SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System

Device Trade Name: WaveLight® EX500 Excimer Laser System, ALLEGRETTO WAVE® EYE-Q Excimer Laser System

Device Procode: LZS

Applicant's Name and Address: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P020050/S023

Date of FDA Notice of Approval: November 21, 2016

The original PMA (P020050) was approved on October 7, 2003 for WaveLight Allegretto WAVE Excimer Laser System indicated for use in Laser Assisted in situ Keratomileusis (LASIK) treatment for the following:

- The reduction or elimination of myopia of up to -12.0 diopters (D) of sphere and up to -6.0 D of astigmatism at the spectacle plane;
- Patients who are 18 years of age or older; and
- Patients with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery.

The SSED to support the indication is available on the CDRH website at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P020050 and is incorporated by reference here.

The current supplement was submitted to expand the indication for the ALLEGRETTO WAVE® EYE-Q and WaveLight® EX500 for use in photorefractive keratectomy (PRK) treatments.

II. INDICATIONS FOR USE

The WaveLight® EX500 Excimer Laser System and ALLEGRETTO WAVE® Eye-Q Excimer Laser Systems are indicated for use in Photorefractive Keratectomy (PRK) treatments for:

- the reduction or elimination of up to -6.0 diopters (D) of spherical equivalent myopia or myopia with astigmatism, with up to -6.0 D of spherical component and up to -3.0 D of astigmatic component at the spectacle plane,
- patients who are 18 years of age or older and,
- patients with documentation of a stable manifest refraction defined as ≤ 0.5 D preoperative spherical equivalent shift over one year prior to surgery.

III. CONTRAINDICATIONS

The device is contraindicated if any of the following conditions exist:

- progressive myopia with or without astigmatism, acute or recurrent ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone,
- patients with a weakened immune system, including diagnosed collagen vascular, atopic syndrome, autoimmune or immunodeficiency disease,
- patients with degeneration of structures of the cornea, diagnosed keratoconus or any clinical pictures suggestive to keratoconus,
- patients with recurrent corneal erosion. This condition can lead to serious corneal problems during and after PRK,
- patients with uncontrolled diabetes,
- patients with a thin cornea and which is not thick enough to undergo the necessary ablation for the PRK procedure,
- patients with uncontrolled glaucoma. It is unknown whether PRK is safe and effective for such patients,
- patients with eyes that have a calculated esidual stromal bed thickness that is less than 250 microns, and
- patients with severe dry eyes.
- Eyes with unstable visual acuity by manifest refraction (change of more than 0.5 diopter in myopia or astigmatism) over the prior 12 months preceding surgery.

- Herpes (herpes simplex or herpes zoster) eye infection within the past year or corneal damage from prior herpes eye infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ALLEGRETTO WAVE® Eye-Q and WaveLight® EX500 Excimer Laser Systems labeling.

V. DEVICE DESCRIPTION

Two (2) devices are included in this submission, ALLEGRETTO WAVE EYE-Q Excimer Laser System (EYE-Q) and WAVELIGHT EX500 Excimer Laser System (EX500). These two (2) systems are similar. The primary difference between them is the frequency of the laser pulse, 400 Hz for EYE-Q and 500 Hz for EX500. The functional similarity for LASIK between the two (2) devices was approved by FDA on November 23, 2011 under P020050/S006 and P030008/S006 in which a study demonstrated that the ablation profiles on the bovine cornea were identical for 200 Hz, 400 Hz, and 500 Hz pulse frequencies.

ALLEGRETTO WAVE EYE-Q Excimer Laser System

The EYE-Q is a scanning-spot Excimer laser system used in refractive surgery for the treatment of refractive errors of the human eye. The system consists of a compact excimer laser with high pulse frequency, a galvanometer scanner for positioning the laser spot, and a fast eye-tracker for determining eye position and laser beam direction. The integrated eye-tracker offers automatic centration of the ablation and tracking of eye movements. The specially shaped profile of the treatment laser beam and the small spot size ensure the required accuracy to achieve the desired contour of the treated corneal surface.

The WaveNet™ Planning Software (WPS) allows the physician to plan treatments on a portable notebook computer outside the surgical area in the same way as if directly on the device. The software is made available to the surgeon on a standard DVD-ROM and can be used with any notebook computer meeting the specified hardware requirements.

WaveLight EX500 Laser System

EX500 uses the same scanning technique for positioning the laser spot and same eyetracker to determine the eye position and laser mean direction as in EYE-Q. Similarly the WaveNet Planning Software is used for planning treatment. As for treatment parameter, EX500 provides the same wavelength, fluence, beam diameter, and ablation zone as EYE-Q.

The comparison of the technical specifications of lasers used in EYE-Q and EX500 are the follows.

	EYE-Q	**EX500**
Laser Source	ArF excimer laser	ArF excimer laser
Laser Class	4	4
Wavelength	193 nm	193 nm
Pulse Frequency	400 Hz	500 Hz
Pulse Duration	10 ns + 5 ns	6 ns + 2 ns

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative methods for the correction of myopia and myopia with astigmatism include the following: wearing prescription spectacles or contact lenses, laser-assisted in situ keratomileusis (LASIK), phakic intraocular lens (IOL) implantation, radial keratotomy, and automated lamellar keratoplasty. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their physicians to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The WaveLight® EX500 is the 3rd generation of the WaveLight stationary scanning-spot excimer laser system. The 1st and 2nd generations are the ALLEGRETTO WAVE and the ALLEGRETTO WAVE EYE-Q, respectively. As of January, 2015 the following number of excimer laser systems have been installed worldwide:

- 528 ALLEGRETTO WAVE,
- 1220 ALLEGRETTO WAVE Eye-Q, and
- 728 WaveLight® EX500

Of those, 106 ALLEGRETTO WAVE, 312 ALLEGRETTO WAVE Eye-Q, and 125 WaveLight® EX500 laser systems have been installed in the USA. The WaveLight® EX500 is CE marked and is approved in Argentina, Australia, Belarus, Brazil, Canada, China, Colombia, Costa Rica, Honduras, Indonesia, Israel, Kazakhstan, Malaysia, Mexico, New Zealand, Philippines, Peru, Russia, Serbia, Singapore, South Africa, South Korea, Sri Lanka, Taiwan, Thailand, Turkey, Ukraine, USA, Uruguay,Venezuela, and Vietnam.

These devices have not been marketed in the United States for the indication of Photorefractive Keratectomy (PRK).

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with PRK include the following: Loss of best spectacle corrected visual acuity (BSCVA), under- or over-correction of refractive error, induced astigmatism, worsening of patient complaints (such as double vision, sensitivity to bright lights, glare, increased difficulty with night vision, fluctuations in vision, starbursts, halos), dry eyes, eye pain and/or burning feeling in eyes, foreign body sensation in eyes, watery eyes, increased intraocular pressure (IOP), corneal haze, corneal infiltrate or ulcer, corneal epithelial defect, corneal edema.

The occurrence of these events may involve the necessity of secondary (additional) surgical intervention, such as the possibility of corneal transplant due to corneal complications.

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

IX. SUMMARY OF NON-CLINICAL STUDIES

No new nonclinical studies were performed for the new PRK indication proposed in this submission. Previous nonclinical study for LASIK was conducted for the ALLEGRETTO device in the original PMA submission (P020050). A nonclinical study for WaveLight WaveLight EX500 (500 Hz) was conducted for PMA Supplement 6 (P020050/S006) for LASIK indication to demonstrate the same functional performance as ALLEGRETTO WAVE EYE-Q (400 Hz). This study demonstrated that the ablation profiles on the bovine cornea were identical for 200 Hz, 400 Hz, and 500 Hz pulse frequencies.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Alcon Laboratories, Inc. performed a clinical study to demonstrate a reasonable assurance of safety and effectiveness of photorefractive keratectomy (PRK) with only the ALLEGRETTO WAVE EYE-Q excimer laser system for the elimination of up to -6.0 diopters (D) of spherical equivalent myopia or myopia with astigmatism, with up to -6.0 D of spherical component and up to -3.0 D of astigmatic component at the spectacle plane under IDE G120133. 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 treated between August 2012 and June 2014. The database for this P020050/S023 reflected data collected through September 19, 2014 and included 161 patients. There were 8 investigational sites.

The study was a prospective, multi-center, single-arm, open-label, 24-month

clinical study conducted in two (2) stages. In the first, 66 eyes of 34 participants were treated. An interim analysis was conducted after 44 eyes of 22 participants had completed the Month 3 visit to evaluate the adequacy of the treatment nomogram. In the second stage, additional participants were enrolled for a total cohort of 320 eyes (of 161 participants). There were 17 scheduled study visits. The planned duration of follow-up for each participant is 24 months after the surgery (Day 0 visit).

Treatment planning was done with wavefront-optimized corneal profiles, with all eyes targeted for emmetropia. The laser software used the nomogram-adjusted manifest refraction data to determine the treatment plan for PRK. Mitomycin-C was not used during the PRK procedure.

The study design and analyses were planned according to recommendations in ANSI Z80.11.2007 and the methodology described by Eydelman et al (2006) for the standardized analysis of correction of astigmatism by laser systems. No effectiveness or safety hypothesis tests were planned for this study. The analyses of the primary endpoints were based solely on observed rates. The observed rate is defined as the number of eyes meeting the objective divided by the number of eyes with data at the time point of refractive stability. The objectives were considered to have been met if the point estimate for each endpoint met or outperformed the target rate. For analysis of refractive outcomes, the sphere component of the manifest refraction tested at 4.0 meters was adjusted for optical infinity by adding -0.25 D to the sphere magnitude. Manifest refraction spherical equivalent (MRSE) was calculated using the adjusted manifest sphere value. For vector analyses of astigmatism, manifest refraction results were converted to cross cylinder form, adjusted for a vertex distance of 12 mm, then converted to plus cylinder form.

Analyses of the rates of ocular serious adverse events (SAEs) were based on observed cumulative rates, defined as the number of eyes experiencing the SAE at any time during the study divided by the number of eyes in the intent-to-treat (ITT) analysis set. A safety objective was considered to have been met if the point estimate for a safety endpoint is lower than the target rate. Cumulative rates for protocol-specific AEs were defined in the same way as the rates of ocular SAEs. No targets were specified for the protocol-specific AEs. Cumulative rates, by-visit rates, and participant listings were provided for all other types of AEs collected in the study. All other safety parameters were summarized at the visit at which the data were collected.

