CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SECONDARY REVIEW

NDA/BLA #:	NDA 203324
Supplement #	0043 (Resubmission)
Drug Name:	Riboflavin ophthalmic solution/KXL® System
Proposed Indication:	(1) Treatment of progressive keratoconus (2) Treatment of corneal ectasia following refractive surgery
Applicant:	Avedro, Inc.
Date(s):	Original Submission: September 16, 2013 First Resubmission: September 29, 2014 Second Resubmission: October 16, 2015 PDUFA date: April 15, 2016
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Keywords: Open-label, progressive keratoconus, corneal ectasia following refractive surgery, LASIK, photorefractive keratectomy (PRK), corneal collagen cross-linking (CXL), maximum corneal curvature (Kmax), missing data

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1 INTRODUCTION

This is the second resubmission for NDA 203324, seeking approval of a combination product (drug and device) for the treatment of progressive keratoconus and the treatment of corneal ectasia following refractive surgery. The drug component of the combination product is riboflavin ophthalmic solution and the device component is the KXL system for the ultraviolet A (UVA) light source. The applicant has received two Complete Response letters: one for the original NDA and one for the first resubmission. The two resubmissions did not include new clinical data. The first resubmission included additional literature and sensitivity analyses to further support the efficacy analysis methods and results from the three pivotal studies (UVX-001, UVX-002, and UVX-003) in the original NDA. The second resubmission provided responses to the device related issues. After reviewing the original NDA and the first resubmission, the statistical review team concluded that the three pivotal studies demonstrated evidence of efficacy of corneal collagen cross-linking (CXL) (using riboflavin ophthalmic solution and the UV-X system for the UVA light source) for the improvement of maximum corneal curvature (Kmax) in subjects with progressive keratoconus and subjects with corneal ectasia following refractive surgery. The two primary statistical reviews conducted by Dr. Dongliang Zhuang were finalized on February 28, 2014 and March 12, 2015, and my secondary review was finalized on March 15, 2015.

I conducted this current review for three purposes: (1) to provide recommendations for the CLINICAL STUDIES section of the drug labeling, (2) to include the updated efficacy results for Study UVX-002 after making corrections to the non-physiological Kmax values, and (3) to perform subgroup analyses by age, illumination diameter, refractive surgery, and corneal thickness to assist the clinical review team in evaluating the robustness of the efficacy results for the overall population.

My recommendations for the drug labeling are presented in Section 2. They provide relevant details for the study designs and populations of the pivotal studies, and include an informative graph depicting the efficacy results. The updated efficacy results for Study UVX-002 are presented in Section 3. Although less favorable for the test product, the updated results still support the overall positive efficacy conclusion reached in the aforementioned statistical reviews. The results of the subgroup analyses by age, illumination diameter, refractive surgery, and corneal thickness are summarized in Section 4. They are generally consistent with the results for the overall population.

2 LABELING RECOMMENDATIONS FOR THE CLINICAL STUDIES SECTION

The following are my recommendations for the CLINICAL STUDIES section of the drug labeling.

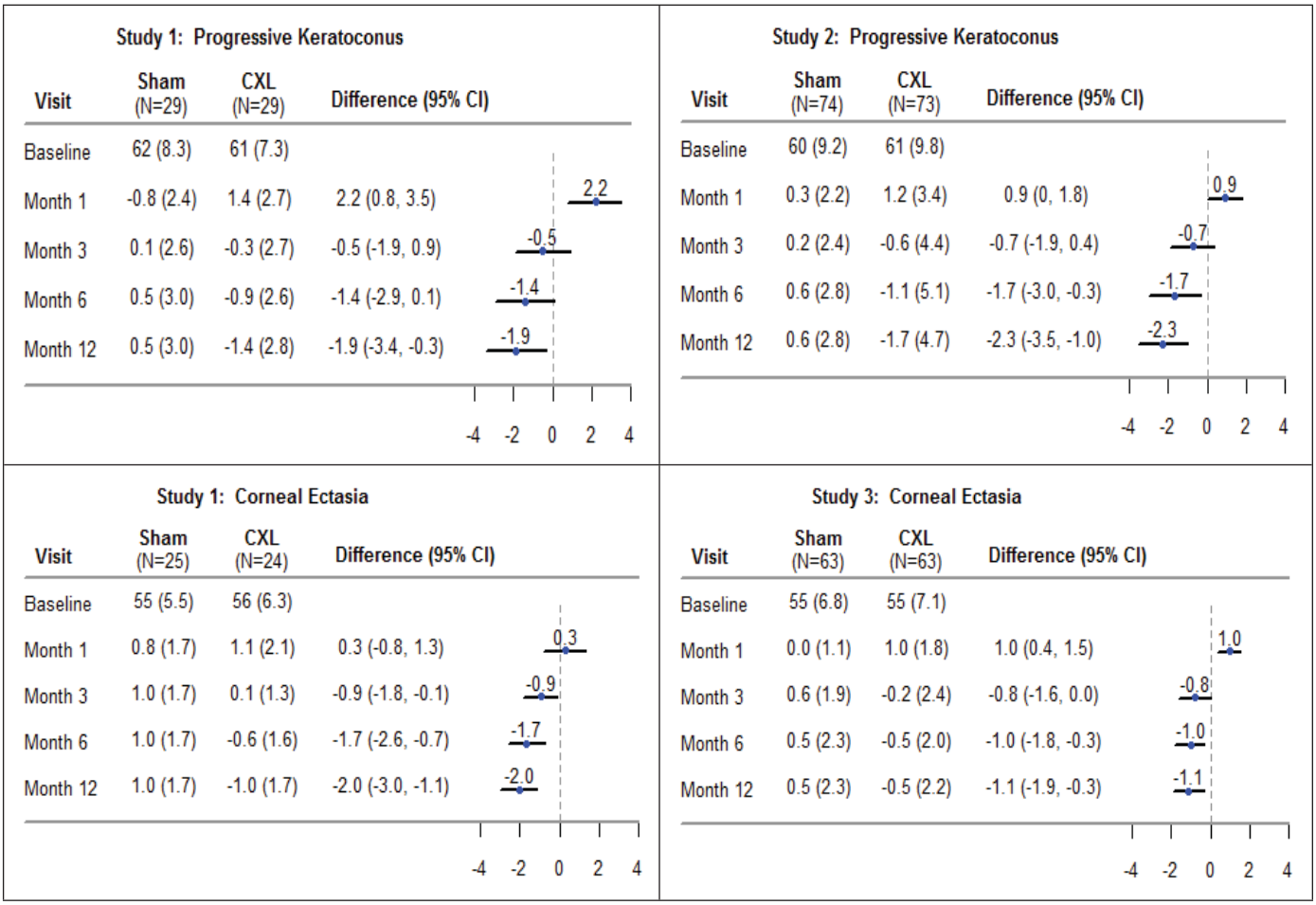
14. CLINICAL STUDIES

Three prospective, randomized, parallel-group, open-label, sham-controlled trials were conducted to evaluate the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing CXL in the eyes of subjects with progressive keratoconus or corneal ectasia following refractive surgery. These trials were sham-controlled for the first 3 months and had a total duration of 12 months for safety and efficacy evaluations. Study 1 enrolled 58 subjects with progressive keratoconus and 49 subjects with corneal ectasia following refractive surgery. Study 2 enrolled 147 subjects with progressive keratoconus, and Study 3 enrolled 130 subjects with corneal ectasia following refractive surgery. The enrolled subjects had one eye designated as the study eye and were randomized to receive one of two study treatments (CXL or sham) in their study eyes at the baseline visit. The study subjects were evaluated at Day 1, Week 1, and Months 1, 3, 6, and 12. At month 3 or later, subjects had the option of receiving CXL treatment in both the sham study eyes and non-study eyes and were followed-up for 12 months from the time of receiving CXL treatment. For keratoconus subjects in Studies 1 and 2, approximately 56% and 89% of the subjects received CXL treatment in their sham study eyes by Month 3 and Month 6, respectively. For corneal ectasia subjects in Studies 1 and 3, approximately 60% and 90% of the subjects received CXL treatment in their sham eyes by Month 3 and Month 6, respectively.

The average age was 33 years for the progressive keratoconus subjects and 43 years for the corneal ectasia subjects. The average baseline Kmax values were 61 diopters for the progressive keratoconus subjects and 55 diopters for the corneal ectasia subjects. A majority (93%) of the corneal ectasia subjects had LASIK only, 5 (3%) subjects had photorefractive keratectomy (PRK) only, and 8 (4%) subjects had both LASIK and PRK.

In each study, the maximum corneal curvature (Kmax) was assessed at baseline, Months 1, 3, and 12. The CXL-treated eyes showed increasing improvement in Kmax from Month 3 through Month 12 (Figure 1). For keratoconus subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 while the sham eyes had an average increase of 0.5 diopter in Study 1 and 0.6 diopter in Study 2; the difference (95% CI) between the CXL and sham groups in the mean change from baseline Kmax was -1.9 (-3.4, -0.3) diopters in Study 1 and -2.3 (-3.5, -1.0) diopters in Study 2. For corneal ectasia subjects, at Month 12, the CXL-treated eyes had an average Kmax reduction of 1.0 diopter in Study 1 and 0.5 diopter in Study 3 while the sham eyes had an average increase of 1.0 diopter in Study 1 and 0.5 diopter in Study 3; the treatment difference between the CXL and sham groups was: -2.0 (-3.0, -1.1) diopters in Study 1 and -1.1 (-1.9, -0.3) diopters in Study 3.

Figure 1: Mean (SD) (Diopter) Change from Baseline Kmax



All randomized subjects were included in the analysis except for four CXL-treated subjects who had missing baseline Kmax values in Study 3. Post-baseline missing data were imputed using last available K_{max} value. For the sham study eyes that received CXL treatment after baseline, the last K_{max} measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

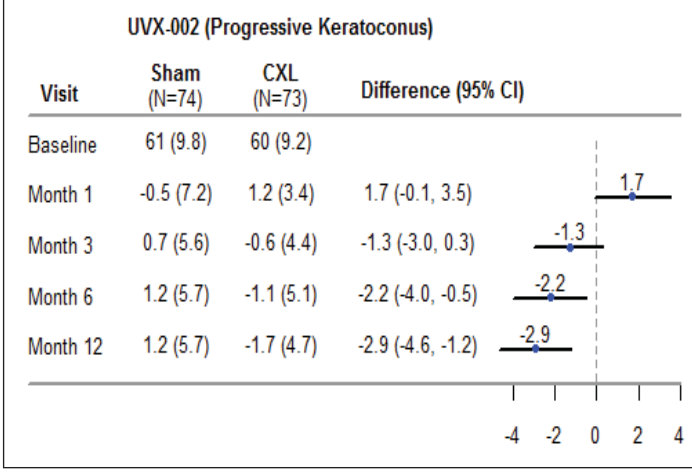
3 UPDATED EFFICACY RESULTS FOR STUDY UVX-002

Three sham study eyes, one in Study UVX-001 and two in Study UVX-002, had Kmax values that were considered non-physiological values (Table 5 in Appendix). These values should have been treated as missing and imputed using the last observation carried forward (LOCF) method in the FDA's efficacy analysis. However, upon checking the efficacy results presented in both the FDA briefing document and the presentation slides for the advisory committee (AC) meeting held on February 24, 2015, I found that only the non-physiological value in Study UVX-001 was treated as missing and imputed using the LOCF method. Thus, I conducted the analysis for Study UVX-002 in the same manner as was done for Study UVX-001. In the updated analysis (Figure 2), compared with the results presented in the FDA AC briefing document, the magnitude of the average increase from baseline Kmax is reduced by approximately half diopter in the sham group from Month 3 through Month 12. Consequently, the average CXL treatment effect (relative to the sham group) is reduced by approximately half diopter. However, since the upper limit of the 95% confidence interval for the treatment difference is one diopter below zero at Month 12, the updated analysis results still demonstrate statistically significant CXL treatment effect for the improvement of Kmax from baseline.

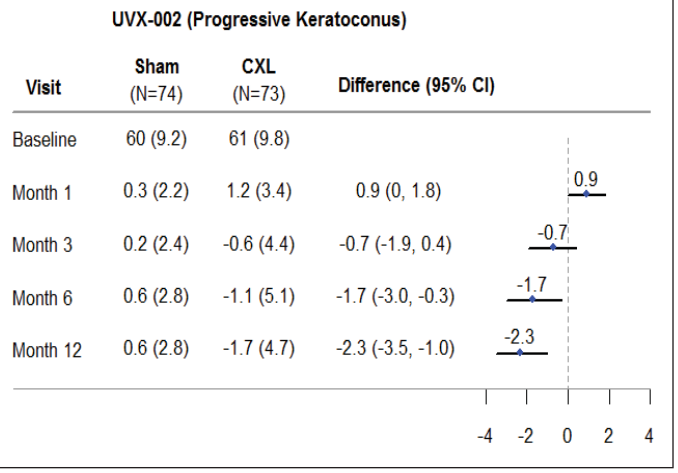
The updated results for Study UVX-002 are included in Section 2 for the labeling recommendations.

Figure 2: Study UVX-002: Mean (SD) (Diopter) Change from Baseline Kmax

Results in the AC Briefing Document (No Data Correction)



Updated Results after Data Corection



Source: reviewer's analysis. All randomized study eyes were included. Post-baseline missing values were imputed using last available K_{max} measurement. For sham study eyes that received CXL treatment after baseline, the last K_{max} measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

For easy access to the FDA's detailed primary efficacy analysis results, I include my analysis results in Table 6 and Table 7 (Appendix) for the three pivotal studies. My analyses used the applicant's datasets located at: \\CDSESUB1\evsprod\NDA203324\0000\m5\datasets (raw datasets for baseline characteristics) and \\CDSESUB1\evsprod\NDA203324\0007\m5\datasets\ise\analysis\ adam\datasets (the efficacy analysis dataset).

4 SUBGROUP ANALYSES

The primary statistical review (February 28, 2014) for the original NDA included the applicant's subgroup analyses by gender, race, and keratoconus severity. The results of these subgroup analyses were consistent with the results for the overall population. This review includes additional subgroup analyses by age, illumination diameter, refractive surgery, and corneal thickness. I conducted these subgroup analyses to assist the clinical review team in evaluating the robustness of the primary efficacy results for the overall population. The results of these additional subgroup analyses are summarized in the following four subsections, and they are generally consistent with the results for the overall population.

4.1 Subgroup Analyses by Age

The protocol-specified inclusion criterion for age was "*14 years of age or older*" (Table 8 in Appendix). The enrolled subjects ranged in age from 14 to 63 years in the keratoconus studies and 22 to 63 years in the corneal ectasia studies (Table 1). On average, the keratoconus subjects were approximately 10 years younger than the corneal ectasia subjects: 33 years for the keratoconus subjects and 43 years for the corneal ectasia subjects. While the corneal ectasia studies did not enroll pediatric subjects, the keratoconus studies enrolled 10 (5%) and 33 (16%) pediatric subjects 14-17 years old and 14-22 years old, respectively. Note that the upper threshold for pediatric population was 17 years for CDER and 22 years for CDRH. These thresholds were presented during the AC meeting to discuss the applicability of extrapolation from adult data to the pediatric population with progressive keratoconus (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM436466.pdf).

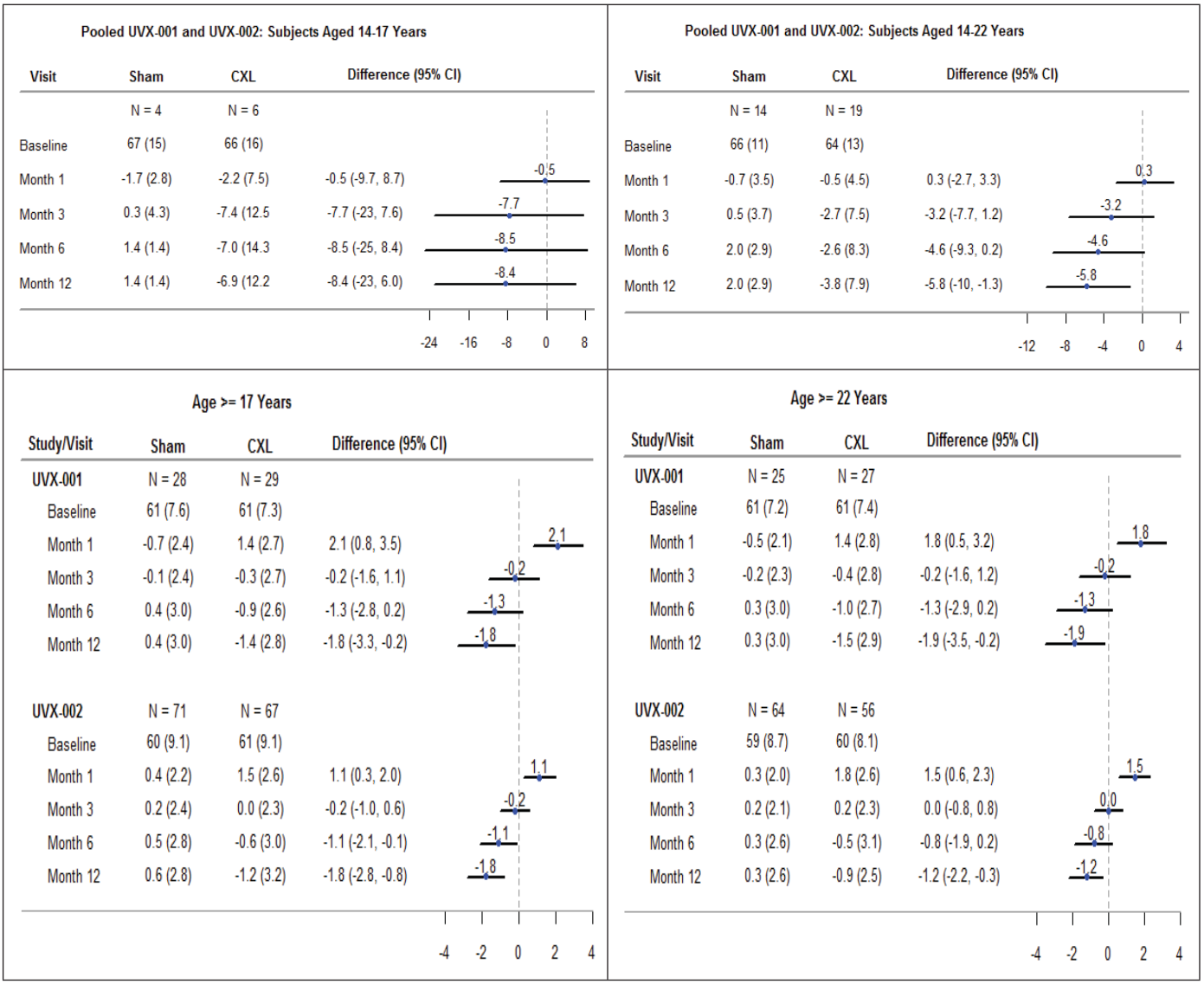
Table 1: **Summary Statistics of Age**

	UVX-001 (Keratoconus)		**UVX-002 (Keratoconus)**		**Overall**
	Sham (N=29)	**CXL (N=29)**	**Sham (N=74)**	**CXL (N=73)**	**N=205**
Mean (SD)	37 (13)	33 (8)	34 (12)	30 (10)	33 (11)
Min, Max	16, 60	20, 50	15, 63	14, 57	14, 63
14-17 Years [1]	1	0	3	6	**10 (5%)**
14-22 Years [2]	4	2	10	17	**33 (16%)**
	UVX-001 (Corneal Ectasia)		**UVX-003 (Corneal Ectasia)**		
	Sham (N=25)	**CXL (N=24)**	**Sham (N=63)**	**CXL (N=67)**	**N=179**
Mean (SD)	40 (8)	45 (9)	43 (9)	43 (9)	43 (9)
Min, Max	24, 57	28, 63	24, 62	22, 60	22, 63

[1] Age ≥ 14 and < 17 years. [2] Age ≥ 14 and < 22 years.
Source: reviewer's analysis. Table 13 in the applicant's study reports contained the summary data for mean, minimum, and maximum. The age variable was calculated based on subjects' informed consent date and the birth date.

For the keratoconus subjects, the subgroup analyses were conducted for four age groups: 14-17 years, 14-22 years, ≥17 years, and ≥22 years. For the two pediatric age groups (14-17 years and 14-22 years), the analyses were conducted based on the pooled data from Studies UVX-001 and UVX-002 because of the small sample sizes in these two age groups. As shown in Figure 3, the results of these subgroup analyses are consistent with the results for the overall population. The CXL treatment effect appeared to be larger in the pediatric subjects than the adult subjects from Month 3 through Month 12; at Month 12, relative to the sham group, the CXL-treated pediatric subjects had an average Kmax reduction of more than 5 diopters whereas the adult subjects had an average Kmax reduction of less than 2 diopters.

