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EpiSmart Crosslinking for Keratoconus: A Phase 2 Study

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Purpose: The aim of this study was to assess changes in visual acuity after epithelium-on ("epi-on") corneal crosslinking after a diagnosis of keratoconus.

Methods: Subjects with corneal ectatic diseases were enrolled in a prospective, randomized, controlled, open-label, multicenter trial. Subjects were randomized to 1 of 3 treatment groups and treated with an epi-on crosslinking system including riboflavin/sodium iodide and pulsed UVA exposure (EpiSmart, CXL Ophthalmics, Encinitas, CA). The UVA treatment groups were 2.4 J/cm^2 over 20 minutes, 3.6 J/cm^2 over 20 minutes, and 3.6 J/cm^2 over 30 minutes. The primary end point was logarithm of the minimum angle of resolution corrected distance visual acuity (CDVA). Secondary end points were logarithm of the minimum angle of resolution uncorrected distance visual acuity (UCVA), maximum corneal curvature (Kmax), and minimum corneal thickness. Data were assessed 6 and 12 months post-operatively, using *t*-tests for differences from baseline.

Results: Two thousand two hundred twenty-eight subjects were treated with epi-on crosslinking. One thousand nine hundred twenty-two subjects had a diagnosis of keratoconus; other treated eyes had postsurgical and other ectasias. At 6 and 12 months, the subjects with keratoconus demonstrated significant improvements in CDVA, UCVA, and Kmax; minimum corneal thickness was unchanged. One hundred ninety-five subjects (8.7%) reported at least 1 adverse event (AE). A mild corneal epithelial defect was reported in 31 cases (1.4%) and was the only AE reported in >1% of subjects. There were no serious AEs related to the treatment.

Conclusions: EpiSmart epi-on crosslinking resulted in mean improvements in CDVA, UCVA, and Kmax at both 6 and 12 months and an excellent safety and efficacy profile in subjects with keratoconus, with few significant side effects. Differences between UVA treatment groups were not significant.

Key Words: corneal ectasia, crosslinking, epithelium-on, keratoconus

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Keratoconus causes an asymmetry of corneal shape and thickness which can markedly impair vision due to progressive corneal thinning, steepening, and resultant irregular astigmatism. Recent population-based epidemiological research using modern topographic or tomographic diagnostics has shown a prevalence of 1% to 4%, with significant regional and ethnic variation,[1–4] suggesting a large unmet need for noninvasive treatment. Current nonsurgical treatments include soft or rigid contact lenses or spectacles. As the disease progresses, these treatments typically do not provide adequate functional improvement. Implantable intracorneal ring segments can improve visual acuity in some cases, but they do not prevent disease progression and can be associated with significant complications. Historically, many patients with keratoconus have required corneal transplantation due to disease progression.

Since the introduction of the Dresden protocol in 2003,[5] corneal collagen crosslinking (CXL) has provided a method of stiffening the cornea, thus slowing or halting ectasia progression.[6–11] Standard CXL requires epithelial debridement ("epi-off") to achieve saturation of the corneal stroma with riboflavin ophthalmic solution and illumination with ultraviolet A (365 nm) radiation. Side effects of epithelial debridement include prolonged pain, delayed epithelial healing, infection, scarring, and slow visual recovery.[12–14] By contrast, an epithelium-on technique ("epi-on") that leaves an intact and nondisrupted epithelium may halt progression while reducing postoperative (post-op) pain, minimizing the likelihood of significant complications, and promoting faster visual recovery. A number of "epi-on" protocols have been reported, with varying results.[15–17]

The EpiSmart epi-on crosslinking procedure (CXL Ophthalmics, Encinitas, CA) has been shown in animal models to obtain adequate stromal riboflavin levels across an intact epithelium[18] and to maintain a sustained riboflavin

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concentration without supplemental riboflavin drops throughout ultraviolet-A (UVA) exposure.[19] Stulting et al[10] reported on 308 patients with keratoconus treated with EpiSmart who showed improvements in vision and improvements in keratometric end points, each sustained over 24 months. This same report also demonstrated significant improvement in coma which can account for some of the significant visual improvements seen. We report in this article the largest study to date evaluating the safety and effectiveness of this investigational epi-on procedure in subjects with corneal ectasia due to keratoconus.

MATERIALS AND METHODS

The study was a prospective, randomized, controlled, open-label, multicenter trial conducted in the United States under Food and Drug Administration (FDA) IND 124062 and registered with www.ClinicalTrials.gov (NCT03029104). Good Clinical Practice and Health Insurance Portability and Accountability Act (HIPPA) guidelines were followed throughout. Ethics Board approval for this study was granted on November 18, 2016, by the Chesapeake IRB (6940 Columbia Gateway, Suite 110, Columbia, MD 21046). Informed consent or guardian assent for subjects younger than 18 years was obtained and documented in writing before the initiation of any study procedures. The required follow-up period was 6 months post-op, and subjects were also subsequently encouraged to return for 12-month follow-up examinations when possible.