The sample size was determined based on the ANSI A80.11-2007 recommendation of a minimum number of eyes required to adequately detect SAEs with an expected rate or 1% or greater. With 300 eyes, any ocular SAE that occurs in at least 1% of the population undergoing the procedure would be observed in the study at least once with approximately 95% probability. Therefore, it was planned that up to 350 eyes

should be enrolled with the goal that at least 300 treated eyes would complete the Month 12 visit.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ALLEGRETTO WAVE EYE-Q excimer laser system for PRK treatment study was limited to patients who met the following inclusion criteria:

   - Subjects 18 years of age or older
   - Subjects desiring refractive correction of myopia up to -6.0 D sphere with or without astigmatism 0 to -3.0 D, and up to -6.0 D MRSE at the spectacle plane measured by manifest refraction
   - Intended treatment targeted for emmetropia
   - Bilateral intended treatment
   - Minimum BSCVA in the treated eye of 20/25
   - UCVA of 20/40 or worse in the treated eye
   - Less than 0.75 D spherical equivalent (SE) difference between cycloplegic and manifest refractions
   - Stable refraction (within ± 0.5 D), as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive manifest refractions and/or medical records or glasses prescription history or lensometry of the glasses
   - Demonstrated stable refraction for contact lens wearers (any contact lens use in the 3 months before screening) within ± 0.5 D MRSE on 2 consecutive exam dates under the following conditions:

     (a) lenses were not worn for at least 3 weeks (hard lenses), 2 weeks (toric lenses), or 3 days (soft lenses) prior to the first refractionused to establish stability and through the day of surgery

     (b) the 2 refractions were performed at least 7 days apart

   - Signed informed consent document
   - Willing and able to comply with schedule for follow-up visits

Patients were not permitted to enroll in the ALLEGRETTO WAVE EYE-Q excimer laser system for PRK treatment study if they met any of the following exclusion criteria:

- Females who were pregnant, lactating, or planning a pregnancy or not using an adequate method of birth control during the time course of the study, or had another condition associated with the fluctuation of hormones that could lead to refractive changes

- Participation in other clinical trials during the present study

- Acute or chronic disease or illness that would have increased the operative risk or confounded the outcomes of the study (immuno-compromised, connective tissue disease, clinically significant atopic disease, diabetes, etc)

- Dry eye syndrome, as determined by the short questionnaire for dry eye Syndrome

- Systemic medications that may have confounded the outcome of the study or increased the risk to the subject by affecting wound healing or tissue repair, including, but not limited to steroids, antimetabolites, immune response modifying drugs, etc.

- Nystagmus or any other condition that would have prevented a steady gaze during the PRK treatment or other diagnostic tests

- Mixed astigmatism refractive error

- Ocular condition that predisposed the subject to future complications, for example:

  (a) history or evidence of active or inactive corneal disease (herpes simplex keratitis, herpes zoster keratitis, recurrent erosion syndrome, corneal dystrophy, or cornea guttae, etc.)

  (b) history of keloid formation

  (c) evidence of retinal vascular disease

  (d) keratoconus or keratoconus suspect

  (e) glaucoma or glaucoma suspect (including IOP > 23 mmHg) by exam findings and/or family history (mother, father, blood sibling with glaucoma)

(f) evidence of pellucid marginal degeneration or other topographic abnormality

(g) pathologic alterations of the anterior eye segment/chamber

(h) pathologies of the iris, e.g., coloboma, other irregular changes to the iris margin

(i) acute or recurring ocular pathology

- Subjects with eyes that had predicted residual stromal bed
- thickness < 250 μm
- Previous intraocular or corneal surgery
- Subjects who desired monovision
- A known sensitivity to medications used for study procedures, including PRK
- Presence or history of any condition or finding that made the subject unsuitable as a candidate for PRK or study participation or may have confounded the outcome of the study, in the opinion of the Investigator.

2. Follow-up Schedule

All eyes were evaluated according to the following schedule of assessments (Table 1):

Table 1. Schedule of Visits

Visit Schedule	Visit Type	Visit Name*
Day -30 to -1	Screening	Visit 1
Day 0	Surgery	Visit 2A/2B
Day 1	Re-epithelialization	Visit 3A/3B
Day 2-4	Postoperative	Visit 4A/4B
Day 5-9	Postoperative	Visit 5A/5B
Day 21-35	Postoperative	Visit 6A/6B
Day 70-98	Postoperative	Visit 7A/7B
Day 147-182	Postoperative	Visit 8
Day 245-301	Postoperative	Visit 9
Day 330-420	Postoperative	Visit 10
Day 690-810	Postoperative	Visit 11

* Visit A is for the 1st eye while Visit B for 2nd eye.

Study procedures included the following: uncorrected distance and near visual

acuity (UCVA), best spectacle-corrected distance visual acuity (BSCDVA), photopic and mesopic contrast sensitivity, manifest refraction, cycloplegic refraction, pupillometry, keratometry, corneal topography, pachymetry, tonometry, measurement of axial length by ultrasound, aberrometry, slit-lamp examination, dilated fundus examination, administration of the VSARC questionnaire (Visual Symptoms Associated with Refractive Correction), administration of the RSVP questionnaire (Refractive Status and Vision Profile), and documentation of adverse events and complications.

3. Clinical Endpoints

The key safety and effectiveness endpoints were evaluated at the time of refractive stability and are summarized below.

i. Safety endpoints and objectives

- Ocular serious adverse events: <1% of treated eyes with each ocular SAE type.

- Decrease in best spectacle-corrected visual acuity (BSCVA): At refractive stability, <5% of treated eyes with BSCVA decrease of ≥2 lines from baseline; at refractive stability, <1% of treated eyes whose preoperative BSCVA was 20/20 or better with BSCVA worse than 20/40.

- Induced manifest refractive cylinder (MRC): <5% of eyes with >2.00 D of induced manifest refractive cylinder magnitude at refractive stability compared to baseline.

Photopic and mesopic contrast sensitivity and responses on the VSARC and RSVP questionnaires were evaluated.

ii. Effectiveness endpoints and objectives

- Visual acuity: At refractive stability, ≥85% of eyes with preoperative BSCVA of 20/20 or better should achieve UCVA of 20/40 or better.

- Refractive predictability: At refractive stability, ≥75% of eyes should achieve MRSE and MRC within ±1.0 D of zero. ≥50% of eyes should achieve MRSE and MRC within ±0.5 D of zero.

- Refractive stability: ≥95% of eyes should have a change of ≤1.0 D in MRSE and MRC between 2 refractions, performed at 1 and 3 months postoperatively, or over a minimum 3 month period thereafter.

Cylinder vector and non-vector variables were evaluated.

B. Accountability of PMA Cohort

At the time of database lock, of 176 patients enrolled in the PMA study, 88.6 % (156) patients are available for analysis at the completion of the study, the 12 month post-operative visit (Table 2). 161 participants had one or both eyes treated; in two (2) participants, one eye was treated. A total of 320 eyes were treated (Table 3).

Table 2. Subject Disposition, (All Enrolled)

	n	(%)
Enrolled	176	
Screen Failures	15	
Treated[a]	161	(100.0)
Completed Study	152	(94.4)
Discontinued	9	(5.6)
Lost to Follow-up	7	(4.3)
Unable to Make Future Office Visits	2	(1.2)

n = Number of subjects in category

[a] Subjects 1001 and 1002 had only one eye treated.

Table 3. Postoperative Visit Status by Eye (Intent-to-Treat Population)

	Visit 3 Day 1		Visit 4 Re-epithelialization		Visit 5 Week 1		Visit 6 Month 1		Visit 7 Month 3		Visit 8 Month 6		Visit 9 Month 9		Visit 10 Month 12	
Status	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Treated (N=320)																
Available for Analysis	320	(100.0)	318	(99.4)	320	(100.0)	320	(100.0)	317	(99.1)	315	(98.4)	315	(98.4)	311	(97.2)
Active	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missed Visit																
Discontinued																
Retreatment	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 Causes	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.6)	2	(0.6)	2	(0.6)
Lost to Follow-up	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	3	(0.9)	3	(0.9)	7	(2.2)
Missed visit, but seen at later visit	0	(0.0)	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Not seen, but status obtained (e.g. phone)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
% Accountability		(100.0)		(99.4)		(100.0)		(100.0)		(99.7)		(99.1)		(99.1)		(97.8)

N = Number of eyes in ITT analysis set

n = Number of eyes in category

% Accountability = Available for Analysis / (Treated - Discontinued - Active)

Active = Number of eyes that have not yet reached the visit

C. Study Population Demographics and Baseline Parameters

The demographics of the study cohort are presented in Table 4 below. 78.3% of the cohort is white and 88.8% non-Hispanic or Latino. The mean age is 31.5±7.4 years (range 19 to 56).

Table 4. Demographic Statistics (Intent-to-Treat)

	(N=161) n (%)
Age (Years)	
Mean (SD)	31.5 (7.4)
Median	30.0
(Min, Max)	(19, 56)
Age Category	
18-64	161 (100.0)
≥ 65	0 (0.0)
Sex	
Male	89 (55.3)
Female	72 (44.7)
Race	
White	126 (78.3)
Black or African American	13 (8.1)
Asian	12 (7.5)
Native Hawaiian or Other Pacific Islander	3 (1.9)
Other	7 (4.3)
Ethnicity	
Hispanic or Latino	18 (11.2)
Not Hispanic or Latino	143 (88.8)

N = Number of subjects in ITT analysis set
n = Number of subjects in category
SD = Standard deviation, Min = Minimum, Max = Maximum

The baseline refractive characteristics of the cohort are provided in the following (Table 5):

Table 5. Baseline Characteristics by Eye, (Intent-to-Treat)

Baseline Characteristic	Statistic	Results
Manifest Sphere	**n**	320
	Mean	-2.957
	SD	1.4843
	Median	-2.75
	(Min, Max)	(-6.00, -0.25)
	95% CI	(-3.120, -2.794)
Manifest Cylinder	**n**	320
	Mean	-0.788
	SD	0.8191
	Median	-0.50
	(Min, Max)	(-3.00, 0.00)
	95% CI	(-0.878, -0.697)
MRSE	**n**	320

Baseline Characteristic	Statistic	Results
	Mean	-3.351
	SD	1.4191
	Median	-3.25
	(Min, Max)	(-6.00, -0.75)
	95% CI	(-3.507, -3.195)
UCVA	**n**	320
	Mean	0.870
	SD	0.2656
	Median	0.92
	(Min, Max)	(0.28, 1.40)
	95% CI	(0.841, 0.900)
BSCVA	**n**	320
	Mean	-0.085
	SD	0.0741
	Median	-0.10
	(Min, Max)	(-0.28, 0.12)
	95% CI	(-0.093, -0.076)

n = Number of eyes in ITT analysis set with data
SD = Standard deviation, Min = Minimum, Max = Maximum
CI = Confidence Interval
MRSE = Manifest refraction spherical equivalent
UCVA = Uncorrected visual acuity
BSCVA = Best-spectacle corrected visual acuity

A total of 18 dioptric bins were defined based on each combination of preoperative sphere (0.0 D to -6.0 D) and cylinder (0.0 D to -3.0 D) as shown in Table 6 below. Eligible participants were assigned to dioptric bins based on their preoperative manifest refraction results. The distribution of treated eyes within each dioptric bin was based on a minimum of 20 eyes per bin, except for the bin of less than or equal to 0.5 D cylinder (planned of minimum 75 eyes).