Figure 3: Subgroup Analyses by Age for Keratoconus Subjects: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis.

4.2 Subgroup Analyses by Illumination Diameter

For the UVA light source, the applicant's proposed device (KXL system) for post-marketing use is not the device (UV-A system) used in the pivotal studies. In the original NDA and the first resubmission, the proposed device has a fixed illumination diameter of 9.0 mm. In the second resubmission, the proposed device has a fixed illumination diameter of 9.5 mm. The device used in the pivotal studies however had varied illumination diameters: small (7.5 mm), medium (9.5 mm), and large (11.0 mm). As shown in Table 2, for the combined CXL treatment groups, no eyes were treated with the small diameter, 170 (88%) eyes were treated with the medium diameter, 17 (9%) eyes were treated with the large diameter, and 6 (3%) eyes had missing data. Note that the UV-X device was not turned on for the sham study eyes and the measurement for illumination diameter was not recorded for these eyes. Thus, I include all the sham eyes in the subgroup analyses by illumination diameter.

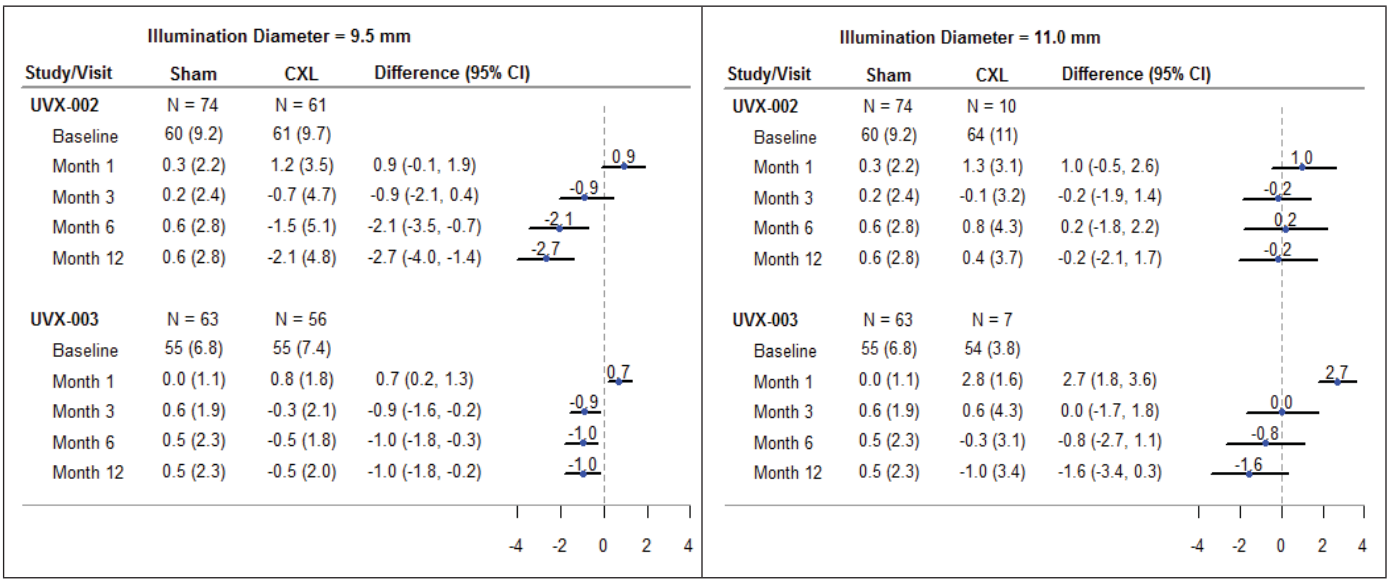
Table 2: Number of Study Eyes by Illumination Diameter for the CXL Groups

	Keratoconus		Corneal Ectasia		Overall
	UVX-001 (N=29)	UVX-002 (N=73)	UVX-001 (N=24)	UVX-003 (N=67)	N=193
Samll (7.5 mm)	0	0	0	0	0
Medium (9.5 mm)	29 (100%)	61 (84%)	24 (100%)	56 (84%)	170 (88%)
Large (11.0 mm)	0	10 (13%)	0	7 (10%)	17 (9%)
Missing data	0	2 (3%)	0	4 (6%)	6 (3%)

Source: Adapted from Table 2 in the first resubmission at \\CDSESUB1\evsprod\NDA203324\0028\m1\us\111-info-amend.

As all the CXL study eyes were treated with the medium (9.5 mm) diameter in Study UVX-001 (Table 2), I conducted the subgroup analyses by illumination diameter for Study UVX-002 and UVX-003 only (Figure 4). In these two studies, the efficacy results for the eyes treated with the medium (9.5 mm) diameter were similar to those for the overall study population. For the eyes treated with the large (11.0 mm) diameter, although the sample size was small, the efficacy results appeared to be consistent with those for the overall population.

Figure 4: Subgroup Analyses by Illumination Diameter: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis.

4.3 Subgroup Analyses by Refractive Surgery

In corneal ectasia Studies UVX-001 and UVX-003, one key inclusion criterion was "*having a diagnosis of corneal ectasia after corneal refractive surgery (e.g., LASIK, photorefractive keratectomy (PRK), or epi-LASIK)*" (Table 8 in Appendix). These two studies enrolled 166 (93%) subjects with LASIK only, 5 (3%) subjects with PRK only, and 8 (4%) subjects with both LASIK and PRK (Table 3).

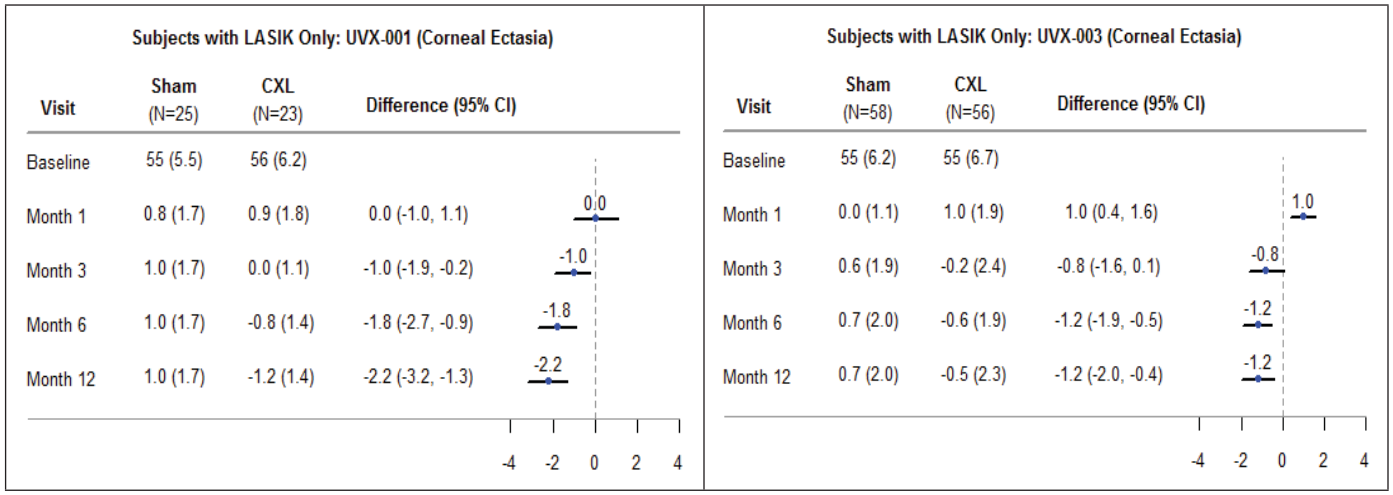
Table 3: Number of Study Eyes by Refractive Surgery

	UVX-001 (Corneal Ectasia)		UVX-003 (Corneal Ectasia)		Overall
	Sham (N=25)	CXL (N=24)	Sham (N=63)	CXL (N=67)	N=179
LASIK only	25 (100%)	23 (96%)	58 (92%)	60 (90%)	166 (93%)
PRK only	0	0	1 (2%)	4 (6%)	5 (3%)
LASIK and PRK	0	1 (4%)	4 (6%)	3 (4%)	8 (4%)

Source: adapted from Table 2 from the first NDA resubmission at \\CDSESUB1\evsprod\NDA203324\0028\m1\us\111-info-amend

As shown in Figure 5, the results for subjects with LASIK only are similar to the results for the overall population.

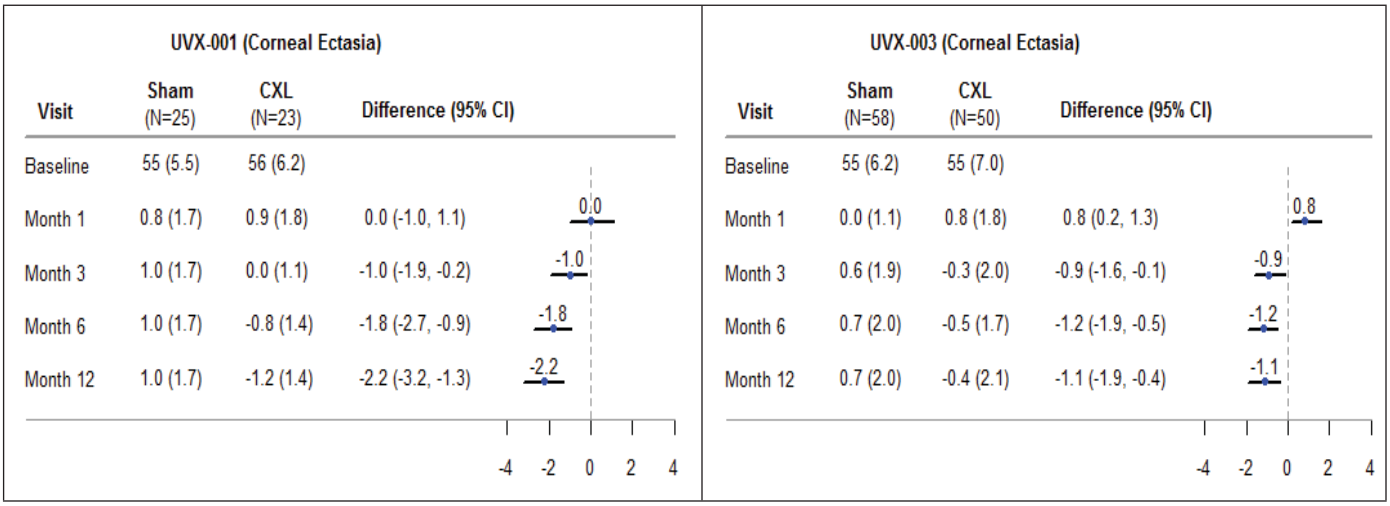
Figure 5: Subgroup Analyses for Subjects with LASIK Only: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis. Four CXL-treated subjects had a missing baseline Kmax value and were excluded from the analysis in Study UVX-003.

I also conducted subgroup analysis for the subjects with LASIK only and treated with a 9.5 mm illumination diameter because the clinical review team was interested in this subgroup analysis. The results of this subgroup analysis are similar to the results for the overall population (Figure 6). Note that for Study UVX-001, the analysis results presented in Figure 6 are the same as in Figure 5 because all the CXL study eyes in this study were treated with a 9.5 mm illumination diameter.

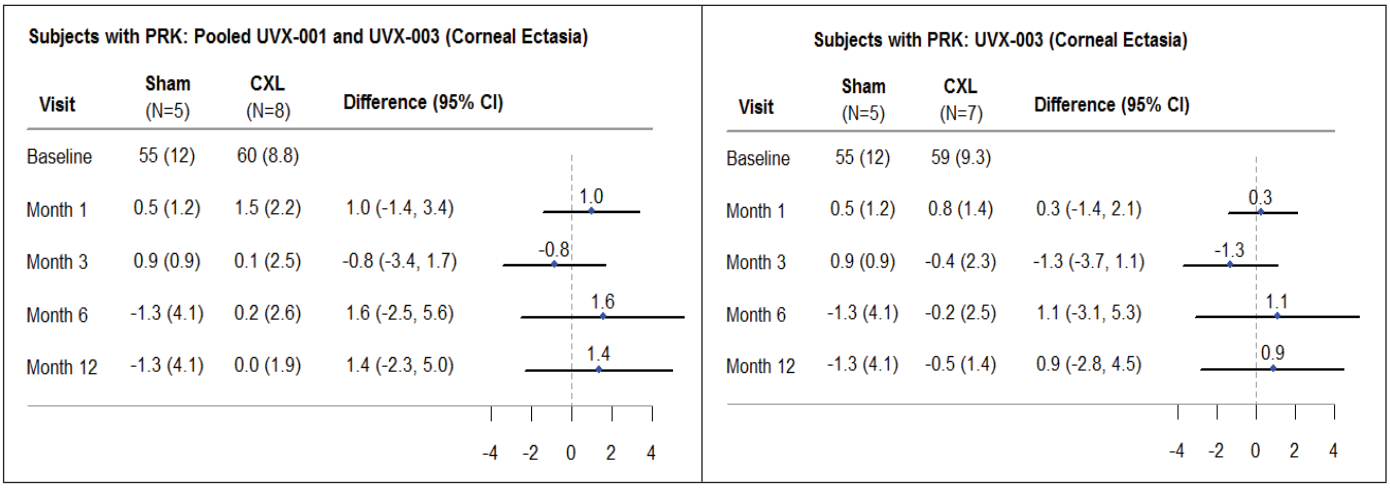
Figure 6: Subgroup Analyses for Subjects with LASIK Only and Treated with a 9.5 mm Illumination Diameter: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis.

I conducted the subgroup analysis for the subjects with PRK using data from Study UVX-003 alone and the pooled data from Studies UVX-001 and UVX-003 because Study UVX-001 had only one subject with PRK (Table 3). This subgroup analysis yielded an average reduction in Kmax of 1.3 diopters in the sham group and no more than half diopter in the CXL group at Months 6 and 12 (Figure 7). As a result, this subgroup analysis did not show numerically favorable results for the CXL group. However, given the small sample size and the wide confidence intervals for the treatment difference, from a statistical perspective, one cannot make a definitive conclusion regarding the CXL treatment effect on Kmax for the subjects with PRK. Thus I defer to the clinical review team to determine the applicability of extrapolation from the efficacy results of the subjects with LASIK only to the population with PRK.

Figure 7: Subgroup Analyses for Subjects with PRK: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis.

4.4 Subgroup Analyses by Corneal Thickness

According to the study protocols, subjects who meet the following criterion (Table 8 in Appendix) would be excluded from the studies:

"Corneal pachymetry at the screening exam that is < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the Medio-Cross (b) (4) *riboflavin solution alone will be used or < 300 microns when the* (b) (4) *riboflavin will be used"*

As shown in Table 4, the range of corneal thickness was 306 to 561 microns for the keratoconus subjects and 308 to 599 microns for the corneal ectasia subjects. Overall, the mean corneal thickness was 440 microns for the keratoconus subjects and 431 microns for the corneal ectasia subjects. A majority of the subjects, 80% of the keratoconus subjects and 73% of the corneal ectasia subjects, had a corneal thickness of at least 400 microns; and 19% of the keratoconus subjects and 26% of the corneal ectasia subjects had corneal thickness between 300-400 microns.

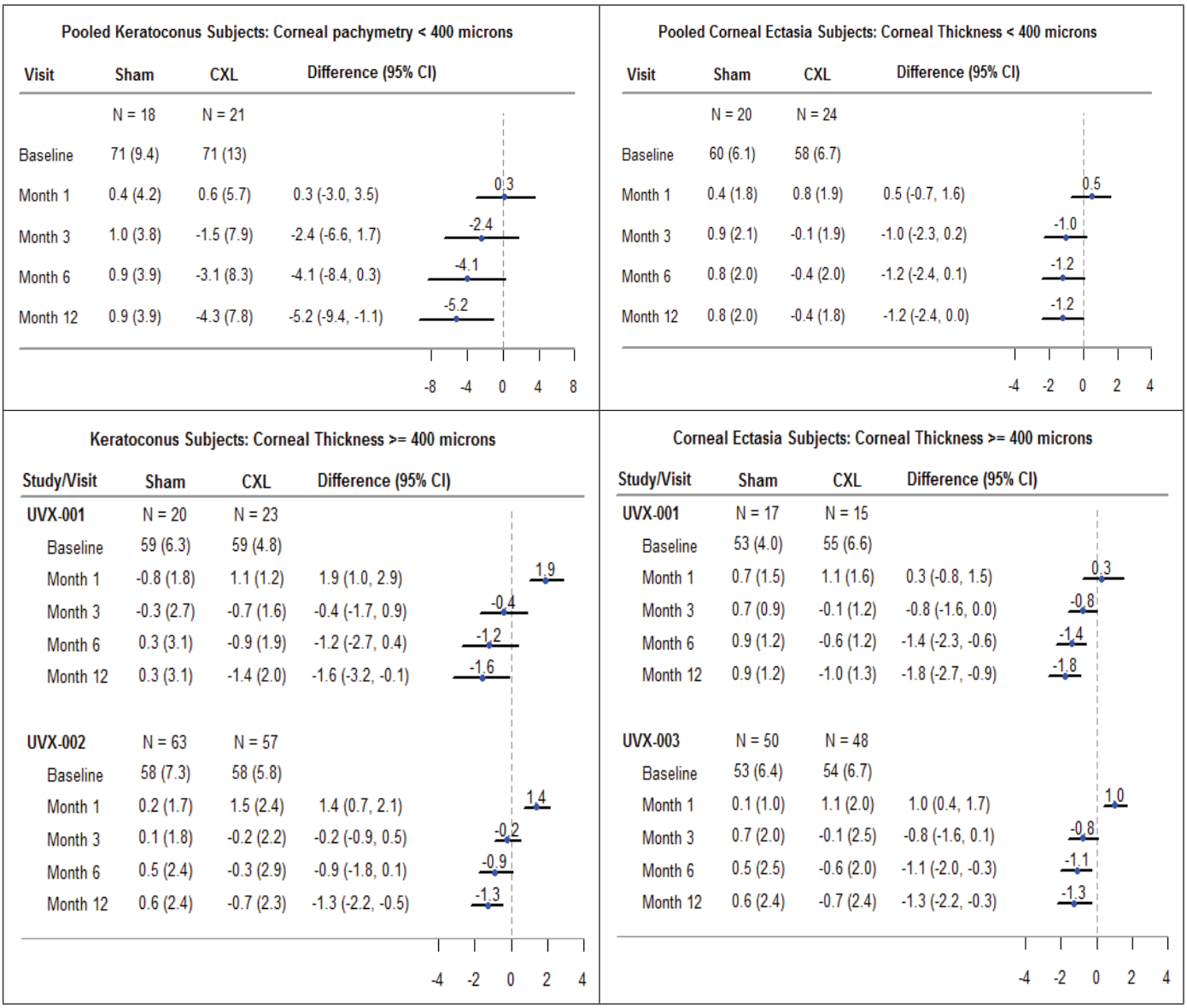
Table 4: **Summary Statistics of Corneal Thickness (micron)**

	UVX-001 (Keratoconus)		**UVX-002 (Keratoconus)**		**Overall**
	Sham (N=29)	**CXL (N=29)**	**Sham (N=74)**	**CXL (N=73)**	**N=205**
Observed data	28	29	73	72	202
Mean (SD)	429 (52)	441 (49)	443 (46)	440 (47)	440 (53)
Min, Max	330, 527	358, 548	306, 538	328, 561	306, 561
300 - 400 microns	8 (28)	6 (21%)	10 (14%)	15 (21%)	39 (19%)
> 400 microns	20 (69%)	23 (79%)	63 (85%)	57 (78%)	163 (80%)
Missing data	1	0	1	1	3 (1%)
	UVX-001 (Corneal Ectasia)		**UVX-003 (Corneal Ectasia)**		
	Sham (N=25)	**CXL (N=24)**	**Sham (N=63)**	**CXL (N=67)**	**N=178**
Observed data	25	24	62	67	177
Mean (SD)	413 (41)	427 (60)	439 (54)	431 (54)	431 (53)
Min, Max	336, 478	346, 599	308, 554	320, 568	308, 599
300 - 400 microns	8 (32%)	9 (38%)	12 (19%)	18 (27%)	47 (26%)
> 400 microns	17 (68%)	15 (62%)	50 (79%)	49 (73%)	131 (73%)
Missing data	0	0	1	0	1 (1%)

Source: reviewer's analysis using variable "PREPACH" in the dataset "TX.XPT" at \\CDSESUB1\evsprod\NDA203324\0000\m5\datasets.

