SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Femtosecond Laser System for refractive correction

Device Trade Name: VisuMax Femtosecond Laser

Device Procode: OTL

Applicant's Name and Address: Carl Zeiss Meditec, Inc.
5160 Hacienda Drive
Dublin, California 94568

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150040/S003

Date of FDA Notice of Approval: October 4, 2018

The original PMA (P150040) was approved on September 13, 2016 and is indicated for use in small incision lenticule extraction (SMILE) for the reduction or elimination of myopia ≥ -1.00 D to ≤ -8.00 D, with ≤ -0.50 D cylinder and Manifest Refraction Spherical Equivalent (MRSE) ≤ -8.25 D in the eye to be treated in patients who are 22 years of age or older with documentation of stable manifest refraction over the past year as demonstrated by a change of ≤ 0.50 D MRSE. The SSED to support the indication is available on the CDRH website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150040 and is incorporated by reference here. The current supplement was submitted to expand the indication for the VisuMax Femtosecond Laser to include treatment of myopia with astigmatism.

II. INDICATIONS FOR USE

The VisuMax Femtosecond Laser is indicated for use in small incision lenticule extraction (SMILE) for the reduction or elimination of myopia with or without astigmatism:

- For spherical refractive error (in minus cylinder format) from -1.00 diopters through -10.00 diopters,
- For cylinder from -0.75 diopters through -3.00 diopters,
- When refraction spherical equivalent is no greater in magnitude than 10.00 diopters,

in patients 22 years of age or older with documentation of stable manifest refraction over the past year as demonstrated by a change in sphere and cylinder of ≤ 0.50 D in magnitude.

III. CONTRAINDICATIONS

VisuMax Femtosecond Laser lenticule removal for the correction of myopia with or without astigmatism is contraindicated in patients with:

- a residual stromal bed thickness that is less than 250 microns from the corneal endothelium;
- abnormal corneal topographic findings, e.g. keratoconus, pellucid marginal degeneration;
- ophthalmoscopic signs of progressive or unstable myopia or keratoconus (or keratoconus suspect);
- irregular or unstable (distorted/not clear) corneal mires on central keratometry images;
- severe dry eye;
- active eye infection or inflammation;
- recent herpes eye infection or problems resulting from past infection;
- active autoimmune disease or connective tissue disease;
- uncontrolled diabetes;
- uncontrolled glaucoma.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the VisuMax Femtosecond Laser labeling.

V. DEVICE DESCRIPTION

The VisuMax Femtosecond Laser (**Figure 1**) is a precision ophthalmic surgical laser designed for the creation of incisions in the cornea. The action of the VisuMax and other femtosecond lasers mimics the cutting action of mechanical or blade-based keratomes. The VisuMax accomplishes this by scanning tightly focused patterns of femtosecond laser pulses in the cornea at precise and predefined positions and depths. Each laser pulse produces a micro-photodisruption in tissue of only a few microns in size. Patterns of contiguous, focused laser pulses result in the creation of continuous cut surfaces in the cornea.

Figure 1. VisuMax Femtosecond Laser

Table 1. The VisuMax Femtosecond Laser System consists of the following major components:

Laser Console	The Laser Console houses the femtosecond laser source, the scanning delivery system, the computer and software-hardware control system, an uninterruptible electrical power supply, the power supply distribution electronics, a visualization system and surgical microscope, two slit illumination units, the interface hardware for the Treatment Pack, user controls and user interface.
Patient Supporting System	The Patient Supporting System (PSS) is used to support the patient in a supine position during corneal surgery with the VisuMax Femtosecond Laser. The PSS is also used to properly position the patient with respect to the Treatment Pack affixed to the treatment objective lens in the Laser Console. The joystick control on the PSS is manipulated by the user to position the patient with respect to the Treatment Pack, and to applanate and immobilize the eye of the patient in preparation for laser treatment.
Accessories - Treatment Pack	The VisuMax Treatment Pack is a commercially available, pre-sterilized, single-use disposable accessory to the VisuMax Femtosecond Laser. It consists of disposable elements that allow for the laser beam to be properly coupled onto a patient's cornea in a precise and controlled manner. No cleaning, disinfection or re-sterilization by the user is required or permitted. The Treatment Pack is contained in the blister pack that has been tested to maintain the sterility of the inner contents during the labeled shelf life using accepted international standards and accelerated test conditions accompanied by real life testing.

For the small incision lenticule extraction procedure, an intrastromal lenticule is created with the femtosecond laser in a shape corresponding to the desired refractive correction

in the intact cornea. The femtosecond incisions for the spherical only SMILE procedure consist of four separate cuts (posterior cut, side cut for the lenticule, cap cut (anterior cut), and side cut for the opening incision), which are completed in succession in the procedure. For spherocylindrical lenticules, there is an additional transition zone cut between the lenticule posterior curved surface and the edge of the lenticule. The lenticule is subsequently accessed and removed by the surgeon through the opening incision.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative methods of correcting spherical or spherocylindrical myopia include: spectacle correction (glasses), contact lenses, Laser-Assisted In Situ Keratomileusis (LASIK, including conventional LASIK, wavefront-guided LASIK, and topography-guided LASIK), photorefractive keratectomy (PRK), and phakic intraocular lenses.

Each alternative has its own advantages and disadvantages. A prospective patient should fully discuss these alternatives with his/her eye care provider to select the correction method that is best for the patient.

VII. MARKETING HISTORY

The ZEISS VisuMax Femtosecond Laser including the lenticule removal procedure is commercially available in more than 200 countries, including the following: Algeria, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, China, Croatia, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Iceland, Ireland, Kazakhstan, Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Morocco, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Arab Emirates, United Kingdom, and Vietnam.

The ZEISS VisuMax Femtosecond Laser has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential adverse effects (e.g., complications) associated with the VisuMax SMILE procedure include, but are not limited to:

- Loss of best spectacle corrected visual acuity (BSCVA) or contrast sensitivity;
- Over-correction or under-correction;
- Increase in refractive cylinder;
- Difficulty with night driving;
- Headache or eyestrain due to imbalance between the eyes;
- Worsening of patient complaints such as glare, halos, starbursts, hazy or blurred vision, distortion, double or ghost images, fluctuation of vision, focusing difficulty, difficulty with depth perception, light sensitivity; grittiness, and ocular pain/soreness;

- Transient light sensitivity syndrome;
- Dry eye;
- Ptosis;
- Increase in IOP;
- Lens opacity;
- Conjunctivitis;
- Iritis;
- Corneal haze/scar/infection/inflammation/infiltrate/ulcer/epithelial defect/epithelium in the interface/ edema/decompensation/striae or microstriae/ectasia;
- Perforated, miscreated, or melting of the cap;
- Treatment interruption, difficult lenticule removal with tissue damage or retained lenticule; ocular penetration;
- Retinal detachment/posterior vitreous detachment/vascular accidents.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The following additional testing was conducted to support the new indication. Testing conducted under the original PMA (P150040) is incorporated by reference here.

i. Pattern Generator Testing

The VisuMax Pattern Generator software module used to produce the three-dimensional patterns for the SMILE treatment was tested against a separate implementation of the SMILE cut pattern algorithms in order to verify that the SMILE refractive geometric parameters are correctly predicted by the Pattern Generator software implementation. Test results for the Pattern Generator software module implementation for spherocylindrical myopia treatments were found to correctly predict all tested SMILE refractive parameters within test acceptance criteria.

ii. Cut Shape Verification Testing

Cut shape verification testing was performed for the VisuMax for the sphere-only SMILE procedures that were the subject of P150040. This verification testing of cut shapes was repeated for the implementation of spherocylindrical SMILE treatments.

A series of laser scanning microscope images were made of the cross sections of ex vivo porcine corneas in which lenticule cuts were completed by the VisuMax Femtosecond Laser. The laser scanning images demonstrated that lenticule cut surface shapes and the lenticule cut positions were produced in corneas with good geometric fidelity and good accuracy.

All test criteria were met, demonstrating that cut surface shapes and cut positioning were created in corneas with good geometric fidelity and good quality.

iii. Cut Geometry Verification Testing

Performance testing was undertaken in which all geometric or laser scanning parameters were verified for the complete range of spherocylindrical VisuMax SMILE treatments that are the subject of this PMA supplement.

In the same manner as the tests reported in P150040, the verification test consisted of SMILE cuts made in a number of porcine globes for SMILE scanning patterns. The test procedure consists of verifying cut dimensions, laser scanning direction, feature orientations, the presence or absence of particular features associated with cut types, etc. Dimensions, positioning and orientations of all geometric and laser scan parameters that could be directly observed were all positively verified.

In addition to verifying the laser scanning parameters, geometric parameters and cut features, proper dissection or separation of tissue planes at the various cut surfaces was verified. Additional verification steps included verification that opening incisions could be accessed, verification that the laser-cut lenticules could be removed, and verification of the quality of side cuts, lamellar cuts, corneal flap cuts and side cut incisions. This aspect of the verification test demonstrates the ability of the VisuMax to cut spherocylindrical lenticules with transition zones with good cut quality and tissue dissection.

B. <u>Additional Studies</u>

i. Electrical Safety, Electromagnetic Compatibility, and Laser Safety Testing

The VisuMax Femtosecond Laser was tested by accredited third-party laboratories to ensure compliance with the applicable international standards for electromagnetic compatibility, electrical safety and laser safety. These standards include IEC 60601-1 (General Requirements for Safety), IEC 60601-1-2 (Electromagnetic Compatibility Requirements and Tests), IEC 60601-1-4 (Programmable Electrical Medical Systems), IEC 60601-2-22 (Particular Requirements for the Safety of Diagnostic and Therapeutic Laser Equipment), IEC 60825-1 (Safety of Laser Products, Part 1 - Equipment Classification, and Requirements), and IEC 60825-5 (Safety of Laser Products – Manufacturer's Checklist). Additionally, the VisuMax Femtosecond Laser meets all relevant design and performance standards for light-emitting products as defined in 21 CFR Part 1040.

ii. Software Validation Testing

ZEISS procedures require the establishment and review of specifications, development of risk analysis, and adequate verifications and validation of software and hardware prior to release. Risk management procedures were applied according to current ISO 14791 and IEC 60601-1 standards.

Software testing was performed in accordance with IEC 60601-1-4 to verify and validate module and system level functions. The results of the overall validation testing demonstrate that the VisuMax Femtosecond Laser meets all software specifications and requirements.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the SMILE procedure with the VisuMax Femtosecond Laser in subjects with myopia with or without astigmatism in the US under IDE # G140232. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between February 18, 2015 and July 29, 2016 at 5 investigational sites. The database for this PMA supplement reflected data collected from 357 treated subjects.