Table 6. Frequency of Eyes by Preoperative Sphere & Cylinder Bin (Intent-to-Treat)

	Cylinder				
Myopia Sphere	0.00 to -0.500	-0.501 to -1.000	-1.001 to -2.000	-2.001 to -3.000	Eyes per Sphere Bin
-0.000 to -1.000	11	7	5	11	34
-1.001 to -2.000	39	12	20	7	78
-2.001 to -3.000	38	13	12	7	70
-3.001 to -4.000	32	10	5	6	53
-4.001 to -5.000	33	11	9	1	54
-5.001 to -6.000	27	4	0	0	31
Eyes per Cylinder Bin	180	57	51	32	320

D. Safety and Effectiveness Results

Determination of refractive stability per ANSI Z80.11-2007 was performed using refractive outcomes from the consistent cohort (CC) analysis set (n=310 eyes; defined as all eyes in the ITT analysis set that completed all post-operative visits up to Month 12). Based on these analyses, the time point of refractive stability for the CC set was established at Month 6 (Visit 8)(Table 7). The following conditions were met at the Month 3 to Month 6 interval in order to establish refractive stability:

- 99.7% and 100% of eyes had a change of MRSE and manifest refractive cylinder of ≤ 1.0 D, respectively.
- The mean rate of change per year was -0.019 D and 0.038 D for MRSE and manifest refractive cylinder, respectively.
- The 95% confidence interval for the mean rate of change included zero.
- The mean rate of change decreased towards zero over time, although there was clinically non-significant increase or decrease in mean change in MRSE and manifest refractive cylinder between consecutive intervals starting at the Month 3 to Month 6 interval.

Table 7. Criteria for Refractive Stability by Eye, (Intent-to-Treat)

		Week 1 to Month 1 (N=320)	Month 1 to Month 3 (N=317)	Month 3 to Month 6 (N=314)	Month 6 to Month 9 (N=314)	Month 9 to Month 12 (N=310)
Change of MRSE ≤ 1.0 D	**n (%)**	306 (95.6)	310 (97.8)	313 (99.7)	314 (100.0)	309 (99.7)
Change of MRSE in Diopters	**Mean**	-0.017	0.019	-0.005	0.012	0.025
	SD	0.5216	0.4292	0.2611	0.2415	0.2341
	95% CI	(-0.075, 0.040)	(-0.028, 0.067)	(-0.034, 0.024)	(-0.014, 0.039)	(-0.001, 0.051)
Change of MRSE per Year	**Mean**	-0.206	0.116	-0.019	0.049	0.100

		Week 1 to Month 1 (N=320)	Month 1 to Month 3 (N=317)	Month 3 to Month 6 (N=314)	Month 6 to Month 9 (N=314)	Month 9 to Month 12 (N=310)
	SD	6.2589	2.5752	1.0444	0.9658	0.9363
	95% CI	(-0.895, 0.482)	(-0.169, 0.401)	(-0.135, 0.097)	(-0.058, 0.157)	(-0.005, 0.205)
Change of Cylinder ≤ 1.0 D	**n (%)**	303 (94.7)	310 (97.8)	314 (100.0)	314 (100.0)	310 (100.0)
Change of Cylinder in Diopters	**Mean**	-0.009	0.168	0.010	0.023	0.003
	SD	0.5391	0.4081	0.2285	0.2078	0.1799
	95% CI	(-0.069, 0.050)	(0.123, 0.213)	(-0.016, 0.035)	(0.000, 0.046)	(-0.017, 0.023)
Change of Cylinder per Year	**Mean**	-0.113	1.008	0.038	0.092	0.013
	SD	6.4696	2.4483	0.9141	0.8313	0.7195
	95% CI	(-0.824, 0.599)	(0.737, 1.278)	(-0.063, 0.140)	(0.000, 0.185)	(-0.068, 0.093)

Cylinder is manifest refractive cylinder
N = Number of eyes with non-missing Cylinder and non-missing MRSE at both visits in visit interval
n = Number of eyes in category
SD = Standard deviation, Min = Minimum, Max = Maximum
CI = Confidence Interval

1. Safety Results

The analysis of safety was based on the cohort of 320 treated eyes (Intent-to-Treat (ITT) cohort) available for the 12 month evaluation. A summary of key safety variables over time is listed below.

- Ocular SAEs – The cumulative rate of any ocular SAE was 0.9%. This meets the primary safety objective of <1% of treated eyes experiencing each ocular SAE type.

- Decrease in BSCVA –
  - No eyes had BSCVA decrease of ≥ 2 lines from baseline at Month 6. This meets the primary safety objective of <5% of treated eyes with BSCVA decrease of ≥2 lines from baseline.
  - No eyes had BSCVA worse than 20/40 (in eyes with BSCVA of 20/20 or better preoperatively) at Month 6. This meets the primary safety objective of <1% of treated eyes whose preoperative BSCVA was 20/20 or better with BSCVA worse than 20/40.

- Induced MRC – No eyes had > 2.0 D of induced manifest refraction cylinder at Month 6 compared to baseline. This meets the primary safety objective of <5% of eyes with >2.00 D of induced manifest refractive cylinder magnitude at refractive stability compared to baseline.

The key safety outcomes for this study are presented below in Tables 8 to 24. Results of the other co-primary safety endpoints are presented in Table 8 below.

Table 8. Best Spectacle Corrected Visual Acuity and Manifest Cylinder by Eye, (Intent-to-Treat)

Visit	Parameter	n	/ N	(%)	95% CI†
Visit 5 - Week 1	BSCVA decrease of ≥ 2 lines from baseline	80	/ 320	(25.0)	(20.4, 30.1)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	8	/ 299	(2.7)	(1.2, 5.2)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 320	(0.0)	(0.0, 1.1)
Visit 6 - Month 1	BSCVA decrease of ☐ 2 lines from basel	13	/ 320	(4.1)	(2.2, 6.8)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	0	/ 299	(0.0)	(0.0, 1.2)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 320	(0.0)	(0.0, 1.1)
Visit 7 - Month 3	BSCVA decrease of ☐ 2 lines from basel	1	/ 317	(0.3)	(0.0, 1.7)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	0	/ 297	(0.0)	(0.0, 1.2)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 317	(0.0)	(0.0, 1.2)
Visit 8 - Month 6	BSCVA decrease of ☐ 2 lines from basel	0	/ 314	(0.0)	(0.0, 1.2)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	0	/ 294	(0.0)	(0.0, 1.2)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 314	(0.0)	(0.0, 1.2)
Visit 9 - Month 9	BSCVA decrease of ☐ 2 lines from basel	0	/ 314	(0.0)	(0.0, 1.2)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	0	/ 294	(0.0)	(0.0, 1.2)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 314	(0.0)	(0.0, 1.2)
Visit 10 - Month 12	BSCVA decrease of ☐ 2 lines from basel	0	/ 311	(0.0)	(0.0, 1.2)
	BSCVA worse than 20/40 (BSCVA 20/20 or better preop)	0	/ 291	(0.0)	(0.0, 1.3)
	Increase of > 2.00 D of induced manifest refraction cylinder	0	/ 311	(0.0)	(0.0, 1.2)

N = Number of eyes in ITT analysis set with data at visit
n = Number of eyes in category
† 95% confidence interval from Binomial distribution

Adverse effects are reported in Tables 9 to 14.

Adverse effects that occurred in the PMA clinical study:

The cumulative rate of ocular SAEs is presented in Table 9.

Table 9. Cumulative Incidence of Ocular Serious Adverse Events by Eye (Intent-to-Treat)

	(N=320)		
Adverse Event	**n**	**(%)**	**E**
Eyes with any AE	3	(0.9)	3
Corneal infiltrates	2	(0.6)	2
Corneal oedema	1	(0.3)	1

Adverse Event	n	(N=320) (%)	E

N = Number of eyes in ITT analysis set
n = Number of eyes with events
E = Number of events
If an eye has multiple occurrences of an AE, the eye is presented only once in the respective count column (n) for the corresponding AE. Events are counted each time in the event (E) column.
Denominators for percentages are the number of treated eyes
AEs coded using MedDRA version 15.0

The two (2) cases of corneal infiltrates were treated with topical antibiotic ophthalmic drops and a short course of oral antibiotics. The infiltrates were found to be resolved 14 and 2 days post-operatively.

The cumulative rates of ocular non-serious AEs are presented in Table 10. The most frequently observed event was corneal opacity/corneal haze, with a rate of 5.6%. All cases, with the exception of one event, were reported as resolved. One incidence of corneal opacity at Month 6 was device-related. The event was assessed as mild and resolved with treatment by post-operative month 12 month.

Table 10. Cumulative Incidence of Ocular Non-Serious Adverse Events by Eye (Intent-to-Treat)

Adverse Event	n	(N=320) (%)	E
Eyes with any AE	60	(18.8)	86
Altered visual depth perception	1	(0.3)	2
Chalazion	1	(0.3)	2
Conjunctival hyperaemia	1	(0.3)	1
Conjunctivitis	2	(0.6)	2
Conjunctivitis allergic	5	(1.6)	5
Conjunctivitis viral	1	(0.3)	1
Corneal abrasion	3	(0.9)	3
Corneal disorder	1	(0.3)	1
Corneal epithelium defect	3	(0.9)	3
Corneal erosion	3	(0.9)	3
Corneal oedema	1	(0.3)	1
Corneal opacity	18	(5.6)	20
Dry eye	4	(1.3)	4
Episcleritis	1	(0.3)	1
Eye allergy	6	(1.9)	6
Eye pain	3	(0.9)	3
Eyelid oedema	1	(0.3)	1
Foreign body sensation in eyes	1	(0.3)	1
Halo vision	1	(0.3)	1
Hordeolum	1	(0.3)	1

Adverse Event	n	(N=320) (%)	E
Iritis	1	(0.3)	1
Keratitis	3	(0.9)	3
Meibomian gland dysfunction	2	(0.6)	2
Photophobia	2	(0.6)	2
Photopsia	1	(0.3)	1
Punctate keratitis	5	(1.6)	7
Vision blurred	3	(0.9)	3
Visual acuity reduced	1	(0.3)	1
Visual impairment	2	(0.6)	2
Vitreous floaters	2	(0.6)	2

N = Number of eyes in ITT analysis set
n = Number of eyes with events
E = Number of events
If an eye has multiple occurrences of an AE, the eye is presented only once in the respective count column (n) for the corresponding AE. Events are counted each time in the event (E) column.
Denominators for percentages are the number of treated eyes
AEs coded using MedDRA version 15.0

Table 11 presents the summary of reported corneal haze by severity. The highest rate of grade 1 or greater corneal haze was at Month 1 (9.7%) and progressively decreased through Month 12 to 1.0%.