Subjects were enrolled if they were diagnosed with a corneal ectatic disorder. Documentation of progression was *not* required for enrollment. The focus of our efficacy analysis was on patients with a diagnosis of keratoconus, with the remainder analyzed for additional safety data.

Enrollment occurred at 9 clinical sites between December 21, 2016, and June 28, 2019. Subjects who were at least 8 years old, with a minimum corneal thickness ≥375 μm, were not pregnant or breastfeeding, without active *Herpes simplex* corneal disease, without severe nystagmus, or without conditions that would present a contraindication to any of the study materials or procedures were enrolled.

After informed consent was obtained, the subjects were given a computer-generated randomization code and assigned 1:1:1 to 1 of 3 groups with predefined treatment protocols. Randomization was stratified by indication: keratoconus, postsurgical ectasia, and "other ectatic diagnoses." Both eyes of subjects undergoing bilateral simultaneous treatments were assigned to the same treatment group. Each had a complete baseline eye examination, including refractive assessments for manifest refraction, uncorrected distance visual acuity (UCVA), corrected distance visual acuity (CDVA), Scheimpflug corneal tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany), intraocular pressure, slit-lamp examination, and dilated fundus examination.

Corneal Crosslinking Treatments

Subjects were treated with the EpiSmart system (CXL Ophthalmics, LLC), comprising ophthalmic sponges for the preparation of the cornea and drug delivery (EpiPrep; CXL Ophthalmics),[10,18] riboflavin 5′-phosphate and sodium iodide (0.5%/0.015%) ophthalmic solution (RiboStat; CXL Ophthalmics),[18,19] and an ultraviolet-A illuminator (CXL Ophthalmics) that delivers ultraviolet light (365 nm wavelength) in a 12-mm diameter circular pattern onto the corneas in 15-second on/15-second off cycles.[10,18,19] The technique was as previously described by Stulting et al.[10] Proparacaine anesthetic was instilled in the eye(s) immediately before treatment. The sterile ophthalmic sponge wand was hydrated with proparacaine solution and used to remove lipids, mucus, and any other debris from the surface of the cornea without disruption of the epithelium. A lid speculum was placed in the eye(s) undergoing treatment, and the sterile corneal loading sponge was then applied to the corneal epithelial surface. This sponge was saturated with several drops of the riboflavin ophthalmic solution and kept moist by application of 1 to 2 drops of riboflavin ophthalmic solution every 1 to 3 minutes until the surgeon confirmed adequate saturation of the cornea, using a slitlamp.[10] Riboflavin loading of the corneal stroma proceeded for 20 minutes before checking for saturation at the slitlamp. Saturation was confirmed by referencing a chart of slit-lamp images depicting a validated 5-point scale of riboflavin saturation[18] and with which sites were trained. Riboflavin exposure could be extended to achieve adequate loading, and the time to achieve corneal saturation with riboflavin was recorded. After visually confirming adequate stromal saturation, the corneal surface was irrigated with artificial tears for 30 seconds before UVA illumination to minimize the UVA light absorbance effect of riboflavin on the corneal surface or within the epithelium.

The UVA illuminator was calibrated, its beam(s) centered within the corneal limbus before each treatment, and 1 of the 3 preassigned UVA treatment protocols was initiated by swiping an assigned treatment card through the magnetic card reader on the UVA illumination device. The 3 protocols were as follows, by randomization group:

Group 1. 2.4 J/cm^2 over 20 minutes, as 4 mW/cm^2 cycled on/off at 15-second intervals.
Group 2. 3.6 J/cm^2 over 20 minutes, as 6 mW/cm^2 cycled on/off at 15-second intervals.
Group 3. 3.6 J/cm^2 over 30 minutes, as 4 mW/cm^2 cycled On/Off at 15-second intervals.

For simultaneous bilateral treatments, riboflavin/sodium iodide solution was applied to both eyes, and UVA was delivered to each eye with separate but synchronized optical heads. Riboflavin ophthalmic solution was not instilled during UVA light application. Artificial tears or other lubricating solutions were applied every 30 to 60 seconds during the UVA light application to avoid corneal drying. After completion of the procedure, the lid speculum was removed, and broad-spectrum antibiotic and antiinflammatory drops were instilled in the eye(s). No bandage contact lenses were applied.

Subjects were assessed at post-op day 1 and at 3 and 6 months post-op. Optional study assessments were performed, at the discretion of the investigator and subject, at 12 months when possible. The 3-, 6-, and 12-month post-op assessments included all ocular examinations performed at baseline.

Outcome Measures

The original primary efficacy analysis was based on 6-month post-op assessments. Subjects were then encouraged to return for 12-month post-op assessments when possible.

When assessments were scheduled, subjects were instructed to remove contact lenses before the visit—2 weeks before for rigid gas-permeable contact lenses and 3 days before for soft or scleral lenses—unless the subject had no suitable vision correction option. Because the primary objective of this study was to assess changes in visual acuity resulting from the crosslinking procedure, all visual acuity measurements were made by an observer who was masked to the treatment group to which study subjects were assigned.