This was a prospective, multi-center, single-armed, unmasked clinical study. Subjects were followed for 12 months postoperatively.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the study was limited to patients who met the following inclusion criteria:

   1. Male and female subjects age 22 years of age and older;
   2. Spherical myopia from ≥ -1.00 diopter (D) to ≤ -10.00 D, with ≤ -3.00 D cylinder and manifest refraction spherical equivalent (MRSE) ≤ -11.50 D, in the eye to be treated;
   3. A stable refraction for the past year, as demonstrated by a change in MRSE of ≤ 0.50 D in the eye to be treated;
   4. A difference between cycloplegic and manifest refractions of < 0.75 D spherical equivalent in the eye to be treated. (SE) is the difference between cycloplegic and manifest refractions;
   5. Uncorrected visual acuity (UCVA) worse than 20/40 in the eye to be treated;
   6. Best spectacle corrected visual acuity (BSCVA) at least 20/20 in the eye to be treated;
   7. Discontinue use of contact lenses for at least 2 weeks (for hard lenses) or 3 days (for soft lenses) prior to the preoperative examination, and through the day of surgery; All contact lens wearers must demonstrate a stable refraction (within ±0.5 D), as determined by MRSE, on two consecutive examinations at least 1 week apart, in the eye to be treated;
   8. Central corneal thickness of at least 500 microns in the eye to be treated;
   9. Willing and able to return for scheduled follow-up examinations;

10. Able to provide written informed consent and follow study instructions in English.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

1. Mesopic pupil diameter > 8.0 mm;
2. Cylinder greater than -3.00 D;
3. Treatment depth is less than 250 microns from the corneal endothelium;
4. Eye to be treated is targeted for monovision;
5. Fellow eye has BSCVA worse than 20/40;
6. Keratometry readings via Sim-K values less than 40.00 D;
7. Abnormal corneal topographic findings, e.g., keratoconus, pellucid marginal degeneration, in either eye;
8. History of or current anterior segment pathology, including cataracts in the eye to be treated;
9. Clinically significant dry eye syndrome unresolved by treatment in either eye;
10. Residual, recurrent, active ocular or uncontrolled eyelid disease, corneal scars or other corneal abnormality such as recurrent corneal erosion or severe basement membrane disease in the eye to be treated;
11. Ophthalmoscopic signs of progressive or unstable myopia or keratoconus (or keratoconus suspect) in either eye;
12. Irregular or unstable (distorted/not clear) corneal mires on central keratometry images in either eye;
13. History of ocular herpes zoster or herpes simplex keratitis;
14. Deep orbits, strong blink, anxiety, pterygium, or any other finding suggesting difficulty in achieving or maintaining suction;
15. Difficulty following directions or unable to fixate;
16. Previous intraocular or corneal surgery of any kind in the eye to be treated, including any type of surgery for either refractive or therapeutic purposes;
17. History of steroid-responsive rise in intraocular pressure, glaucoma, or preoperative intraocular pressure (IOP) > 21 mmHg in either eye;
18. History of diabetes, diagnosed autoimmune disease, connective tissue disease or clinically significant atopic syndrome;
19. Immunocompromised or requires chronic systemic corticosteroids or other immunosuppresive therapy that may affect wound healing;
20. History of known sensitivity to planned study medications;
21. Participating in any other ophthalmic drug or device clinical trial during the time of this clinical investigation;
22. Pregnant, lactating, or of child-bearing potential and not practicing a medically approved method of birth control.

2. Follow-up Schedule
All patients who agreed to participate in the study were to return for follow-up examinations per the following schedule:

Preoperative Evaluation: Day -60 to Day -1
Operative Evaluation: Day 0, day of surgery
Postoperative Day 1: Days 1
Postoperative Week 1: Days 5 to 9
Postoperative Month 1: Days 21 to 35 (Weeks 3 to 5)
Postoperative Month 3: Days 70 to 98 (Weeks 10 to 14)
Postoperative Month 6: Days 147 to 182 (Weeks 21 to 26)
Postoperative Month 9: Days 245 to 301 (Weeks 35 to 43)
Postoperative Month 12: Days 330 to 420 (Months 11 to 14)
Patient Exit.

The parameters to be measured preoperatively and postoperatively during the study are summarized in **Table 2** below.

Table 2. Visit Schedule

Visits	Preop	Operative Visit	1 Day	7 Days	1 Month	3 Months	6 Months	9 Months	12 Months	Interim Visits [1]
UCVA	x		x	x	x	x	x	x	x	
BSCVA	x			x	x [2]	x [2]	x [2]	x [2]	x [2]	x [2,3]
Manifest refraction	x			x	x	x	x	x	x	x [2,3]
Cycloplegic refraction	x								x	
Computerized corneal topography	x					x	x	x	x	
Central keratometry	x					x	x	x	x	
Pupil size (mesopic)	x					x	x	x	x	
Wavefront Analysis	x					x			x	
Dilated fundus examination	x					x			x	
Pachymetry	x				x					
Slit lamp exam	x		x	x	x	x	x	x	x	x
Intraocular pressure	x				x	x	x	x	x	
Mesopic contrast sensitivity	x					x	x	x	x	
Subject Questionnaire	x					x	x	x	x	
Intraoperative events		x								
Adverse events		x	x	x	x	x	x	x	x	x

[1] Clinical assessments performed at interim visits were at investigator's discretion based on the patient's condition at presentation.

[2] If the visual acuity with spectacle correction is 2 or more lines below that obtained preoperatively, a rigid contact lens over refraction should be performed to estimate the best possible corrected visual acuity. Rigid CL over-refraction is required at all scheduled postoperative visits at 1 month or beyond. In addition, it is suggested for unscheduled visits if deemed appropriate by the study investigator based on the subject's clinical presentation.

[3] For interim visits < 7 days postoperative or any interim visit in which the subject presents with a condition that precludes performing a manifest refraction (e.g., central corneal abrasion), pinhole acuity will be obtained.

The patient reported outcomes (PRO) instrument ("subject questionnaire") used in IDE clinical study consisted of the Quality of Vision (QoV) questionnaire with accompanying photographs, and 2 of the 3 domains of the Ocular Surface Disease Index (OSDI). The modified QoV used in this trial could not be determined to be a reliable measure of visual symptoms by the FDA. Therefore, the reported prevalence and severity of symptoms may not be accurate. The study protocol specified that the PRO instrument was to be administered at the preoperative visit and at 3, 6, 9, and 12 months postoperatively. Study subjects self-administered the PRO instrument directly to reduce the potential for bias from an interviewer. The QoV instrument had three domains (frequency, severity, and bothersome) each consisting of 10 items that evaluate glare, halos, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuation of vision, focusing difficulties, and judging distance or depth perception. The two domains of the OSDI included all questions related to ocular symptoms and all questions related to environmental triggers.

Adverse events and complications were to be recorded at all visits.

The key postoperative time points were the point of refractive stability for the cohort (6 months) and the 12-month visit.

3. Clinical Endpoints

With regards to safety, the key outcomes for the study were:

1. Preservation of Best-Spectacle Corrected Visual Acuity (BSCVA)

a. In eyes with preoperative BSCVA 20/20 or better, percentage of eyes with BSCVA worse than 20/40 at the postoperative interval at which stability has been established.
b. Percentage of eyes with ≥ 2 lines BSCVA loss.

2. Induced Manifest Refractive Astigmatism

Percentage of eyes with induced cylinder of >2.00D at the postoperative interval at which stability has been established.

3. Loss of Contrast Sensitivity

a. Mean of "within-eye" loss of contrast sensitivity from baseline to 12 months with the 1-sided 95% confidence interval for each spatial frequency.
b. The percentage of eyes showing ≥ 0.3 log units loss at two or more spatial frequencies.

4. Incidence of Adverse Events

The counts and percentages of eyes for each adverse event.

Patient reported symptoms, stratified by pupil size and fellow eye status, are a secondary safety outcome.

Additional safety outcomes include corneal topography and wavefront aberrometry results.

With regards to effectiveness, the key outcomes for the study were:

1. **Predictability:**
   The percentage of eyes at the point at which stability is first achieved with MRSE:
   a. Within ± 1.00 D of the intended outcome.
   b. Within ± 0.50 D of the intended outcome.
2. **Improvement in uncorrected visual acuity (UCVA) following treatment:**
   a. The percentage of eyes that achieve UCVA of 20/40 or better at the postoperative interval at which stability has been established
   b. Percentage of eyes -that achieve UCVA of 20/20 or better

Stability is considered to have been achieved at the latter of two postoperative refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, if at least three of the four following stability criteria are met:

1. At least 95% of the treated eyes should have a change ≤ 1.00 D of MRSE at the latter of two postoperative refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval;
2. The mean rate of change in MRSE, as determined by paired analysis, is ≤ 0.5 D per year (0.04 D/month) over the same time period;
3. The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;
4. The 95% confidence interval for the mean rate of change includes zero or a rate of change attributable to normal aging.

Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup.

For eyes treated for astigmatic myopia, the following additional outcomes were analyzed:

Predictability: the percentage of eyes achieving manifest refraction cylinder (MRCYL) within ± 1.00 D of the intended outcome, and within ± 0.50 D of the intended outcome at the point at which stability is first achieved

Vector analysis: |Intended Refractive Correction (IRC)|, |Surgically Induced Refractive Correction (SIRC)|, |Error Vector (EV)|, Correction Ratio (CR), Error Ratio (ER) pooled and stratified by baseline magnitude of cylinder

Stability of MRCYL: the percentage of eyes with a change in MRCYL within 1.0 D and 0.5 D, the mean change in MRCYL and the 95% confidence interval of the mean change, the monthly mean change in MRCYL between two consecutive postoperative visits

Accountability of PMA Cohort

At the time of database lock, of the 357 patients who underwent surgery in the PMA study, 98.9% (n=349) patients were available for analysis at the completion of the study, the 12month post-operative visit. Accountability for all treated eyes through 12 months is presented in **Table 3**

Table 1. Accountability - All Treated Eyes:

Treated (N = 357)	Day 1	Week 1	Month 1	Month 3	Month 6	Month 9	Month 12
Available for analysis	357 (100.0%)	357 (100.0%)	357 (100.0%)	357 (100.0%)	348 (97.5%)	352 (98.6%)	349 (97.8%)
Active	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (2.5%)	5 (1.4%)	8 (2.2%)
Discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.1%)	4 (1.1%)	4 (1.1%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alternative treatment*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.1%)	4 (1.1%)	4 (1.1%)
Missed visit	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.4%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	4 (1.1%)
% Accountability	357/357 (100.0%)	357/357 (100.0%)	357/357 (100.0%)	357/357 (100.0%)	348/353 (98.6%)	352/353 (99.7%)	349/353 (98.9%)

Status categories were based on ANSI-Z80.11-2012.