Table 11. Corneal Haze by Severity and Visit (Intent-to-Treat)

Severity		Visit 1 Screening	Visit 6 Month 1	Visit 7 Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12
0 - 0.5	**n/N**	320/320	289/320	290/317	288/314	303/314	308/311
	%	100.0	90.3	91.5	91.7	96.5	99.0
	95% CI†	(98.9, 100.0)	(86.5, 93.3)	(87.8, 94.3)	(88.1, 94.5)	(93.8, 98.2)	(97.2, 99.8)
1	**n/N**	0/320	30/320	25/317	22/314	10/314	3/311
	%	0.0	9.4	7.9	7.0	3.2	1.0
	95% CI†	(0.0, 1.1)	(6.4, 13.1)	(5.2, 11.4)	(4.4, 10.4)	(1.5, 5.8)	(0.2, 2.8)
2	**n/N**	0/320	1/320	2/317	4/314	1/314	0/311
	%	0.0	0.3	0.6	1.3	0.3	0.0
	95% CI†	(0.0, 1.1)	(0.0, 1.7)	(0.1, 2.3)	(0.3, 3.2)	(0.0, 1.8)	(0.0, 1.2)
3	**n/N**	0/320	0/320	0/317	0/314	0/314	0/311
	%	0.0	0.0	0.0	0.0	0.0	0.0
	95% CI†	(0.0, 1.1)	(0.0, 1.1)	(0.0, 1.2)	(0.0, 1.2)	(0.0, 1.2)	(0.0, 1.2)
4	**n/N**	0/320	0/320	0/317	0/314	0/314	0/311
	%	0.0	0.0	0.0	0.0	0.0	0.0
	95% CI†	(0.0, 1.1)	(0.0, 1.1)	(0.0, 1.2)	(0.0, 1.2)	(0.0, 1.2)	(0.0, 1.2)

Severity	Visit 1 Screening	Visit 6 Month 1	Visit 7 Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12

n = Number of eyes in category
N = Number of eyes in ITT analysis set with data at visit
† 95% confidence interval from Binomial distribution

Non-serious, protocol-specified AEs

The following non-serious protocol specified adverse events were documented (Tables 12-14):

- Corneal edema between 1 week and 1 month after the procedure
- Peripheral corneal epithelial defect at 1 month or later
- Recurrent corneal erosion at 1 month or later
- Foreign body sensation at 1 month or later
- Pain at 1 month or later
- Ghost/double images in the operative eye
- Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later which the investigator has determined is not easily resolved when the subject is wearing correction or has some simple explanation unrelated to the treatment.
- Clinical signs consistent with marked to severe dry eye at 6 months or later
- Any symptoms of dry eye that significantly affect comfort or activities of daily living (as reported to the investigator) at 6 months or later
- Any symptoms of glare or haloes that significantly affect comfort or activities of daily living (as reported to the investigator) at 6 months or later

The overall rate of "Any symptom marked moderate or severe on the VSARC questionnaire at Month 6 or later" was 18.4%. Within this category, the highest rates were observed for dryness in eyes (10.9%), eyes sensitive to light (5.9%), foreign body sensation (4.4%) and pain in eyes (4.1%).

Table 12. Cumulative Incidence of Non-Serious Protocol-Specified Adverse Events by Eye

Adverse Event	n	(N=320) (%)	E
Recurrent corneal erosion at 1 month or later	3	(0.9)	3
Any symptoms of dry eye that significantly affect comfort or activities of daily living at 6 months or later	64	(20.0)	64
Any symptoms of glare or haloes that significantly affect comfort or activities of daily living at 6 months or later	14	(4.4)	18
Clinical signs consistent with marked to severe dry eye at 6 months or later	1	(0.3)	1
Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later	59	(18.4)	128
1 - Pain in eyes	13	(4.1)	13

Adverse Event	n	(N=320) (%)	E
2 - Dryness in eyes	35	(10.9)	35
3 - Burning feeling in eyes	10	(3.1)	10
4 – Glare	2	(0.6)	2
5 - Eyes sensitive to light	19	(5.9)	19
6 - Halos (circle shapes around lights)	10	(3.1)	10
7 - Starbursts (star shapes around lights)	4	(1.3)	4
8 - Blurry vision	6	(1.9)	8
10 - Fluctuation (changes) in vision	6	(1.9)	6
11 - Difficulty focusing in dim or low light	2	(0.6)	2
12 - Watery Eyes / Tearing	5	(1.6)	5
13 - Foreign body sensation (feeling like something is in your eye)	14	(4.4)	14
Foreign body sensation at 1 month or later	23	(7.2)	29
Ghost/double images in the operative eye	30	(9.4)	31
Pain at 1 month or later	22	(6.9)	26

N = Number of eyes in ITT analysis set
n = Number of eyes with events
E = Number of events
If an eye has multiple occurrences of an AE, the eye is presented only once in the respective count column (n) for the corresponding AE. Events are counted each time in the event (E) column.
Denominators for percentages are the number of treated eyes.

Table 13. Cumulative Incidence of Ocular Protocol Specified Adverse Event – Severity

Protocol Specified Adverse Event Category	Adverse Event	E	Mild N	Mild (%)	Moderate n	Moderate (%)	Severe n	Severe (%)
Corneal edema between 1 week and 1 month after the procedure	Corneal Oedema	1	1	(100.0)	0	(-)	0	(-)
Corneal infiltrate or ulcer	Corneal Infiltrates	2	2	(100.0)	0	(-)	0	(-)
Recurrent corneal erosion at 1 month or later	Corneal Erosion	3	2	(66.7)	1	(33.3)	0	(-)
Any symptoms of dry eye that significantly affect comfort or activities of daily living at 6 months or later	Dry Eye	64	37	(57.8)	23	(35.9)	4	(6.3)
Any symptoms of glare or haloes that significantly affect comfort or activities of daily living at 6 months or later	Glare	10	10	(100.0)	0	(-)	0	(-)
	Halo Vision	8	6	(75.0)	0	(-)	2	(25.0)
Clinical signs consistent with marked to severe dry eye at 6 months or later	Dry Eye	1	1	(100.0)	0	(-)	0	(-)
Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later	Dry Eye	35	12	(34.3)	19	(54.3)	4	(11.4)
	Eye Irritation	10	0	(-)	8	(80.0)	2	(20.0)
	Eye Pain	13	1	(7.7)	10	(76.9)	2	(15.4)
	Foreign Body Sensation In Eyes	14	2	(14.3)	10	(71.4)	2	(14.3)
	Glare[a]	2	2	(100.0)	0	(-)	0	(-)
	Halo Vision[a]	10	2	(20.0)	6	(60.0)	2	(20.0)

Protocol Specified Adverse Event Category	Adverse Event	E	Mild N	Mild (%)	Moderate n	Moderate (%)	Severe n	Severe (%)
	Lacrimation Increased	5	3	(60.0)	2	(40.0)	0	(-)
	Photophobia	19	2	(10.5)	15	(78.9)	2	(10.5)
	Photopsia	4	2	(50.0)	2	(50.0)	0	(-)
	Vision Blurred[a]	10	0	(-)	10	(100.0)	0	(-)
	Visual Impairment	6	2	(33.3)	4	(66.7)	0	(-)
Foreign body sensation at 1 month or later[b]	Foreign Body Sensation In Eyes	186	167	(89.8)	17	(9.1)	2	(1.1)
Ghost/double images in the operative eye[b]	Diplopia	86	60	(69.8)	19	(22.1)	7	(8.1)
Pain at 1 month or later[b]	Eye Pain	139	121	(87.1)	16	(11.5)	2	(1.4)

E = Number of events
n = Number of events in severity category
Percentage is calculated as n/E.
[a] The events glare (n=2, E=4), halos (n=2, E=6), and blurry vision (n=1, E=2) were reported by investigators as AEs based on VSARC responses. Although these events do not meet the protocol specified definition of "Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later", Alcon considers that they are best accounted for in this table.
[b] Events for these categories were identified through the VSARC questionnaire. Self- reported responses other than none were reported as adverse events.