CDVA and UCVA were assessed and recorded in Snellen units and converted to logarithm of the minimum angle of resolution (logMAR). Scheimpflug tomography was performed at each visit with the Pentacam (Oculus GmbH, Wetzlar, Germany). Tomogram-derived maximum corneal curvature (Kmax) and minimum corneal thickness were recorded for analysis.

All subjects were evaluated for adverse events (AEs) from the day crosslinking was performed through the last study visit. All AEs, regardless of severity and whether or not they were attributed to the study treatment, were recorded in the source documents and case report forms using standard medical terminology. All AEs were evaluated beginning with onset, and the evaluation continued until resolution was noted or until the investigator determined that the subject's condition was stable. Any medication necessary for the treatment of an AE was recorded on the concomitant medication case report form. A list of "anticipated adverse events" was included in the clinical protocol.

Safety Analysis

AEs were recorded at each visit post-op and at any other time they were reported. The timing and severity were recorded. It was noted if an AE was deemed serious and if so, its relation to treatment. AEs were recorded in common medical language and later coded according to MedDRA 16.0 by term and by system. They were then reviewed individually by an ophthalmologist masked to the treatment group. AEs were tabulated by the treatment group, and event rates were calculated as percentages of subjects affected. Both eyes were analyzed for safety analysis in those subjects with bilateral treatments.

Efficacy Analysis

The efficacy analysis was performed per eye. Because subjects were qualified for treatment based on diagnosis in 1 eye and further to avoid correlations within subjects, 1 eye per subject was analyzed. When 2 eyes were treated, the primary study eye was determined based on a worse baseline CDVA. In cases where eyes had equivalent baseline CDVA, the eye with greater baseline Kmax was chosen for analysis.

The disposition of subjects was tabulated, including diagnosis, treatment group, assessments completed, and discontinuations. Baseline demographic features were tabulated, including age (mean ± SD), sex, race, and ethnicity; baseline CDVA, UCVA, Kmax, and minimum corneal thickness were summarized as means and standard deviations. Efficacy metrics at 3, 6, and 12 months post-op were computed by subtracting baseline values to yield change-from-baseline values.

The primary end point (logMAR CDVA) was analyzed to describe expected changes post-op in end point parameters and to test for differences between groups. The primary measures of efficacy were the mean change from baseline in logMAR CDVA in the primary eye at month 6 post-op for each treatment group. As a supportive analysis to the primary end point, the mean change from baseline and treatment differences were estimated at 3 and 12 months post-op (using all available data for patients within each subgroup). Categorical changes in CDVA were also calculated based on the differences in the number of Snellen lines read at follow-up visits versus baseline.

Separately for each time point, analysis of variance (ANOVA) was used to obtain point estimates and 95% CIs for the change from baseline in logMAR CDVA for each group. ANOVA was also used to obtain point estimates and CIs for all pairwise comparisons between groups. *P* values were calculated for descriptive purposes for the changes in CDVA from baseline to 6 and 12 months post-op based on paired two-sample *t*-tests, using observed data only (no imputation).

As a supportive analysis, the secondary end points of UCVA and Kmax were computed and analyzed in the same way as the primary end points. As exploratory analyses, distributions of categorical changes in CDVA (by-line of vision) were summarized for baseline to 12 months post-op, and changes in minimum corneal thickness were analyzed for baseline to 3, 6, and 12 months post-op. As a sensitivity analysis for pediatric patients, the subset of treated subjects ≤21 years of age at the time of treatment were also analyzed separately.

RESULTS

Subjects

A total of 2228 subjects were randomized and treated in this study (treated analysis set). The demographics of the treated population are summarized in Table 1. Subjects averaged 32 ± 13 years (mean ± SD) of age and ranged from 8 to 79. The average baseline CDVA in the population was 0.316 logMAR (20/41 Snellen), and the average UCVA was 0.875 logMAR (20/150 Snellen). The average Kmax (±SD) was 59 ± 10 diopters. One thousand five hundred eighty-three (71%) of these subjects received bilateral, simultaneous treatments. A small number (n = 19) opted to have their second eye treated at a later visit. For safety results, all data for all subjects are presented.

Keratoconus was diagnosed in 1922 subjects (86.3%) of the study population. Of these subjects, 1315 (68.4%) were treated bilaterally. The efficacy analysis was performed in the 1605 subjects (83.5%) who complied with the study protocol requirements at baseline. Table 2 details the disposition of subjects among the treatment groups.