% = n ÷ N × 100.

% Accountability = available ÷(treated - discontinued - active) × 100

* After discontinuation of the SMILE treatment, study eyes received treatment with an approved refractive laser procedure.

Of the 357 subjects that underwent surgery, four subjects underwent alternative treatments. Out of the 353 subjects in the effectiveness cohort, 348 were available for analysis at the 6-month postoperative time point and 349 were available for analysis at the 12-month postoperative time point.

B. Study Population Demographics and Baseline Parameters

The demographics of the study population are summarized in **Table 4** below. The baseline preoperative refractive parameters are summarized in **Table 5** below.

Table 4. Demographics - All Treated Eyes:

Demographics	Treated for Spherical Myopia Only		Treated for Astigmatic Myopia		All Treated Eyes	
	Number	Percentage	Number	Percentage	Number	Percentage
NUMBER OF EYES & SUBJECTS	50 Eyes of 50 Subjects		307 Eyes of 307 Subjects		357 Eyes of 357 Subjects	
GENDER						
Male	20	40.0%	128	41.7%	148	41.5%
Female	30	60.0%	179	58.3%	209	58.5%
RACE						
White	39	78.0%	249	81.1%	288	80.7%
Black	4	8.0%	10	3.3%	14	3.9%
Asian	2	4.0%	15	4.9%	17	4.8%
Other	5	10.0%	33	10.7%	38	10.6%
SURGICAL EYE						
Right	13	26.0%	140	45.6%	153	42.9%
Left	37	74.0%	167	54.4%	204	57.1%
AGE (In Years)						
Mean (SD)	33.1 (7.1)		33.1 (7.3)		33.1 (7.2)	
Min., Max.	23.0, 59.0		22.0, 58.0		22.0, 59.0	
FELLOW-EYE STATUS						
Excimer Laser Refractive Surgery	49	98.0%	304	99.0%	353	98.9%
Untreated	1	2.0%	3	1.0%	4	1.1%

Table 5. Preoperative Refraction Parameters - All Treated Eyes:

Manifest Sphere: Mean (SD): -4.815 (2.389) Min, Max: -10.000, -1.000	**Manifest Cylinder: Mean (SD): -1.335 (0.799), Min, Max: -3.00, 0.00**								**Total**	
	0.00 to -0.50 D		**-0.75 to -1.00 D**		**-1.01 to -2.00 D**		**-2.01 to -3.00 D**			
	%	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**
-1.00 to -2.00 D	0.8%	(3/357)	4.5%	(16/357)	5.3%	(19/357)	3.1%	(11/357)	13.7%	(49/357)
-2.01 to -3.00 D	2.0%	(7/357)	3.9%	(14/357)	5.9%	(21/357)	3.6%	(13/357)	15.4%	(55/357)
-3.01 to -4.00 D	2.0%	(7/357)	5.3%	(19/357)	5.3%	(19/357)	3.4%	(12/357)	16.0%	(57/357)
-4.01 to -5.00 D	1.7%	(6/357)	4.8%	(17/357)	3.9%	(14/357)	4.8%	(17/357)	15.1%	(54/357)
-5.01 to -6.00 D	0.6%	(2/357)	5.0%	(18/357)	3.1%	(11/357)	1.4%	(5/357)	10.1%	(36/357)
-6.01 to -7.00 D	1.4%	(5/357)	3.9%	(14/357)	2.8%	(10/357)	1.4%	(5/357)	9.5%	(34/357)
-7.01 to -8.00 D	1.7%	(6/357)	2.8%	(10/357)	1.7%	(6/357)	0.8%	(3/357)	7.0%	(25/357)
-8.01 to -9.00 D	2.2%	(8/357)	2.2%	(8/357)	1.4%	(5/357)	0.8%	(3/357)	6.7%	(24/357)
-9.01 to -10.00 D	1.7%	(6/357)	2.0%	(7/357)	1.7%	(6/357)	1.1%	(4/357)	6.4%	(23/357)
Total	14.0%	(50/357)	34.5%	(123/357)	31.1%	(111/357)	20.4%	(73/357)	100%	(357/357)

Shaded cells were eyes treated for spherical myopia only.

C. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the full cohort of 357 patients who underwent surgery. The key safety outcomes for this study are presented below in **Tables 6 to 7**. Adverse effects are reported in **Tables 8 to 11**. The secondary safety outcomes on patient reported symptoms are presented below in **Tables 12 to 13**. Additional safety outcomes are presented below in **Tables 14 to 20**.

Table 6. Summary of Key Variables for Preservation of BSCVA and Increase in Astigmatism at 6-Month Point of Refractive Stability - All Treated Eyes:

Key Variable	n/N	%	95% CI[1]
Loss of ≥ 2 lines BSCVA	0/348	0.0%	(0.0%, 1.1%)
BSCVA worse than 20/40 if 20/20 or better preoperatively	0/348	0.0%	(0.0%, 1.1%)
Increased manifest refractive astigmatism > 2.0D	0/348	0.0%	(0.0%, 1.1%)

N = Number of CRFs received with non-missing values at each visit.
[1] 95% CI was calculated based on Clopper-Pearson exact method.

Table 7. Log Contrast Sensitivity Change from Preoperative Visit - All Treated Eyes:

Frequency	Statistics	Month 3	Month 6	Month 9	Month 12
A (1.5 cpd)	N	357	348	352	349
	Mean	0.028	0.059	0.073	0.076
	SD	0.172	0.167	0.183	0.179
	< 0.85[1] at preop only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	< 0.85[1] at postop only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	< 0.85[1] at both preop & postop	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
B (3 cpd)	N	357	348	352	349
	Mean	> 0.060	> 0.096	> 0.093	> 0.110
	SD	> 0.192	> 0.191	> 0.191	> 0.183
	< 1.00[1] at preop only	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
	< 1.00[1] at postop only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	< 1.00[1] at both preop & postop	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
C (6 cpd)	N	357	348	352	349
	Mean	> 0.051	> 0.114	> 0.120	> 0.129
	SD	> 0.227	> 0.233	> 0.230	> 0.216
	< 1.08[1] at preop only	9 (2.5%)	10 (2.9%)	10 (2.8%)	8 (2.3%)
	< 1.08[1] at postop only	4 (1.1%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
	< 1.08[1] at both preop & postop	3 (0.8%)	1 (0.3%)	1 (0.3%)	3 (0.9%)
D (12 cpd)	N	357	348	352	349
	Mean	> 0.016	> 0.054	> 0.087	> 0.096
	SD	> 0.226	> 0.226	> 0.258	> 0.243
	< 0.90[1] at preop only	36 (10.1%)	40 (11.5%)	39 (11.1%)	36 (10.3%)
	< 0.90[1] at postop only	22 (6.2%)	16 (4.6%)	12 (3.4%)	11 (3.2%)
	< 0.90[1] at both preop & postop	44 (12.3%)	38 (10.9%)	39 (11.1%)	41 (11.7%)
Gained ≥0.3 Log Unit at ≥2 frequencies[2]		50 (14.0%)	72 (20.7%)	78 (22.2%)	89 (25.5%)
No Change[2]		294 (82.4%)	270 (77.6%)	269 (76.4%)	256 (73.4%)
Lost ≥0.3 Log Unit at ≥2 frequencies[2]		13 (3.6%)	6 (1.7%)	5 (1.4%)	4 (1.1%)

N = Number of CRFs received with non-missing values at preop and postop visit. Not Reported = Number of CRFs received with missing values at preop or postop visit.

[1] Number of subjects that could not read any patch at the respective spatial frequency. 0.85, 1.00, 1.08, and 0.90 are the lowest measurable contrast sensitivity values at 1.5, 3, 6, and 12 cpd, respectively. **Per FDA request, these lowest values were used for statistical calculation**. If unmeasurable values (i.e. zero patches reported at preop or postop) are included in the calculation of mean values, the means are designated as "<" (less than) the numerical values and corresponding standard deviation estimates are designated as ">" (greater than) the numerical values. Corresponding minimum and maximum values are represented respectively with "<" and ">" the numerical values. If there were more unmeasurable values at preop than at postop, a "~" symbol precedes the numerical value for the 95% CL of Mean.

[2] Change from non-zero patches preoperatively to zero patches postoperatively was considered as a loss of at least 0.3 log units. Change from zero patches preoperatively to non-zero patches postoperatively was considered a gain of at least 0.3 log units.

Adverse effects that occurred in the PMA clinical study:

Table 8. Intraoperative Adverse Events:

N = 357	Number	Percent
Cap tear (Difficult lenticule removal with tissue damage)	3	0.8%
Number of Subjects with at least one Event	3	0.8%

Multiple events could be reported for each subject. Percent = Number/N ×100.

Table 9. Intraoperative Events - All Treated Eyes:

N = 357	Number	Percent
Difficult lenticule removal without tissue damage	2	0.6%
Loss of suction: completed treatment	10	2.8%
Loss of suction: discontinued treatments	4	1.1%
Temporary release of suction by the surgeon	1	0.3%
Decentered treatment[1]	5	1.4%
Number of Subjects with at least one Event	20	5.6%

Multiple events could be reported for each subject. Percent = Number/N ×100.

[1] Identified based on postoperative topography

Table 10. Postoperative Ophthalmic Adverse Events - All Treated Eyes:

AE	D1 N=357	W1 N=357	M1 N=357	M3 N=357	M6 N=348	M9 N=352	M12 N=349	Uns N=21	Cum N=357
Diffuse lamellar keratitis (Stage 3 or above)	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Corneal infiltrate or ulcer	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Any persistent corneal epithelial defect at 1 month or later	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Corneal edema at 1 month or later	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Epithelium in the interface with loss of ≥ 2 lines (≥ 10 letters) of BSCVA	0 0.0%	1 0.3%	1 0.3%	1 0.3%	0 0.0%	0 0.0%	0 0.0%	1	1 0.3%
Melting of the cap	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
IOP increase of > 10 mmHg above baseline or IOP > 30 mmHg on 2 consecutive exams	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Haze beyond 6 months with loss of ≥ 2 lines (≥ 10 letters) of BSCVA	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Decrease in BSCVA of ≥ 2 lines (≥ 10 letters) not due to irregular astigmatism as shown by hard contact lens refraction at 3 months or later	0 0.0%	0 0.0%	0 0.0%	1* 0.3%	0 0.0%	0 0.0%	0 0.0%	1*	1* 0.3*%
Retinal Detachment	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Retinal vascular accidents	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Ocular penetration	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Any other vision-threatening event	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Other									
Conjunctivitis, allergic	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 0.3%	0 0.0%	1	2 0.6%
Epithelium in the interface present at 6 months or later requiring surgical removal	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1	1 0.3%

Hypertensive Retinopathy	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 0.3%	0	1 0.3%
Iritis	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1	1 0.3%
Krukenbergs Spindle	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 0.3%	1 0.3%	1 0.3%	1	1 0.3%

Multiple events could be reported for each subject.
Uns = interim visit, N is the number of eyes with interim visits, and incidence is the number of eyes with the reported events during the interim visits.
Cum = cumulative, N is the number of all treated eyes with postoperative visits, and incidence is the number of eyes with the reported events during the study.
* This AE of BSCVA loss is associated with the case of Epithelium in the interface with loss of ≥ 2 lines BSCVA.