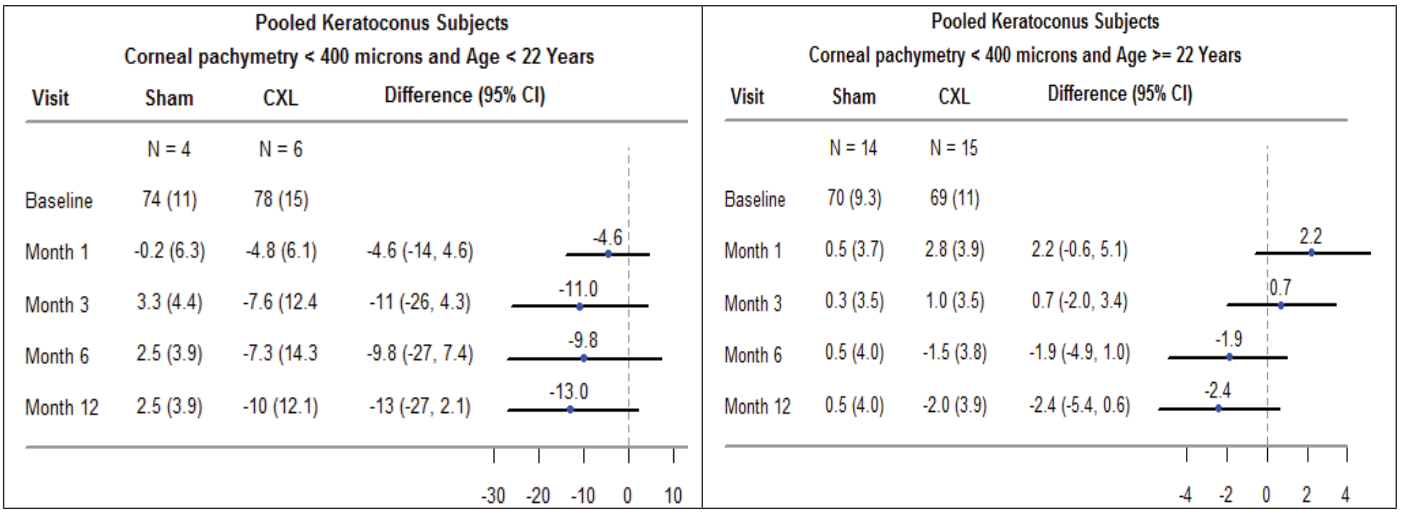
The subgroup analyses for the subjects with corneal thickness of at least 400 microns were conducted for each of the three studies separately; however, because of the small sample sizes, the subgroup analyses for the subjects with corneal thickness less than 400 microns were conducted for the pooled data. As shown in Figure 8, the results of these subgroup analyses were consistent with the results for the overall population. For the keratoconus studies, the CXL-treatment effect appeared to be larger in the subjects with corneal thickness of less than 400 microns than the subjects with corneal thickness of at least 400 microns; at Month 12, relative to the sham group, the CXL-treated subjects who had corneal thickness less than 400 microns had an average Kmax reduction of 5.2 diopters whereas the subjects with corneal thickness of at least 400 microns showed an average reduction of 1.3 to 1.6 diopters. This observed larger CXL-treatment effect for the keratoconus subjects with corneal thickness less than 400 microns appeared to be mainly contributed by the subjects who were younger than 22 years old (Figure 9).

Figure 8: Subgroup Analyses by Corneal Thickness: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis. In the CXL group of Study UVX-003, three eyes with corneal thickness < 400 microns and one eye with corneal thickness ≥ 400 microns were excluded from the analysis because of missing baseline Kmax values.

Figure 9: Subgroup Analyses by Corneal Thickness and Age: Mean (SD) Change from Baseline Kmax



Source: reviewer's analysis

5 APPENDIX

Table 5: Data Listing of Three Sham Eyes That Had Non-physiological Kmax Values

Progressive Keratoconus	Subject ID	Treatment	Visit	Visit Date	Raw Kmax	Imputed Kmax Using LOCF
UVX-001	(b) (6)	Receiving Sham	Baseline	13-Nov-08	62	
			Month 1	2-Apr-09	**-0.3**	**62**
			Month 3	5-Jun-09	68.6	
		Receiving CXL		5-Jun-09		
			Month 1	21-Jul-09	64.4	
			Month 3	28-Aug-09	70.7	
			Month 6	18-Nov-09	67.3	
UVX-002	(b) (6)	Receiving Sham	Baseline	20-Jun-08	58.4	
			Month 1	2-Sep-08	**0**	**58.4**
			Month 3	21-Nov-08	57.5	
		Receiving CXL		21-Nov-08		
			Month 1	20-Jan-09	59.9	
			Month 3	10-Mar-09	59.9	
			Month 6	24-Apr-09	59.5	
			Month 12	21-May-10	60.8	
UVX-002	(b) (6)	Receiving Sham	Baseline	28-Oct-08	64.4	
			Month 1	13-Jan-09	63.6	
			Month 3	25-Feb-09	**108**	**63.6**
		Receiving CXL		25-Feb-09		
			Month 1	20-May-09	61.7	
			Month 3	8-Jul-09	60.9	
			Month 6		.	
			Month 12	4-Aug-10	59.1	

Source: reviewer's analysis

Table 6: Efficacy Results of Kmax and Change from Baseline Kmax (Keratoconus Studies UVX-001 and UVX-002)

		Kmax		Change from Baseline in Kmax		
Study	**Statistic**	**CXL**	**Sham**	**CXL**	**Sham**	**Difference (95% CI) [1]**
UVX-001		**N=29**	**N=29**			
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)			
	Median	59.2	62.0			
	Min, Max	49.5, 79.2	47.7, 81.3			
Month 1	Mean (SD)	62.0 (8.4)	61.2 (8.3)	1.4 (2.7)	-0.8 (2.4)	2.2 (0.8, 3.5)
	Median	60.1	60.2	0.9	-0.2	
	Min, Max	51.5, 89.4	47.5, 78.6	-1.4, 13.9	-7.9, 4.8	
Month 3	Mean (SD)	60.3 (8.2)	62.0 (9.4)	-0.3 (2.7)	0.1 (2.6)	-0.5 (-1.9, 0.9)
	Median	58.3	60.8	-0.7	-0.1	
	Min, Max	48.0, 86.2	47.5, 87.4	-5.4, 10.7	-7.4, 6.6	
Month 6	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)	-1.4 (-2.9, 0.1)
	Median	57.7	60.8	-1.1	0	
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	
Month 12	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	-1.9 (-3.4, -0.3)
	Median	58.4	60.8	-1.0	0	
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	
UVX-002		**N=73**	**N=74**			
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)			
	Median	58.0	57.5			
	Min, Max	47.8, 96.4	48.3, 90.3			
Month 1	Mean (SD)	62.2 (9.4)	60.1 (9.6)	1.2 (3.4)	0.3 (2.2)	0.9 (-0.0, 1.8)
	Median	59.4	57.7	1.0	0.0	
	Min, Max	49.3, 93.8	47.5, 91.3	-16.8, 8.1	-7.4, 8.0	
Month 3	Mean (SD)	60.4 (8.9)	59.9 (9.4)	-0.6 (4.4)	0.2 (2.4)	-0.7 (-1.9, 0.4)
	Median	58.4	57.8	0	-0.1	
	Min, Max	47.8, 89.5	48.8, 91.5	-32.7, 5.5	-8.5, 8.2	
Month 6	Mean (SD)	59.9 (8.3)	60.4 (9.8)	-1.1 (5.1)	0.6 (2.8)	-1.7 (-3.0, -0.3)
	Median	57.9	58.0	-0.5	-0.1	
	Min, Max	47.3, 87.5	49.4, 91.1	-36.2, 11.6	-8.5, 13.8	
Month 12	Mean (SD)	59.3 (8.5)	60.4 (11.3)	-1.7 (4.7)	0.6 (2.8)	-2.3 (-3.5, -1.0)
	Median	58.0	58.0	-1.0	-0.1	
	Min, Max	46.6, 90.9	49.4, 91.1	-31.6, 7 3	-8.5, 13.8	

[1] Difference in mean change from baseline in Kmax (CXL – Sham).

Source: Reviewer's Analysis. In Study UVX-001, an erroneous Kmax value at Month 1 for sham subject (b) (6) was imputed by the baseline value (Table 5). In Study UVX-002, an erroneous Kmax value at Month 1 for sham subject (b) (6) was imputed by the baseline value; a potentially erroneous Kmax value at Month 3 for sham subject (b) (6) was imputed by the value at Month 1 (Table 5).

Table 7: Efficacy Results of Kmax and Change from Baseline Kmax (Ectasia Studies UVX-001 and UVX-003)

		Kmax		Change from Baseline in Kmax		
Study	**Statistic**	**CXL**	**Sham**	**CXL**	**Sham**	**Difference (95% CI)[1]**
UVX-001		**N=24**	**N=25**			
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)			
	Median	56.2	55.2			
	Min, Max	47.4, 71.6	47.0, 68.2			
Month 1	Mean (SD)	57.4 (7.6)	55.8 (6.0)	1.1 (2.1)	0.8 (1.7)	0.3 (-0.8, 1.3)
	Median	57.2	55.5	0.9	0.5	
	Min, Max	42.9, 77.0	47.7, 67.1	-4.5, 6.0	-3.0, 6.5	
Month 3	Mean (SD)	56.4 (7.0)	56.0 (6.4)	0.1 (1.3)	1.0 (1.7)	-0.9 (-1.8, -0.1)
	Median	55.1	56.0	0.0	0.7	
	Min, Max	47.6, 73.8	47.6, 70.4	-2.5, 3.3	-1.0, 7.3	
Month 6	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)	-1.7 (-2.6, -0.7)
	Median	53.2	56.6	-0.8	0.6	
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	
Month 12	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	-2.0 (-3.0, -1.1)
	Median	53.3	56.6	-0.9	0.6	
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	
UVX-003		**N=63**	**N=63**			
Baseline[2]	Mean (SD)	55.1 (7.1)	54.7 (6.8)			
	Median	53.9	52.9			
	Min, Max	44.9, 74.5	42.9, 76.3			
Month 1	Mean (SD)	56.0 (7.0)	54.7 (6.7)	1.0 (1.8)	0.0 (1.1)	1.0 (0.4, 1.5)
	Median	55.7	53.4	0.6	0.1	
	Min, Max	45.2, 75.8	43.4, 75.1	-3.1, 5.8	-2.2, 2.4	
Month 3	Mean (SD)	54.9 (7.0)	55.3 (6.8)	-0.2 (2.4)	0.6 (1.9)	-0.8 (-1.6, -0.0)
	Median	53.4	53.8	0.1	0.5	
	Min, Max	44.8, 77.3	43.4, 77.6	-8.6, 6.8	-2.7, 11.9	
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)	-1.0 (-1.8, -0.3)
	Median	53.3	53.8	-0.2	0.5	
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	
Month 12	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	-1.1 (-1.9, -0.3)
	Median	53.5	54.1	-0.3	0.5	
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3 8	-8.6, 11.9	

[1] Difference in mean change from baseline in Kmax (CXL – Sham). [2] In Study UVX-003, four subjects in the CXL group had missing baseline K_{max} values and were excluded from the analysis.

Source: reviewer's analysis.

Table 8: **Key Inclusion and Exclusion Criteria for Studies UVX-001, UVX-002, and UVX-003**

Key Inclusion Criteria for Keratoconus Studies UVX-001 and UVX-002	
1	14 years of age or older
2	Having a diagnosis of progressive keratoconus defined as one or more of the following changes over a period of 24 months or less before randomization: a. An increase of ≥ 1.00 D in the steepest keratometry value (or simK) b. An increase of ≥ 1.00 D in regular astigmatism evaluated by subjective manifest refraction c. A myopic shift (decrease in the spherical equivalent) of ≥ 0.50 D on subjective manifest refraction d. A decrease ≥ 0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers where other information is not available. [NOTE: Patients with a clear history of progression but without prior documentation may be followed and re-examined at a later visit to confirm progression.]
3	Presence of central or inferior steepening on the Pentacam map
4	Axial topography consistent with keratoconus
5	Presence of one or more findings associated with keratoconus, such as: a. Fleischer ring b. Vogt striae c. Corneal thinning d. Corneal scarring e. Scissoring of the retinoscopic reflex
6	Steepest keratometry (Kmax) value ≥ 47.00 D
7	I-S ratio > 1.5 on the Pentacam map or topography map
8	BSCVA worse than 20/20 (<53 letters on ETDRS chart)
9	Contact Lens Wearers Only: removal of contact lenses for the required period of time prior to the screening refraction: Contact Lens Type — Minimum Discontinuation Time Soft — 3 Days Soft Extended Wear — 1 Week Soft Toric — 2 Weeks Rigid gas permeable — 2 Weeks
Key Exclusion Criteria for Keratoconus Studies UVX-001 and UVX-002	
1	Eyes classified as either normal, atypical normal, or keratoconus suspect on the severity grading scheme
2	A history of previous corneal surgery or the insertion of Intacs in the eye(s) to be treated
3	Corneal pachymetry at the screening exam that is < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the Medio-Cross (b) (4) riboflavin solution alone will be used or < 300 microns when (b) (4) riboflavin will be used
4	Previous ocular condition (other than refractive error) in the eye(s) to be treated that may predispose the eye for future complications, for example: a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.) b. Clinically significant corneal scarring in the CXL treatment zone that is not related to keratoconus or, in the investigator's opinion, will interfere with the cross-linking procedure
5	A history of chemical injury or delayed epithelial healing in the eye(s) to be treated
6	Pregnancy (including plan to become pregnant) or lactation during the course of the study
7	A known sensitivity to study medications
8	Patients with nystagmus or any other condition that would prevent a steady gaze during the CXL treatment or other

	diagnostic tests
9	Patients with a current condition that, in the investigator's opinion, would interfere with or prolong epithelial healing
10	Taking Vitamin C (ascorbic acid) supplements within 1 week of the cross-linking treatment
Key Inclusion Criteria for Keratoconus Studies UVX-001 and UVX-003	
1	14 years of age or older Having a diagnosis of corneal ectasia after corneal refractive surgery (e.g., LASIK, photorefractive keratectomy [PRK], or epi-LASIK)
2	Presence of central or inferior steepening on the Pentacam map
3	Axial topography consistent with corneal ectasia
4	BSCVA worse than 20/20 (<55 letters on ETDRS chart)
5	Contact Lens Wearers Only: removal of contact lenses for the required period of time prior to the screening refraction: Contact Lens Type — Minimum Discontinuation Time Soft — 3 Days Soft Extended Wear — 1 Week Soft Toric — 2 Weeks Rigid gas permeable — 2 Weeks
Key Exclusion Criteria for Keratoconus Studies UVX-001 and UVX-003	
1	Corneal pachymetry at the screening exam that is < 400 microns at the thinnest point measured by Pentacam in the eye(s) to be treated when the Medio-Cross (b) (4) riboflavin solution alone will be used or < 300 microns when (b) (4) riboflavin will be used
2	Previous ocular condition (other than refractive error) in the eye(s) to be treated that may predispose the eye for future complications, for example: a. History of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.) b. Clinically significant corneal scarring in the CXL treatment zone that is not related to the corneal ectasia or prior refractive surgery or, in the investigator's opinion, will interfere with the cross-linking procedure
3	A history of chemical injury or delayed epithelial healing in the eye(s) to be treated
4	Pregnancy (including plan to become pregnant) or lactation during the course of the study
5	A known sensitivity to study medications
6	Patients with nystagmus or any other condition that would prevent a steady gaze during the CXL treatment or other diagnostic tests
7	Patients with a current condition that, in the investigator's opinion, would interfere with or prolong epithelial healing
8	Taking Vitamin C (ascorbic acid) supplements within 1 week of the cross-linking treatment

Source: Section 6 of the protocols amended July 6, 2010, original January 15, 2008; located at: \\CDSESUB1\evsprod\NDA203324\0007\m5.

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/s/

YAN WANG
04/08/2016

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Concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SECONDARY REVIEW

NDA/BLA #:	NDA 203324
Supplement #	0028 (Resubmission)
Drug Name:	Riboflavin ophthalmic solution/KXL® System
Proposed Indication:	(1) Treatment of progressive keratoconus
	(2) Treatment of corneal ectasia following refractive surgery
Applicant:	Avedro, Inc.
Date(s):	Stamp date: September 29 , 2014
	PDUFA date: March 29, 2015
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Team:	Statistical Reviewer: Dongliang Zhuang, Ph.D.
	Statistical Team Leader: Yan Wang, Ph.D.
	Division Director: Dionne Price, Ph.D.
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Medical Reviewer and Team Leader: William Boyd, M.D.
	Deputy Division Director: Wiley Chambers, M.D.
	Division Director: Renata Albrecht, M.D.
Project Manager:	Jacquelyn Smith

Keywords: Missing data, open-label, progressive keratoconus, corneal ectasia following refractive surgery, corneal collagen cross-linking, maximum keratometry (Kmax), 2-sample t-test, ANCOVA, nonparametric Wilcoxon test

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1 INTRODUCTION

In this NDA resubmission, the applicant sought approval of a combination product, riboflavin ophthalmic solution and KXL system, for the treatment of progressive keratoconus and the treatment of corneal ectasia following refractive surgery. The applicant did not provide new clinical data in this resubmission; they provided additional literature and sensitivity analyses to further support the efficacy analysis methods and results from the three pivotal studies (UVX-001, UVX-002, and UVX-003) included in the original NDA. Of note: the device (UV-X system) used in these pivotal studies was not the same as the KXL system proposed to be marketed by the applicant, and this issue is addressed in the CDRH reviews.

Extensive statistical reviews for both the original NDA and the current NDA resubmission were conducted by the primary statistical reviewer, Dr. Dongliang Zhuang (see DARRTS entries dated on 2 February 2014 and 12 March 2015). The primary statistical reviewer concluded that the three pivotal studies demonstrated evidence of efficacy of corneal collagen cross-linking (CXL) (using riboflavin ophthalmic solution and UV-X system for ultraviolet A irradiation) for the improvement of corneal curvature for subjects with progressive keratoconus and subjects with corneal ectasia following refractive surgery. I concur with this conclusion. In this secondary review, I will provide my perspective on the statistical issues encountered in the efficacy evaluation of the three pivotal studies and summarize the totality of efficacy results.

2 STATISTICAL ISSUES

Two major statistical issues were encountered in the efficacy evaluation. They were related to the change of the primary efficacy endpoint from Month 3 to Month 12 and the analysis method of the endpoint at Month 12.

2.1 Change of the Primary Efficacy Endpoint from Month 3 to Month 12

In the three pivotal studies, the primary efficacy outcome was the corneal curvature over time, measured by maximum keratometry (Kmax) in the study eye at baseline, Months 1, 3, 6, and 12. The baseline value was defined as the last measurement prior to Day 0 (randomization/treatment day) in the study eye. The protocol-defined primary efficacy endpoint was the change from baseline in Kmax at Month 3. However, the statistical analysis plan (SAP) changed the time point of the primary efficacy endpoint to Month 12. The applicant provided the following justification for this change in the Clinical Study Reports:

> *At the time the study was initially planned, a review of the existing literature suggested that the primary efficacy endpoint could be analyzed at 3 months post-procedure. However, subsequent additional literature suggested that later time points are better suited for evaluating the long-term clinical significance of the CXL procedure because the corneal stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize (Wittig-Silva et al,2008; Wollensak and*

Iomdina, 2009; Caporossi et al, 2010). This is consistent with the FDA's comments, whereby the Agency strongly recommended that the Sponsor evaluate later time points. Based on the findings of this additional literature, and consistent with the FDA's recommendations, the Sponsor decided to extend the time point of the primary efficacy endpoint analysis to 12 months.

In principle, I find the above justification acceptable based on the literature submitted by the applicant. However, the change of the primary endpoint in the SAP occurred more than one year after all subjects completed Study UVX-001. The SAP was prepared after the applicant had acquired the studies from the previous sponsors and after a portion of the study results from Studies UVX-002 and UVX-003 was submitted for publication. The dates of some key study events are summarized in Table 2 in the Appendix of this review. This late change of the primary endpoint raised multiplicity concerns due to the opportunity to choose the most favorable result from two or more analyses. Additionally, the studies were designed to allow subjects randomized to sham to receive CXL at Month 3 or 6, after the timing of the original primary endpoint. The majority of the sham subjects did receive CXL at Month 6 or earlier (Table 1): 86% in Study UVX-001 (keratoconus), 91% in Study UVX-002 (keratoconus), 84% in Study UVX-001 (corneal ectasia), and 92% in Study UVX-003 (corneal ectasia). By Month 12, only four sham subjects (two in UVX-002 and two in UVX-003) did not receive CXL. Therefore, close to 100% of the sham subjects had missing data for the SAP-defined endpoint at Month 12.