TABLE 1. Demographics of the Treated Analysis Set

	Group 1	Group 2	Group 3
Age (yr)			
N	745	735	748
Mean	32.6	32.4	32.6
SD	13.04	13.11	12.94
Min, Max	8, 76	8, 78	9, 79
<21	175 (23.5%)	163 (22.2%)	175 (23.4%)
≥21	570 (76.5%)	572 (77.8%)	573 (76.6%)
Race			
American Indian or Alaska Native	2 (0.3%)	2 (0.3%)	3 (0.4%)
Asian	32 (4.3%)	38 (5.2%)	31 (4.1%)
Black or African American	92 (12.3%)	89 (12.1%)	99 (13.2%)
Native Hawaiian or other Pacific Islander	3 (0.4%)	7 (1.0%)	2 (0.3%)
White	582 (78.1%)	573 (78.0%)	584 (78.1%)
Other	34 (4.6%)	26 (3.5%)	29 (3.9%)
Sex			
Male	524 (70.3%)	518 (70.5%)	528 (70.6%)
Female	221 (29.7%)	217 (29.5%)	220 (29.4%)
Ethnicity	142 (19.1%)	118 (16.1%)	138 (18.4%)
Hispanic or Latino			
Not Hispanic or Latino	603 (80.9%)	617 (83.9%)	609 (81.4%)

The subjects in the efficacy analysis set had moderate to advanced disease at baseline based on a mean Kmax of 59.1 diopters for primary eyes for all subjects and 60.0 diopters for the ≤21 year subset. Baseline values for each group are enumerated in Table 3 with the primary and secondary end points. The average time to saturation of the corneal stroma with riboflavin was 22.3 minutes across all subjects.

Primary and Secondary End Points

Of the 1605 subjects with keratoconus with complete baseline assessments, 1400 (87.2%) completed the 6-month post-op outcome primary efficacy assessments. Seven hundred eighty-four subjects were then assessed at 12 months post-op. The lower number of subjects seen at 12 months was due to the initially planned 6 months termination of enrollment. Based on data suggesting more than sufficient statistical power, enrollment concluded on June 28, 2019. Data collection continued for 6 months, but the subjects enrolled in the final 6-month enrollment period did not have an opportunity for longer follow-up. For the first 60% of subjects enrolled, 67% of subjects contributed 12-month follow-up data; for the last 40% of subjects enrolled, 3% contributed 12-month follow-up data.

A summary of CDVA across time and treatment groups is provided in Table 3. The overall mean change in CDVA was −0.06 and −0.07 logMAR at 6 and 12 months post-op, respectively ($P < 0.001$ for improvement in each of 3 groups), with the average visual acuity improving from 20/41 at baseline to 20/35 Snellen at 12 months post-op. Figure 1 summarizes the changes in CDVA over time post-op. ANOVA analysis showed CDVA improvements after treatment for all groups at each time point, and no statistically significant difference in CDVA among the 3 active treatment groups for any time point.

A summary of UCVA across time and treatment groups is provided in Table 3. Overall, UCVA was significantly improved by about 1 line of vision at 6 and 12 months post-op ($P < 0.001$ for improvement at both time points and for each group), with the average uncorrected visual acuity improving from 20/150 at baseline to 20/120 Snellen at 12 months post-op. ANOVA analysis showed no statistically significant difference between the 3 active treatment groups at any time point. Figure 2 summarizes the changes in UCVA over time post-op.

A summary of Kmax across time and treatment groups is provided in Table 4. Overall, Kmax was significantly flattened by −0.45 ± 0.09 D (mean ± SE) at 12 months post-op ($P < 0.05$ in each treatment group). ANOVA analysis showed no statistically significant difference between the 3 active treatment groups for any time point. Figure 3 summarizes the changes in Kmax over time post-op.

Post Hoc End Points

A summary of minimum corneal thickness across time and treatment groups is provided in Table 4. There were no substantial changes in minimum corneal thickness in any group. There was a trend toward thickening, with marginal statistical significance at 12 months post-op. The 95% confidence intervals exclude a change in thickness of more than +6 or −6 μm in any group at any time point. Figure 4 summarizes the changes in minimal thickness over time post-op.

The primary and secondary analyses were repeated in the subset of subjects aged 21 years or younger. Mean end point results were similar, with a trend toward larger gains in CDVA in younger patients. The CDVA change from baseline to month 12 post-op in group 1 subjects (n = 65) was −0.116

TABLE 2. Disposition: Treated Analysis Set

	Group 1	Group 2	Group 3
Subjects randomized and treated	745 (100%)	735 (100%)	748 (100%)
Safety analysis set*	750	745	752
Subjects with keratoconus	644 (86.4%)	635 (86.4%)	643 (86%)
Subject's initial treatment			
OD	85 (13.2%)	105 (16.5%)	87 (13.5%)
OS	93 (14.4%)	98 (15.4%)	103 (16%)
OU	457 (71.0%)	428 (67.4%)	430 (66.9%)
Efficacy analysis set†	542 (84.2%)	534 (84.1%)	529 (82.3%)

*Safety analysis set double counts 19 patients who were in 2 treatment groups for 2 eyes.

†Efficacy analysis set includes subjects with a keratoconus diagnosis and complied with study requirements.