Through the point of data lock, a total of 9 subjects were reported with 11 ocular adverse events (AEs) over the course of the study. Three intraoperative events were reported as AEs. Six subjects experienced adverse events postoperatively.

Table 11. Complications - All Treated Eyes:

Complications	**D0 N=357**	**D1 N=357**	**W1 N=357**	**M1 N=357**	**M3 N=357**	**M6 N=348**	**M9 N=352**	**M12 N=349**	**Uns N=21**	**Cum N=357**
Clinical signs and/or subject symptoms consistent with dry eye	0 0.0%	2 0.6%	4 1.1%	4 1.1%	4 1.1%	1 0.3%	0 0.0%	0 0.0%	3	13 3.6%
Corneal edema between 1 week and 1 month after procedure	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Corneal scarring	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1	1 0.3%
Crystalline lens opacity	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Diffuse lamellar keratitis (Stage 2 or less)	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Epithelium in the interface	0 0.0%	2 0.6%	2 0.6%	3 0.8%	3 0.8%	5 1.4%	5 1.4%	5 1.4%	2	9 2.5%
Foreign body sensation at 1 month or later	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Ghost/double images in the operative eye*	0* 0.0%	0* 0.0%	0* 0.0%	0* 0.0%	0* 0.0%	0* 0.0%	0* 0.0%	0* 0.0%	0*	0* 0.0%
Interface debris, such as lint, pigment, air bubbles, and meibomian gland secretions	0 0.0%	1 0.3%	2 0.6%	1 0.3%	0 0.0%	1 0.3%	0 0.0%	0 0.0%	0	4 1.1%
Moderate or severe glare	0 0.0%	0 0.0%	0 0.0%	0 0.0%	13 3.6%	7 2.0%	6 1.7%	2 0.6%	0	24 6.7%
Moderate or severe halos	0 0.0%	0 0.0%	0 0.0%	0 0.0%	9 2.5%	5 1.4%	3 0.9%	2 0.6%	0	16 4.5%
Pain at 1 month or later	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Striae/microstriae	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	0 0.0%
Transient light sensitivity syndrome (TLSS)	0 0.0%	0 0.0%	0 0.0%	1 0.3%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0	1 0.3%

Multiple events could be reported for each subject.
Uns = interim visit, N is the number of eyes with interim visits, and incidence is the number of eyes with the reported events during the interim visits.
Cum = cumulative, N is the number of all treated eyes with postoperative visits, and incidence is the number of eyes with the reported events during the study.
*Note that numbers presented here only indicate reports directly given by the patient to the investigator. Numbers are not consistent with responses provided in the Quality of Vision (QoV) questionnaire. See Table 13 for these numbers and those of other moderate to severe symptoms reported in the QoV. Additional information on patient symptoms from questionnaires is provided in the section on Patient Reported Outcomes.

Three secondary interventions were performed over the course of the study, one at Day 1, one at Month 1, and one at an interim visit after Month 12, all involving irrigation to remove epithelial cells from the interface.

Secondary Safety Outcomes: Patient Reported Symptoms

The PRO instrument ("subject questionnaire" or questionnaire) used in IDE clinical study consisted of the QoV questionnaire with accompanying photographs, and 2 of the 3 domains of the OSDI. The modified QoV used in this trial could not be determined to be a reliable measure of visual symptoms by the FDA. Therefore, the reported prevalence and severity of symptoms may not be accurate. The study protocol specified that the PRO instrument was to be administered at the preoperative visit and at 3, 6, 9, and 12 months postoperatively. Study subjects self-administered the PRO instrument directly to reduce the potential for bias from an interviewer. The QoV instrument had three domains (frequency, severity, and bothersome) each consisting of 10 items which evaluate glare, halos, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuation of vision, focusing difficulties, and judging distance or depth perception. The two domains of the OSDI included all questions related to ocular symptoms and all questions related to environmental triggers.

Results from the questionnaire are summarized in **Tables 12 and 13** below.

Table 12. Frequency of Moderate and Severe Dry Eye Symptoms Classified by OSDI Scores All Treated Eyes:

Severity of Dry Eye Symptoms	Preop	Month 6	Month 12	Last Available Visit
N	357	348	349	357
Moderate	19 (5%)	20 (6%)	21 (6%)	21 (6%)
Severe	9 (3%)	7 (2%)	10 (3%)	10 (3%)
Not Reported	0	0	0	0

OSDI score = (sum of scores) x 25/(# of questions answered). The responses of N/A were excluded.
Moderate: OSDI score ≥ 23 to < 33. Severe: OSDI score ≥ 33.
Scoring based on Miller et al. Minimal Clinically Important Difference for the Ocular Surface Disease Index *Arch Ophthalmol*. 2010;128(1):94-101.

Table 13. Two Highest Categories of Bothersome and Severity for Each QoV Symptom at 12 Months:

Visual Symptom	Number of Patient Out of 349 Total			
	Bothersome		Severity	
Glare	Quite	0 (0.0%)	Moderate	2 (0.6%)
	Very	1 (0.3%)	Severe	0 (0.0%)
	Total	1 (0.3%)	Total	2 (0.6%)
Halos	Quite	3 (0.9%)	Moderate	2 (0.6%)
	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	3 (0.9%)	Total	2 (0.6%)
Starbursts	Quite	8 (2.3%)	Moderate	13 (3.7%)
	Very	2 (0.6%)	Severe	1 (0.3%)
	Total	10 (2.9%)	Total	14 (4.0%)
Hazy Vision	Quite	3 (0.9%)	Moderate	2 (0.6%)
	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	3 (0.9%)	Total	2 (0.6%)
Blurred	Quite	5 (1.4%)	Moderate	3 (0.9%)

Vision	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	5 (1.4%)	Total	3 (0.9%)
Distortion	Quite	0 (0.0%)	Moderate	0 (0.0%)
	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	0 (0.0%)	Total	0 (0.0%)
Double or Multiple Images	Quite	1 (0.3%)	Moderate	2 (0.6%)
	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	1 (0.3%)	Total	2 (0.6%)
Fluctuation	Quite	2 (0.6%)	Moderate	0 (0.0%)
	Very	0 (0.0%)	Severe	0 (0.0%)
	Total	2 (0.6%)	Total	0 (0.0%)
Focusing	Quite	3 (0.9%)	Moderate	5 (1.4%)
	Very	1 (0.3%)	Severe	1 (0.3%)
	Total	4 (1.1%)	Total	6 (1.7%)
Judging Distance or Depth Perception	Quite	0 (0.0%)	Moderate	1 (0.3%)
	Very	1 (0.3%)	Severe	0 (0.0%)
	Total	1 (0.3%)	Total	1 (0.3%)

Additional Safety Outcomes and Analyses:

Table 14. Topography Findings - All Treated Eyes:

	Preop n/N (%)	**Month 3 n/N (%)**	**Month 6 n/N (%)**	**Month 9 n/N (%)**	**Month 12 n/N (%)**
Evaluable	357	355	347	351	348
Irregular Astigmatism	0/357 (0.0%)	0/355 (0.0%)	0/347 (0.0%)	0/351 (0.0%)	0/348 (0.0%)
Ectasia	0/357 (0.0%)	0/355 (0.0%)	0/347 (0.0%)	0/351 (0.0%)	0/348 (0.0%)
Tear Film Artifacts	0/357 (0.0%)	0/355 (0.0%)	1/347 (0.3%)	1/351 (0.3%)	1/348 (0.3%)
Decentration	NA	5/355 (1.4%)	5/347 (1.4%)	5/351 (1.4%)	5/348 (1.4%)
Other	1/357 (0.3%)	4/355 (1.1%)	4/347 (1.2%)	5/351 (1.4%)	5/348 (1.4%)
Central area of steepening	1/357 (0.3%)	0/355 (0.0%)	0/347 (0.0%)	0/351 (0.0%)	0/348 (0.0%)
Distorted mires	0/357 (0.0%)	2/355 (0.6%)	2/347 (0.6%)	3/351 (0.9%)	3/348 (0.9%)
Superior area of flattening	0/357 (0.0%)	2/355 (0.6%)	2/347 (0.6%)	2/351 (0.6%)	2/348 (0.6%)
Topography image quality not sufficient	0	1	0	0	1
Topography not performed	0	1	1	1	0
Total	357	357	348	352	349

N = Number of eyes with non-missing values at each visit. % = n/N ×100.

Five subjects showed consistent decentration greater than 1 mm at all four scheduled postoperative visits.

Table 15. Change in Wavefront Aberrometry from Preoperative Stratified by Largest Scan Size (mm) Treated Eyes with Preoperative, 3-Month, and 12-Month Visits:

Scan Size	Parameters	Statistics	Month 3	Month 12
4.0	**Change in Wavefront from Preoperative (μm)**			
	Total Higher Order RMS	N	123	123
		Mean (SD)	-0.001 (0.203)	-0.019 (0.175)
		Min, Max	-0.984, 1.133	-1.082, 0.319
	Coma	Mean (SD)	0.030 (0.141)	0.015 (0.112)
		Min, Max	-0.349, 1.005	-0.447, 0.314
	Spherical	Mean (SD)	-0.019 (0.088)	-0.015 (0.065)
		Min, Max	-0.343, 0.578	-0.382, 0.136
5.0	**Change in Wavefront from Preoperative (μm)**			
	Total Higher Order RMS	N	96	96
		Mean (SD)	0.028 (0.188)	0.028 (0.218)
		Min, Max	-1.085, 0.443	-0.978, 1.204
	Coma	Mean (SD)	0.071 (0.144)	0.066 (0.160)
		Min, Max	-0.512, 0.379	-0.391, 0.552
	Spherical	Mean (SD)	-0.013 (0.091)	-0.004 (0.102)
		Min, Max	-0.224, 0.296	-0.302, 0.223
6.0	**Change in Wavefront from Preoperative (μm)**			
	Total Higher Order RMS	N	18	18
		Mean (SD)	0.069 (0.276)	0.088 (0.336)
		Min, Max	-0.336, 0.469	-0.451, 0.788
	Coma	Mean (SD)	0.122 (0.302)	0.158 (0.354)
		Min, Max	-0.371, 0.651	-0.257, 0.955
	Spherical	Mean (SD)	0.132 (0.235)	0.158 (0.241)
		Min, Max	-0.259, 0.591	-0.259, 0.585
Overall	**Change in Wavefront from Preoperative (μm)**			
	Total Higher Order RMS	N	237	237
		Mean (SD)	0.016 (0.204)	0.008 (0.210)
		Min, Max	-1.085, 1.133	-1.082, 1.204
	Coma	Mean (SD)	0.054 (0.161)	0.047 (0.166)
		Min, Max	-0.512, 1.005	-0.447, 0.955
	Spherical	Mean (SD)	-0.005 (0.113)	0.003 (0.112)
		Min, Max	-0.343, 0.591	-0.382, 0.585

N = Number of CRFs received with non-missing values at each visit.
The largest scan size was 4.0, 5.0, or 6.0 mm, depending on the largest scan size obtained at all the preoperative and postoperative visits.