Table 1: Number of Sham Subjects Receiving CXL or Withdrawing from Study

Number of Sham Subjects Receiving CXL				
	Progressive Keratoconus		**Corneal Ectasia**	
Visit	**UVX-001 (N=29)**	**UVX-002 (N=74)**	**UVX-001 (N=25)**	**UVX-003 (N=63)**
Month 1		2 (3%)		
Month 3	9 (31%)	47 (64%)	11 (44%)	42 (67%)
Month 6	16 (55%)	18 (24%)	10 (40%)	16 (25%)
Total	25 (86%)	67 (91%)	21 (84%)	58 (92%)
Number of Sham Subjects Receiving CXL or Withdrawing from Study Prior to Month 12				
Total	29 (100%)	72 (97%)	25 (100%)	61 (97%)

Because of the issue of multiplicity and the lack of sham data at Month 12, our efficacy assessment should not be limited to the applicant's late-defined primary analysis at 12 months. Rather we should focus on the totality of the results and consider a broad set of analyses including the12-month analysis and also weighing heavily on the 3-month results and noting the FDA's recommendation of evaluating later time points as well. Before discussing the totality of the results, the problem with lack of sham data at Month 12 is discussed further in the next section.

2.2 Use of the Last Observation Carried Forward (LOCF) Method in the Analysis of the Efficacy Endpoint at Month 12

The applicant's efficacy analyses were conducted on all randomized and treated subjects (ITT population). Subjects were analyzed according to the randomized arm and were excluded from the analyses if they had missing baseline values. The applicant's primary efficacy analysis used a two-sample t-test to compare the two treatment groups. In this analysis, the LOCF method was used to impute missing data resulting from subject withdrawal or intermittent missed visits, as well as to impute data for sham subjects who received CXL after Day 0 (randomization/treatment day). For sham subjects who received CXL after Day 0, their last observed Kmax value prior to receiving CXL was carried forward in the analysis for later time points. The applicant's justification for the use of the LOCF method was summarized below (on page 16 of the applicant's Advisory Committee briefing document):

> *The LOCF approach is valid for imputation of study data because keratoconus and post-refractive ectasia are progressive corneal ectatic conditions. Keratoconus and corneal ectasia patients do not experience spontaneous remission or become free of disease, rather a majority continue to progress and become worse as shown in the published literature. The LOCF approach does not account for any continued progression of disease in the control group, making it more difficult to demonstrate differences in mean change from baseline Kmax with CXL. As a result, the LOCF approach provides a conservative measure of success of the cross-linking procedure.*

Based on the literature submitted by the applicant, Kmax measurements remained stable or worsened over time for a majority of untreated eyes with keratoconus or corneal ectasia. Thus, in principle, in the absence of substantial missing data, I find the use of the LOCF method within this context acceptable. However, because the variability of the Kmax data can increase overtime (Wittig-Silva 2014), we cannot assert that this LOCF approach provides a conservative measure of the treatment effect in terms of the 95% confidence interval and the p-value for testing the treatment difference. Additionally, we need to examine the pattern of the missing data in order to make a final conclusion regarding the appropriateness of any pre-specified missing data handling method and to have a sound interpretation of the analysis results.

In Studies UVX-001, UVX-002, and UVX-003, for the CXL groups, the missing data at Month 12 were mainly due to lost to follow-up or administrative decision (none were due to adverse events or lack of efficacy). In Studies UVX-002 and UVX-003, 5% (4/73) and 22% (15/67) of the subjects had missing data, respectively. In Study UVX-001, 31% (9/29) of the progressive keratoconus subjects and 17% (4/24) of the corneal ectasia subjects had missing data, respectively. As shown in Figure 1, the Kmax profiles for subjects with missing data appeared similar to those for subjects without missing data, and using the LOCF method to impute the missing data seemed reasonable and unlikely to inflate the treatment effect of CXL.

For the sham groups, the Kmax values at Month 3 or 6 prior to receiving CXL did not improve from baseline for the majority of subjects (Figure 2). Additionally, the Kmax profiles for subjects receiving CXL at Month 3 appeared similar to those for subjects receiving CXL at Month 6, thus the use of the LOCF method for the treatment group comparison at Month 6 seemed reasonable. However, as discussed in the previous section and as is also apparent from Figure 2, there was essentially no sham data at Month 12 in these three studies. As a result, close to 100% of the sham data at Month 12 were imputed in the applicant's analysis for the endpoint at Month 12. Thus, the applicant's analysis for the endpoint at Month 12 is not a direct comparison of the two treatment groups at Month 12. Instead, it compared the Kmax data at Month 12 in the CXL group to the Kmax data at Month 3 or 6 in the sham group. Although this indirect comparison is acceptable in terms of providing evidence of efficacy in these studies, it is not acceptable in terms of treating it as a direct comparison of the two treatment groups at Month 12.

In summary, though the applicant claimed that the LOCF method should lead to a conservative assessment for the 12-month endpoint, there is a concern when close to 100% of the data from one arm needs imputing and there is no viable observed data to support this claim. It was thus important to assess the robustness of the applicant's analysis results using additional methods. One such analysis, conducted by the primary statistical reviewer, allows for a conservative assessment (Table 5 in the Appendix of this review). Note that in the three studies, sham subjects who received CXL at 6 months or earlier were followed for additional 12 months. In the aforementioned reviewer's analysis, the last observed Kmax value at or prior to 12 months (after randomization) was used to calculate the change from baseline for all subjects, including the sham subjects who had received CXL at Month 6 or earlier. Thus, this analysis evaluated the CXL treatment effect regardless of adherence to the randomized arm. As 84% to 92% of the sham subjects received CXL at 6 months or earlier in the three studies (Table 1), this analysis primarily compared the effect of prompt treatment (treated at the randomization day for the subjects in the CXL group) to the effect of delayed treatment (treated at 3 or 6 months after randomization day for the subjects in the sham group). Positive results of this analysis should provide further evidence of efficacy of the CXL treatment.

Figure 1: Observed Kmax for CXL Subjects: BLACK -- with missing data at Month 12; RED -- without missing data at Month 12.

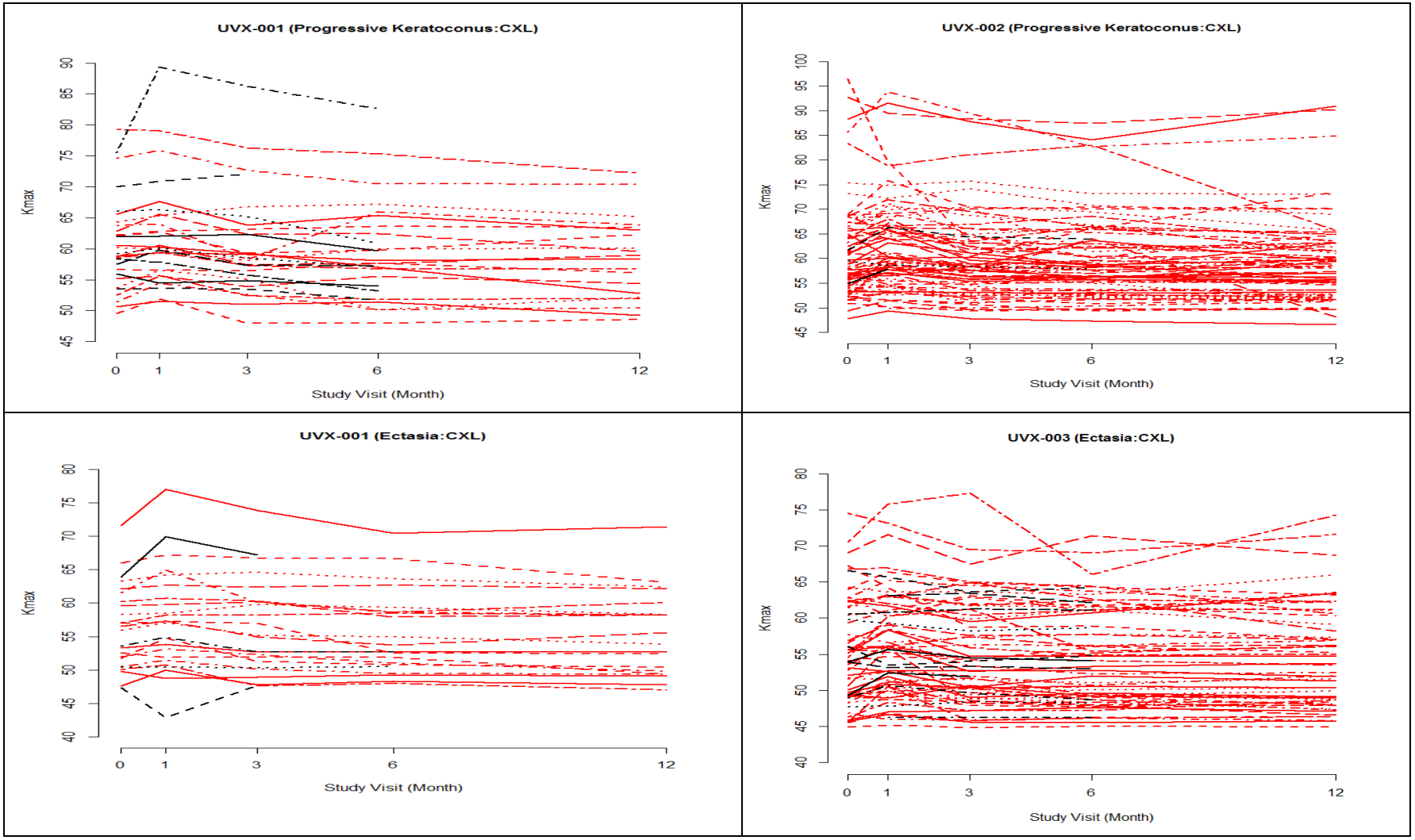
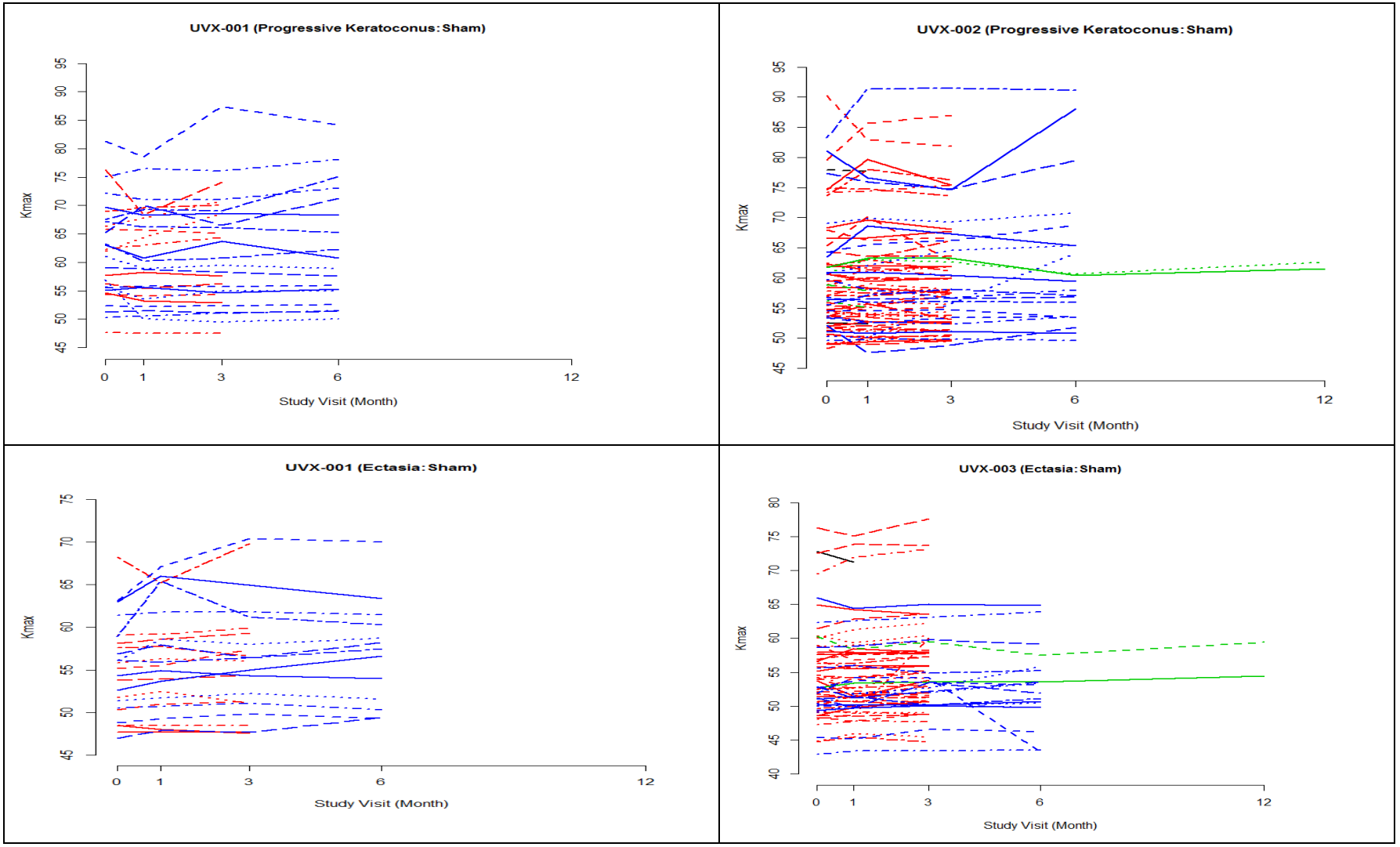


Figure 2: Observed Kmax for Sham Subjects: RED -- received CXL at Month 3; BLUE -- received CXL Month 6; GREEN – did not receive CXL by Month 12.



3 Totality of Evidence of Efficacy

As discussed in the previous sections, two major statistical issues were encountered in the efficacy evaluation of the three pivotal studies included in the original NDA. The first one relates to the change of the primary endpoints leading to a multiplicity issue due to the opportunity to choose the most favorable result from two or more analyses. The second issue pertains to the imputation of missing data and the interpretation of the analysis results for the endpoint at Month 12 due to the lack of sham data at Month 12. Despite these issues, I conclude that the three pivotal studies demonstrated evidence of efficacy of CXL treatment for the improvement of Kmax for subjects with progressive keratoconus and subjects with corneal ectasia following refractive surgery based on the following totality of the efficacy results (Tables 3-6 in the Appendix of this review).

In the corneal ectasia Study UVX-001 and Study UVX-003:

(1) A statistically significant treatment difference was observed in the applicant's analyses at Months 3, 6 and 12 (Table 4). In Study UVX-001, the treatment differences were -0.9 [95% CI: (-1.8, -0.1)], -1.7 [95% CI: (-2.6, -0.7)], and -2.0 [95% CI: (-3.0, -1.1)] diopter at Months 3, 6, and 12, respectively. In Study UVX-003, the treatment differences were -0.8 [95% CI: (-1.6, 0)], -1.0 [95% CI: (-1.8, -0.3)], and -1.1 [95% CI: (-1.9, -0.3)] diopter at Months 3, 6, and 12, respectively.

(2) A numerically favorable treatment difference was observed in the primary reviewer's sensitivity analysis (prompt vs. delayed treatments) at Month 12 (Table 5). The treatment differences were -1.8 [95% CI: (-3.4, -0.2)] diopter in Study UVX-001 and -0.4 [95% CI: (-1.3, 0.5)] diopter in Study UVX-003.

(3) Kmax improvement from baseline was observed at Months 6 and 12 in the CXL group whereas no Kmax improvement was observed at Months 3 and 6 in the sham group (Table 4). In Study UVX-001, the Kmax was reduced from baseline by 0.6 diopter at Month 6 and 1.0 diopter at Month 12 in the CXL group, whereas the Kmax was increased from baseline by 1.0 diopter at both Months 3 and 6 in the sham group. In Study UVX-003, the Kmax was reduced from baseline by 0.5 diopter in the CXL group at both Months 6 and 12, whereas the Kmax was increased from baseline by approximately 0.5 diopter at both Months 3 and 6 in the sham group.

(4) A numerically favorable treatment difference was observed in the percentage of subjects who had a reduction of at least 1.0 diopter in Kmax from baseline at Months 3, 6 and 12 (Table 6). For example, in Study UVX-001, 38% and 4% of subjects had a reduction of at least 1.0 diopter in Kmax from baseline at Month 6 in the CXL and sham groups, respectively, with a treatment difference of 34% [95% CI: (13%, 54%)]. In Study UVX-003, 27% and 13% of subjects had a reduction of at least 1.0 diopter in Kmax from baseline at Month 6 for the CXL and sham groups, respectively, with a treatment difference of 14% [95% CI: (1%, 28%)].

In the progressive keratoconus Study UVX-001 and Study UVX-002:

(1) A numerically favorable treatment difference was observed in the applicant's analyses at Months 3 and 6 (Table 3). In Study UVX-001, the treatment differences were -0.5 [95% CI: (-1.9, 0.9)] and -1.4 [95% CI: (-2.9, 0.1)] diopter at Months 3 and 6, respectively. In Study UVX-002, the treatment differences were -1.3 [95% CI: (-3.0, 0.3)] and -2.2 [95% CI: (-4.0, -0.5)] diopter at Months 3 and 6, respectively.

(2) A statistically significant treatment difference was observed in the applicant's analyses at Month 12 (Table 3). The treatment differences were -1.9 [95% CI: (-3.4, -0.3)] diopter in Study UVX-001 and -2.9 [95% CI: (-4.6, -1.2)] diopter in Study UVX-002.

(3) A numerically favorable treatment difference was observed in the primary reviewer's sensitivity analysis (prompt vs. delayed treatments) at Month 12 (Table 5). The treatment differences were -1.1 [95% CI: (-2.9, 0.8)] diopter in Study UVX-001 and -1.5 [95% CI: (-2.8, -0.3)] diopter in Study UVX-002.

(4) Kmax improvement from baseline was observed at Months 6 and 12 in the CXL group whereas no Kmax improvement was observed at Months 3 and 6 in the sham group (Table 3). In Study UVX-001, the Kmax was reduced from baseline by 0.9 diopter at Month 6 and 1.4 diopter at Month 12 in the CXL group, whereas the Kmax was increased from baseline by 0.1 diopter at Month 3 and 0.5 diopter at Month 6 in the sham group. In Study UVX-002, the Kmax was reduced from baseline by 1.1 diopter at Month 6 and 1.7 diopter at Month 12 in the CXL group, whereas the Kmax was increased from baseline by 0.7 diopter at Month 3 and 1.2 diopter at Month 6 in the sham group.

(5) A numerically favorable treatment difference was observed in the percentage of subjects who had a reduction of at least 1.0 diopter in Kmax from baseline at Months 3, 6 and 12 (Table 6). For example, in Study UVX-001, 52% and 31% of subjects had a reduction of at least 1.0 diopter in Kmax from baseline at Month 6 in the CXL and sham groups, respectively, with a treatment difference of 21% [95% CI: (-4%, 46%)]. In Study UVX-002, 44% and 19% of subjects had a reduction of at least 1.0 diopter in Kmax from baseline at Month 6 in the CXL and sham groups, respectively, with a treatment difference of 25% [95% CI: (11%, 39%)].