TABLE 3. Visual Acuity Efficacy End Points

Group	logMAR Visual Acuity: Baseline and Change From Baseline			
	Baseline, Mean ± SD (N)	3 Months Post-op, Mean ± SE (N)	6 Months Post-op, Mean ± SE (N)	12 Months Post-op, Mean ± SE (N)
CDVA				
Group 1 (2.4 J/cm²; 20 min)	0.314 ± 0.284 (542)	−0.040 ± 0.009 (526)*	−0.058 ± 0.009 (472)*	−0.074 ± 0.012 (264)*
Group 2 (3.6 J/cm²; 20 min)	0.313 ± 0.305 (534)	−0.053 ± 0.008 (514)*	−0.068 ± 0.009 (461)*	−0.060 ± 0.013 (247)*
Group 3 (3.6 J/cm²; 30 min)	0.323 ± 0.318 (529)	−0.039 ± 0.010 (511)*	−0.064 ± 0.010 (467)*	−0.071 ± 0.018 (273)*
UCVA				
Group 1 (2.4 J/cm²; 20 min)	0.872 ± 0.515 (541)	−0.076 ± 0.014 (521)*	−0.085 ± 0.015 (469)*	−0.088 ± 0.019 (263)*
Group 2 (3.6 J/cm²; 20 min)	0.848 ± 0.520 (533)	−0.079 ± 0.013 (512)*	−0.110 ± 0.015 (461)*	−0.070 ± 0.020 (247)**
Group 3 (3.6 J/cm²; 30 min)	0.907 ± 0.517 (528)	−0.092 ± 0.014 (508)*	−0.099 ± 0.015 (468)*	−0.124 ± 0.021 (272)*

*$P < 0.0001$, **$P < 0.0005$.

logMAR ($P < 0.001$), with the average visual acuity improving from 20/42 at baseline to 20/32 Snellen at 12 months post-op.

Distributions of cumulative CDVA changes, expressed as Snellen lines, from baseline to 12 months post-op are shown in Figure 5. Overall, 81% of patients with keratoconus maintained or improved their vision, with 14% gaining 3 lines or more of CDVA. The distribution for group 1 is very similar to the distribution overall. In patients 21 years old or younger in group 1, 89% of subjects had stable or improved vision, with 25% gaining 3 or more lines of CDVA. Overall, 31 of the 784 (4%) of subjects lost 3 lines or more of CDVA between baseline and month 12. In their medical records, 17 (55%) of these reported other concomitant ocular conditions during the study that may have affected vision, including dry eye, cataracts, and glaucoma.

Safety End Points

The safety profile demonstrated that this treatment was fairly benign, with only 195 (8.8%) of patients reporting any AE (Table 5). Most were mild and transient. There was no significant difference between the UVA treatment protocol groups in rates of AEs. The events reported in the largest proportion of subjects were corneal epithelial defects associated with treatment (1.4%), meibomian gland dysfunction (0.7%), punctate keratitis (0.5%), and dry eye (0.4%). AEs in 59 subjects (2.6%) were judged by the treating physicians to be probably or possibly related to the CXL treatment. Of the 31 epithelial defects reported, 25 (90%) were reported at 1 site; 30 were mild and resolved within 1 week, and 1 was moderate and resolved in 11 days. There were no instances of corneal striae, infection, or other serious AEs related to the treatment.

DISCUSSION

This study included the largest number of patients with keratoconus in an interventional crosslinking study to date. This epithelium-on ("epi-on") technique induced AEs at rates markedly lower than typically reported for conventional (epithelium-off, "epi-off") crosslinking, as would be expected with a noninvasive treatment. Seventy-one percent of subjects were treated in both eyes simultaneously, and typically, they were able to resume all normal activities in 24 to 48 hours post-op. The AEs most observed were corneal epithelial defects in 1.4% of subjects, which was in all but 1 case minor and resolved within 1 week. Most of these events (90%) were reported at 1 site with 28 such epithelial defects reported and was a technique-dependent finding related to the cornea preparation with the EpiPrep sponge wand, which resolved after retraining. Furthermore, the statistical significance of efficacy end point improvement suggests that the technique is effective without the need for inducing notable injury to the epithelium in even a small proportion of patients.

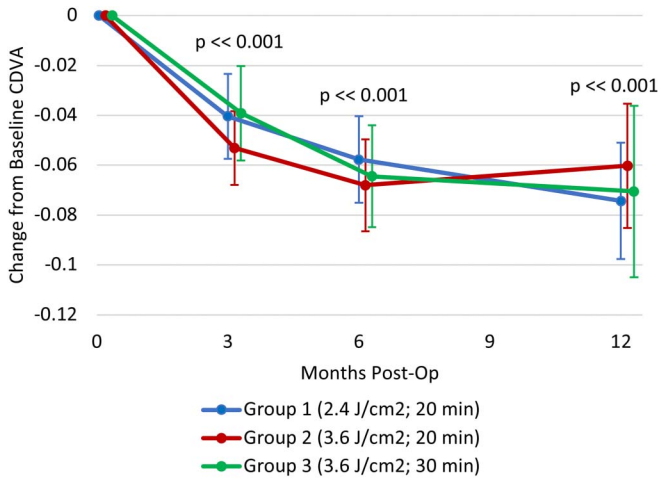

FIGURE 1. Change in CDVA post-op by treatment group (mean ± 95% CI). The average improvements were highly significant for all time points and in each group. (The full color version of this figure is available at www.corneajrnl.com.)