Table 16. Summary of Key Safety Variables for Preservation of BSCVA and Increase in Astigmatism at Last Available Visit All Treated Eyes:

Key Safety Variables	n/N	%	95% CI[1]
Loss of ≥ 2 lines BSCVA	0/357	0.0%	(0.0%, 1.1%)
BSCVA worse than 20/40 if 20/20 or better preoperatively	0/357	0.0%	(0.0%, 1.1%)
Increased manifest refractive astigmatism > 2.0D	0/357	0.0%	(0.0%, 1.1%)

N = Number of CRFs received with non-missing values at each visit.
[1] 95% CI was calculated based on Clopper-Pearson exact method.

Table 17. Change in Best Spectacle-Corrected Visual Acuity (BSCVA) from Preop
All Treated Eyes:

BSCVA Change	Week 1 n (%)	Month 1 n (%)	Month 3 n (%)	Month 6 n (%)	Month 9 n (%)	Month 12 n (%)
Available (N)	357	357	357	348	352	349
Lost > 2 lines (>10 letters)	29 (8.1%)	3 (0.8%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost 2 lines (10 letters)	4 (1.1%)	6 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost 1 line (5-9 letters)	80 (22.4%)	46 (12.9%)	28 (7.8%)	14 (4.0%)	11 (3.1%)	8 (2.3%)
Unchanged (< 5 letters)	235 (65.8%)	273 (76.5%)	293 (82.1%)	263 (75.6%)	259 (73.6%)	257 (73.6%)
Gained 1 line (5-9 letters)	9 (2.5%)	27 (7.6%)	34 (9.5%)	68 (19.5%)	79 (22.4%)	78 (22.3%)
Gained 2 lines (10 letters)	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (0.6%)	1 (0.3%)	5 (1.4%)
Gained > 2 lines (>10 letters)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
Not reported	0	0	0	0	0	0
Total	357	357	357	348	352	349

N = Number of CRFs received with non-missing values at each visit.

Table 18. QoV Score Change from Preoperative - All Treated Eyes:

Sub-scale		Month 3	Month 6	Month 9	Month 12
Frequency	**N**	**357**	**348**	**352**	**349**
	Worse	176/357 (49%)	133/348 (38%)	118/352 (34%)	110/349 (32%)
	Same	63/357 (18%)	74/348 (21%)	82/352 (23%)	79/349 (23%)
	Improved	118/357 (33%)	141/348 (41%)	152/352 (43%)	160/349 (46%)
	Not Reported	0	0	0	0
Severity	**N**	**357**	**348**	**352**	**349**
	Worse	156/357 (44%)	125/348 (36%)	106/352 (30%)	93/349 (27%)
	Same	70/357 (20%)	74/348 (21%)	85/352 (24%)	79/349 (23%)
	Improved	131/357 (37%)	149/348 (43%)	161/352 (46%)	177/349 (51%)
	Not Reported	0	0	0	0
Bothersome	**N**	**357**	**348**	**352**	**349**
	Worse	136/357 (38%)	107/348 (31%)	96/352 (27%)	86/349 (25%)
	Same	79/357 (22%)	105/348 (30%)	106/352 (30%)	108/349 (31%)
	Improved	142/357 (40%)	136/348 (39%)	150/352 (43%)	155/349 (44%)
	Not Reported	0	0	0	0

Change = Postop - Preop (pairwise); these changes may not necessarily represent a clinically meaningful improvement or worsening in the QoV scores.
Worse: Change > 0. Same: Change = 0. Improved: Change < 0.
Not Reported = Number of eyes with missing values at each visit.

Table 19. Changes of 2 or More Grades in QoV Symptoms at 12 Months:

Symptom	Outcomes	Better n/N (%)	Worse n/N (%)
Glare	Frequency	4/349 (1.1%)	1/349 (0.3%)
	Severity	5/349 (1.4%)	0/349 (0.0%)
	Bothersome	6/349 (1.7%)	1/349 (0.3%)
	# of Subjects	11/349 (3.2%)	2/349 (0.6%)
Halos	Frequency	2/349 (0.6%)	3/349 (0.9%)
	Severity	1/349 (0.3%)	2/349 (0.6%)
	Bothersome	2/349 (0.6%)	3/349 (0.9%)
	# of Subjects	4/349 (1.1%)	3/349 (0.9%)
Starbursts	Frequency	6/349 (1.7%)	6/349 (1.7%)
	Severity	12/349 (3.4%)	6/349 (1.7%)
	Bothersome	11/349 (3.2%)	6/349 (1.7%)
	# of Subjects	18/349 (5.2%)	10/349 (2.9%)
Hazy Vision	Frequency	1/349 (0.3%)	3/349 (0.9%)
	Severity	2/349 (0.6%)	1/349 (0.3%)
	Bothersome	4/349 (1.1%)	3/349 (0.9%)
	# of Subjects	4/349 (1.1%)	4/349 (1.1%)
Blurred Vision	Frequency	4/349 (1.1%)	3/349 (0.9%)
	Severity	5/349 (1.4%)	2/349 (0.6%)
	Bothersome	5/349 (1.4%)	3/349 (0.9%)
	# of Subjects	7/349 (2.0%)	5/349 (1.4%)
Distortion	Frequency	0/349 (0.0%)	0/349 (0.0%)
	Severity	0/349 (0.0%)	0/349 (0.0%)
	Bothersome	0/349 (0.0%)	0/349 (0.0%)
	# of Subjects	0/349 (0.0%)	0/349 (0.0%)
Double or Multiple Images	Frequency	1/349 (0.3%)	1/349 (0.3%)
	Severity	1/349 (0.3%)	1/349 (0.3%)
	Bothersome	2/349 (0.6%)	1/349 (0.3%)
	# of Subjects	2/349 (0.6%)	1/349 (0.3%)
Fluctuation	Frequency	1/349 (0.3%)	1/349 (0.3%)
	Severity	3/349 (0.9%)	0/349 (0.0%)
	Bothersome	2/349 (0.6%)	2/349 (0.6%)
	# of Subjects	3/349 (0.9%)	2/349 (0.6%)
Focusing	Frequency	4/349 (1.1%)	3/349 (0.9%)
	Severity	6/349 (1.7%)	4/349 (1.1%)
	Bothersome	8/349 (2.3%)	1/349 (0.3%)
	# of Subjects	9/349 (2.6%)	4/349 (1.1%)
Judging Distance Depth Perception	Frequency	6/349 (1.7%)	0/349 (0.0%)
	Severity	6/349 (1.7%)	0/349 (0.0%)
	Bothersome	9/349 (2.6%)	1/349 (0.3%)
	# of Subjects	12/349 (3.4%)	1/349 (0.3%)
	# of Subjects	43/349 (12.3%)	19/349 (5.4%)

N = Number of eyes with non-missing values the 12-Month visit. % = n/N ×100.
Symptoms with the highest rates of 2-grades of worsening or more within each subscale are shaded. The assessment of symptom improvement or worsening by changes of 2 or more grades might be limited due the questionnaire design with four response options per questions.

Table 20. OSDI Score Change from Preoperative All Treated Eyes:

Sub-scale		Month 3	Month 6	Month 9	Month 12
Experienced Symptoms during the Last Week	**N**	**357**	**348**	**352**	**349**
	Worse	148/357 (41%)	121/348 (35%)	106/352 (30%)	101/349 (29%)
	Same	139/357 (39%)	144/348 (41%)	155/352 (44%)	163/349 (47%)
	Improved	70/357 (20%)	83/348 (24%)	91/352 (26%)	85/349 (24%)
	NA	0	0	0	0
	Not Reported	0	0	0	0
Felt Uncomfortable in Situations during the Last Week	**N**	**330**	**323**	**318**	**318**
	Worse	139/330 (42%)	116/323 (36%)	102/318 (32%)	109/318 (34%)
	Same	126/330 (38%)	116/323 (36%)	134/318 (42%)	126/318 (40%)
	Improved	65/330 (20%)	91/323 (28%)	82/318 (26%)	83/318 (26%)
	NA	27	25	34	31
	Not Reported	0	0	0	0

Change = Postop - Preop (pairwise).
Worse: Change > 0. Same: Change = 0. Improved: Change < 0.
NA = Number of subjects with "Not applicable" response to all questions of the sub-scale. The NA responses were not included in the OSDI score calculation. Subjects with NA to all questions of the sub-scale were excluded from the analyses.
Not Reported = Number of eyes with missing values at each visit.

2. Effectiveness Results

The analysis of effectiveness was based on the 348 evaluable effectiveness cohort patients at the stability 6-month time point. Preoperatively, there were no eyes with UCVA of 20/40 or better. Key effectiveness outcomes are presented in **Tables 21**. Analysis of stability is presented in **Table 22** below.

