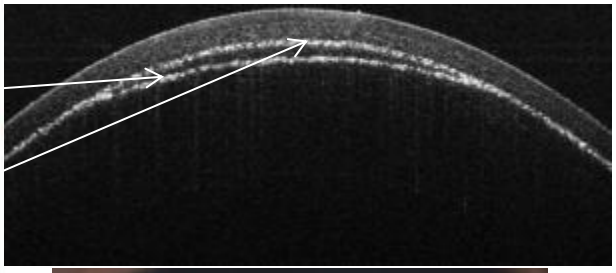
Lenticule Extraction Procedure

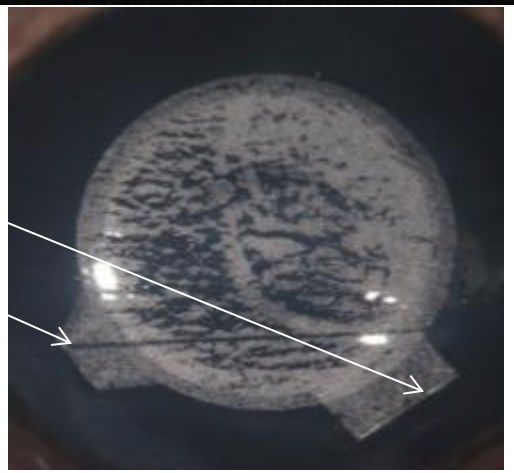
This procedure employs an investigational femtosecond laser (low pulse energy and high pulse repetition rate) with a wavelength of 345 nm to create a lenticule of intrastromal corneal tissue

Procedure Steps:

1. Creation of lower boundary of intrastromal lenticule
2. Creation of upper boundary of intrastromal lenticule in the stroma
3. Creation of channels for extraction of intrastromal lenticule
4. Manipulation and extraction of lenticule manually by surgeon
5. Lenticule removal complete







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Methods: Treatment Groups

Parameter	Group 1 IR-Femtosecond LASIK with Excimer Ablation (Control)	Group 2 UV-Femtosecond ILE Anticipated Clinical Exposure	Group 3 UV-Femtosecond ILE 5.5-fold Anticipated Clinical Exposure
Correction (diopters)	-5.0	-5.0	-5.0
Energy	800 nJ (femtosecond laser)	80 nJ	120 nJ
Spot Separation	7 µm x 7 µm (femtosecond laser)	4 µm x 4 µm	1.5 µm x 1.5 µm
Optical Zone	5.5 mm	5.5 mm	5.5 mm
Lenticule Depth / Flap Thickness	150 µm	150 µm	150 µm
Central Ablation Depth / Lenticule Thickness	55 µm	55 µm	55 µm
Animals on Study	16	16	16
Duration of Study	~ 6 months	~ 6 months	~ 6 months

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Methods: Observations

Parameter	Observation Schedule
Slit Lamp	PS, SDs 3, 7, 14, 21 and 28, monthly thereafter
Indirect Biomicroscopy	PS, SDs 3, 14 and 28, monthly thereafter
Intraocular Pressure	PS, SDs 7, 14, 21 and 28, monthly thereafter
Pachymetry	PS, SDs 7, 14, 21 and 28, monthly thereafter
Specular Microscopic Endothelial Analysis	PS, and SDs 12, 26 and 180
Histopathology (eyes and adnexa only)	Approximately 4 weeks (4 animals) and ~6 months (6 animals)