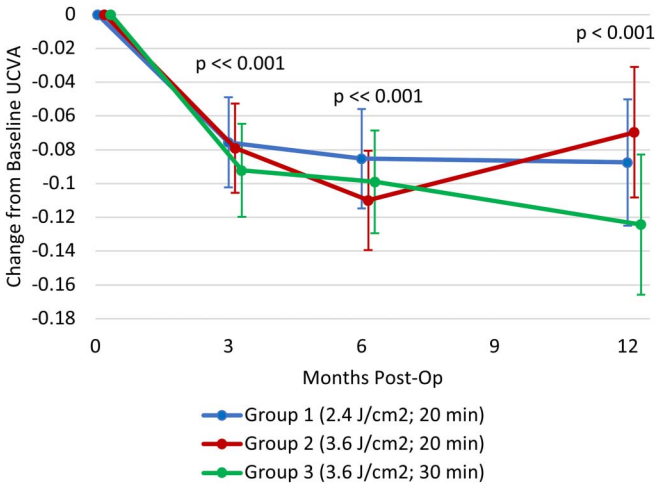

FIGURE 2. Change in UCVA post-op by treatment group (mean ± 95% CI). The average improvements were highly significant for all time points and in each group. (The full color version of this figure is available at www.corneajrnl.com.)

Compared with epi-off crosslinking, a far smaller incidence of AEs was observed. Epithelial defects or abrasions were observed in <2% of subjects, compared with 100% for epi-off, with 23% lasting over a week.[20,21] "Corneal opacity" noted here in 0.3% of subjects can be compared with "corneal haze" reported in 64% of patients after epi-off crosslinking.[21] Although haze after epi-off crosslinking is commonly observed, peaking at 1 to 3 months post-op, it is not correlated with positive or negative outcomes.[22] Corneal striae are seen at a rate of 24% in epi-off procedures[20] but were not seen in this study. Finally, corneal infection is a risk with epithelial removal[13,23]: notably, no infections occurred with the epi-on procedure reported in this article.

The prespecified efficacy end points were CDVA (primary), UCVA (secondary), and Kmax (secondary). The statistical significance of mean CDVA and UCVA end points is high for each group and at each time point, even with the most conservative control of type 1 error rate (eg, Bonferroni correction might adjust the P value from 0.05 to 0.05/27 = 0.00185 to account for 27 comparisons for 3 time points, 3 groups, and 3 metrics). The visual end points indicate improvements in both corrected and uncorrected visual acuity of about 1 line of vision sustained up to 12 months post-op. These gains are consistent with a previous study using the present epi-on CXL technique.[10] The gains in visual acuity observed here are also similar in magnitude to those seen after epi-off crosslinking.[9,11,20]

The Kmax end points were also statistically significant overall. The degree of Kmax improvement is smaller in magnitude than that typically seen in epi-off crosslinking, consistent with a previous study of this technique in particular[10] and of epi-on crosslinking more generally.[15–17,24] Higher than normal Kmax is a hallmark of keratoconus and correlated with disease progression before CXL treatment.[25] However, Kmax flattening has not been shown to correlate well with improvements in visual acuity after crosslinking treatment.[10,11,26] Visual acuity improvements do correlate with regularization of the corneal surface which is observable in coma and higher-order aberrations, both of which were shown to be improved after treatment with the present epi-on technique.[10]

Overall, 80% of the patients in this study had stable or improved CDVA at 12 months post-op. In patients 21 years or younger, 89% had stable or improved vision. This is consistent with the large magnitude of average CDVA improvement in younger patients at 12 months post-op. The age effect may be the result of greater pliability or responsiveness to treatment of young corneas, often observed to

TABLE 4. Tomography-Derived Efficacy End Points

	Corneal Geometric Parameters: Baseline and Change From Baseline			
Group	**Baseline, Mean ± SD (N)**	**3 Months Post-op, Mean ± SE (N)**	**6 Months Post-op, Mean ± SE (N)**	**12 Months Post-op, Mean ± SE (N)**
Kmax (diopters)				
Group 1 (2.4 J/cm²; 20 min)	58.9 ± 9.3 (542)	−0.16 ± 0.11 (521)	−0.20 ± 0.10 (471)	−0.29 ± 0.12 (263)*
Group 2 (3.6 J/cm²; 20 min)	58.7 ± 9.7 (533)	−0.33 ± 0.12 (512)*	−0.40 ± 0.12 (460)**	−0.53 ± 0.17 (246)**
Group 3 (3.6 J/cm²; 30 min)	59.8 ± 10.8 (527)	−0.39 ± 0.14 (508)**	−0.37 ± 0.11 (465)**	−0.53 ± 0.17 (270)**
Min corneal thickness (microns)				
Group 1 (2.4 J/cm²; 20 min)	455 ± 48 (548)	0.57 ± 0.88 (527)	1.02 ± 1.12 (478)	3.86 ± 1.28 (269)*
Group 2 (3.6 J/cm²; 20 min)	461 ± 49 (543)	−2.02 ± 1.06 (522)	1.03 ± 0.91 (468)	3.07 ± 1.42 (252)*
Group 3 (3.6 J/cm²; 30 min)	456 ± 52 (531)	−2.89 ± 1.3 (512)*	0.32 ± 1.22 (469)	3.39 ± 1.63 (272)*

*$P < 0.05$, **$P < 0.005$.