Table 14. Cumulative Incidence of Ocular Protocol Specified Adverse Event – Resolution

Protocol Specified Adverse Event Category	Adverse Event	E	Resolved n	Resolved (%)	Not Resolved n	Not Resolved (%)	Unknown n	Unknown (%)
Corneal edema between 1 week and 1 month after the procedure	Corneal Oedema	1	1	(100.0)	0	(-)	0	(-)
Corneal infiltrate or ulcer	Corneal Infiltrates	2	2	(100.0)	0	(-)	0	(-)
Recurrent corneal erosion at 1 month or later	Corneal Erosion	3	2	(66.7)	1	(33.3)	0	(-)
Any symptoms of dry eye that significantly affect comfort or activities of daily living at 6 months or later	Dry Eye	64	29	(45.3)	33	(51.6)	2	(3.1)
Any symptoms of glare or haloes that significantly affect comfort or activities of daily living at 6 months or later	Glare	10	6	(60.0)	4	(40.0)	0	(-)
	Halo Vision	8	4	(50.0)	4	(50.0)	0	(-)
Clinical signs consistent with marked to severe dry eye at 6 months or later	Dry Eye	1	1	(100.0)	0	(-)	0	(-)
Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later	Dry Eye	35	11	(31.4)	22	(62.9)	2	(5.7)
	Eye Irritation	10	4	(40.0)	4	(40.0)	2	(20.0)
	Eye Pain	13	4	(30.8)	7	(53.8)	2	(15.4)
	Foreign Body Sensation In Eyes	14	6	(42.9)	8	(57.1)	0	(-)
	Glare[a]	2	2	(100.0)	0	(-)	0	(-)
	Halo Vision[a]	10	10	(100.0)	0	(-)	0	(-)
	Lacrimation Increased	5	0	(-)	3	(60.0)	2	(40.0)
	Photophobia	19	7	(36.8)	10	(52.6)	2	(10.5)
	Photopsia	4	4	(100.0)	0	(-)	0	(-)
	Vision Blurred[a]	10	4	(40.0)	6	(60.0)	0	(-)
	Visual Impairment	6	4	(66.7)	2	(33.3)	0	(-)
Foreign body sensation at 1 month or later[b]	Foreign Body Sensation In Eyes	186	156	(83.9)	28	(15.1)	2	(1.1)

Protocol Specified Adverse Event Category	Adverse Event	E	Resolved n	Resolved (%)	Not Resolved n	Not Resolved (%)	Unknown n	Unknown (%)
Ghost/double images in the operative eye[b]	Diplopia	86	84	(97.7)	0	(-)	2	(2.3)
Pain at 1 month or later[b]	Eye Pain	139	94	(67.6)	40	(28.8)	5	(3.6)

E = Number of events
n = Number of events in resolution category
Percentage is calculated as n/E.
[a]The events glare (n=2, E=4), halos (n=2, E=6), and blurry vision (n=1, E=2) were reported by investigators as AEs based on VSARC responses. Although these events do not meet the protocol specified definition of "Any symptom marked moderate or severe on the VSARC questionnaire at month 6 or later", Alcon considers that they are best accounted for in this table.
[b]Events for these categories were identified through the VSARC questionnaire. Self-reported responses other than none were reported as adverse events.

Contrast sensitivity

Contrast sensitivity (CS) testing was performed on all subjects to evaluate clinically significant changes from baseline. CS testing was performed in photopic conditions with and without glare at spatial frequencies of 3, 6, 12, and 18 cd/m^2, and in mesopic conditions with and without glare at spatial frequencies of 1.5, 3, 6, and 12 cd/m^2.

For each lighting condition, the percentage of eyes with a clinically significant increase or decrease in CS, defined as either an increase or decrease from baseline of greater than or equal to 0.3 log units (at 2 or more spatial frequencies), was evaluated. In addition, a transition from seeing to not seeing, or from not seeing to seeing a grating at the highest available contrast, was considered equivalent to greater than or equal to 0.3 log units of change, and assessed as clinically significant.

At all visits and lighting conditions, a higher percentage of eyes showed a clinically significant increase from baseline in contrast sensitivity compared to those with a clinically significant decrease from baseline in CS, although most eyes had no significant change in contrast sensitivity. A clinically significant decrease in CS under photopic lighting conditions was observed in no more than 6.8% and 5.1% of eyes when tested with and without a glare source, respectively. Furthermore, a clinically significant decrease from baseline in contrast sensitivity from baseline under mesopic lighting conditions was observed in no more than 9.8% and 10.4% of eyes when tested with and without a glare source, respectively (Table 15).

Table 15. Proportion of Eyes with Clinically Significant Change from Preoperative Measurement in Contrast Sensitivity, (Intent-to-Treat)

			Clinically Significant Increase n / N	Clinically Significant Increase (%)	Clinically Significant Decrease n / N	Clinically Significant Decrease (%)
Visit 7 Month 3	Mesopic	With Glare	74 / 317	(23.3)	31 / 317	(9.8)
		Without Glare	52 / 317	(16.4)	33 / 317	(10.4)

	Photopic	With Glare	36 / 317	(11.4)	8 / 317	(2.5)
		Without Glare	27 / 317	(8.5)	14 / 317	(4.4)
Visit 8						
Month 6	Mesopic	With Glare	74 / 314	(23.6)	26 / 314	(8.3)
		Without Glare	80 / 314	(25.5)	32 / 314	(10.2)
	Photopic	With Glare	48 / 314	(15.3)	17 / 314	(5.4)
		Without Glare	30 / 314	(9.6)	16 / 314	(5.1)
Visit 9						
Month 9	Mesopic	With Glare	84 / 314	(26.8)	20 / 314	(6.4)
		Without Glare	65 / 314	(20.7)	29 / 314	(9.2)
	Photopic	With Glare	36 / 314	(11.5)	20 / 314	(6.4)
		Without Glare	25 / 314	(8.0)	15 / 314	(4.8)
Visit 10						
Month 12	Mesopic	With Glare	88 / 311	(28.3)	19 / 311	(6.1)
		Without Glare	70 / 311	(22.5)	20 / 311	(6.4)
	Photopic	With Glare	42 / 311	(13.5)	21 / 311	(6.8)
		Without Glare	33 / 311	(10.6)	10 / 311	(3.2)

N = Number of eyes in ITT analysis set with data at visit n = Number of eyes in category

VSARC Questionnaire

Results for the VSARC questionnaire are presented in Table 16 and were used to assess post-operative symptoms and protocol-specified adverse events. Of note, the VSARC was not found to reliably measure patient symptoms. At all postoperative visits, most participants rated their symptoms as none or mild. However, it is not known whether subjects reported their symptoms in the presence or absence of corrective lenses. Furthermore, the VSARC questionnaire does not measure the functional impact of these symptoms; instead, the investigators determined the significance of the impact.

Table 16. Visual Symptoms Associated with Refractive Correction Questionnaire by Subject

	Visit 1 Screening		Visit 6A Month 1		Visit 6B Month 1		Visit 7A Month 3		Visit 7B Month 3		Visit 8 Month 6		Visit 9 Month 9		Visit 10 Month 12	
Question/Result	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
1. Pain in eyes																
None	152	(94.4)	127	(80.9)	128	(82.1)	133	(83.6)	132	(83.5)	139	(88.0)	138	(87.3)	135	(86.5)
Mild	7	(4.3)	28	(17.8)	27	(17.3)	20	(12.6)	20	(12.7)	16	(10.1)	14	(8.9)	19	(12.2)
Moderate	2	(1.2)	1	(0.6)	1	(0.6)	6	(3.8)	6	(3.8)	3	(1.9)	5	(3.2)	1	(0.6)
Severe	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.6)
2. Dryness in eyes																
None	140	(87.0)	37	(23.6)	34	(21.8)	61	(38.4)	61	(38.6)	70	(44.3)	78	(49.4)	85	(54.5)
Mild	18	(11.2)	101	(64.3)	103	(66.0)	86	(54.1)	85	(53.8)	81	(51.3)	69	(43.7)	64	(41.0)
Moderate	3	(1.9)	19	(12.1)	19	(12.2)	12	(7.5)	12	(7.6)	6	(3.8)	9	(5.7)	7	(4.5)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	2	(1.3)	0	(0.0)
3. Burning feeling in the eye																

	Visit 1 Screening		Visit 6A Month 1		Visit 6B Month 1		Visit 7A Month 3		Visit 7B Month 3		Visit 8 Month 6		Visit 9 Month 9		Visit 10 Month 12	
Question/Result	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
None	152	(94.4)	134	(85.4)	134	(85.9)	130	(81.8)	130	(82.3)	134	(84.8)	143	(90.5)	139	(89.1)
Mild	6	(3.7)	21	(13.4)	21	(13.5)	25	(15.7)	24	(15.2)	21	(13.3)	11	(7.0)	16	(10.3)
Moderate	1	(0.6)	1	(0.6)	1	(0.6)	4	(2.5)	4	(2.5)	3	(1.9)	3	(1.9)	1	(0.6)
Severe	2	(1.2)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)
4. Glare																
None	132	(82.5)	90	(57.3)	86	(55.1)	125	(78.6)	126	(79.7)	133	(84.2)	136	(86.1)	139	(89.1)
Mild	19	(11.9)	57	(36.3)	62	(39.7)	33	(20.8)	31	(19.6)	25	(15.8)	21	(13.3)	17	(10.9)
Moderate	7	(4.4)	10	(6.4)	8	(5.1)	1	(0.6)	1	(0.6)	0	(0.0)	1	(0.6)	0	(0.0)
Severe	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
5. Eyes sensitive to light																
None	123	(76.4)	54	(34.4)	56	(35.9)	94	(59.1)	95	(60.1)	113	(72.0)	122	(77.2)	126	(80.8)
Mild	30	(18.6)	81	(51.6)	78	(50.0)	56	(35.2)	54	(34.2)	39	(24.8)	32	(20.3)	26	(16.7)
Moderate	7	(4.3)	18	(11.5)	19	(12.2)	8	(5.0)	8	(5.1)	4	(2.5)	3	(1.9)	4	(2.6)
Severe	1	(0.6)	4	(2.5)	3	(1.9)	1	(0.6)	1	(0.6)	1	(0.6)	1	(0.6)	0	(0.0)
6. Halos (circle shapes around lights)																
None	135	(84.4)	90	(57.3)	89	(57.1)	122	(76.7)	124	(78.5)	135	(85.4)	144	(91.1)	141	(90.4)
Mild	21	(13.1)	46	(29.3)	47	(30.1)	33	(20.8)	30	(19.0)	20	(12.7)	12	(7.6)	15	(9.6)
Moderate	2	(1.3)	19	(12.1)	18	(11.5)	3	(1.9)	3	(1.9)	3	(1.9)	2	(1.3)	0	(0.0)
Severe	2	(1.3)	2	(1.3)	2	(1.3)	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
7. Starbursts (star shapes around lights)																
None	147	(91.3)	108	(68.8)	106	(67.9)	129	(81.1)	131	(82.9)	136	(86.1)	138	(87.3)	140	(89.7)
Mild	11	(6.8)	37	(23.6)	39	(25.0)	27	(17.0)	24	(15.2)	20	(12.7)	19	(12.0)	16	(10.3)
Moderate	1	(0.6)	10	(6.4)	9	(5.8)	3	(1.9)	3	(1.9)	2	(1.3)	1	(0.6)	0	(0.0)
Severe	2	(1.2)	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
8. Blurry vision																
None	105	(65.2)	60	(38.2)	57	(36.5)	125	(78.6)	126	(79.7)	133	(84.2)	141	(89.2)	140	(89.7)
Mild	24	(14.9)	77	(49.0)	80	(51.3)	29	(18.2)	29	(18.4)	24	(15.2)	14	(8.9)	15	(9.6)
Moderate	11	(6.8)	18	(11.5)	19	(12.2)	5	(3.1)	3	(1.9)	1	(0.6)	3	(1.9)	1	(0.6)
Severe	21	(13.0)	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
9. Double vision (seeing two images of the same thing)																
None	150	(93.2)	119	(75.8)	118	(75.6)	146	(91.8)	145	(91.8)	153	(96.8)	157	(99.4)	156	(100.0)
Mild	8	(5.0)	23	(14.6)	25	(16.0)	8	(5.0)	9	(5.7)	5	(3.2)	1	(0.6)	0	(0.0)
Moderate	2	(1.2)	12	(7.6)	10	(6.4)	3	(1.9)	3	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Severe	1	(0.6)	3	(1.9)	3	(1.9)	2	(1.3)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)
10. Fluctuation (changes) in vision																
None	147	(91.3)	63	(40.1)	62	(39.7)	125	(78.6)	125	(79.1)	131	(82.9)	140	(88.6)	145	(92.9)
Mild	11	(6.8)	68	(43.3)	70	(44.9)	30	(18.9)	31	(19.6)	25	(15.8)	15	(9.5)	10	(6.4)
Moderate	3	(1.9)	25	(15.9)	23	(14.7)	4	(2.5)	2	(1.3)	2	(1.3)	3	(1.9)	1	(0.6)
Severe	0	(0.0)	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
11. Difficulty focusing in dim or low light																
None	124	(77.0)	98	(62.4)	98	(62.8)	135	(84.9)	136	(86.1)	135	(85.4)	144	(91.1)	145	(92.9)