4 APPENDIX

Table 2: Dates of Key Events of Study Planning, Execution, Analysis, and Reporting

	UVX-001 Progressive Keratoconus, Corneal Ectasia	**UVX-002 Progressive Keratoconus**	**UVX-003 Corneal Ectasia**
Protocol	Version 1.0: Jul. 14, 2007 Version 1.2: Sep. 30, 2007 Version 1.3: Jan. 17, 2008	Version 1.0: Nov. 5, 2007 Version 1.1: Jan. 15, 2008 Version 1.2: Jul. 6, 2010	
First subject enrolled	Jan. 5, 2008	Jan. 5, 2008	Jan. 5, 2008
Last subject completed	Jul. 27, 2010	Apr. 11, 2011	Jan. 27, 2011
Sponsorship transferred to Avedro: Sept. 10, 2010 for UVX-001 and May 7, 2010 for UVX-002 and UVX-003			
Paper by Dr. Peter Hersh for Studies UVX-002 and UVX-003: Submitted: Mar. 2, 2010 Accepted: Jul. 30, 2010 Published: Jan., 2011			
SAP	Same as in UVX-002 and UVX 003	Dec. 16, 2011	Jan. 18, 2012
CSR	Jul. 11, 2013	Jan. 17, 2012	Jan. 20, 2012 Jun. 28, 2013 (Amendment 1)

Table 3: Applicant's Analysis Results: Kmax and Change in Kmax from Baseline in the Study Eye (Keratoconus Studies UVX-001 and UVX-002, ITT Population; LOCF)

		Kmax		Change from Baseline in Kmax		Difference	
Study	**Statistic**	**CXL**	**Sham**	**CXL**	**Sham**	**95% CI [1]**	**p-value[2]**
UVX-001		**N=29**	**N=29**				
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)				
	Median	59.2	62.0				
	Min, Max	49.5, 79.2	47.7, 81.3				
Month 1	Mean (SD)	62.0 (8.4)	61.2 (8.3)	1.4 (2.7)	-0.7 (2.5)	----	0.0007 *
	Median	60.1	60.2	0.9	-0.2	2.1 (0.7, 3.5)	0.0029 **
	Min, Max	51.5, 89.4	47.5, 78.6	-1.4, 13.9	-7.9, 4.8	2.1 (0.7, 3.5)	0.0031 ***
Month 3	Mean (SD)	60.3 (8.2)	62.0 (9.4)	-0.3 (2.7)	0.1 (2.6)	----	0.2048 *
	Median	58.3	60.8	-0.7	-0.1	-0.5 (-1.9, 0.9)	0.5085 **
	Min, Max	48.0, 86.2	47.5, 87.4	-5.4, 10.7	-7.4, 6.6	-0.4 (-1.7, 1.0)	0.5918 ***
Month 6	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)	----	0.0557 *
	Median	57.7	60.8	-1.1	0	-1.4 (-2.9, 0.1)	0.0674 **
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	-1.3 (-2.8, 0.2)	0.0838 ***
Month 12	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	----	0.0170 *
	Median	58.4	60.8	-1.0	0	-1.9 (-3.4, -0.3)	0.0175 **
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	-1.8 (-3.4, -0.3)	0.0217 ***
UVX-002		**N=73**	**N=74**				
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)				
	Median	58.0	57.5				
	Min, Max	47.8, 96.4	48.3, 90.3				
Month 1	Mean (SD)	62.2 (9.4)	59.3 (11.9)	1.2 (3.4)	-0.5 (7.2)	----	0.0009 *
	Median	59.4	57.3	1.0	-0.1	1.7 (-0.1, 3.5)	0.0678 **
	Min, Max	49.3, 93.8	0, 91.3	-16.8, 8.1	-58.4, 8.0	1.7 (-0.1, 3.6)	0.0622 ***
Month 3	Mean (SD)	60.4 (8.9)	60.5 (10.9)	-0.6 (4.4)	0.7 (5.6)	----	0.5076 *
	Median	58.4	57.8	0	-0.1	-1.3 (-3.0, 0.3)	0.1142 **
	Min, Max	47.8, 89.5	48.8, 108.0	-32.7, 5.5	-8.5, 43.6	-1.2 (-2.8, 0.4)	0.1426 ***
Month 6	Mean (SD)	59.9 (8.3)	61.0 (11.3)	-1.1 (5.1)	1.2 (5.7)	----	0.0059 *
	Median	57.9	58.0	-0.5	-0.1	-2.2 (-4.0, -0.5)	0.0129 **
	Min, Max	47.3, 87.5	49.4, 108.0	-36.2, 11.6	-8.5, 43.6	-2.1 (-3.8, -0.4)	0.0177 ***
Month 12	Mean (SD)	59.3 (8.5)	61.0 (11.3)	-1.7 (4.7)	1.2 (5.7)	----	<0.0001*
	Median	58.0	58.0	-1.0	-0.1	-2.9 (-4.6, -1.2)	0.0010 **
	Min, Max	46.6, 90.9	49.4, 108.0	-31.6, 7.3	-8.5, 43.6	-2.8 (-4.5, -1.1)	0.0015 ***

[1] Difference in mean change from baseline in Kmax (CXL – Sham).

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Sham by Wilcoxon test.

** P-value on difference between CXL and Sham by t-test.

*** P-value on difference between CXL and Sham l by ANCOVA with baseline as covariate.

Source: Study UVX-001 CSR Table 14.2.1.1.2, Study UVX-002 CSR Table 14.2.1.1.3, and the primary statistical review for the original NDA.

Note: The results in this table were presented in the FDA's Advisory Committee briefing document on pages 39-40. In Study UVX-001, an erroneous Kmax value at Month 1 for sham subject (b) (6) was imputed by the baseline value (Table 7). In Study UVX-002, an erroneous Kmax value at Month 1 for sham subject (b) (6) was imputed by the baseline value; a potentially erroneous Kmax value at Month 3 for sham subject (b) (6) was imputed by the value at Month 1 (Table 7).

Table 4: Applicant's Analysis Results: Kmax and Change in Kmax from Baseline in the Study Eye (Corneal Ectasia Studies UVX-001 and UVX-003, ITT Population; LOCF)

		Kmax		Change from Baseline in Kmax		Difference	
Study	**Statistic**	**CXL**	**Sham**	**CXL**	**Sham**	**95% CI [1]**	**p-value[2]**
UVX-001		**N=24**	**N=25**				
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)				
	Median	56 2	55.2				
	Min, Max	47.4, 71.6	47.0, 68.2				
Month 1	Mean (SD)	57.4 (7.6)	55.8 (6.0)	1.1 (2.1)	0.8 (1.7)	----	0.1966 *
	Median	57 2	55.5	0.9	0.5	0.3 (-0.8, 1.3)	0.6408 **
	Min, Max	42.9, 77.0	47.7, 67.1	-4.5, 6.0	-3.0, 6.5	0.1 (-0.9,1.1)	0.8622 ***
Month 3	Mean (SD)	56.4 (7.0)	56.0 (6.4)	0.1 (1.3)	1.0 (1.7)	----	0.0374 *
	Median	55.1	56.0	0.0	0.7	-0.9 (-1.8, -0.1)	0.0382 **
	Min, Max	47.6, 73.8	47.6, 70.4	-2.5, 3.3	-1.0, 7.3	-1.1 (-1.8, -0.3)	0.0068 ***
Month 6	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)	----	0.0010 *
	Median	53 2	56.6	-0.8	0.6	-1.7 (-2.6, -0.7)	0.0010 **
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	-1.7 (-2.7, -0.8)	0.0006 ***
Month 12	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	----	<0.0001 *
	Median	53 3	56.6	-0.9	0.6	-2.0 (-3.0, -1.1)	0.0001 **
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	-2.1 (-3.1, -1.2)	<.0001 ***
UVX-003		**N=67**	**N=63**				
Baseline[3]	Mean (SD)	55.1 (7.1)	54.7 (6.8)				
	Median	53.9	52.9				
	Min, Max	44.9, 74.5	42.9, 76.3				
Month 1	Mean (SD)	56.0 (7.0)	54.7 (6.7)	1.0 (1.8)	0.0 (1.1)	----	0.0019 *
	Median	55.7	53.4	0.6	0.1	1.0 (0.4, 1.5)	0.0005 **
	Min, Max	45.2, 75.8	43.4, 75.1	-3.1, 5.8	-2.2, 2.4	1.0 (0.4, 1.5)	0.0004 ***
Month 3	Mean (SD)	54.9 (7.0)	55.3 (6.8)	-0.2 (2.4)	0.6 (1.9)	----	0.0418 *
	Median	53.4	53.8	0.1	0.5	-0.8 (-1.6, 0.0)	0.0386 **
	Min, Max	44.8, 77.3	43.4, 77.6	-8.6, 6.8	-2.7, 11.9	-0.8 (-1.5, 0.0)	0.0417 ***
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)	----	0.0045 *
	Median	53.3	53.8	-0.2	0.5	-1.0 (-1.8, -0.3)	0.0084 **
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	-1.0 -1.7, -0.3)	0.0086 ***
Month 12	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	----	0.0017 *
	Median	53.5	54.1	-0.3	0.5	-1.1 (-1.9, -0.3)	0.0080 **
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3.8	-8.6, 11.9	-1.1 (-1.8, -0.3)	0.0087 ***

[1] Difference in mean change from baseline in Kmax (CXL – Sham).

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Sham by Wilcoxon test.

** P-value on difference between CXL and Sham by t-test.

*** P-value on difference between CXL and Sham by ANCOVA with baseline as covariate.

[3] Four subjects in CXL group did not have a K_{max} measurement at baseline and were excluded from the analysis.

Source: Study UVX-001 CSR Table 14.2.1.1.2, Study UVX-003 CSR Table 14.2.1.1.3, and the primary statistical review for the original NDA.

Note: The results in this table were presented in the FDA's Advisory Committee briefing document on pages 41-42.

Table 5: The Primary Statistical Reviewer's Sensitivity Analysis at Month 12: Kmax and Change in Kmax from Baseline in the Study Eye (ITT Population; LOCF)

		Kmax		Change from Baseline in Kmax		Difference	
Study	**Statistic**	**CXL**	**Sham**	**CXL**	**Sham**	**95% CI [1]**	**p-value [2]**
UVX-001 (keratoconus)		**N=29**	**N=29**				
	Mean (SD)	59.2 (7.8)	61.5 (9.7)	-1.4 (2.8)	-0.3 (4.1)	----	0.0914 *
	Median	58.4	62.5	-1.0	0.1	-1.1 (-2.9, 0.8)	0.2534 **
	Min, Max	48.6, 82.6	47.7, 89.3	-7.8, 7.1	-12.1, 8.0	-1.0 (-2.9, 0.8)	0.2734 ***
	95% CI			(-2.5, -0.3)	(-1.9, 1.2)		
		N=73	**N=74**				
UVX-002 (keratoconus)	Mean (SD)	59.3 (8.5)	59.7 (9.6)	-1.7 (4.7)	-0.1 (2.7)	----	0.0060*
	Median	58.0	57.5	-1.0	-0.2	-1.5 (-2.8, -0.3)	0.0159 **
	Min, Max	46.6, 90.9	48.6, 90.6	-31.6, 7.3	-10.4, 7.8	-1.4 (-2.6, -0.2)	0.0225 ***
	95% CI			(-2.8, -0.6)	(-0.8, 0.5)		
UVX-001 (corneal ectasia)		**N=24**	**N=25**				
	Mean (SD)	55.3 (6.6)	55.8 (6.9)	-1.0 (1.7)	0.8 (3.4)	----	0.0078 *
	Median	53.3	54.4	-0.9	0.4	-1.8 (-3.4, -0.2)	0.0243 **
	Min, Max	47.0, 71.4	47.4, 78.8	-4.6, 3.3	-2.9, 15.7	-1.9 (-3.5, -0.3)	0.0207 ***
	95% CI			(-1.7, -0.3)	(-0.6, 2.2)		
UVX-003 (corneal ectasia)		**N=67**	**N=63**				
	Mean (SD)	54.5 (6.8)	54.5 (6.4)	-0.5 (2.2)	-0.2 (2.7)	----	0.4235 *
	Median	53.5	53.6	-0.3	-0.1	-0.4 (-1.3, 0.5)	0.3791 **
	Min, Max	44.9, 74.3	43.3, 72.1	-10.2, 3.8	-8.6, 12.9	-0.3 (-1.2, 0.5)	0.4199 ***
	95% CI			(-1.1, 0.0)	(-0.8, 0.5)		

Last observation carried forward method (LOCF) was used to impute missing data at Month 12 for all subjects, including sham subjects who received CXL at Month 6 or earlier.

[1] Difference = CXL – Sham.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Sham by Wilcoxon test.

** P-value on difference between CXL and Sham by t-test.

*** P-value on difference between CXL and Sham by ANCOVA with baseline as covariate.

Source: Tables 11-12 in the primary statistical review for the original NDA. In Study UVX-003, four subjects with missing baseline Kmax values were excluded from the analysis. In Study UVX-002, sham subject (b) (6) received CXL at Month 3 and with a potentially erroneous Kmax value at this time point; this Kmax value was imputed by the value at Month 1 (Table 7).

Table 6: Proportion (%) of Subjects with a Deduction of at Least 1.0 Diopter in Kmax from Baseline in the Study Eye (ITT Population; LOCF)

Study	CXL	Sham	Difference (95% CI)	P-value (Chi-square)
UVX_001 (Keratoconus)	**N=29**	**N=29**		
Month 1	1 (3%)	11 (38%)	-35 (-53, -16)	0.0012
Month 3	13 (45%)	8 (28%)	17 (-7, 42)	0.1719
Month 6	15 (52%)	9 (31%)	21 (-4, 46)	0.1097
Month 12	15 (52%)	9 (31%)	21 (-4, 46)	0.1097
UVX_002 (Keratoconus)	**N=73**	**N=74**		
Month 1	9 (12%)	15 (20%)	-8 (-20, 4)	0.1927
Month 3	22 (30%)	15 (20%)	10 (-4, 24)	0.1681
Month 6	32 (44%)	14 (19%)	25 (11, 39)	0.0011
Month 12	37 (51%)	13 (18%)	33 (19, 48)	<.0001
UVX_001 (Corneal Ectasia)	**N=24**	**N=25**		
Month 1	2 (8%)	1 (4%)	4 (-9, 18)	0.5271
Month 3	3 (13%)	1 (4%)	9 (-7, 24)	0.2773
Month 6	9 (38%)	1 (4%)	34 (13, 54)	0.0036
Month 12	10 (42%)	1 (4%)	38 (17, 59)	0.0016
UVX_003 (Corneal Ectasia)	**N=63**	**N=63**		
Month 1	5 (8%)	13 (21%)	-13 (-25, -1)	0.0417
Month 3	17 (27%)	6 (10%)	18 (4, 31)	0.0112
Month 6	17 (27%)	8 (13%)	14 (1, 28)	0.0444
Month 12	18 (29%)	7 (11%)	18 (4, 31)	0.0140

Last observation carried forward method (LOCF) was used to impute missing data resulting from subject withdrawal or intermittent missed visit, as well as to impute data for sham subjects who received CXL during the study. For sham subjects who received CXL after randomization day, their last observed Kmax value prior to receiving CXL was carried forward in the analysis for later time points.

Source: secondary reviewer's analysis. In Study UVX-003, four subjects with missing baseline Kmax values were excluded from the analysis. In Study UVX-001, at Month 1, an erroneous Kmax value for sham subject (b) (6) was replaced by the baseline value (Table 7). In Study UVX-002, at Month 1, an erroneous Kmax value for sham subject (b) (6) was replaced by the baseline value; at Month 3, a potentially erroneous Kmax value for sham subject (b) (6) was replaced by the value at Month 1 (Table 7).

During the review for the original NDA, the statistical reviewer provided a data listing of subjects whose values of Kmax change from baseline were above 20 diopters to Dr. Wiley Chambers to examine the reliability of these data. According to Dr. Chambers, the values highlighted in red in the following table were considered non-physiological values. These non-physiological values were imputed using the values observed at the earlier visit time point (highlighted in blue) for the analyses presented in Tables 3-6 and Figures 1-2.

Table 7: Data Listing of Three Sham Subjects Who Had Non-physiological Kmax Values in the Study Eye

Progressive Keratoconus	Subject ID	Treatment	Visit	Visit Date	Raw Kmax	Imputed Kmax
UVX-001	(b) (6)	Receiving Sham	Baseline	13-Nov-08	62	
			Month 1	2-Apr-09	**-0.3**	**62**
			Month 3	5-Jun-09	68.6	
		Receiving CXL		5-Jun-09		
			Month 1	21-Jul-09	64.4	
			Month 3	28-Aug-09	70.7	
			Month 6	18-Nov-09	67.3	
UVX-002	(b) (6)	Receiving Sham	Baseline	20-Jun-08	58.4	
			Month 1	2-Sep-08	**0**	**58.4**
			Month 3	21-Nov-08	57.5	
		Receiving CXL		21-Nov-08		
			Month 1	20-Jan-09	59.9	
			Month 3	10-Mar-09	59.9	
			Month 6	24-Apr-09	59.5	
			Month 12	21-May-10	60.8	
UVX-002	(b) (6)	Receiving Sham	Baseline	28-Oct-08	64.4	
			Month 1	13-Jan-09	63.6	
			Month 3	25-Feb-09	**108**	**63.6**
		Receiving CXL		25-Feb-09		
			Month 1	20-May-09	**61.7**	
			Month 3	8-Jul-09	**60.9**	
			Month 6		**.**	
			Month 12	4-Aug-10	**59.1**	

Reference

Wittig-Silva C, et al. A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus, Three-Year Results. Ophthalmology 2014; 121 (4):812-821.

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/s/

YAN WANG
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203324
Supplement #:	0028 (Resubmission)
Drug Name:	Riboflavin ophthalmic solution/KXL® System
Indication(s):	(b) (4)
Applicant:	Avedro, Inc.
Date(s):	Received: September 29, 2014 PDUFA due date: March 29, 2015
Review Priority:	Priority
Biometrics Division:	Division IV
Statistical Reviewer:	Dongliang Zhuang, PhD
Concurring Reviewers:	Yan Wang, PhD
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Medical Reviewer: William Boyd, MD Deputy Division Director: Wiley Chambers, MD Division Director: Renata Albrecht, MD
Project Manager:	Jacquelyn Smith

Keywords: Missing data, open-label, keratoconus, corneal ectasia following refractive surgery, corneal collagen cross-linking, nonparametric Wilcoxon test

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1 SUBMISSION BACKGROUND

The applicant, Avedro, first submitted NDA 203324 (SN 0007) on 16 September 2013 to provide evidence for the safety and efficacy of corneal collagen cross-linking (CXL) using riboflavin ophthalmic solution and the KXL System (b) (4) The submission included three randomized, parallel-group, open-label, sham-controlled, 12-month studies. Clinically meaningful and statistically significant efficacy results for CXL treatment were observed in two corneal ectasia studies (Study UVX-001 and Study UVX-003). However, several deficiencies were noted for the keratoconus studies (Study UVX-001 and Study UVX-002). As a result, a Complete Response (CR) letter was issued on 14 March 2014. Deficiencies outlined in the CR letter included the following two items:

- The clinical studies did not meet the protocol-specified primary endpoints at 3 months.
- The analysis of data at month 12 was not a direct comparison between the CXL arm and the control arm at month 12.

In order to resolve the above deficiencies, the Agency advised the applicant to submit clinical data from adequate and well-controlled studies evaluating CXL for the treatment of keratoconus. The study results should meet their protocol-specified primary endpoint.

A Type A meeting was held on 6 August 2014 to discuss the deficiencies listed in the CR letter. In the meeting briefing package, the applicant provided responses to the issues identified in the CR letter and sought the Agency's agreement. The Agency responded with preliminary comments. The Agency found the applicant's responses acceptable and further stated that the next step in the process was to resubmit NDA 203324 and the resubmission would need to address all the issues in the CR letter and in the Agency's preliminary comments.

The applicant resubmitted NDA 203324 for review on 29 September 2014. There were no new clinical data in the resubmission. In the original NDA submission, the applicant provided a number of publications to provide information on the natural history of keratoconus as well as to support the efficacy analyses and results. In addition to several publications elucidating the background information for keratoconus further, the resubmission included an article by Wittig-Silva, et al published in 2014. In the article, the authors evaluated the long-term effects of CXL treatment as well as progression of the disease as measured by Kmax over a 3-year follow-up period in a controlled trial. The applicant also submitted additional sensitivity analyses to support the efficacy results presented in the original NDA.

An extensive statistical review was conducted for the original submission. This review of the resubmission will focus on the information that was submitted to address the deficiencies in the original submission.

A joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Ophthalmic Device Panel was held on 24 February 2015. Various topics were discussed, including concerns regarding the use of the last observation carried forward (LOCF)

methodology in the applicant's primary efficacy analysis and the change of the time at which the primary outcome was assessed.

2 STATISTICAL EVALUATION

In the study protocols of the original NDA submission, the primary efficacy endpoint was defined as the change from baseline in the maximum corneal curvature, as measured by the maximum keratometry (Kmax, in the unit of diopter [D]), at Month 3. The applicant extended the time-point for the primary efficacy analysis from Month 3 to Month 12 after the studies had been completed. A statistically significant difference in the mean change in Kmax from baseline between the CXL group and the control group was demonstrated at both Month 3 and Month 12 in UVX-001 and UVX-003, respectively, for corneal ectasia subjects (Table 1). Although the applicant's primary efficacy analysis at Month 12 resulted in statistically significant and clinically meaningful improvements in Kmax for keratoconus subjects, the efficacy of CXL treatment observed in keratoconus subjects was neither clinically meaningful nor statistically significant at Month 3 (Table 2). Furthermore, since most subjects in the control arm received CXL treatment at Month 3 or later, the analysis at Month 12 was complicated by the lack of sham data. In the applicant's analysis, the data at Month 3 or Month 6 was used to impute Month 12 data for control subjects receiving CXL treatment. This was analogous to last observation carried forward approach in the analysis.