Table 21. Summary of Key Effectiveness Variables Effectiveness Cohort Eyes (key outcomes highlighted with grey background):

Key Effectiveness Variables	Week 1 n/N (%) 95% CI	Month 1 n/N (%) 95% CI	Month 3 n/N (%) 95% CI	Month 6 n/N (%) 95% CI	Month 9 n/N (%) 95% CI	Month 12 n/N (%) 95% CI
UCVA, 20/16 or better	39/353 (11.0%) (8.0%, 14.8%)	99/353 (28.0%) (23.4%, 33.0%)	141/353 (39.9%) (34.8%, 45.3%)	174/348 (50.0%) (44.6%, 55.4%)	184/352 (52.3%) (46.9%, 57.6%)	207/349 (59.3%) (54.0%, 64.5%)
UCVA, 20/20 or better	156/353 (44.2%) (38.9%, 49.5%)	233/353 (66.0%) (60.8%, 70.9%)	294/353 (83.3%) (79.0%, 87.0%)	293/348 (84.2%) (79.9%, 87.9%)	312/352 (88.6%) (84.8%, 91.8%)	312/349 (89.4%) (85.7%, 92.4%)
UCVA, 20/25 or better	253/353 (71.7%) (66.7%, 76.3%)	309/353 (87.5%) (83.6%, 90.8%)	333/353 (94.3%) (91.4%, 96.5%)	333/348 (95.7%) (93.0%, 97.6%)	337/352 (95.7%) (93.1%, 97.6%)	333/349 (95.4%) (92.7%, 97.4%)
UCVA, 20/32 or better	317/353 (89.8%) (86.2%, 92.8%)	336/353 (95.2%) (92.4%, 97.2%)	343/353 (97.2%) (94.9%, 98.6%)	341/348 (98.0%) (95.9%, 99.2%)	347/352 (98.6%) (96.7%, 99.5%)	342/349 (98.0%) (95.9%, 99.2%)
UCVA, 20/40 or better	339/353 (96.0%) (93.4%, 97.8%)	347/353 (98.3%) (96.3%, 99.4%)	349/353 (98.9%) (97.1%, 99.7%)	343/348 (98.6%) (96.7%, 99.5%)	350/352 (99.4%) (98.0%, 99.9%)	345/349 (98.9%) (97.1%, 99.7%)
MRSE, Attempted vs. Achieved, ±0.25D	253/353 (71.7%) (66.7%, 76.3%)	279/353 (79.0%) (74.4%, 83.2%)	295/353 (83.6%) (79.3%, 87.3%)	291/348 (83.6%) (79.3%, 87.4%)	306/352 (86.9%) (83.0%, 90.3%)	303/349 (86.8%) (82.8%, 90.2%)
MRSE, Attempted vs. Achieved, ±0.50D	318/353 (90.1%) (86.5%, 93.0%)	324/353 (91.8%) (88.4%, 94.4%)	341/353 (96.6%) (94.1%, 98.2%)	326/348 (93.7%) (90.6%, 96.0%)	338/352 (96.0%) (93.4%, 97.8%)	331/349 (94.8%) (92.0%, 96.9%)
MRSE, Attempted vs. Achieved, ±1.00D	348/353 (98.6%) (96.7%, 99.5%)	348/353 (98.6%) (96.7%, 99.5%)	349/353 (98.9%) (97.1%, 99.7%)	345/348 (99.1%) (97.5%, 99.8%)	351/352 (99.7%) (98.4%, 100.0%)	346/349 (99.1%) (97.5%, 99.8%)
MRSE, Attempted vs. Achieved, ±2.00D	353/353 (100.0%)	353/353 (100.0%)	353/353 (100.0%)	348/348 (100.0%)	352/352 (100.0%)	349/349 (100.0%)

	(99.0%, 100.0%)	(99.0%, 100.0%)	(99.0%, 100.0%)	(98.9%, 100.0%)	(99.0%, 100.0%)	(98.9%, 100.0%)

N = Number of CRFs received with non-missing values at each visit.
95% CI was calculated based on Clopper-Pearson exact method.

Stability:

Table 22. Stability of Manifest Refraction Spherical Equivalent (MRSE) Effectiveness Population:

Change in MRSE	Between 1 and 3 Months	Between 3 and 6 Months	Between 6 and 9 Months	Between 9 and 12 Months
Pairwise Sequential Visits				
Eyes within 0.50 D change (n/N, %, [% CI][1])	340/353 (96.3%) (93.8%, 98.0%)	334/348 (96.0%) (93.3%, 97.8%)	340/347 (98.0%) (95.9%, 99.2%)	342/349 (98.0%) (95.9%, 99.2%)
Eyes within 1.00 D change (n/N, %, [% CI][1])	352/353 (99.7%) (98.4%, 100.0%)	347/348 (99.7%) (98.4%, 100.0%)	346/347 (99.7%) (98.4%, 100.0%)	348/349 (99.7%) (98.4%, 100.0%)
Mean change between visits SD 95% CI	0.035 0.254 (0.009, 0.062)	0.008 0.226 (-0.016, 0.032)	0.000 0.204 (-0.022, 0.022)	0.016 0.192 (-0.004, 0.037)
Mean change per month	0.018	0.003	0.000	0.005
Mean change per year (change per month × 12)	0.212	0.033	0.000	0.066
12-Month Consistent Cohort				
Eyes within 0.50 D change (n/N, %, [% CI][1])	332/345 (96.2%) (93.6%, 98.0%)	331/345 (95.9%) (93.3%, 97.8%)	338/345 (98.0%) (95.9%, 99.2%)	338/345 (98.0%) (95.9%, 99.2%)
Eyes within 1.00 D change (n/N, %, [% CI][1])	344/345 (99.7%) (98.4%, 100.0%)	344/345 (99.7%) (98.4%, 100.0%)	344/345 (99.7%) (98.4%, 100.0%)	344/345 (99.7%) (98.4%, 100.0%)
Mean change between visits SD 95% CI	0.035 0.256 (0.008, 0.062)	0.009 0.227 (-0.015, 0.033)	0.000 0.205 (-0.022, 0.022)	0.017 0.193 (-0.004, 0.037)
Mean change per month	0.017	0.003	0.000	0.006
Mean change per year (change per month × 12)	0.209	0.036	0.000	0.067

Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam.
Consistent Cohort = All eyes examined at 1, 3, 6, 9 and 12 months.
[1] 95% CI was calculated based on Clopper-Pearson method.

Additional Effectiveness Analyses:

The results of key effectiveness variables were stratified by pre-operative manifest refraction spherical equivalent (MRSE) as shown in **Table 23** below.

Table 23. Summary of Key Effectiveness Variables at 6 Months Stratified By Preoperative MRSE Effectiveness Population**:**

Key Effectiveness Variable	Preop MRSE					
	-1.00 to -2.00 D n/N (%)	-2.01 to -3.00 D n/N (%)	-3.01 to -4.00 D n/N (%)	-4.01 to -5.00 D n/N (%)	-5.01 to -6.00 D n/N (%)	-6.01 to -7.00 D n/N (%)
UCVA, 20/16 or better	8/19 (42.1%)	18/40 (45.0%)	35/64 (54.7%)	28/49 (57.1%)	25/45 (55.6%)	18/36 (50.0%)
UCVA, 20/20 or better	15/19 (78.9%)	31/40 (77.5%)	55/64 (85.9%)	41/49 (83.7%)	38/45 (84.4%)	32/36 (88.9%)
UCVA, 20/25 or better	18/19 (94.7%)	36/40 (90.0%)	63/64 (98.4%)	48/49 (98.0%)	43/45 (95.6%)	35/36 (97.2%)
UCVA, 20/32 or better	18/19 (94.7%)	40/40 (100.0%)	63/64 (98.4%)	49/49 (100.0%)	43/45 (95.6%)	36/36 (100.0%)
UCVA, 20/40 or better	19/19 (100.0%)	40/40 (100.0%)	63/64 (98.4%)	49/49 (100.0%)	43/45 (95.6%)	36/36 (100.0%)
MRSE, Attempted vs. Achieved, ±0.25D	17/19 (89.5%)	31/40 (77.5%)	55/64 (85.9%)	42/49 (85.7%)	39/45 (86.7%)	28/36 (77.8%)
MRSE, Attempted vs. Achieved, ±0.50D	18/19 (94.7%)	36/40 (90.0%)	63/64 (98.4%)	47/49 (95.9%)	43/45 (95.6%)	32/36 (88.9%)
MRSE, Attempted vs. Achieved, ±1.00D	19/19 (100.0%)	40/40 (100.0%)	64/64 (100.0%)	49/49 (100.0%)	45/45 (100.0%)	36/36 (100.0%)
MRSE, Attempted vs. Achieved, ±2.00D	19/19 (100.0%)	40/40 (100.0%)	64/64 (100.0%)	49/49 (100.0%)	45/45 (100.0%)	36/36 (100.0%)

Key Effectiveness	Preop MRSE				Total
	-7.01 to -8.00 D n/N (%)	-8.01 to -9.00 D n/N (%)	-9.01 to -10.00 D n/N (%)	> -10.00 D n/N (%)	n/N (%)
UCVA, 20/16 or better	14/36 (38.9%)	12/26 (46.2%)	11/23 (47.8%)	5/10 (50.0%)	174/348 (50.0%)
UCVA, 20/20 or better	32/36 (88.9%)	22/26 (84.6%)	18/23 (78.3%)	9/10 (90.0%)	293/348 (84.2%)
UCVA, 20/25 or better	35/36 (97.2%)	24/26 (92.3%)	21/23 (91.3%)	10/10 (100.0%)	333/348 (95.7%)
UCVA, 20/32 or better	36/36 (100.0%)	25/26 (96.2%)	21/23 (91.3%)	10/10 (100.0%)	341/348 (98.0%)
UCVA, 20/40 or better	36/36 (100.0%)	25/26 (96.2%)	22/23 (95.7%)	10/10 (100.0%)	343/348 (98.6%)
MRSE, Attempted vs. Achieved, ±0.25D	29/36 (80.6%)	21/26 (80.8%)	19/23 (82.6%)	10/10 (100.0%)	291/348 (83.6%)
MRSE, Attempted vs. Achieved, ±0.50D	34/36 (94.4%)	22/26 (84.6%)	21/23 (91.3%)	10/10 (100.0%)	326/348 (93.7%)
MRSE, Attempted vs. Achieved, ±1.00D	35/36 (97.2%)	25/26 (96.2%)	22/23 (95.7%)	10/10 (100.0%)	345/348 (99.1%)
MRSE, Attempted vs. Achieved, ±2.00D	36/36 (100.0%)	26/26 (100.0%)	23/23 (100.0%)	10/10 (100.0%)	348/348 (100.0%)

N = Number of CRFs received with non-missing values for each group.

Shaded cells: Treatment of -10.01 through -11.00 D MRSE will present a flagged warning to the user indicating that correction of these powers is outside the range of the approved indications for use. Treatments of more than -11.00 D MRSE are locked out.

The tables below summarize additional information related to the effectiveness results from the pivotal clinical trial.