Abbreviations: PS = prescreen, SD = Study Day

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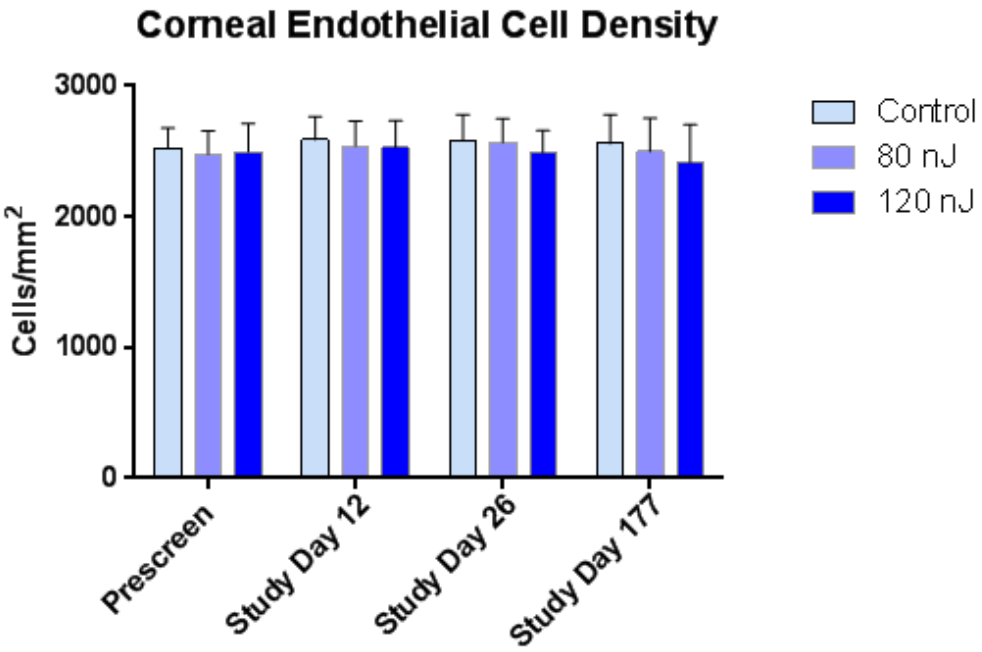
Results: Corneal Endothelium Stable out to Six Months

- No significant differences were noted between groups throughout study for:
  - Mean Corneal Endothelial Cell Density
  - Mean Endothelial Cell Area
  - Coefficient of Variation of Mean Cell Size
  - Percent Hexagonal Cells

N Values*			
Time Point	Control	80 nJ	120 nJ
Prescreen	16	16	16
Study Day 12	10	13	6
Study Day 26	9	13	13
Study Day 177	5	6	6

*Variation in n values on SDs 12 through 177 are due to:
- Attrition due to 48 hr interim sacrifice
- Dislocated flaps in control Group
- Stromal haze on Study Day 12 in 120 nJ Group



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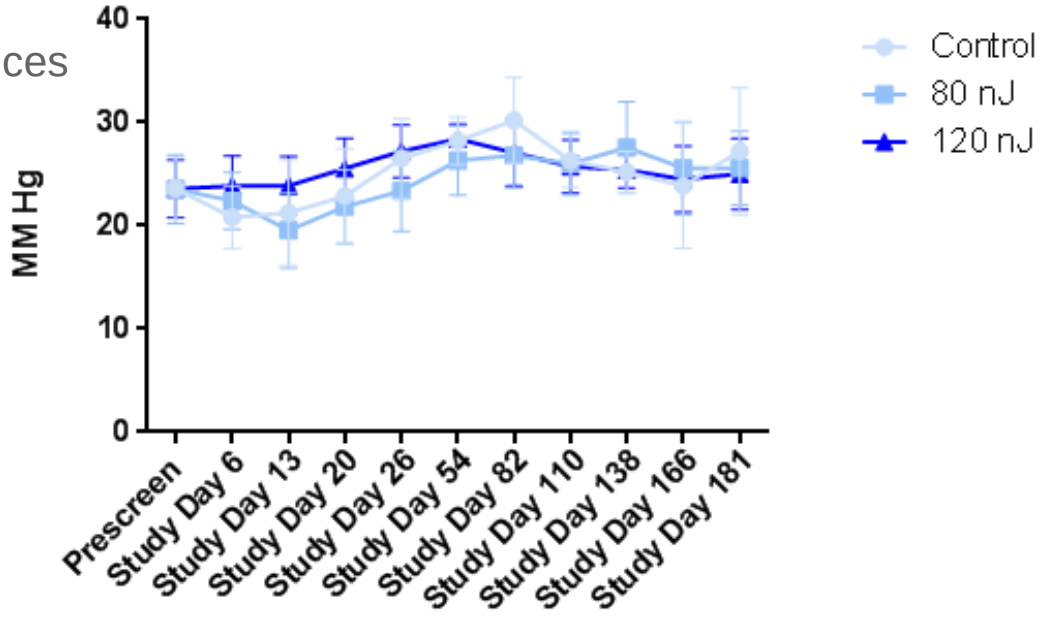
Results: Intraocular Pressure Unaffected by Lenticule Extraction