Table 1: Analysis of the Mean Change from Baseline in Kmax for Corneal Ectasia Subjects (Studies UVX-001 and UVX-003, ITT, LOCF)

	UVX-001		UVX-002	
Visit/Category	CXL (N=24)	Sham (N=25)	CXL (N=67)	Sham (N=63)
Baseline (BL)	56.3 (6.3)	55.0 (5.5)	55.1 (7.1)	54.7 (6.8)
Month 3				
Change from BL	0.1 (1.3)	1.0 (1.7)	-0.2 (2.4)	0.6 (1.9)
Diff. (95% CI) [1]	-0.9 (-1.8, -0.1)		-0.8 (-1.6, -0.0)	
P-value [2]	0.0382		0.0386	
Month 12				
Change from BL	-1.0 (1.7)	1.0 (1.7)	-0.5 (2.2)	0.5 (2.3)
Diff. (95% CI) [1]	-2.0 (-3.0, -1.1)		-1.1 (-1.9, -0.3)	
P-value [2]	0.0001		0.0080	

[1] Difference = CXL – Sham.
[2] P-value on difference between CXL and Sham by t-test.

Table 2: Analysis of the Mean Change from Baseline in Kmax for Progressive Keratoconus Subjects (Studies UVX-001 and UVX-002, ITT, LOCF)

	UVX-001		UVX-002	
Visit/Category	CXL (N=29)	Sham (N=29)	CXL (N=73)	Sham (N=74)
Baseline (BL)	60.6 (7.3)	61.9 (8.3)	61.0 (9.8)	59.8 (9.2)
Month 3				
Change from BL	-0.3 (2.7)	0.1 (2.6)	-0.6 (4.4)	0.7 (5.6)
Diff. (95% CI) [1]	-0.5 (-1.9, 0.9)		-1.3 (-3.0, 0.3)	
P-value [2]	0.5085		0.1142	
Month 12				
Change from BL	-1.4 (2.8)	0.5 (3.0)	-1.7 (4.7)	1.2 (5.7)
Diff. (95% CI) [1]	-1.9 (-3.4, -0.3)		-2.9 (-4.6, -1.2)	
P-value [2]	0.0175		0.0010	

[1] Difference = CXL – Sham.
[2] P-value on difference between CXL and Sham by t-test.

From a statistical perspective, the following two key issues need to be addressed in this resubmission for the primary efficacy evaluation:

- Adequate time-point for efficacy evaluation (i.e., 3 months vs. 12 months),
- Justification of the use of the efficacy data at Month 3 or Month 6 for the analysis at Month 12.

2.1 Adequate Time-point for Efficacy Evaluation

In the discussion of primary efficacy analysis, the applicant acknowledged that a 3 month timeframe for analysis of cross-linking for keratoconus was too short to evaluate the benefit of this procedure. Instead, the appropriate time frame for the efficacy analysis was at least 6 months.

According to the applicant, the change in the time-point of the primary efficacy analysis from 3 months to 12 months occurred after obtaining the UVX cross-linking studies from the original sponsor, Peschke Meditrade. This change was implemented prior to database lock and the finalization of the Statistical Analysis Plan. The decision was based on the advancements in the science of cross-linking and an understanding that corneal stromal remodeling associated with the healing response following CXL procedure required 6-12 months to stabilize. The effect of CXL treatment in flattening and regularizing the keratoconic shape of the cornea was not evident until 6 months after the procedure. The applicant also noted that many studies in the literature used 12 months or a longer timeframe for the efficacy evaluation.

Therefore, the applicant concluded that the change in timing of analysis to 12 months for the UVX studies was consistent with scientific data and standards for cross-linking studies in keratoconus.

2.2 Use of Kmax Data at Earlier Time-points for Month 12 Analysis

The study design allowed sham subjects to receive CXL treatment at Month 3 or later. For sham subjects who received CXL treatment, their Kmax values after receiving CXL treatment were treated as missing and were imputed using the Kmax values at an earlier visit prior to CXL treatment. The applicant contended that this approach was valid for imputation because of the progressive nature of keratoconus. Moreover, the applicant stated that there were no data to demonstrate that keratoconus subjects experienced spontaneous remission, became free of disease or improved. As a result, the applicant concluded that the LOCF approach provided a conservative measure of success of the cross-linking procedure. The applicant provided publications to support the notion that keratoconus is either stable or progressive. In the following, the reviewer provides a brief summary of the findings from some of those publications.

The natural history of keratoconus was evaluated in Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study (Wagner 2007). The study was designed to prospectively characterize changes in vision, corneal curvature, corneal status (including corneal scarring), and quality of life in patients with keratoconus and to identify the factors associated with these changes over time. The study enrolled 1209 eligible patients at 16 participating clinics across the United States between31 May 1995 and 29 June 1996. At the time of enrollment, patients were (1) aged 12 years or older; (2) exhibited an irregular cornea, as determined by distortion of keratometric mires and/or scissoring of the retinoscopic reflex; and (3) demonstrated at least one biomicroscopic sign, including Vogt's striae, Fleicher's ring of 2 mm or more of arc, or corneal scarring typical of keratoconus. Patients were examined annually for 8 years.

Corneal curvature (including flat keratometric reading and steep keratometric reading) was measured with manual keratometry. In addition, the study used the first definite apical clearance lens (FDACL) as a supplementary measure of corneal curvature. FDACL was developed specifically for the CLEK Study; it was an alternative procedure to quantify the severity and progression of corneal steepening in keratoconus. A series of rigid contact lenses was applied to the keratoconic corneas to determine FDACL, the flattest lens that showed an apical clearance fluorescein pattern after equilibration. The FDACL procedure was designed to assess disease progression in keratoconus in a way that would also provide information on contact lens fitting in keratoconus, beyond that obtainable from keratometry or videokeratography (Edrington 1998).

CLEK Study patients were approximately 40 years old at baseline, 69% were White, and 57% were male. The mean (SD) flat keratometric reading for 1204 patients at baseline was 47.96 ± 5.50 D, and the mean steep keratometric reading for 1204 patients was 50.89 ± 5.79 D. The mean FDACL at baseline (n = 1182 patients) was 50.94 ± 5.69 D.

There were 1062 patients with at least one study-eligible eye and at least one slope generated from longitudinal data for FDACL or the flat keratometric reading. There were 1940 eyes from 1020 patients for FDACL and 1988 eyes from 1028 patients for flat keratometry. CLEK patients exhibited a gradual increase in corneal curvature during follow-up. The slope of the change in the FDACL (0.18 ± 0.60 D/year) and in the flat keratometric reading (0.20 D ± 0.80 D/year) over 8 years translated into expected 8-year increases of 1.44 D in the FDACL and 1.60 D in the flat keratometric reading. Therefore, this long term observational study of keratoconus patients demonstrated a gradual increase in corneal curvature, supporting the notion that keratoconus is a progressive disease.

The findings from the CLEK Study were further supported by the results from other clinical studies. Wittig-Silva et al. reported three-year results of a prospective, unmasked, randomized controlled trial of corneal collagen cross-linking in progressive keratoconus (Wittig-Silva 2014). Keratoconus was considered to be progressive if there was a subjective deterioration in vision and at least one of the following criteria were met over the preceding 12 months: an increase of at least 1 diopter (D) in the steepest simulated keratometry value derived from computerized videokeratography or in the steepest meridian measured by manual keratometry, an increase of at least 1.0 D in astigmatism as determined by manifest subjective refraction, or a 0.1 mm or more decrease in the back optic zone radius of the best-fitting contact lens.

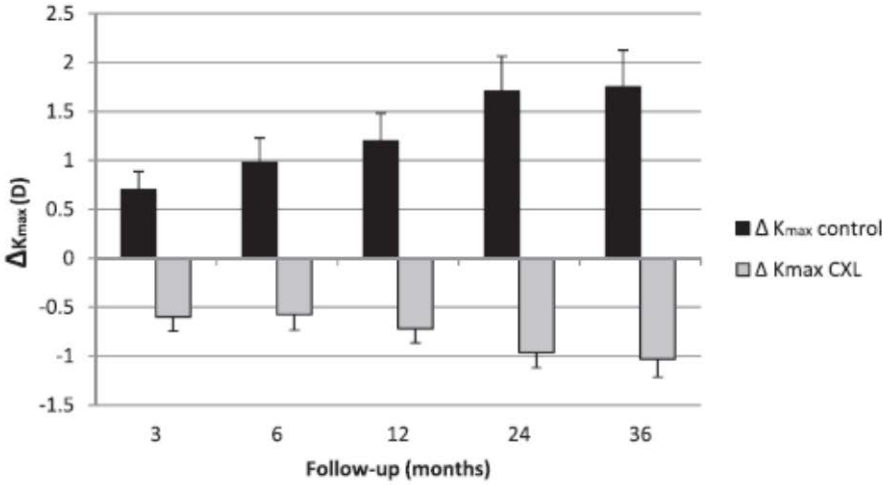
A total of 100 eyes with progressive keratoconus were randomized into the CXL treatment or control groups. Each eye was randomized independently if both eyes of a patient qualified for participation in the study.

A total of 50 eyes were randomized to the control group. At baseline, the mean age was 25.8 ± 6.4 years for the control group. The follow-up visits occurred at Month 3, 6, 12, 24, and 36. The number of the control eyes at these visits was 48, 46, 41, 31, and 27, respectively. The study allowed patients in the control group to receive compassionate CXL treatment after a minimum of 6 months of follow-up, provided that continuous significant disease progression was

documented. Data collection was terminated for compassionately treated eyes at the time of the CXL procedure, and the LOCF approach was used to complete the follow-up data.

The relatively large number of patients who stayed in the control group allowed a meaningful assessment of the disease progression. The mean change from baseline in the maximum simulated keratometry Kmax is shown in Figure 1. In control eyes (n=48), a steepening in the corneal curvature progressed over time. Kmax increased by a mean (± SE) of 1.20 ± 0.28 D, 1.70 ± 0.36 D, and 1.75 ± 0.38 D at 12, 24, and 36 months, respectively, from the baseline Kmax (± SD) of 51.18 ± 4.03 D. Most of the change in corneal curvature occurred during the first 24 months, whereas changes were less marked during the third year.

Figure 1: Mean change (± SE) from baseline in maximum simulated keratometry value (Kmax) in diopters (D)



Changes in minimum simulated keratometry mirrored the changes in Kmax, with a steepening in control eyes by a mean (± SE) of 0.66 ± 0.22 D, 1.31 ± 0.32 D, and1.35 ± 0.34 D at 12, 24, and 36 months, respectively, from the baseline Kmin (± SD) of 46.62 ±3.27 D.

Despite the difference in the patient population (keratoconus in the CLEK Study vs. progressive keratoconus in Wittig-Silva 2014), these two long-term studies demonstrated that keratoconus patients experienced worsening of the condition (Kmax and Kmin increased) over time. Similar findings were observed in other reported clinical studies (Jordan 2012, Caporossi 2010, and Vinciguerra 2009).

Keratoconus patients were also observed to continue to maintain active disease status over time. O'Brart 2011 reported the study results from a randomized, bilateral, observer-masked, prospective study, in which twenty-four subjects with early to moderate bilateral keratoconus with reported progression were recruited. One eye of each was randomly assigned to undergo cross-linkage, with the other eye remaining untreated as a control over the 18-month follow-up period. Preoperatively, the mean simulated keratometry in untreated eyes was 47.14 D, and at 18 months, it was unchanged at 47.26 D.

In summary, these studies support the notion that, if left untreated, keratoconus is either stable or progressive. As a result, Kmax remains the same or increases over time for untreated eyes. This observation supports the use of the Kmax data at earlier time-points for the treatment comparison at a later time-point. The applicant asserted that their analysis at Month 12 using LOCF approach was conservative in estimating the treatment effect. However, it is worth noting that the statistical testing for the treatment difference also depends on the variability of the treatment effect. Thus, the applicant's analysis may not always produce conservative results.

3 SUMMARY AND CONCLUSIONS

There were two statistical issues associated with the applicant's primary efficacy analysis, which was based on the treatment comparison at Month 12.

The first issue is the change of the time-point for the primary efficacy analysis from Month 3 to Month 12 after the studies had been completed. The practice of changing the time-point of the primary efficacy analysis after the study completion can compromise the credibility of the study conduct and the study results. From a statistical perspective, a multiplicity issue could arise as a result of the change of the primary efficacy endpoint from Month 3 and Month 12 after the study completion. This statistical review would not be able to address this issue.

In addressing the first issue, the applicant acknowledged that the choice to evaluate the effectiveness at the 3 month time-period was not appropriate. Existing literature suggests that corneal healing after epithelial debridement is continuing at 3 months. The change from Month 3 to Month 12 for the primary efficacy endpoint seems justified from a clinical point of view.

The second issue concerns the lack of data in the control group at Month 12 in applicant's analysis. The study design allowed the subjects in the control group to cross over to receive the CXL treatment in the study eyes after Month 3. As a result, no subjects or only very few subjects in the respective control groups remained in the assigned treatment and had efficacy data at Month 12. Therefore, the studies did not have adequate data to allow a direct treatment comparison at Month 12. In the applicant's analyses, the comparison between the CXL group and the control group after Month 3 was based on the imputed data using LOCF approach.

The validity of the applicant's analysis at Month 12 depends on the assumptions that keratoconus and post-refractive corneal ectasia are progressive diseases and consequently, the patients' corneal curvature will worsen over time. The applicant submitted literature including an observational study to evaluate the natural history of keratoconus and clinical studies that showed the progression of the disease as measured by Kmax over a long follow-up period in a controlled setting. Our review of the literature, including those provided by the applicant, concludes that Kmax increases over time or remains stable for untreated eyes and therefore, the sham subjects' data at an earlier time-point prior to receiving CXL could be used for the treatment comparison at a later time-point.

Although the study design did not allow a direct treatment comparison at Month 12, the analysis that uses the Kmax prior to receiving CXL treatment for sham subjects seems reasonable to establish the treatment effect at Month 12. Therefore, when it is viewed aside from potential multiplicity issue, the applicant's analysis demonstrated statistically significant and clinically meaningful efficacy of CXL in the treatment of keratoconus and post-refractive corneal ectasia.

The activity of CXL treatment in keratoconus and post-refractive corneal ectasia subjects was further supported by an alternative analysis that we conducted according to the intent-to-treat principle in the review of the first submission. Sham subjects' efficacy data after receiving CXL treatment were included in the analysis. In contrast, the applicant's analysis had excluded these data. Therefore, our analysis compared the efficacy in subjects who were treated with CXL at the randomization day to the efficacy in subjects whose CXL treatment was delayed by three months or six months depending on the visit at which the subject received CXL treatment. A statistically significant and clinically meaningful improvement in Kmax was demonstrated in UVX-002 for keratoconus subjects and in UVX-001 for corneal ectasin subjects. When compared to the applicant's analysis results, our analysis showed that subjects in the sham group experienced an improvement in the corneal curvature at Month 12, reflecting the delayed effect of CXL treatment.

In my view, the two statistical issues in the CR letter have been adequately addressed in this resubmission. Based on the applicant's analysis at Month 12, sufficient evidence of a CXL treatment effect for the improvement of Kmax has been demonstrated for both indications.

The following is the applicant's proposal for the CLINICAL STUDIES section and my recommendations for this section are marked by track changes.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONGLIANG ZHUANG
03/12/2015

YAN WANG
03/12/2015
Concur with overall conclusions and see my secondary review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203324
Drug Name:	Riboflavin ophthalmic solution/KXL® System
Indication(s):	(b) (4)
Applicant:	Avedro, Inc.
Date(s):	Received: September 16, 2013 PDUFA due date: March 16, 2014
Review Priority:	Priority
Biometrics Division:	Division IV
Statistical Reviewer:	Dongliang Zhuang, PhD
Concurring Reviewers:	Yan Wang, PhD
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	William Boyd, MD
Project Manager:	Jacquelyn Smith

Keywords: Missing data, open-label, keratoconus, corneal ectasia following refractive surgery, corneal collagen cross-linking, nonparametric Wilcoxon test

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1 EXECUTIVE SUMMARY

This statistical review evaluates the clinical studies submitted by Avedro, Inc., in support of their new drug application for corneal collagen cross-linking using riboflavin ophthalmic solution and Avedro's KXL® System (b) (4) Keratoconus is a naturally occurring ocular condition, whereas corneal ectasia is a complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK). Both conditions are characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity. Corneal collagen cross-linking is a procedure that uses UVA light and a photosensitizer (riboflavin) to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma. Avedro's KXL® System delivers a dose of UVA light to irradiate a targeted treatment area of cornea to induce cross-linking.

The efficacy and safety of riboflavin ophthalmic solution/UVA irradiation for the treatment of keratoconus and corneal ectasia following refractive surgery were evaluated in three clinical trials, UVX-001, UVX-002, and UVX-003. UVX-001 had a mixed population of subjects with either keratoconus or corneal ectasia, UVX-002 enrolled only keratoconus subjects, and UVX-003 enrolled only corneal ectasia subjects. All 3 studies were designed as randomized, parallel-group, open-label, sham-controlled, 12-month trials. After randomization on Day 0 to receive single CXL treatment (riboflavin/UVA irradiation) or single sham treatment in the study eye, subjects attended visits at Day 1, Week 1, and 1, 3, 6, and 12 months post-treatment. At Month 3 or later, subjects had the option to have CXL performed on their untreated eyes, including fellow eyes in both groups and the study eyes in control group.

The primary efficacy evaluation was based on the change from baseline in the maximum corneal curvature as measured by the maximum keratometry (K_{max}, in the unit of diopter [D]). When the statistical evaluation of the efficacy was based on data at Month 3 as originally planned in the protocols, a statistically significant difference in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was observed in UVX-001 and UVX-003, respectively, for corneal ectasia subjects. The difference observed in both studies (0.9 D and 0.8 D for UVX-001 and UVX-003, respectively) was close to 1.0 D, a threshold considered to be a clinical success. However, the efficacy of CXL treatment observed in keratoconus subjects was neither clinically meaningful nor statistically significant. A difference of 0.5 D and 1.3 D in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was reported in UVX-001 and UVX-002, respectively. The difference observed in UVX-001 was less than 1.0 D, the threshold for clinical success. The difference observed in UVX-002 was greater than 1.0 D, but the difference is not statistically significant. The observed difference of 1.3 D was likely driven by one large decrease in K_{max} experienced by one subject in the CXL group and one large increase in K_{max} experienced by one subject in the control group. These two groups were not differentiable in terms of the median (0 vs -0.1 D).

The Applicant extended the time-point of the primary efficacy analysis from Month 3 to Month 12 after the studies were completed. Their analysis indicated that CXL treatment resulted in statistically significant and clinically meaningful improvements in K_{max} for both indications in

all three studies. This was concluded from an analysis that included a significant amount of imputed data at Month 12 for the control group. The study design allowed the subjects in the control group to cross over to receive the CXL treatment in the study eyes after Month 3. As a result, no subjects or only two subjects in the control groups for the respective studies remained in the assigned treatment (i.e., control) and had efficacy data at Month 12. Therefore, a direct comparison of treatment effect at Month 12 cannot be made. In the Applicant's primary efficacy analysis, the efficacy data at Month 3 or Month 6 prior to cross-over was carried forward to Month 12; the treatment comparison at Month 12 was essentially a comparison of CXL at Month 12 with the control at Month 3 and Month 6. The estimate of the treatment effect could be unreliable if the efficacy data at Month 3 and Month 6 is not representative of the efficacy data at Month 12.

In addition to concerns regarding the lack of data in the control group at Month 12, the last observation carried forward (LOCF) imputation strategy has the limitation of using only one observed value and ignoring other available values, and consequently it does not take into account the uncertainty of the missing values. To further evaluate the study results based on the LOCF approach, a multiple imputation was carried out to handle missing data for the K_{max} parameter at post-baseline visits. The multiple imputation procedure used a regression model including K_{max} observed at previous visits. Due to the lack of data at Month 12, the multiple imputation procedure was not implemented at Month 12. At Month 6, the treatment effect estimated using LOCF was not consistent with the treatment effect estimated using multiple imputation in UVX-003. In the other two studies, LOCF and multiple imputation yielded similar estimates of the treatment effects.