Table 24. Postoperative Uncorrected Visual Acuity (UCVA) Compared to Preoperative Best Spectacle Corrected Visual Acuity (BSCVA) Effectiveness Cohort Eyes:

UCVA vs BSCVA	Day 1 n (%)	Week 1 n (%)	Month 1 n (%)	Month 3 n (%)
Available (N)	353	353	353	353
UCVA >2 Lines Better than Preop BSCVA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
UCVA 2 Lines Better than Preop BSCVA	0 (0.0%)	0 (0.0%)	2 (0.6%)	7 (2.0%)
UCVA 1 Line Better than Preop BSCVA	6 (1.7%)	19 (5.4%)	51 (14.4%)	75 (21.2%)
UCVA Equal to Preop BSCVA	47 (13.3%)	80 (22.7%)	126 (35.7%)	161 (45.6%)
UCVA 1 Line Worse than Preop BSCVA	98 (27.8%)	122 (34.6%)	108 (30.6%)	74 (21.0%)
UCVA 2 Lines Worse than Preop BSCVA	85 (24.1%)	66 (18.7%)	38 (10.8%)	22 (6.2%)
UCVA >2 Lines Worse than Preop BSCVA	117 (33.1%)	66 (18.7%)	28 (7.9%)	13 (3.7%)
UCVA Better than or Equal to Preop BSCVA	53 (15.0%)	99 (28.0%)	179 (50.7%)	244 (69.1%)
Not reported	0	0	0	0
Total	353	353	353	353

UCVA vs BSCVA	Month 6 n (%)	Month 9 n (%)	Month 12 n (%)
Available (N)	348	352	349
UCVA >2 Lines Better than Preop BSCVA	0 (0.0%)	1 (0.3%)	1 (0.3%)
UCVA 2 Lines Better than Preop BSCVA	14 (4.0%)	21 (6.0%)	23 (6.6%)
UCVA 1 Line Better than Preop BSCVA	94 (27.0%)	100 (28.4%)	112 (32.1%)
UCVA Equal to Preop BSCVA	141 (40.5%)	147 (41.8%)	147 (42.1%)
UCVA 1 Line Worse than Preop BSCVA	74 (21.3%)	60 (17.0%)	42 (12.0%)
UCVA 2 Lines Worse than Preop BSCVA	14 (4.0%)	13 (3.7%)	13 (3.7%)
UCVA >2 Lines Worse than Preop BSCVA	11 (3.2%)	10 (2.8%)	11 (3.2%)
UCVA Better than or Equal to Preop BSCVA	249 (71.6%)	269 (76.4%)	283 (81.1%)
Not reported	0	0	0
Total	348	352	349

N = Number of CRFs received with non-missing values at each visit.

Accuracy of the IRC, with respect to manifest refractive spherical equivalent (MRSE), is shown in **Table 25** for the 6-month consistent effectiveness cohort. This cohort consists of all eyes from the effectiveness cohort with every follow-up exam from 1 week onward to the 6-month point of stability.

Table 25. Accuracy of MRSE — Attempted vs. Achieved - 6-Month Consistent Effectiveness Cohort:

MRSE Deviation	Week 1 n/N (%)	Month 1 n/N (%)	Month 3 n/N (%)
Available (N)	348	348	348
± 0.25 D	248/348 (71.3%)	274/348 (78.7%)	290/348 (83.3%)
± 0.50 D	313/348 (89.9%)	319/348 (91.7%)	336/348 (96.6%)
± 1.00 D	343/348 (98.6%)	343/348 (98.6%)	344/348 (98.9%)
± 2.00 D	348/348 (100.0%)	348/348 (100.0%)	348/348 (100.0%)
Overcorrected > 1.00 D	1/348 (0.3%)	1/348 (0.3%)	1/348 (0.3%)
Overcorrected > 2.00 D	0/348 (0.0%)	0/348 (0.0%)	0/348 (0.0%)
Undercorrected > 1.00 D	4/348 (1.1%)	4/348 (1.1%)	3/348 (0.9%)
Undercorrected > 2.00 D	0/348 (0.0%)	0/348 (0.0%)	0/348 (0.0%)
Mean (SD)	-0.036 (0.354)	-0.065 (0.333)	-0.030 (0.282)
Range	-1.500, 1.375	-1.750, 1.750	-1.750, 1.250
Not reported	0	0	0
Total	348	348	348

MRSE Deviation	Month 6 n/N (%)	Month 9 n/N (%)	Month 12 n/N (%)
Available (N)	348	347	345
± 0.25 D	291/348 (83.6%)	301/347 (86.7%)	299/345 (86.7%)
± 0.50 D	326/348 (93.7%)	333/347 (96.0%)	327/345 (94.8%)
± 1.00 D	345/348 (99.1%)	346/347 (99.7%)	342/345 (99.1%)
± 2.00 D	348/348 (100.0%)	347/347 (100.0%)	345/345 (100.0%)
Overcorrected > 1.00 D	0/348 (0.0%)	0/347 (0.0%)	0/345 (0.0%)
Overcorrected > 2.00 D	0/348 (0.0%)	0/347 (0.0%)	0/345 (0.0%)
Undercorrected > 1.00 D	3/348 (0.9%)	1/347 (0.3%)	3/345 (0.9%)
Undercorrected > 2.00 D	0/348 (0.0%)	0/347 (0.0%)	0/345 (0.0%)
Mean (SD)	-0.022 (0.278)	-0.021 (0.238)	-0.004 (0.253)
Range	-1.500, 1.000	-1.250, 0.750	-1.250, 1.000
Not reported	0	0	0
Total	348	347	345

N = Number of CRFs received with non-missing values at each visit.

Additional information related to the effectiveness of the astigmatic correction are shown in **Tables 26 to 29**.

Accuracy of the intended astigmatic correction, with respect to manifest refractive cylinder, is shown in **Table 26** for the 6-month consistent effectiveness cohort. This cohort consists of all eyes from the effectiveness cohort with every follow-up exam from 1 week onward to the 6-month point of stability. **Table 27** shows analysis of the intended astigmatic correction stratified by MRCYL for the 6-month postoperative follow-up exam.

Table 26. Accuracy of MRCYL — Attempted vs. Achieved
Eyes treated for Astigmatic Myopia — 6-Month Consistent Effectiveness Cohort:

MRCYL Deviation	Week 1 n/N (%)	Month 1 n/N (%)	Month 3 n/N (%)
Available (N)	300	300	300
± 0.25 D	215/300 (71.7%)	202/300 (67.3%)	216/300 (72.0%)
± 0.50 D	266/300 (88.7%)	259/300 (86.3%)	267/300 (89.0%)
± 1.00 D	297/300 (99.0%)	292/300 (97.3%)	297/300 (99.0%)
± 2.00 D	300/300 (100.0%)	300/300 (100.0%)	300/300 (100.0%)
Mean (SD)	-0.221 (0.303)	-0.246 (0.337)	-0.212 (0.318)
Range	-1.250, 0.000	-1.500, 0.000	-1.500, 0.000
Not reported	0	0	0
Total	300	300	300

MRCYL Deviation	Month 6 n/N (%)	Month 9 n/N (%)	Month 12 n/N (%)
Available (N)	300	299	297
± 0.25 D	215/300 (71.7%)	225/299 (75.3%)	227/297 (76.4%)
± 0.50 D	263/300 (87.7%)	271/299 (90.6%)	272/297 (91.6%)
± 1.00 D	292/300 (97.3%)	296/299 (99.0%)	290/297 (97.6%)
± 2.00 D	300/300 (100.0%)	299/299 (100.0%)	297/297 (100.0%)
Mean (SD)	-0.221 (0.334)	-0.187 (0.294)	-0.179 (0.310)
Range	-1.500, 0.000	-1.250, 0.000	-1.500, 0.000
Not reported	0	0	0
Total	300	299	297

N = Number of CRFs received with non-missing values at each visit.

Table 27. Accuracy of MRCYL — Attempted vs. Achieved at 6 Months
Stratified By Preoperative MRCYL
Eyes treated for Astigmatic Myopia — Effectiveness Population

MRCYL Deviation	Preop MRCYL			Total
	-0.75 to -1.00 D n/N (%)	-1.01 to -2.00 D n/N (%)	-2.01 to -3.00 D n/N (%)	n/N (%)
± 0.25 D	102/120 (85.0%)	74/108 (68.5%)	39/72 (54.2%)	215/300 (71.7%)
± 0.50 D	110/120 (91.7%)	94/108 (87.0%)	59/72 (81.9%)	263/300 (87.7%)
± 1.00 D	117/120 (97.5%)	107/108 (99.1%)	68/72 (94.4%)	292/300 (97.3%)
± 2.00 D	120/120 (100.0%)	108/108 (100.0%)	72/72 (100.0%)	300/300 (100.0%)
Mean (SD)	-0.148 (0.303)	-0.222 (0.312)	-0.340 (0.383)	-0.221 (0.334)
Range	-1.500, 0.000	-1.250, 0.000	-1.500, 0.000	-1.500, 0.000

N = Number of CRFs received with non-missing values for each group.

Results of the Vector Analysis at 6 months are shown in **Table 28**.

Table 28. Vector Analysis Summary at 6 Months
Eyes treated for Astigmatic Myopia — Effectiveness Population:

Preoperative Cylinder	n	|IRC| Mean ± SD	|SIRC| Mean ± SD	|EV|[1] Mean ± SD	CR[2] Mean ± SD	ER[3] Mean ± SD
Month 6						
All	300	1.528 ± 0.699	1.444 ± 0.637	0.221 ± 0.334	0.972 ± 0.222	0.155 ± 0.281
-0.75 to -1.00 D	120	0.883 ± 0.125	0.924 ± 0.241	0.148 ± 0.303	1.051 ± 0.274	0.174 ± 0.379
-1.01 to -2.00 D	108	1.542 ± 0.283	1.443 ± 0.371	0.222 ± 0.312	0.936 ± 0.174	0.147 ± 0.211
-2.01 to -3.00 D	72	2.583 ± 0.278	2.311 ± 0.430	0.340 ± 0.383	0.894 ± 0.136	0.133 ± 0.156

Cylinder axis of left eye was flipped around the vertical axis. Then IRC, SIRC, CR and ER were calculated.
1 EV = IRC - SIRC
2 CR = |SIRC|/|IRC|
3 ER = |EV|/|IRC|

The stability analysis of MRCYL is presented in **Table 29**.