	Visit 1 Screening		Visit 6A Month 1		Visit 6B Month 1		Visit 7A Month 3		Visit 7B Month 3		Visit 8 Month 6		Visit 9 Month 9		Visit 10 Month 12	
Question/Result	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Mild	26	(16.1)	50	(31.8)	48	(30.8)	21	(13.2)	20	(12.7)	20	(12.7)	14	(8.9)	10	(6.4)
Moderate	7	(4.3)	7	(4.5)	7	(4.5)	2	(1.3)	2	(1.3)	3	(1.9)	0	(0.0)	1	(0.6)
Severe	4	(2.5)	2	(1.3)	3	(1.9)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
12. Watery eyes/tearing																
None	130	(80.7)	132	(84.1)	130	(83.3)	139	(87.4)	140	(88.6)	145	(91.8)	138	(87.3)	139	(89.1)
Mild	26	(16.1)	22	(14.0)	24	(15.4)	20	(12.6)	18	(11.4)	13	(8.2)	18	(11.4)	14	(9.0)
Moderate	5	(3.1)	2	(1.3)	2	(1.3)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.3)	3	(1.9)
Severe	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
13. Foreign body sensation (feeling like something is in your eye)																
None	142	(88.2)	106	(67.5)	107	(68.6)	117	(73.6)	114	(72.2)	129	(81.6)	138	(87.3)	141	(90.4)
Mild	16	(9.9)	46	(29.3)	45	(28.8)	37	(23.3)	39	(24.7)	24	(15.2)	18	(11.4)	13	(8.3)
Moderate	2	(1.2)	5	(3.2)	4	(2.6)	5	(3.1)	5	(3.2)	4	(2.5)	2	(1.3)	2	(1.3)
Severe	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	0	(0.0)	0	(0.0)

n = Number of subjects in category
Percentages based on number of subjects with data for each question at visit.

RSVP Questionnaire

The RSVP questionnaire (Vitale et al) is designed to measure self-reported functioning, symptoms, health perceptions, and expectations in individuals with refractive error. It contains 42 items covering eight domains: concern, expectations, physical/social functioning, driving, symptoms, optical problems, glare, and problems with corrective lenses. Results for the RSVP questionnaire are presented in Table 17. Information on whether subjects reported their symptoms in the presence or absence of corrective lenses was not collected. The RSVP results show that there was no worsening in vision-related health status post-operatively.

Table 17. Descriptive Statistics for RSVP Subscales by Visit by Subject

Subscale	Statistic	Visit 1 Screening	Visit 6A Month 1	Visit 6B Month 1	Visit 7A Month 3	Visit 7B Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12
Concern	**N**	161	154	154	159	158	158	158	156
	Mean	39.9	23.0	22.6	10.1	9.9	7.9	8.0	6.7
	SD	23.16	16.63	16.56	11.65	11.48	10.91	11.54	10.30
	Median	37.5	20.8	20.8	8.3	4.2	0.0	0.0	0.0
	(Min, Max)	(0.0, 100.0)	(0.0, 75.0)	(0.0, 66.7)	(0.0, 54.2)	(0.0, 54.2)	(0.0, 58.3)	(0.0, 58.3)	(0.0, 66.7)
Driving	**N**	157	135	140	155	152	152	156	155
	Mean	17.2	18.2	17.9	6.3	5.9	5.8	5.0	3.9
	SD	22.78	20.37	20.37	11.61	11.42	13.83	9.91	8.67
	Median	8.3	8.3	8.3	0.0	0.0	0.0	0.0	0.0
	(Min, Max)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 50.0)	(0.0, 50.0)	(0.0, 100.0)	(0.0, 50.0)	(0.0, 41.7)

Subscale	Statistic	Visit 1 Screening	Visit 6A Month 1	Visit 6B Month 1	Visit 7A Month 3	Visit 7B Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12
Expectations	**N**	161	154	154	158	157	157	158	156
	Mean	62.0	64.1	64.2	64.7	64.2	67.3	64.9	66.6
	SD	26.18	27.85	27.97	29.51	29.52	29.50	31.23	30.92
	Median	75.0	75.0	75.0	75.0	75.0	75.0	75.0	75.0
	(Min, Max)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 100.0)
Functioning	**N**	159	139	144	156	153	153	155	155
	Mean	13.7	12.7	12.2	2.1	2.1	2.3	1.3	1.1
	SD	16.61	16.55	16.02	4.10	4.14	8.80	3.38	3.17
	Median	8.3	7.5	7.2	0.0	0.0	0.0	0.0	0.0
	(Min, Max)	(0.0, 86.4)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 25.0)	(0.0, 29.5)	(0.0, 100.0)	(0.0, 20.0)	(0.0, 25.0)
Symptoms	**N**	159	136	141	156	153	153	154	155
	Mean	7.6	15.3	15.0	6.5	6.4	6.1	5.2	4.2
	SD	11.23	13.14	12.33	7.69	7.77	8.09	8.66	6.87
	Median	5.0	15.0	12.5	5.0	5.0	5.0	0.0	0.0
	(Min, Max)	(0.0, 62.5)	(0.0, 70.0)	(0.0, 50.0)	(0.0, 45.0)	(0.0, 45.0)	(0.0, 35.0)	(0.0, 45.0)	(0.0, 35.0)
Optical Problems	**N**	160	137	142	156	153	152	154	155
	Mean	5.0	12.8	12.6	3.5	3.1	2.5	1.8	1.2
	SD	9.87	13.80	13.88	6.61	6.01	5.40	3.91	3.28
	Median	0.0	10.0	10.0	0.0	0.0	0.0	0.0	0.0
	(Min, Max)	(0.0, 75.0)	(0.0, 70.0)	(0.0, 70.0)	(0.0, 30.0)	(0.0, 30.0)	(0.0, 40.0)	(0.0, 20.0)	(0.0, 18.8)
Glare	**N**	158	137	141	156	153	154	156	155
	Mean	9.4	19.2	19.1	7.7	7.6	5.8	5.0	3.7
	SD	13.14	15.59	15.86	9.98	10.05	9.41	8.01	7.90
	Median	0.0	16.7	16.7	0.0	0.0	0.0	0.0	0.0
	(Min, Max)	(0.0, 66.7)	(0.0, 66.7)	(0.0, 66.7)	(0.0, 50.0)	(0.0, 50.0)	(0.0, 41.7)	(0.0, 33.3)	(0.0, 41.7)
Problems with Corrective Lenses	**N**	156	22	20	13	13	20	17	15
	Mean	34.7	20.5	16.9	17.9	16.0	7.3	5.1	0.8
	SD	22.64	25.31	24.43	19.20	19.68	13.64	8.90	3.23
	Median	30.4	18.8	6.3	25.0	0.0	0.0	0.0	0.0
	(Min, Max)	(0.0, 75.0)	(0.0, 100.0)	(0.0, 100.0)	(0.0, 50.0)	(0.0, 50.0)	(0.0, 50.0)	(0.0, 25.0)	(0.0, 12.5)
S	**N**	161	154	154	159	158	158	158	156
	Mean	20.2	19.9	19.3	8.3	8.4	7.8	6.8	5.9

Subscale	Statistic	Visit 1 Screening	Visit 6A Month 1	Visit 6B Month 1	Visit 7A Month 3	Visit 7B Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12
	SD	11.55	12.57	12.48	6.64	6.99	7.22	5.90	4.78
	Median (Min, Max)	18.3 (3.1, 61.2)	17.6 (0.7, 75.7)	17.6 (0.7, 75.7)	6.4 (0.0, 34.4)	6.4 (0.0, 39.3)	5.7 (0.0, 47.9)	4.9 (0.0, 29.9)	4.7 (0.0, 30.6)

n = Number of eyes in category
SD = Standard deviation, Min = Minimum, Max = Maximum
S=Overall score

2. Effectiveness Results

The analysis of effectiveness was based on results from 320 eyes of 161 evaluable patients at the 12-month time point. Key effectiveness outcomes are presented in Tables 18 to 23.

At Month 6, 100% of the 294 eyes with preoperative BSCVA of 20/20 or better had UCVA of 20/40 or better, 99.7% of eyes were within ± 1.0 D of zero MRSE, and 93.3% were within ± 0.5 D of zero MRSE. In addition, at Month 6, 99.0% of eyes had refractive cylinder within ± 1.0 D of zero, and 92.7% of eyes had manifest refractive cylinder within ± 0.5 D of zero. Within the Month 3 to Month 6 interval, 99.7% of eyes had a change in MRSE and manifest refractive cylinder of ≤ 1.0 D in manifest refractive cylinder.