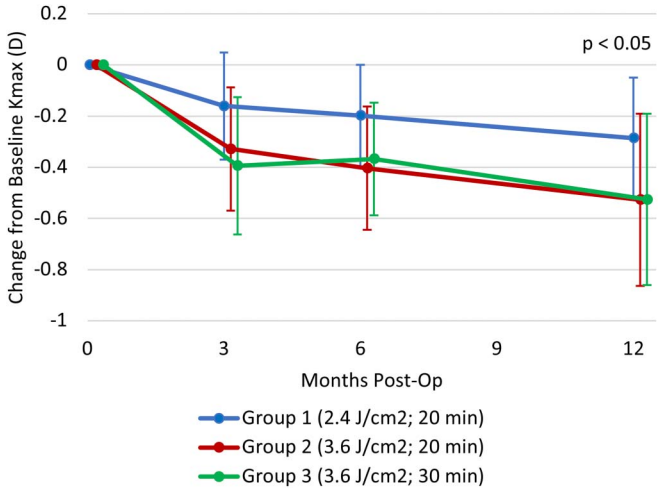

FIGURE 3. Change in Kmax post-op by treatment group (mean ± 95% CI). The topographic flattening was 0.25–0.5 diopter and statistically significant for 2 groups at 6 months and all 3 groups at 12 months. (The full color version of this figure is available at www.corneajrnl.com.)

have rapid progression when diagnosed with keratoconus at a young age,[27–30] or may be the result of concomitant ocular conditions in older patients represented in this study such as nascent age-related macular degeneration (AMD), lens opacities, or previous corneal procedures which may have blunted the positive impact on CDVA conferred by CXL treatment.

No differences in efficacy outcomes were observed between the treatment groups. Each of the 3 groups used full saturation of the corneal stroma with riboflavin. All treatment groups used a dose of UVA similar to or lower than what has been shown safe and effective repeatedly in epi-off crosslinking studies.[9,11,20] Each also used a 15-second on/off cycling that was previously optimized based on theoretical exposure calculations and nonclinical experimentation.[31] The study did not show any group to be optimal, but the results do suggest that all chosen energy levels were sufficient for efficient crosslinking for the duration and intensity of UVA used.

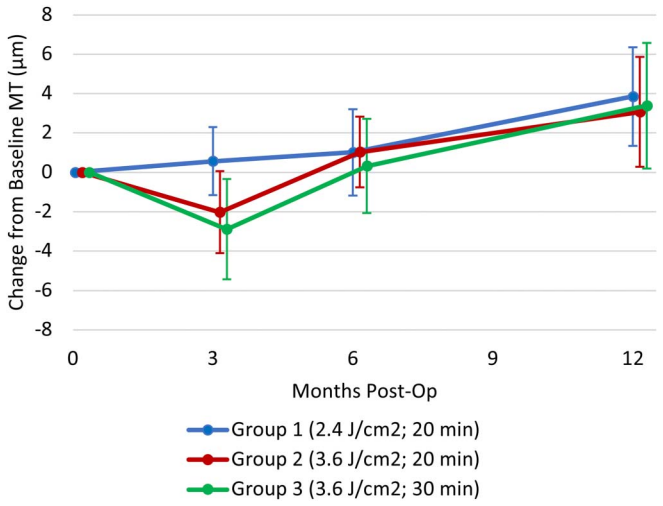

FIGURE 4. Change in minimum corneal thickness post-op by treatment group (mean ± 95% CI). Overall, there were no substantial or clinically significant changes observed in average corneal thickness at the thinnest point. (The full color version of this figure is available at www.corneajrnl.com.)

In group 1, with the lowest UVA dose (2.4 J/cm^2), the CDVA change from baseline to 12 months post-op was −0.074 ± 0.012 (mean ± SE). In this treatment group, 15% of subjects gained 3 or more lines of visual acuity, whereas 25% of patient ≤21 years old gained 3 or more lines. Three lines of VA improvement has been used as a conservative threshold for clinically relevant vision gain in studies of neovascular AMD, and changes of such magnitude are believed to overcome the assumed variability of CDVA measurement. The distribution of changes in CDVA is similar to that observed in previous studies of epi-off crosslinking.[20] Given the well-known progressive nature of keratoconus, it is unlikely that patients with untreated keratoconus would experience a spontaneous regression of visual symptoms of this magnitude.