Table 29. Stability of MRCYL
Eyes treated for Astigmatic Myopia — Effectiveness Population

Change in MRCYL	Between 1 and 3 Months	Between 3 and 6 Months	Between 6 and 9 Months	Between 9 and 12 Months
Pairwise Sequential Visits				
Eyes within 0.50 D change (n/N, %, [% CI][1])	291/304 (95.7%) (92.8%, 97.7%)	286/300 (95.3%) (92.3%, 97.4%)	288/299 (96.3%) (93.5%, 98.1%)	294/300 (98.0%) (95.7%, 99.3%)
Eyes within 1.00 D change (n/N, %, [% CI][1])	303/304 (99.7%) (98.2%, 100.0%)	298/300 (99.3%) (97.6%, 99.9%)	298/299 (99.7%) (98.2%, 100.0%)	299/300 (99.7%) (98.2%, 100.0%)
Mean change between visits SD 95% CI	0.034 0.265 (0.004, 0.064)	-0.009 0.272 (-0.040, 0.022)	0.034 0.233 (0.008, 0.061)	0.008 0.199 (-0.015, 0.030)
Mean change per month	0.017	-0.003	0.011	0.003
Mean change per year (change per month × 12)	0.202	-0.037	0.137	0.030
12-Month Consistent Cohort				
Eyes within 0.50 D change (n/N, %, [% CI][1])	284/297 (95.6%) (92.6%, 97.6%)	283/297 (95.3%) (92.2%, 97.4%)	286/297 (96.3%) (93.5%, 98.1%)	291/297 (98.0%) (95.7%, 99.3%)
Eyes within 1.00 D change (n/N, %, [% CI][1])	296/297 (99.7%) (98.1%, 100.0%)	295/297 (99.3%) (97.6%, 99.9%)	296/297 (99.7%) (98.1%, 100.0%)	296/297 (99.7%) (98.1%, 100.0%)
Mean change between visits SD 95% CI	0.033 0.266 (0.002, 0.063)	-0.008 0.272 (-0.039, 0.024)	0.035 0.234 (0.008, 0.061)	0.008 0.200 (-0.015, 0.030)
Mean change per month	0.016	-0.003	0.012	0.003
Mean change per year (change per month × 12)	0.197	-0.030	0.138	0.030

Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam.
Consistent Cohort = All eyes examined at 1, 3, 6, 9 and 12 months.
1 95% CI was calculated based on Clopper-Pearson method.

3. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 5 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

There were no eyes with preoperative UCVA of 20/40 or better. At the refractive time point of stability of 6 months postoperatively, 98.6% (343/348) and 84.2% (293/348) achieved uncorrected visual acuity of 20/40 or better and 20/20 or better, respectively, with no subjects having best corrected visual acuity worse than 20/40 at their last available visit. Similar results were achieved at the 12-month visit.

Additionally, the MRSE was within ± 1.00 D of attempted correction in over 98 % of eyes at all study visits. No fewer than 79% of eyes were within ±0.25 D, and no fewer than 91.8% of eyes were within ±0.50 D of the targeted MRSE correction from the 1-month through 12-month visits. There were no reports of overcorrection > 1.00 D MRSE at 6 months or later.

Effectiveness and stability of the correction of myopia with up to -3.00 D astigmatism with the VisuMax SMILE procedure was demonstrated in the subgroup of 304 eyes that received a spherocylindrical treatment. At the point of stability, i.e., 6 months postoperatively, 71.7%, 87.7%, and 97.3% of eyes were within ± 0.25 D, ± 0.50 D, and ± 1.00 D of targeted plano MRCYL, respectively. The mean change in MRCYL was -0.003 D per month in the 3 to 6-month interval, and 0.011 and 0.003 D per month for the subsequent 3-months intervals. At least 95 % of eyes receiving an astigmatic correction had changes in MRCYL ≤ 0.5 D between 3 and 6 months; 96.3% and 98.0% had changes ≤ 0.5 D at the 6 to 9-month and the 9 to 12-month interval.

Key effectiveness outcomes are summarized below. (The protocol had no specific targets for successs.)

Predictability of MRSE

- Percent of eyes with MRSE within 1.00 diopter of target (at stability time point): 99.1% (345/348)

The result surpasses the FDA Guidance (Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers (Oct 1996)) recommended target of 75% of eyes achieving MRSE within 1.00 D of the intended target.

- Percent of eyes with MRSE within 0.50 diopter of target (at stability time point): 93.7%% (326/348)

The result surpasses the FDA Guidance recommended target of 50% of eyes achieving MRSE within 0.50 D of the intended target.

Improvement in UCVA

- Percent of eyes with UCVA of ≥20/40 (at stability time point): 98.6% (343/348)

The result surpasses the FDA Guidance target of 85% of eyes achieving 20/40. This is a successful outcome.

- Percent of eyes with UCVA of ≥20/20 (at stability time point): 84.2% (293/348)

There is no recommended target for this outcome (for the percent of eyes to achieve 20/20 UCVA) in the 1996 FDA Guidance. However, the result is very close to meeting the FDA Guidance target of 85% for achieving 20/40; this is a positive result considering that 20/20 is 3 lines better.

Stability of MRSE

At 6 months and beyond:

- >95% of eyes change by ≤1.00 D from the prior scheduled visit
- Mean rate of change (from prior scheduled visit) in MRSE is <0.50 D per year (.04 D per month)
- The 95% confidence interval for mean rate of change (from prior scheduled visit) includes zero
- The mean rate of change (from the prior scheduled visit) is monotonically decreasing [except for 9-12 months, because it is virtually zero over 6 – 9 months and 9 – 12 months].

Based upon the above (in line with DOED prior approvals and recommendations), stability was established at 6 months.

The pivotal clinical trial outcomes support the reasonable assurance of the effectiveness of the device for the proposed indications for use.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory as well as data collected in a clinical study conducted to support PMA approval as described above.

No study subject presented with a loss of ≥ 2 lines BSCVA, with BSCVA worse than 20/40, or with increased manifest refractive astigmatism > 2.00 D at 6 months or at the last available visits. With regard to loss of ≥ 2 lines BSCVA at any point during the study, there were 33 study eyes at Week 1, 9 eyes at Month 1, and 1 eye at Month 3 with this degree of loss.

A total of 9 subjects were reported with 11 ocular adverse events (AEs) over the course of the study. No AE occurred at a rate of 1% or greater per type of event. There were 3 intraoperative AEs all involving cap tear related to difficult lenticule removal with tissue damage. There were an additional 22 intraoperative complications, most related to loss of suction. The postoperative adverse events included one case of transient loss of ≥ 2 lines of BSCVA (not resolved by a rigid contact lens) at 3 months, due to epithelium in the interface, and another case of epithelium in the interface requiring secondary surgical intervention (including irrigation) at 12 months. Two other cases of epithelium in the interface required irrigation at early postoperative visits. Other adverse events included 2 cases of allergic conjunctivitis, and single cases of mild iritis, hypertensive retinopathy, and Krukenberg spindle. Postoperative complications included cases of moderate to severe visual symptoms of glare (24) and haloes (16), dry eye syndrome (13), epithelium in the interface (9), interface debris (4), mild peripheral corneal scar (1), and transient light sensitivity syndrome (1). In the majority of cases, harmful events resolved without severe residual sequelae.

No eyes had induced manifest refractive astigmatism >2.00 D at 6 months postoperatively.

Monocular mean log contrast sensitivity did not show a significant mean loss from pre-treatment at any tested spatial frequency (1.5, 3, 6, and 12 cycles per degree) at 6 months. At 6 months, 6/348 eyes (1.7%) showed a loss of ≥ 0.3 log units at ≥ 2 spatial frequencies (while 72/348 eyes (20.7%) showed a similar gain).

The pivotal clinical study outcomes support the reasonable assurance of the safety of the device for the proposed indications for use.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The main benefit of the treatment to the patient is improved UCVA. While there were no eyes preoperatively with UCVA of 20/40 or better, at the refractive time point of stability of 6 months postoperatively, 98.6% (343/348) and 84.2% (293/348) achieved uncorrected visual acuity of 20/40 or better and 20/20 or better, respectively, with no subjects having best corrected visual acuity worse than 20/40 at their last available visit. Similar results were achieved at the 12-month visit. These results represent significant clinical benefit.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The most serious types of adverse events or complications seen in the study were the three cases of intraoperative cap tears. Also significant were several of the cases of epithelium in the interface: one causing significant temporary loss of BSCVA at 3 months, one requiring secondary surgical intervention (including irrigation) at 12 months. Two other cases of epithelium in the interface required irrigation at early postoperative visits. All objective types of adverse events occurred at rates less than 1%. No objective findings resulted in long-term serious sequelae. No study subject presented with a loss of ≥ 2 lines BSCVA at 6 months or greater from treatment.

Additional factors to be considered in determining probable risks and benefits for the VisuMax Femtosecond Laser device included: the study design was of good quality, the conduct of the study was good, with few eyes missing data, and the fact that the device has been commercially available in more than 200 countries without reports of substantial problems.

Patient perspectives considered during the review included a questionnaire that was administered during the clinical trial to collect information on patient symptoms. However, the modified QoV used in this trial could not be determined to be a reliable measure of visual symptoms by the FDA. Therefore, caution must be used in interpreting the data, given that the reported prevalence and severity of symptoms may not be accurate.

In conclusion, given the available information above, the data support that, for small incision lenticule extraction (SMILE) for the reduction or elimination of myopia with or without astigmatism:

- For spherical refractive error (in minus cylinder format) from -1.00 diopters through -10.00 diopters,
- For cylinder from -0.75 diopters through -3.00 diopters,
- When refraction spherical equivalent is no greater in magnitude than 10.00 diopters,

in patients 22 years of age or older with documentation of stable manifest refraction over the past year, the probable benefits of the device outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The benefit of the device for the indications for use, as demonstrated by the uncorrected distance visual acuity results of the pivotal clinical trial, e.g., at the refractive time point of stability of 6 months postoperatively, 98.6% (343/348) and 84.2% (293/348) achieved uncorrected visual acuity of 20/40 or better and 20/20 or better, outweigh the potential risks, with no eyes showing ≥2 lines loss of BSCVA at the final visit and adverse events occurring at rates of <1% per type of event.

XIII. CDRH DECISION

CDRH issued an approval order on October 4, 2018. The final conditions of approval cited in the approval order are described below.

The applicant will conduct a prospective, multicenter, single arm, open-label, observational, new enrollment post approval study of the SMILE procedure by using the VisuMax Femtosecond Laser. The study is designed to evaluate the patient experience of visual symptoms 6 months after bilateral treatment with the VisuMax SMILE procedure as measured by means of the Patient-Reported Outcomes with LASIK (PROWL) patient questionnaire.

The study will enroll and treat a total of 171 adult patients undergoing bilateral treatment with the approved VisuMax SMILE procedure for the reduction or elimination of myopia with astigmatism from six to ten investigational sites in the U.S. Assuming a 10% of loss-to-follow-up rate, 154 patients are evaluable at 6 months of follow up. Eligible patients will be assessed during preoperative and 6-months postoperative visits.

The primary safety endpoints are the development of postoperative clinically relevant visual symptoms, including: the proportion of patients that developed clinically relevant (i.e. "very" or "extremely" bothersome) postoperative visual symptoms; and the proportion of patients that developed difficulty performing daily activities due to postoperative visual symptoms. The secondary safety endpoints include: the resolution of clinically relevant visual symptoms, the development and resolution of all visual symptoms, dry eye, and patient satisfaction.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.