Table 18 Proportion of Eyes Meeting Visual and Refractive Outcome Criteria (Intent-to-Treat)

Visit	Parameter	n / N	(%)	95% CI†
Visit 5 - Week 1	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	270 / 299	(90.3)	(86.4, 93.4)
	MRSE within ± 1.00 D of emmetropia	307 / 320	(95.9)	(93.2, 97.8)
	MRSE within ± 0.50 D of emmetropia	255 / 320	(79.7)	(74.9, 84.0)
	Manifest refractive cylinder within ± 1.00 D of plano	296 / 320	(92.5)	(89.0, 95.1)
	Manifest refractive cylinder within ± 0.50 D of plano	250 / 320	(78.1)	(73.2, 82.5)
Visit 6 - Month 1	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	293 / 299	(98.0)	(95.7, 99.3)
	MRSE within ± 1.00 D of emmetropia	312 / 320	(97.5)	(95.1, 98.9)
	MRSE within ± 0.50 D of emmetropia	258 / 320	(80.6)	(75.9, 84.8)
	Manifest refractive cylinder within ± 1.00 D of plano	303 / 320	(94.7)	(91.6, 96.9)
	Manifest refractive cylinder within ± 0.50 D of plano	239 / 320	(74.7)	(69.6, 79.4)
Visit 7 - Month 3	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	297 / 297	(100.0)	(98.8, 100.0)
	MRSE within ± 1.00 D of emmetropia	315 / 317	(99.4)	(97.7, 99.9)
	MRSE within ± 0.50 D of emmetropia	293 / 317	(92.4)	(88.9, 95.1)
	Manifest refractive cylinder within ± 1.00 D of plano	314 / 317	(99.1)	(97.3, 99.8)
	Manifest refractive cylinder within ± 0.50 D of plano	292 / 317	(92.1)	(88.6, 94.8)
Visit 8 - Month 6	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	294 / 294	(100.0)	(98.8, 100.0)
	MRSE within ± 1.00 D of emmetropia	313 / 314	(99.7)	(98.2, 100.0)
	MRSE within ± 0.50 D of emmetropia	293 / 314	(93.3)	(90.0, 95.8)
	Manifest refractive cylinder within ± 1.00 D of plano	311 / 314	(99.0)	(97.2, 99.8)

Visit	Parameter	n / N	(%)	95% CI†
	Manifest refractive cylinder within ± 0.50 D of plano	291 / 314	(92.7)	(89.2, 95.3)
Visit 9 - Month 9	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	294 / 294	(100.0)	(98.8, 100.0)
	MRSE within ± 1.00 D of emmetropia	314 / 314	(100.0)	(98.8, 100.0)
	MRSE within ± 0.50 D of emmetropia	300 / 314	(95.5)	(92.6, 97.5)
	Manifest refractive cylinder within ± 1.00 D of plano	311 / 314	(99.0)	(97.2, 99.8)
	Manifest refractive cylinder within ± 0.50 D of plano	300 / 314	(95.5)	(92.6, 97.5)
Visit 10 - Month 12	UCVA 20/40 or better (BSCVA 20/20 or better pre-op)	291 / 291	(100.0)	(98.7, 100.0)
	MRSE within ± 1.00 D of emmetropia	309 / 311	(99.4)	(97.7, 99.9)
	MRSE within ± 0.50 D of emmetropia	294 / 311	(94.5)	(91.4, 96.8)
	Manifest refractive cylinder within ± 1.00 D of plano	308 / 311	(99.0)	(97.2, 99.8)
	Manifest refractive cylinder within ± 0.50 D of plano	297 / 311	(95.5)	(92.6, 97.5)

N = Number of eyes in ITT analysis set with data at visit
n = Number of eyes in category
† 95% confidence interval from Binomial distribution

Table 19 Proportion of Eyes Meeting MRSE and Manifest Refractive Cylinder Change Criteria, (Intent-to-Treat)

Visit Interval	Parameter	n / N	(%)	95% CI†
Visit 5 - Week 1 to Visit 6 - Month 1	Change ≤ 1.00 D in MRSE and manifest refractive cylinder	291 / 320	(90.9)	(87.2, 93.8)
Visit 6 - Month 1 to Visit 7 - Month 3	Change ≤ 1.00 D in MRSE and manifest refractive cylinder	303 / 317	(95.6)	(92.7, 97.6)
Visit 7 - Month 3 to Visit 8 - Month 6	Change ≤ 1.00 D in MRSE and manifest refractive cylinder	313 / 314	(99.7)	(98.2, 100.0)
Visit 8 - Month 6 to Visit 9 - Month 9	Change ≤ 1.00 D in MRSE and manifest refractive cylinder	314 / 314	(100.0)	(98.8, 100.0)
Visit 9 - Month 9 to Visit 10 - Month 12	Change ≤ 1.00 D in MRSE and manifest refractive cylinder	309 / 310	(99.7)	(98.2, 100.0)

N = Number of eyes in ITT analysis set with data at visit
n = Number of eyes in category
An eye must meet the criteria for both MRSE and manifest refractive cylinder to be considered a success.
† 95% confidence interval from Binomial distribution

The following table (Table 20) presents the results for eyes that achieved the visual acuity thresholds. At Month 6, 93.0% of eyes had UCVA of 20/20 or better and 100% of eyes had UCVA of 20/40 or better.

Table 20 Proportion of Eyes Achieving Visual Acuity Threshold, (Intent-to-Treat)

Visit	Parameter	n / N	(%)	95% CI†
Visit 5 - Week 1	UCVA 20/20 or better	93 / 320	(29.1)	(24.1, 34.4)
	UCVA 20/40 or better	285 / 320	(89.1)	(85.1, 92.3)
Visit 6 - Month 1	UCVA 20/20 or better	166 / 320	(51.9)	(46.2, 57.5)

Visit	Parameter	n / N	(%)	95% CI†
	UCVA 20/40 or better	314 / 320	(98.1)	(96.0, 99.3)
Visit 7 - Month 3	UCVA 20/20 or better	288 / 317	(90.9)	(87.1, 93.8)
	UCVA 20/40 or better	317 / 317	(100.0)	(98.8, 100.0)
Visit 8 - Month 6	UCVA 20/20 or better	292 / 314	(93.0)	(89.6, 95.6)
	UCVA 20/40 or better	314 / 314	(100.0)	(98.8, 100.0)
Visit 9 - Month 9	UCVA 20/20 or better	292 / 314	(93.0)	(89.6, 95.6)
	UCVA 20/40 or better	314 / 314	(100.0)	(98.8, 100.0)
Visit 10 - Month 12	UCVA 20/20 or better	294 / 311	(94.5)	(91.4, 96.8)
	UCVA 20/40 or better	311 / 311	(100.0)	(98.8, 100.0)

N = Number of eyes in ITT analysis set with data at visit
n = Number of eyes in category
† 95% confidence interval from Binomial distribution

The summary of the non-vector results for MRSE and visual acuity results at Month 6 are presented in Table 21. All eyes had MRSE within ± 2.0 D of zero. The percentage of eyes undercorrected by greater than 1.0 D was 0.3%; no eyes were overcorrected by more than 1.0 D. The majority of eyes (68.5%) had UCVA at Month 6 that was better than or equal to their preoperative BSCVA. No eyes showed a decrease in BSCVA of 2 lines or greater as compared to baseline.

Table 21 Non-Vector Analyses by Eye at Stability Time Point (Month 6) (Intent-to-Treat)

Parameter	n / N	(%)	95% CI†
MRSE ± 2.00 D of emmetropia	314 / 314	(100.0)	(98.8, 100.0)
Overcorrected by > 1.00 D MRSE	0 / 314	(0.0)	(0.0, 1.2)
Overcorrected by > 2.00 D MRSE	0 / 314	(0.0)	(0.0, 1.2)
Undercorrected by > 1.00 D MRSE	1 / 314	(0.3)	(0.0, 1.8)
Undercorrected by > 2.00 D MRSE	0 / 314	(0.0)	(0.0, 1.2)
UCVA equal to or better than preoperative BSCVA	215 / 314	(68.5)	(63.0, 73.6)
Difference in postoperative and preoperative BSCVA			
< -2 lines	3 / 314	(1.0)	(0.2, 2.8)
-2 lines	7 / 314	(2.2)	(0.9, 4.5)
-1 line	83 / 314	(26.4)	(21.6, 31.7)
0 lines	218 / 314	(69.4)	(64.0, 74.5)
1 line	3 / 314	(1.0)	(0.2, 2.8)
2 lines	0 / 314	(0.0)	(0.0, 1.2)
> 2 lines	0 / 314	(0.0)	(0.0, 1.2)

N = Number of eyes in ITT analysis set with data at visit
n = Number of eyes in category
† 95% confidence interval from Binomial distribution

Table 22 presents the results for eyes with a preoperative cylinder component that achieved accuracy of cylinder to target. At Month 6, 98.7 % of eyes were within ± 1.0 D of the intended target cylinder (zero), and 91.1% were within ± 0.5 D of cylinder target.

Table 22. Accuracy of Cylinder to Target by Eye, (Intent-to-Treat)

Cylinder	Visit 1 Screening	Visit 6 Month 1	Visit 7 Month 3	Visit 8 Month 6	Visit 9 Month 9	Visit 10 Month 12
No. Eyes (N)	230	230	227	224	224	223
Mean ± SD	-1.096 ± 0.77	-0.393 ± 0.43	-0.227 ± 0.30	-0.209 ± 0.29	-0.185 ± 0.28	-0.179 ± 0.29
Attempted change ± SD	1.096 ± 0.77					
Achieved change ± SD		0.702 ± 0.90	0.866 ± 0.78	0.886 ± 0.78	0.910 ± 0.77	0.904 ± 0.76
% of eyes within ± 0.50 D of target		69.1	90.3	91.1	94.2	94.2
% of eyes within ± 1.00 D of target		93.0	98.7	98.7	98.7	98.7

N = Number of eyes with preoperative cylindrical component with data at visit
SD = Standard deviation

Results of the vector analyses at Month 6 are presented in Table 23. The mean error vector (EV), defined as the vector difference between the intended refractive correction and the surgically induced refractive correction (IRC - SIRC), was < 0.2. The mean correction ratio (CR; the ratio of the achieved correction magnitude to the required correction magnitude) was close to 1 in each category. Error ratio (ER; the proportion of the intended correction not successfully treated) showed a progressive decrease in mean with increasing preoperative cylinder.