This review also included an alternative analysis according to the intent-to-treat principle. For subjects in the control group, their efficacy data after cross-over from control to CXL treatment was included in the analysis. This analysis compares the efficacy in subjects who had been treated with CXL for 12 months to the efficacy in subjects whose CXL treatment was delayed by three months or six months depending on when the cross-over occurred for subjects in the control group. Statistically significant and clinically meaningful improvements in K_{max} were demonstrated in UVX-002 for keratoconus subjects and in UVX-001 for corneal ectasia subjects.

Despite the inconsistent results from different analyses, the utility of CXL in treating keratoconus and corneal ectasia was observed in the CXL group. The subjects in this treatment group remained in their assigned treatment and the majority of them had K_{max} measurement through Month 12. The improvement in K_{max} continued or was maintained over time.

In summary, the use of different time-points and methods for the primary efficacy analysis led to varying conclusions. The efficacy of CXL treatment observed in corneal ectasia subjects was statistically significant and clinically meaningful at Month 3 according to the analysis specified in the protocol, but this was not the case for keratoconus subjects. A duration of three months might have been too short for a demonstration of a clinically meaningful treatment effect. Although statistically significant and clinically meaningful improvement in K_{max} was demonstrated in the Applicant's analysis, their analysis relied heavily on imputed data based on the LOCF approach. The Applicant's results were not all confirmed by alternative analyses.

Although CXL does appear to have activity in keratoconus subjects, the study design makes a conclusive recommendation based on the statistical evaluation difficult.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

This submission provided clinical data to support corneal collagen cross-linking using riboflavin ophthalmic solution and Avedro's KXL System (b) (4)

Keratoconus is a naturally occurring ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in increasing myopia, irregular astigmatism, and eventual loss of visual acuity. Corneal ectasia is a complication of refractive surgery, primarily laser in-situ keratomileusis (LASIK) and, more rarely, photorefractive keratectomy. The cornea is weakened by refractive surgery so that it protrudes under the force of intraocular pressure and bows outward. This creates progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity. Currently, there is no FDA-approved medical therapy available in the United States (US) for the treatment of keratoconus or corneal ectasia following refractive surgery.

Corneal collagen crosslinking (CXL) is a procedure to biomechanically stabilize the weak cornea in keratoconus and postoperative corneal ectasia and decrease the clinical progression of these diseases. CXL is performed by removing a small section of the corneal epithelium and pretreating the cornea with riboflavin ophthalmic solution beginning 30 minutes before ultraviolet A (UVA) light exposure to saturate the corneal tissue with the riboflavin. Riboflavin, administered 1 drop every 2 minutes for 30 minutes before commencing UVA irradiation, acts as a photosensitizer for the production of reactive oxygen species (singlet oxygen). The cornea is then irradiated with UVA light (365 nm) at an irradiance of 3 mW/cm^2 for 30 minutes to induce crosslinking.

The Applicant's riboflavin ophthalmic solution/ KXL® System is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered as a photosensitizer in conjunction with UVA. The KXL® System is a portable electronic medical device and acts as a UVA irradiation system. The device's light emitting diode (LED) is used to deliver a metered dose of UVA light to a targeted treatment area for illuminating the cornea during CXL.

2.1.2 History of Drug Development

This 16 September 2013 submission was a resubmission of NDA 203324. The NDA was initially submitted on 08 March 2012 following a Pre-NDA meeting on 21 September 2011. The Agency issued a refusal to file letter on 04 May 2012. The decision was based primarily on the chemical incomparability between the proposed commercial product and the material used in the clinical trials, deficiencies in the clinical study reports, and the lack of English translation of

certain references. A meeting was held on 31 May 2012 to discuss the Agency's comments in the refusal to file letter.

The proposed indications received orphan designation, and the submission was granted priority review status.

One of the three studies to support the submission, Study UVX-001, was conducted under US Investigational New Drug (IND) application 78933 submitted by R. Doyle Stulting, MD, PhD (Atlanta, GA). The other two studies were conducted in the U.S. under IND 77882, which was originally submitted by Peschke Meditrade GmbH (Hüenenberg, Switzerland) on 7 November 2007. Sponsorship of IND 77882 was transferred to Avedro on 7 May 2010.

2.1.3 Study Reviewed

This review includes three clinical trials, UVX-001, UVX-002, and UVX-003, which were conducted in U.S. to evaluate the efficacy and safety of riboflavin ophthalmic solution/UVA irradiation for the treatment of keratoconus and corneal ectasia following refractive surgery. All 3 studies were generally identical in design and conduct. They were randomized, parallel-group, open-label, sham-controlled, 12-month trials. UVX-001 had a mixed population of subjects with either keratoconus or corneal ectasia, UVX-002 enrolled only keratoconus subjects, and UVX-003 enrolled only corneal ectasia subjects.

Eligible subjects were those who were 14 years of age or older and had a diagnosis of corneal ectasia after refractive corneal surgery (UVX-001 and UVX-003) or progressive keratoconus (UVX-001 andUVX-002). In each study, eligible subjects were randomized in a 1:1 ratio into 1 of 2 treatment groups: the CXL group or the sham (control) group. Randomization for subjects with keratoconus was stratified by the severity of keratoconus in the study eye (mild or moderate/severe). One eye was designated as the study eye.

The planned sample size was 160 subjects (80 eyes per treatment group) for UVX-002 and UVX-003. The actual enrollment in these two studies was 147 and 130, respectively. The planned sample size was 320 subjects (160 per indication, with 80 eyes per treatment group) for UVX-001. However, enrollment into UVX-001 was terminated early because the investigator left the study site. At the time of the enrollment termination, the study enrolled a total of 107 subjects, including 58 keratoconus subjects and 49 corneal ectasia subjects.

A summary of these three studies is provided in Table 1.

Table 1: Summary of Clinical Studies Included in this Review

Study Identifier	Phase and Design	Treatment	Number of Subjects
UVX-001	A Phase 3, single-center, prospective, randomized, parallel group, open-label, sham controlled 12-month trial in subjects with keratoconus or corneal ectasia.	Single CXL treatment (riboflavin/UVA irradiation) or single sham exposure in the study eye; optional CXL in the sham eye (sham subjects only) or in the nonstudy fellow eye (both groups).	Keratoconus subjects: CXL: N=29 Sham: N=29 Corneal ectasia subjects: CXL: N=24 Sham: N=25
UVX-002	A Phase 3, multi-center, prospective, randomized, parallel group, open-label, sham controlled 12-month trial in subjects with keratoconus.	Single CXL treatment (riboflavin/UVA irradiation) or single sham exposure in the study eye; optional CXL in the sham eye (sham subjects only) or in the nonstudy fellow eye (both groups).	CXL: N=73 Sham: N=74
UVX-003	A Phase 3, multi-center, prospective, randomized, parallel group, open-label, sham controlled 12-month trial in subjects with corneal ectasia.	Single CXL treatment (riboflavin/UVA irradiation) or single sham exposure in the study eye; optional CXL in the sham eye (sham subjects only) or in the nonstudy fellow eye (both groups).	CXL: N=67 Sham: N=63

2.2 Data Sources

The initial NDA submission included only the raw data for the three studies. The raw data were provided in the study subfolders within the following folder. *\\CDSESUB1\evsprod\NDA203324\0000\m5\datasets*.

In the resubmission of the NDA, analysis datasets (adeff and adribo) in ADaM format were included. They can be found at *\\CDSESUB1\evsprod\NDA203324\0007\m5\datasets\ise\analysis\adam\datasets*.

The updated clinical study reports were included in this resubmission and located at: \\CDSESUB1\evsprod\NDA203324\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud

Analysis programs were included in the following folders: *\\CDSESUB1\evsprod\NDA203324\0007\m5\datasets\uvx-002\analysis\programs* and

\\CDSESUB1\evsprod\NDA203324\0007\m5\datasets\uvx-003\analysis\programs.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The initial NDA submission included only the raw data. These datasets did not conform to any data standards. Substantial efforts were involved in understanding and processing the data.

Upon the Agency's request, the Applicant submitted two analysis datasets (adeff and adribo) in ADaM format for the primary efficacy variable (K_{max}) and riboflavin administration. Data for other variables remained in the same format and was not resubmitted.

The statistical analysis plan (SAP) was not finalized until the study completion. In the SAP, the primary efficacy endpoint was redefined. The protocol defined Month 3 as the time-point for the primary efficacy analysis of improvement in K_{max}. The SAP extended the time-point for the primary efficacy analysis to Month 12. The Applicant claimed that the change was made prior to any formal efficacy analyses.

Overall, the data included in the submission is of low quality, and the statistical analysis did not follow the pre-specified procedure in the study protocols.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The three studies (UVX-001, UVX-002, and UVX-003) included in this NDA submission were randomized, parallel-group, open-label, sham-controlled, 12-month trials. UVX-001 had a mixed population of subjects with either keratoconus or corneal ectasia, UVX-002 enrolled keratoconus subjects, and UVX-003 enrolled corneal ectasia subjects.

Subjects were evaluated at 8 study visits: screening/baseline, Day 0 (randomization/treatment day), Day 1, Week 1, and 1, 3, 6, and 12 months after treatment. On Day 0, subjects in the CXL group had topical anesthetic administered to the study eye and the corneal epithelium was removed. Subjects then received riboflavin ophthalmic solution with dextran in the study eye for 30 minutes (1 drop instilled onto the cornea every 2 minutes). Slit lamp examination was used to confirm complete riboflavin saturation into the cornea. If corneal thickness was < 400 microns in eyes in the CXL group after treatment with riboflavin ophthalmic solution with dextran, a second riboflavin solution without dextran was instilled into the study eye (2 drops instilled every 5 to 10 seconds for 2 minute sessions) until corneal thickness increased to at least 400 microns, as measured with ultrasound pachymetry. After the riboflavin pretreatment regimen was completed, study eyes in the CXL group were exposed to UVA light (365 nm) at an irradiance of 3 mW/cm^2 for 30 minutes, and during this time, riboflavin ophthalmic solution with dextran continued to be administered every 2 minutes.

Subjects in the sham treatment group had topical anesthetic administered to the study eye, but did not have the corneal epithelium removed. Study eyes were treated with riboflavin ophthalmic solution as described above (both pretreatment and during the irradiation procedure). Subjects underwent the same UV irradiation procedure as described for subjects in the CXL treatment group except that the UVA light source was not illuminated during the procedure.

At Month 3 or later, subjects whose eye(s) had not developed any contraindications for performing the CXL treatment were given the option to have CXL performed on their untreated eyes, including fellow eyes in both groups and the study eyes in control group. After treatment, these eyes were followed for 12 months according to the same schedule and protocol as the study eye in the CXL group.

The primary efficacy evaluation was based on the corneal curvature, as measured by the maximum keratometry (K_{max}). K_{max} is a measure of the maximum corneal curvature.

Keratoconus and post-refractive corneal ectasia are characterized by steepening and irregularity of the cornea. Steepness of the cornea can be quantitatively measured using corneal topography instrumentation. Maximum corneal curvature, as measured by K_{max}, quantifies the most pathognomonic feature of keratoconus and corneal ectasia. Therefore, this endpoint was clinically meaningful and an appropriate endpoint to demonstrate efficacy.

K_{max} was evaluated at baseline and at Months 1, 3, 6, and 12. The Applicant defined the study success as having a difference of ≥1 D in the mean change in K_{max} from baseline to Month 12 between the CXL group and the control group. The primary efficacy endpoint was originally planned as the difference between the CXL group and the control group in K_{max} from baseline to Month 3 based on a review of the existing literature at the time of the study initiation. The Applicant claimed that their subsequent additional literature review suggested that the corneal epithelial and stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize. Therefore, the Applicant decided that later time points were better suited for evaluating the long-term clinical benefits of the CXL procedure, and the time-point of the primary efficacy endpoint was extended to 12 months. According to the submission, this change of the primary efficacy endpoint occurred after all subjects completed the study but prior to any formal efficacy analyses.

The Applicant stated this change of the primary efficacy endpoint from Month 3 to Month 12 was consistent with the FDA's recommendation. However, this reviewer did not find formal documentation for such a recommendation. To the contrary, the Agency had considered the primary efficacy endpoint at Month 3 acceptable.

- Protocol UVX-001 was included in the Pre-IND meeting package submitted to IND 78933 on August 16, 2007. In its response to the Agency's comments based on Dr. Rhea Lloyd's clinical review, the Applicant stated that "*The primary efficacy variable is the change in corneal curvature from baseline to Month 3, as measured by maximum keratometry (K_{max}). The objective of the study has been revised to clarify this. The study design and Statistical Analysis have also been revised to clarify that the change in*

corneal curvature (as measured by maximum keratometry) is the primary outcome variable." The protocol UVX-001 was subsequently amended to revise the primary efficacy endpoint and the Agency found the revision acceptable.

- The protocols UVX-002 and UVX-003 were submitted to IND 77882 on November 6, 2007. These two studies had similar design as the study UVX-001. In her review of the protocols UVX-002 and UVX-003, Dr. Lloyd commented that the efficacy endpoint is acceptable. In these two protocols, it was stated that "*The primary efficacy parameter that will be evaluated over time is corneal curvature, as measured by maximum keratometry (K_{max}) in the randomized eyes. Study success is defined as a difference of at least 1 diopter in the mean change in K_{max} from baseline to 3 months between the corneal collagen cross-linking (CCCL) treatment group and control group.*"

This review will include the evaluation of the primary efficacy endpoint at Month 3, in addition to Month 12 considered by the Applicant.

The other efficacy endpoints include the mean changes from baseline in best spectacle-corrected visual acuity (BSCVA) and uncorrected visual acuity（UCVA).

No interim analysis was planned for this study. However, an unplanned analysis of the data (as of March 27, 2009) was conducted by the original Sponsor. The Applicant claimed that this analysis did not have any impact on the conduct of the study or analysis. To account for the unplanned analysis, the statistical inference was performed at an overall alpha-level of 0.049 after allocating 0.001 to the analysis.

3.2.2 Statistical Methodologies

According to the Applicant's SAP, the change in K_{max} from baseline would be evaluated for all eyes randomized to the treatment and control groups. Data would be summarized using descriptive statistics, and the differences in mean changes between the CXL treatment group and the control group at each time point would be evaluated using a two sample t-test. While p-values would be reported for each visit, only p-values at Month 3 and Month 12 would be used for statistical inference. An alpha level of 0.001 was allocated to Month 3 when an unplanned data review was conducted, and an alpha level of 0.049 was allocated to the final analysis at Month 12.

In the study reports, additional analyses were conducted to test robustness of the results of primary efficacy analyses. These analyses include the nonparametric Wilcoxon test and the analysis of covariance (ANCOVA) with baseline K_{max} value as the covariate.

Missing data was imputed using the last observation carried forward (LOCF) approach. For the subjects in the control group, the efficacy data at Month 3 or Month 6 prior to cross-over was carried forward to Month 12.

All efficacy analyses were completed using the intent-to-treat (ITT) population according to the randomized treatment. The ITT population consisted of all treated subjects.

The SAP defined the per protocol (PP) set to include all ITT subjects who had no major protocol deviations as assessed at the end of study. All efficacy analyses of the K_{max} endpoint were to be conducted on the PP population. However, no analyses were performed. The Applicant stated that there was little information that a per-protocol analysis would provide.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Subject disposition for keratoconus subjects is presented in Table 2 and subject disposition for corneal ectasia subjects is presented in Table 3.

In Study UVX-001, the majority of the discontinuation from the study was due to the study termination by the Applicant after the investigator left the site (the reason was noted as 'Administrative' for keratoconus subjects and 'Other' for corneal ectasia subjects). At the time of the study termination, there were more subjects remaining in the study in the control group than in the CXL group.

Reasons for discontinuation in the other two studies (UVX-002 and UVX-003) were voluntary withdrawal (unrelated to safety), lost to follow-up and other. No subjects were reported to discontinue from the study due to AEs.

Table 2: Subject Disposition (ITT Population): UVX-001 (Keratoconus Subjects), UVX-002, and Pooled Studies

	UVX-001		UVX-002		Pooled Studies	
Category, n(%)	**CXL (N=29)**	**Sham (N=29)**	**CXL (N=73)**	**Sham (N=74)**	**CXL (N=102)**	**Sham (N=103)**
Randomized	29	29	73	74	102	103
Completed the study	20 (69.0%)	12 (41.4%)	65 (89.0%)	62 (83.8%)	85 (83.3%)	74 (71.8%)
Discont. from study	9 (31.0%)	17 (58.6%)	8 (11.0%)	12 (16.2%)	17 (16.7%)	29 (28.2%)
Administrative	9 (31.0%)	17 (58.6%)	0	0	9 (8.8%)	17 (16.5%)
Voluntary withdrawal	0	0	3 (4.1%)	8 (10.8%)	3 (2.9%)	8 (7.8%)
Lost to follow-up	0	0	5 (6.8%)	4 (5.4%)	5 (4.9%)	4 (3.9%)

Source: UVX-001 CSR Table 7 and UVX-002 CSR Table 6.

Table 3: Subject Disposition (ITT Population): UVX-001 (Corneal Ectasia Subjects), UVX-003, and Pooled Studies

	UVX-001		UVX-003		Pooled Studies	
Category, n(%)	CXL (N=24)	Sham (N=25)	CXL (N=67)	Sham (N=63)	CXL (N=91)	Sham (N=88)
Randomized	24	25	67	63	91	88
Completed the study	20 (83.3%)	11 (44.0%)	56 (83.6%)	48 (76.2%)	76 (83.5%)	59 (67.0%)
Discont. from study	4 (16.7%)	14 (56.0%)	11 (16.4%)	15 (23.8%)	15 (16.5%)	29 (33.0%)
Administrative	0	1 (4.0%)	0	0	0	1 (1.1%)
Voluntary withdrawal	0	0	0	5 (7.9%)	0	5 (5.7%)
Lost to follow-up	1 (4.2%)	3 (12.0%)	6 (9.0%)	3 (4.8%)	7 (7.7%)	6 (6.8%)
Other	3 (12.5%)	10 (40.0%)	5 (7.5%)	7 (11.1%)	8 (8.8%)	17 (19.3%)

Source: UVX-001 CSR Table 8 and UVX-003 CSR Table 6.

The demographics, baseline characteristics, ocular risk factors and contact lens wear are presented for keratoconus subjects in Tables A.1 and A.2 and for corneal ectasia subjects in Tables A.3 and A.4, respectively. These tables are included in the Appendices.

For keratoconus subjects, demographic characteristics were generally comparable between the CXL and control groups in UVX-001 and UVX-002. Subjects were, on average, over 30 years of age. The majority of subjects were Caucasian. More than 60% of subjects in each study were male. The proportion of Hispanic/Latino subjects was approximately 10% in UVX-001. Ethnicity was not reported for nearly half of subjects in UVX-002.

The most frequent ocular risk factors for keratoconus at baseline were eye rubbing and ocular history. The types of contact lenses worn most frequently by keratoconus subjects were rigid gas permeable and soft.

For corneal ectasia subjects, demographic characteristics were generally comparable between the CXL and control groups in UVX-001 and UVX-003. Subjects were, on average, over 43 years of age. More than two-thirds of subjects in each study were Caucasian. The majority of subjects were male. The proportion of Hispanic/Latino subjects was less than 10% in UVX-001. Ethnicity was not reported for more than half of subjects in UVX-003.

The most frequent ocular risk factors for corneal ectasia at baseline were ocular history and eye rubbing. The types of contact lenses worn most frequently by subjects were rigid gas permeable and soft.

3.2.4 Results and Conclusions

3.2.4.1 Change from Baseline in K_{max}

After the study completion, the Applicant redefined the primary efficacy endpoint as the difference in the mean change in K_{max} from baseline to Month 12 between the CXL group and the control group. However, because the study design allowed the subjects in the control group

to cross over to receive the CXL treatment after Month 3, no subjects or only 2 subjects in the control groups remained in the assigned treatment and had efficacy data at Month 12 (Table 4 and Table 5).

Tabulations of subjects remaining on study, subjects remaining on randomized treatment, timing of CXL crossover for subjects in the control group, and subjects with K_{max} measurements were presented in the study reports. They are included in the Appendices.

Table 4: Number of Subjects Remaining on Randomized Treatment and with K_{max} Measurements by Visit: UVX-001 (Keratoconus Subjects) and UVX-002

	UVX-001		UVX-002	
Visit	CXL (N=29)	Sham (N=29)	CXL (N=73)	Sham (N=74)
Baseline	29	29	73	74
Month 1	29	28	70	73
Month 3	29	29	67	67
Month 6	28	18	67	21
Month 12	20	0	69	2

Source: Reviewer's analysis.