- Intraocular Pressure in Study Group 3 (120nJ) was significantly higher on Study Day 6 when compared to control, however, Group 3 IOP was similar to untreated control and baseline values so finding is not considered biologically significant

- No other statistically significant differences were noted for intraocular pressure

N Values			
Time Point	Control	80 nJ	120 nJ
Prescreen	15	16	16
Study Days 6-26	12	13	13
Study Days 54-177	5	6	6

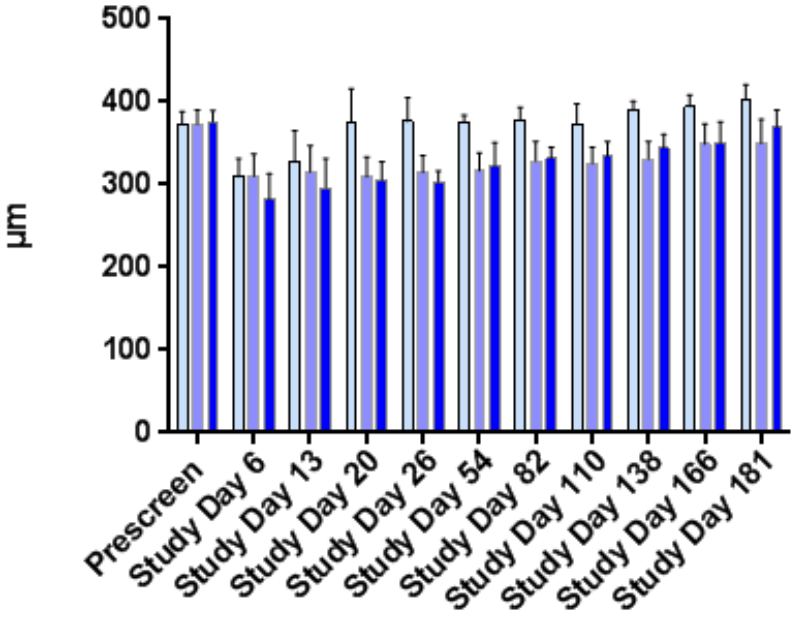


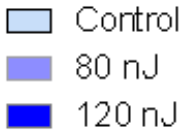
Results: Corneal Thickness Stable following Lenticule Extraction

- Pachymetry measurements indicate stable corneal thickness following surgery for both the 80 and 120 nJ UV-FSL groups