Table 23. Vector Analysis Summary at Stability Time Point (Month 6) (Intent-to-Treat)

Preoperative Cylinder	n	|IRC| (Mean ± SD)	|SIRC| (Mean ± SD)	|EV| (Mean ± SD)	CR (Mean ± SD)	ER (Mean ± SD)
All Eyes (N)	224	1.013 ± 0.7161	1.130 ± 0.7722	0.159 ± 0.2449	1.180 ± 0.4493	0.229 ± 0.4261
0.0 D to ≤0.5 D	89	0.397 ± 0.1075	0.502 ± 0.2241	0.120 ± 0.1943	1.302 ± 0.5989	0.343 ± 0.5763
>0.5 D to ≤1.0 D	54	0.808 ± 0.1186	0.908 ± 0.3467	0.174 ± 0.2664	1.115 ± 0.4018	0.216 ± 0.3570
>1.0 D to ≤2.0 D	50	1.450 ± 0.2240	1.628 ± 0.3866	0.189 ± 0.2827	1.122 ± 0.1950	0.129 ± 0.1899
>2.0 D to ≤3.0 D	31	2.434 ± 0.2510	2.514 ± 0.4194	0.198 ± 0.2670	1.033 ± 0.1450	0.085 ± 0.1209

n = Number of eyes with preoperative cylindrical component with data at visit
SD = Standard deviation, Min = Minimum, Max = Maximum
IRC = Intended Refractive Correction, SIRC = Surgically Induced Refractive Correction, EV = Error Vector, CR = Correction Ratio, ER = Error Ratio

The outcomes summarized above provide reasonable assurance of safety and effectiveness for the device.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: baseline sphere bin, baseline cylinder bin, MRSE, investigator site, age, sex, race, and total treatment zone size. Although statistically significant differences were found across sites in the endpoints MRSE within ± 0.50 D of emmetropia (p=0.0002) and Manifest Refractive Cylinder within ± 0.50 D of emmetropia (p=0.0236), the absolute magnitudes of these differences across sites are not considered clinically significant, and furthermore, the results at all sites still surpass the success criteria of at least 50% rate. For the endpoint of MRC within ±0.5 D of emmetropia, a statistically significant difference (p=0.0281) was found between male and female participants (89.7% versus 96.4%, respectively). However, the absolute magnitude of this difference is not considered clinically significant, and furthermore, these stratified results still surpass the target of at least 50% achieving MRC within 0.5 D of emmetropia.

4. Pediatric Extrapolation

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

E. 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 8 investigators of which none was full-time or part-time employees of the sponsor and 6 of investigators 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 of investigators.
- Significant payment of other sorts: 6 of investigators.
- Proprietary interest in the product tested held by the investigator: none of investigators.
- Significant equity interest held by investigator in sponsor of covered study: none of investigators.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by the applicant and reviewed 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Three (3) published studies were presented to further support approval the PRK indication:

1) Falavarjani et al, 2010 – The authors conducted a prospective, randomized, contralateral study of topography-guided versus wavefront-optimized PRK on 40 eyes of 20 participants with low to moderate myopia with or without astigmatism. The excimer laser used was an earlier version of the Allegretto system (200-Hz). At post-operative month 6, UDVA was similar between the two (2) groups, and no participant lost any lines of visual acuity. Post-operatively, the mean contrast sensitivity score increased in both groups. There were no complications (including corneal infection or haze) observed. However, 6-month data were available only on 10 participants.

2) Kymionis et al, 2008 – This was a retrospective study to compare PRK outcomes between the 200-Hz and 400-Hz Allegretto laser systems. 70 eyes of 35 participants were treated with the 200-Hz device and 58 eyes of 29 were treated with the 400-Hz device. Mean follow-up time was 13.22±1.16 months. At one year post-operatively, 94.2% of the 200-Hz eyes and 96.6% of the 400-Hz eyes were within ±1.00 D of targeted correction. Corneal haze at post-operative month 3 was observed in 29% of the 200-Hz and 46% of the 400-Hz eyes (p=0.03), which cleared over subsequent months; all eyes were clear in both groups by post-operative month 12.

3) Costa et al, 2011 – This was a retrospective study of 222 eyes of 151 participants who underwent PRK for myopia or combined myopia and astigmatism using the Wave Eye-Q system. By post-operative month 6, 86.6% achieved UCVA 20/20 or better and 96.6% achieved UCVA 20/25 or better (but n=119 eyes). There were two (2) cases (0.9%) of mild corneal haze accompanied by BSCVA decrease of one line. No participant lost two (2) or more lines of BSCVA and none required retreatment. There were no significant complications (including severe haze, infectious keratitis, ocular hypertension).

Protocol deviations

The primary clinical study included 16 major protocol deviations related to the Health Insurance Portability and Accountability (HIPAA) form, informed consent, the incorrect application of treatment nomogram, missing Month 6 monocular BSCVA assessment, missing Month 6 monocular UCVA, and out-of-window Month 6 visits. Because of the infrequency of these deviations, it was concluded that these major deviations did not impact the outcomes of the study.

The most frequently occurring minor protocol deviation relates to aberrometry testing (109 instances for 43 participants at five study sites). During aberrometry, either the pupil size was not appropriately captured, or the pupil size was captured as <6 mm. The second most frequently occurring minor deviation relates to lighting conditions for contrast sensitivity assessment. In 43 instances, the ambient lighting from the posterboard was "out of range" (normal should be 80-160 cd/m^2). In 34 of these, the range was between 70-80 cd/m^2.

Site-level deviations included the following:

- At five (5) of the eight (8) investigative sites, BSCVA testing at four (4) meters was conducted with the manifest refraction adjusted for optical infinity (-0.25 D added to the manifest refraction at 4 m). BSCVA methodology was consistent across the five (5) sites, where the -0.25 D adjustment was applied for all subjects at all visits that BSCVA was assessed. Because presbyopes may be impacted by the -0.25 D adjustment due to reduced accommodative amplitude, a summary of the eyes from subjects 40 years or older in the study was provided. A total of 12.5% of eyes in the study were considered presbyopic; more than half were enrolled at the sites where the deviation did not occur. The table below presents an analysis, based on a t-test, comparing BSCVA between the five (5) sites with -0.25 D added to the manifest refraction at 4m and the three (3) sites without -0.25 D added to the manifest refraction at 4m for the 20 subjects (39 eyes) over the age of 40. One subject was excluded from this analysis, Subject C10084.4563.1020, who was over 40 years old but did not have a measurement for BSCVA at Month 6 (OS). The analysis does not indicate a difference in the mean BSCVA between these two groups (p-value = 0.1241) (Table 24).

Table 24. BSCVA at Stability Time Point (Month 6) in Presbyopic Eyes by Sites with and without -0.25 D Added to the Manifest Refraction at 4m

	With -0.25 D Added	Without -0.25 D Added	p-value
n	24	15	
Mean	-0.098	-0.133	0.1241
SD	0.0667	0.0675	
Median	-0.100	-0.140	
(Min, Max)	(-0.20, 0.00)	(-0.26, 0.00)	

n = Number of presbyopic eyes in ITT analysis set with data at visit
P-value from t-test

- Sites did not prospectively report one of the VSARC-based AE ("Any symptom marked moderate or severe on the VSARC questionnaire at Month 6 or later which the Investigator had determined was not easily resolved when the subject is wearing correction or had some simple explanation unrelated to the treatment"). Therefore, this data was captured retrospectively.

- Sites were instructed to use the VSARC questionnaire to report certain AEs (foreign body sensation at 1 month or later, pain 1 month or later, ghost/double images in the operative eye, any symptoms of dry eye significantly affecting comfort or activities of daily living (as reported to the Investigator) at 6 months or later, any symptoms of glare or haloes significantly affecting comfort or ADLs as reported to the Investigator at 6 months or later) even though the protocol did not pre-specify this. Therefore, this data was captured retrospectively.

- At one site, monthly scheduled calibration of the study tonometer was not completed. At another site, two (2) different tonometers were used for IOP measurements. This deviation was determined to not impact the study outcomes.

XII. 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 Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness outcomes from the clinical study of wavefront-optimized PRK performed by the Wave EYE-Q excimer laser system to correct myopia with and without astigmatism met all pre-specified success criteria. Refractive stability was achieved at post-operative month 6. At this time point, the proportion of eyes with pre-operative BSCVA of 20/20 or better that achieved UCVA of 20/40 or better exceed targeted values. In addition, the proportions of eyes achieving MRSE within 0.5 D and 1.0 D of emmetropia and MRC within 0.5 D of emmetropia all exceed targeted values.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. The cumulative rate of any ocular SAE was 0.9%. No eyes had BSCVA decrease of $\geq$ 2 lines from baseline at Month 6. Of the eyes with BSCVA of 20/20 or better preoperatively, no eyes had BSCVA worse than 20/40 (in eyes) at Month 6. No eyes had > 2.0 D of induced manifest refraction cylinder at Month 6 compared to baseline. These outcomes met safety targets and were found to be acceptable.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA approval as described above. At the time point of refractive stability, 100% of participants who had pre-operative best spectacle-corrected visual acuity (BSCVA) of 20/20 achieved a post-operative uncorrected distance visual acuity of 20/40 or better. 93.3% of participants achieved a manifest refractive spherical equivalent within ±0.5 D of emmetropia. The frequency of ocular serious adverse events was less than 1%.

Additional factors to be considered in determining probable risks and benefits for the EYE-Q and EX500 excimer laser devices included: Safety and effectiveness were

evaluated only on the EYE-Q system, not the EX500 system. Non-clinical testing results were used to demonstrate that safety and effectiveness outcomes obtained for the EYE-Q system may be applicable to the EX500 system. See Section IX (SUMMARY OF NON-CLINICAL STUDIES) for additional information.

1. Patient Perspectives
   Patient perspectives considered during the review included: Patient-reported outcomes were collected through the administration of the VSARC questionnaire. However, this instrument does not reliably measure patient symptoms. The VSARC questionnaire does not measure the functional impact of these symptoms; instead, the investigators determined the significance of the impact. Therefore, the presented rates may not accurately reflect the impact of visual or ocular symptoms on prospective patients. The questionnaires also do not capture patient-centric information directly pertaining to relative desirability or acceptability of outcomes, the value placed on the treatment, the tolerance for risk to achieve benefit, or how well patients understand the benefits and risks.

In conclusion, given the available information above, the data support that for the reduction or elimination of up to -6.0 D of spherical equivalent myopia or myopia with astigmatism (with up to -6.0 D of spherical component and up to -3.0 D of astigmatic component at the spectacle plane) in patients who are 18 years of age or older and with documentation of a stable manifest refraction defined as ≤ 0.5 D preoperative spherical equivalent shift over one year prior to surgery, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The clinical data in this application demonstrate the safety and effectiveness of this device when used in accordance with the indications for use. All effectiveness objectives were met at post-operative month 6. All safety objectives were met at post-operative month 6, with low overall rates of serious adverse events, no loss of BSCVA ≥2 lines, and minimal induced MRC. Based on these results, there is reasonable assurance of the safety and effectiveness of wavefront-optimized PRK correction of myopic refractive errors for the proposed indication.

XIV. CDRH DECISION

CDRH issued an approval order on November 21, 2016.

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

XV. 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.

XVI. REFERENCES

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