The minimum corneal thickness derived from Pentacam studies was recorded in this study to investigate the effect of epi-on crosslinking. No thinning was observed after treatment, with only small average changes observed at each time point. This confirms a pilot study which also observed no change in minimal thickness with the EpiSmart technique.[32]

Study Limitations

The initial protocol design was for a 6-month study. Patients were subsequently requested to return for a 12-month post-op examination, when possible, after we became aware of other similar studies where the FDA requested 12-month data. About half of the patients with keratoconus with qualifying baseline data returned for a 12-month follow-up. However, the potential for bias is somewhat reduced because of the enrollment logistics: roughly two thirds of the first 60% of patients enrolled returned for the 12-month post-op visit. At that point, the study was terminated because of sufficient enrollment. The database was locked, and data were analyzed after all patients had returned for the 6-month follow-up. Thus, only 3% of the last 40% of patients enrolled had the opportunity for 12-month follow-up within the study observation period. Because these 12-month data were missing based only on time relative to the decision to halt enrollment, the potential for bias is small. In any case, the 6-month data are highly significant for the same end point changes that are also observed at 12 months. The 6-month end point results of those subjects who completed 12 months of follow-up are indistinguishable from those who did not. Furthermore, results are consistent with a previous study by a group using a similar protocol with up to 24 months of follow-up.[10]

Most of the enrolled patients (70%) were male subjects. No significant differences in outcomes were noted between the male and female subjects in this large sample; however, interpretation of results should consider the relatively lower weight of evidence that is specific to female subjects.

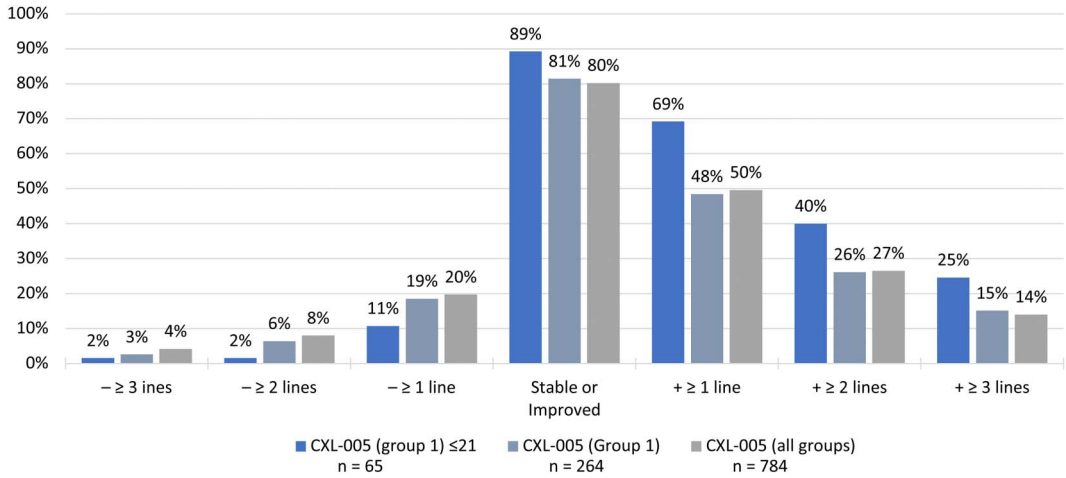

FIGURE 5. Snellen lines of CDVA: Histogram of cumulative changes from baseline to month 12 for the whole, group 1, and ≤ 21 subsets. Most (80%–89%) of patients had stable or improved vision at 12 months and 14% to 25% gained 3 lines or more of vision. (The full color version of this figure is available at www.corneajrnl.com.)

Given the expectation of progression in patients with keratoconus and to maximize the number of treated subjects for comparison, this phase 2 study did not include a placebo/sham control. For this reason, the data are not conclusive regarding the CXL treatment effect. A phase 3 study is planned that will require a masked placebo/sham arm to specifically observe the benefit of this epi-on CXL treatment over 12 months.

CONCLUSIONS

This study examined the response of 1605 patients with keratoconus to an "epi-on" CXL procedure using a novel technique for riboflavin delivery and 3 variations of UVA exposure protocol. No one active treatment arm demonstrated any superiority in efficacy or safety compared with the others. Robust improvements were observed in visual acuity sustained over 12 months in a keratoconus population (not known to spontaneously regress), including a large subset of young subjects 21 years old or younger, with minimal AEs. The results support our contention that this represents a safer, noninvasive crosslinking to arrest the progression of keratoconus. The data support further controlled studies of epi-on crosslinking for the treatment of keratoconus.

TABLE 5. Summary of Treatment-Emergent AEs

	n = 2228
Number of subjects with at least 1 treatment-emergent AE	195 (8.8%)
Corneal epithelial defect	31 (1.4%)
Meibomian gland dysfunction	16 (0.7%)
Punctate keratitis	12 (0.5%)
Dry eye	10 (0.4%)
Conjunctivitis allergic	8 (0.4%)
Corneal opacity	6 (0.3%)
Keratitis	6 (0.3%)
Photophobia	6 (0.3%)
Hypertension	6 (0.3%)
Corneal abrasion	6 (0.3%)
Ophthalmic *Herpes simplex*	6 (0.3%)
Corneal infiltrates	5 (0.2%)
Cataract	5 (0.2%)
Cataract nuclear	4 (0.2%)
Pinguecula	4 (0.2%)
Conjunctivitis	4 (0.2%)

All AEs reported at any visit in > 3 subjects (>0.13%) are listed, regardless of relatedness to procedures.

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