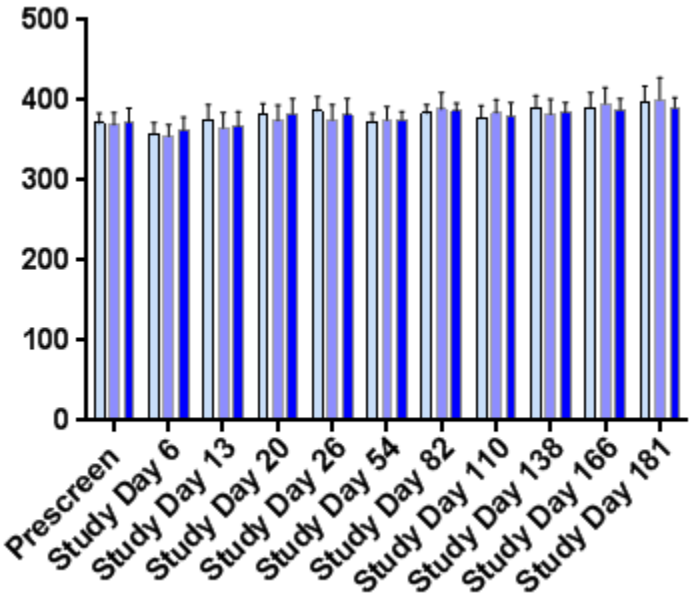
N Values			
Time Point	Control	80 nJ	120 nJ
Prescreen	15	16	16
Study Days 6-26	12	13	13
Study Days 54-177	5	6	6

Treated Eyes





Untreated Controls



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Results: Summary of Biomicroscopic Observations

- Following surgery, minimal to mild conjunctival congestion and aqueous flare were observed spontaneously with similar frequency and severity among groups.

- Corneal Cloudiness was observed in all three groups:
  - Highest severity on Study Day 3 (score of 2) was most frequent in Group 3 (exaggerated exposure group)
  - By Study Day 8, Animals in all groups had minimal corneal haze (score of 1 or less) scores with no haze observed grossly
  - By Study Day 29, only faint corneal haze (score of 0.5 or less) was observable by slit-lamp at the lenticule removal ports in Group 2 (anticipated clinical exposure group)
  - Minimal haze (score of 1) persisted in Group 3 (exaggerated exposure group) at Study Day 29 resolving to faint corneal haze (score of 0.5) observable at lenticule removal port by slit-lamp at Study Day 55 and barely perceptible after Study Day 110

- No changes to the crystalline lens or retina through Study Day 177

Results: Summary of in-life Findings

Parameter	Study Day	IR-Femtosecond LASIK with Excimer Ablation (Control)	UV-FSL 80 nJ	UV-FSL 120 nJ
Corneal endothelium (specular microscopy)	177	Stable	Stable	Stable
IOP	177	Stable	Stable	Stable
Pachymetry	177	Stable	Stable	Stable
Corneal Haze *via* Slit Lamp Biomicroscopy	177	Haze perceptible at flap margin at Study Day 29 By Day 177, Haze is barely perceptible restricted to flap location/faint ring around flap margin	Haze barely perceptible at lenticule removal port only by Study Day 29, Haze no longer perceptible at lenticule removal port By Study Day 177	Haze barely perceptible at lenticule removal port only by Study Day 55, Haze no longer perceptible at lenticule removal port By Study Day 177
Cataract formation	177	No findings	No findings	No findings
Retina	177	No findings	No findings	No findings

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Results: Histopathology

- Treatment related effects were expected and included:
  - **All Groups**: Zone of corneal disorganization consistent with flap creation (Control) or lenticule removal (UV-FSL groups) at four weeks and still visible at six months
  - **All Groups**: Mild corneal epithelial hyperplasia. Less prominent in the UV-Femtosecond Laser groups compared to FS-200 control noted at four weeks and six months.
  - **UV-FSL 120 nJ (High Power) Group**: Minimal hypertrophy of corneal stromal keratocytes in the area of corneal disorganization at four weeks and no longer visible at six months
- No microscopic changes to the corneal endothelium, lens or retina in all three groups throughout study

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Conclusion

The ocular tolerability of a novel 345nm UV femtosecond laser utilized to perform an ILE procedure was characterized in a 6-month safety study in pigmented rabbits. Results indicate that the UV femtosecond laser at anticipated clinical exposure demonstrates a similar post-operative risk profile as LASIK in this preclinical model.

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