Table 5: Number of Subjects Remaining on Randomized Treatment and with K_{max} Measurements by Visit: UVX-001 (Corneal Ectasia Subjects) and UVX-003

	UVX-001		UVX-003	
Visit	CXL (N=24)	Sham (N=25)	CXL (N=67)	Sham (N=63)
Baseline	24	25	63	63
Month 1	24	25	64	61
Month 3	23	24	65	61
Month 6	22	13	62	19
Month 12	20	0	52	2

Source: Reviewer's analysis.

According to input from the Clinical Reviewers, the efficacy evaluation at Month 3 is considered clinically acceptable. Therefore, this review will include the treatment comparison at Month 3 when the majority of the subjects remained in their assigned treatment and had efficacy data. For completeness, the Applicant's analysis results at Month 6 and Month 12 are included in Table 6 to Table 9 along with Month 3 results. The reviewer confirmed the Applicant's analysis results.

The efficacy of CXL treatment observed in keratoconus subjects at Month 3 was neither clinically meaningful nor statistically significant. A difference of 0.5 D and 1.3 D in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was observed in UVX-001 and UVX-002, respectively (Table 6 for UVX-001 and Table 7 for UVX-002). The difference observed in UVX-001 was less than 1.0 D and therefore, it was not considered clinically meaningful. The difference observed in UVX-002 crossed the threshold of 1.0 D for the clinical success, but the difference was not statistically significant (p-value > 0.1).

The observed difference of 1.3 D was likely driven by one large decrease in K_{max} (-32.7 D) experienced by one subject in CXL group and one large increase in K_{max} (43.6 D) experienced by one subject in control group. These two groups were not differentiable in terms of the median (0 vs -0.1 D), which was further supported by the nonparametric Wilcoxon test.

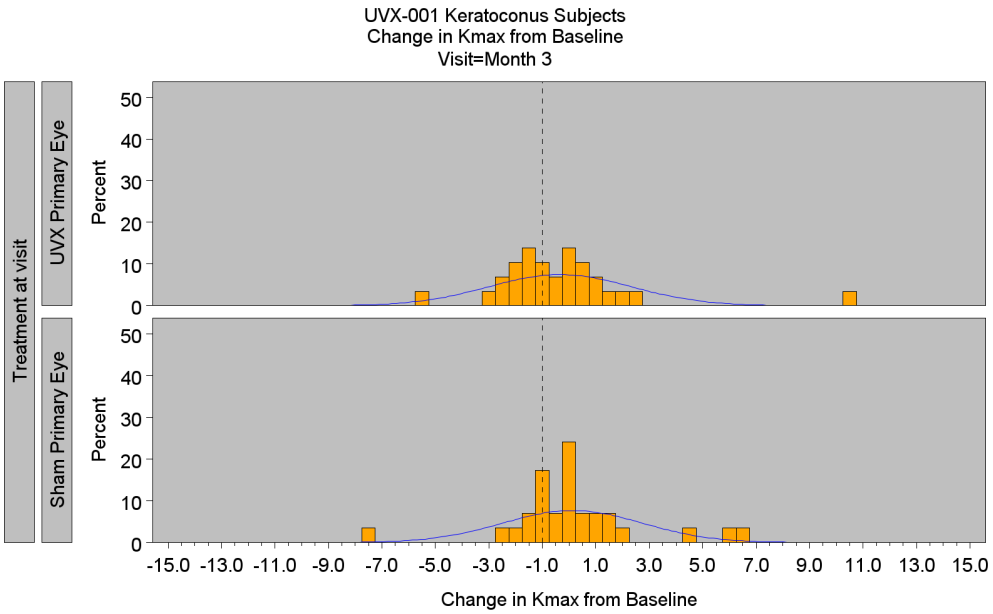
The estimated treatment difference and the associated p-value based on a t-test were consistent with that based on ANCOVA analysis with baseline as covariate, despite of the difference of approximate 1.0 D in baseline K_{max} in both studies.

At Month 1, subjects treated with CXL experienced a worsening in K_{max} as indicated by an increase of 1.4 D and 1.2 D from the baseline in UVX-001 and UVX-002, respectively. On the contrary, subjects in the control group appeared to experience an improvement in K_{max}. Their K_{max} decreased from baseline by 2.9 D and 0.5 D in UVX-001 and UVX-002, respectively. However, upon further examination of the data, these changes in K_{max} might be caused by errors in K_{max}. In UVX-001, a decrease of 62.3 D was reported for subject (b) (6), whose K_{max} reading at Month 1 is -0.3 (baseline 62.0 D). Because K_{max} reading is non-negative, the K_{max} reading for this subject could be erroneous. Subject (b) (6) in UVX-002 had a reduction of 58.4 D in K_{max} at Month 1 from baseline. The subject's K_{max} at baseline, Month 1, and Month 3 was 58.4, 0, and 57.5, respectively. The K_{max} of 0 at Month 1 is questionable. These potentially erroneous values for K_{max} raise concern about the quality of the data.

Subjects in CXL group remained in their assigned treatment group, and the majority of them had K_{max} measurement through Month 12. The improvement in K_{max} continued over time and reached 1.4 D and 1.7 D at Month 12 in UVX-001 and UVX-002, respectively. Therefore, the studies showed the potential benefit of CXL in keratoconus subjects.

Table 6: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline CXL (N=29)	Change from Baseline Control (N=29)	Difference[1]	p-value [2]
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)				
	Median	59.2	62.0				
	Min, Max	49.5, 79.2	47.7, 81.3				
Month 1	Mean (SD)	62.0 (8.4)	58.9 (14.1)	1.4 (2.7)	-2.9 (11.7)	----	0.0002 *
	Median	60.1	58.9	0.9	-0.3	4.3 (-0.1,8.8)	0.0563 **
	Min, Max	51.5, 89.4	-0.3, 78.6	-1.4, 13.9	-62.3, 4.8	4.3 (-0.2,8.9)	0.0587 ***
Month 3	**Mean (SD)**	**60.3 (8.2)**	**62.0 (9.4)**	**-0.3 (2.7)**	**0.1 (2.6)**	**----**	**0.2048 ***
	Median	**58.3**	**60.8**	**-0.7**	**-0.1**	**-0.5 (-1.9,0.9)**	**0.5085 ****
	Min, Max	**48.0, 86.2**	**47.5, 87.4**	**-5.4, 10.7**	**-7.4, 6.6**	**-0.4 (-1.7,1.0)**	**0.5918 *****
Month 6	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)	----	0.0557 *
	Median	57.7	60.8	-1.1	0	-1.4 (-2.9,0.1)	0.0674 **
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	-1.3 (-2.8,0.2)	0.0838 ***
Month 12	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	----	0.0170 *
	Median	58.4	60.8	-1.0	0	-1.9 (-3.4,-0.3)	0.0175 **
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	-1.8 (-3.4,-0.3)	0.0217 ***



[1] Difference = CXL – Control.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Control by Wilcoxon test.

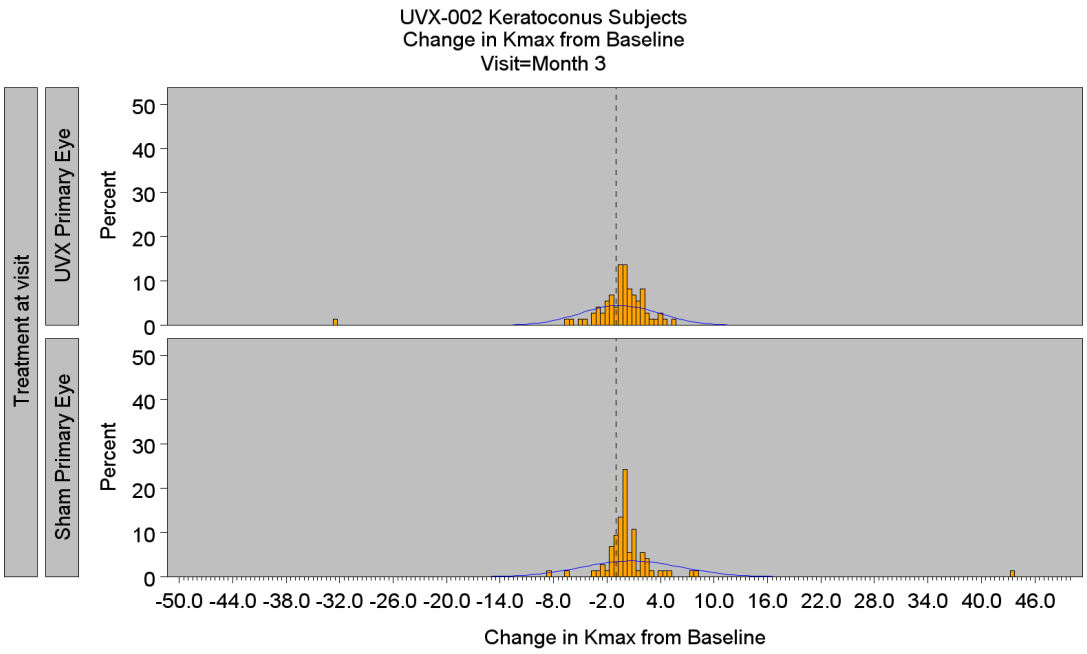
** P-value on difference between CXL and Control by t-test.

*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 7: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-002, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline CXL (N=73)	Change from Baseline Control (N=74)	Difference[1]	p-value [2]
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)				
	Median	58.0	57.5				
	Min, Max	47.8, 96.4	48.3, 90.3				
Month 1	Mean (SD)	62.2 (9.4)	59.3 (11.9)	1.2 (3.4)	-0.5 (7.2)	----	0.0009 *
	Median	59.4	57.3	1.0	-0.1	1.7 (-0.1,3.5)	0.0678 **
	Min, Max	49.3, 93.8	0, 91.3	-16.8, 8.1	-58.4, 8.0	1.7 (-0.1,3.6)	0.0622 ***
Month 3	**Mean (SD)**	**60.4 (8.9)**	**60.5 (10.9)**	**-0.6 (4.4)**	**0.7 (5.6)**	**----**	**0.5076 ***
	Median	**58.4**	**57.8**	**0**	**-0.1**	**-1.3 (-3.0,0.3)**	**0.1142 ****
	Min, Max	**47.8, 89.5**	**48.8, 108.0**	**-32.7, 5.5**	**-8.5, 43.6**	**-1.2 (-2.8,0.4)**	**0.1426 *****
Month 6	Mean (SD)	59.9 (8.3)	61.0 (11.3)	-1.1 (5.1)	1.2 (5.7)	----	0.0059 *
	Median	57.9	58.0	-0.5	-0.1	-2.2 (-4.0,-0.5)	0.0129 **
	Min, Max	47.3, 87.5	49.4, 108.0	-36.2, 11.6	-8.5, 43.6	-2.1 (-3.8,-0.4)	0.0177 ***
Month 12	Mean (SD)	59.3 (8.5)	61.0 (11.3)	-1.7 (4.7)	1.2 (5.7)	----	<0.0001*
	Median	58.0	58.0	-1.0	-0.1	-2.9 (-4.6,-1.2)	0.0010 **
	Min, Max	46.6, 90.9	49.4, 108.0	-31.6, 7.3	-8.5, 43.6	-2.8 (-4.5,-1.1)	0.0015 ***



[1] Difference = CXL – Control.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Control by Wilcoxon test.

** P-value on difference between CXL and Control by t-test.

*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-002 CSR Table 14.2.1.1.3 and Reviewer's analysis.

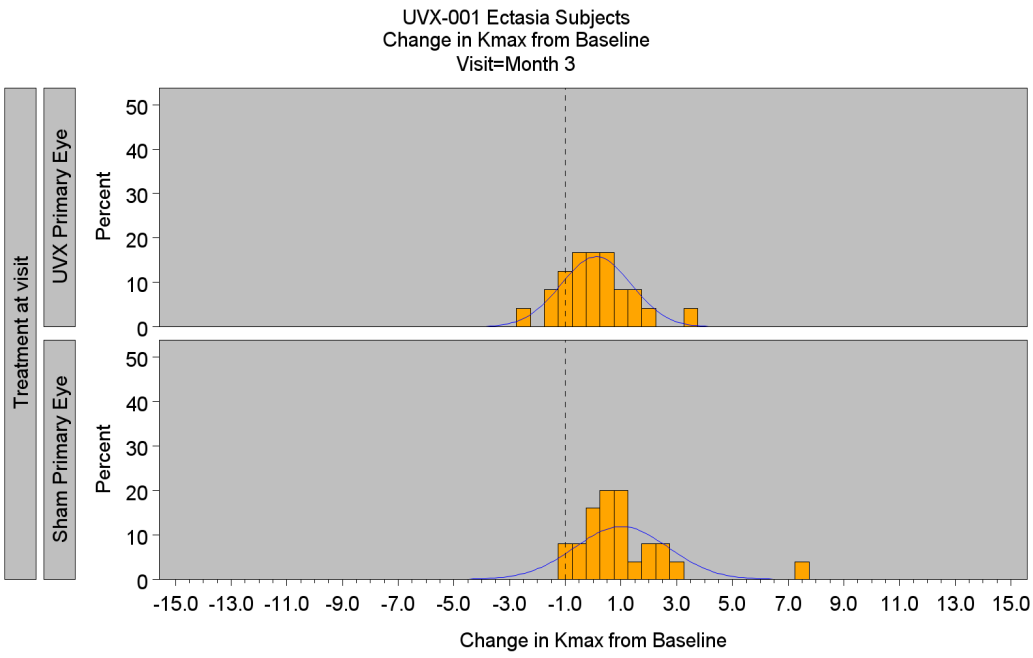
For corneal ectasia subjects, a difference of 0.9 D and 0.8 D in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was observed in UVX-001 and UVX-003, respectively (Table 8 for UVX-001 and Table 9 for UVX-003). The difference observed in both studies is less than 1.0 D, a threshold considered for clinical success. But both studies achieved statistical significance (p-value < 0.05). The estimated treatment difference and/or the associated p-value based on a t-test were further supported by the nonparametric Wilcoxon test and ANCOVA analysis with baseline as covariate.

At Month 1, subjects treated with CXL experienced a worsening in K_{max} as indicated by an increase of approximate 1.0 D from the baseline in both studies. The worsening in K_{max} in subjects in the control group appeared to be less than that in CXL group.

Subjects in CXL group remained in their assigned treatment group and the majority of them had K_{max} measurement through Month 12. The improvement in K_{max} continued or was maintained over time. At Month 12, the improvement in K_{max} was 1.0 D and 0.5 D in UVX-001 and UVX-003, respectively.

Table 8: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline: CXL (N=24)	Change from Baseline: Control (N=25)	Difference 95% CI [1]	p-value [2]
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)				
	Median	56.2	55.2				
	Min, Max	47.4, 71.6	47.0, 68.2				
Month 1	Mean (SD)	57.4 (7.6)	55.8 (6.0)	1.1 (2.1)	0.8 (1.7)	----	0.1966 *
	Median	57.2	55.5	0.9	0.5	0.3 (-0.8,1.3)	0.6408 **
	Min, Max	42.9, 77.0	47.7, 67.1	-4.5, 6.0	-3.0, 6.5	0.1 (-0.9,1.1)	0.8622 ***
Month 3	**Mean (SD)**	**56.4 (7.0)**	**56.0 (6.4)**	**0.1 (1.3)**	**1.0 (1.7)**	**----**	**0.0374 ***
	Median	**55.1**	**56.0**	**0.0**	**0.7**	**-0.9 (-1.8,-0.1)**	**0.0382 ****
	Min, Max	**47.6, 73.8**	**47.6, 70.4**	**-2.5, 3.3**	**-1.0, 7.3**	**-1.1 (-1.8,-0.3)**	**0.0068 *****
Month 6	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)	----	0.0010 *
	Median	53.2	56.6	-0.8	0.6	-1.7 (-2.6,-0.7)	0.0010 **
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	-1.7 (-2.7,-0.8)	0.0006 ***
Month 12	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	----	<0.0001 *
	Median	53.3	56.6	-0.9	0.6	-2.0 (-3.0,-1.1)	0.0001 **
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	-2.1 (-3.1,-1.2)	<.0001 ***



[1] Difference = CXL – Control.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Control by Wilcoxon test.

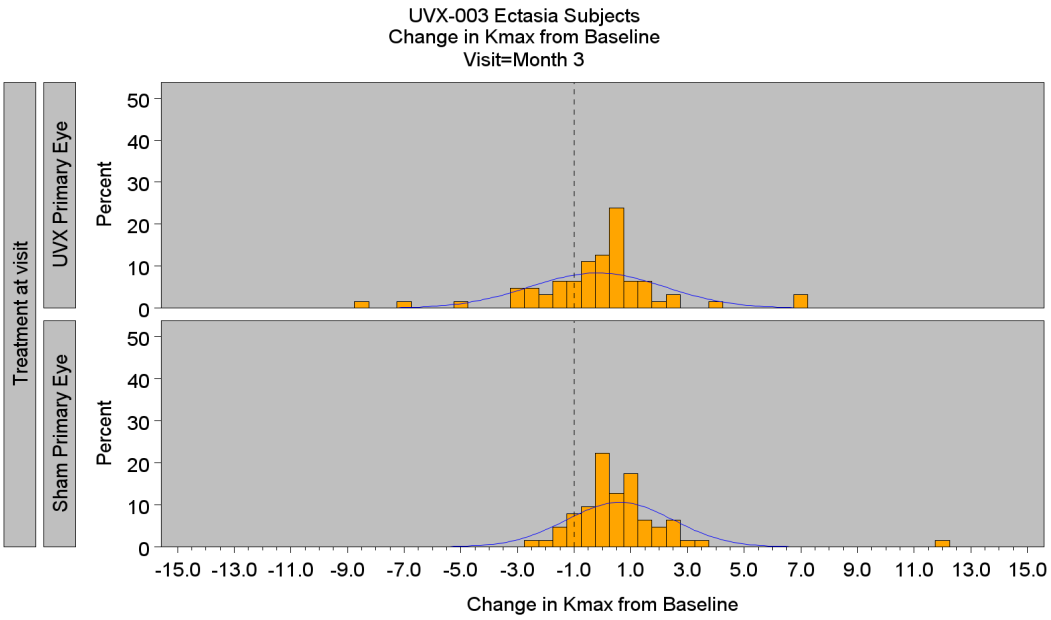
** P-value on difference between CXL and Control by t-test.

*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Source: UVX-001 CSR Table 14.2.1.1.2 and Reviewer's analysis.

Table 9: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-003, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline CXL (N=67)	Change from Baseline Control (N=63)	Difference[1]	p-value [2]
Baseline [3]	Mean (SD)	55.1 (7.1)	54.7 (6.8)				
	Median	53.9	52.9				
	Min, Max	44.9, 74.5	42.9, 76.3				
Month 1	Mean (SD)	56.0 (7.0)	54.7 (6.7)	1.0 (1.8)	0.0 (1.1)	----	0.0019 *
	Median	55.7	53.4	0.6	0.1	1.0 (0.4,1.5)	0.0005 **
	Min, Max	45.2, 75.8	43.4, 75.1	-3.1, 5.8	-2.2, 2.4	1.0 (0.4,1.5)	0.0004 ***
Month 3	**Mean (SD)**	**54.9 (7.0)**	**55.3 (6.8)**	**-0.2 (2.4)**	**0.6 (1.9)**	**----**	**0.0418 ***
	Median	**53.4**	**53.8**	**0.1**	**0.5**	**-0.8 (-1.6,-0.0)**	**0.0386 ****
	Min, Max	**44.8, 77.3**	**43.4, 77.6**	**-8.6, 6.8**	**-2.7, 11.9**	**-0.8 (-1.5,-0.0)**	**0.0417 *****
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)	----	0.0045 *
	Median	53.3	53.8	-0.2	0.5	-1.0 (-1.8,-0.3)	0.0084 **
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	-1.0 -1.7,-0.3)	0.0086 ***
Month 12	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	----	0.0017 *
	Median	53.5	54.1	-0.3	0.5	-1.1 (-1.9,-0.3)	0.0080 **
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3.8	-8.6, 11.9	-1.1 (-1.8,-0.3)	0.0087 ***



[1] Difference = CXL – Control.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Control by Wilcoxon test.

** P-value on difference between CXL and Control by t-test.

*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

[3] Four subjects in CXL group did not have a K_{max} measurement at baseline.

Source: UVX-003 CSR Table 14.2.1.1.3 and Reviewer's analysis.

In this submission, the Applicant's primary efficacy analysis was based on the treatment comparison at Month 12. They concluded that a clinically meaningful and statistically significant difference in the mean change in K_{max} from baseline to Month 12 was observed between the CXL group and the control group. In their analysis, the comparison between the CXL group and the control group after Month 3 was based on imputed data using the last observation carried forward (LOCF) approach. The efficacy data at Month 3 or Month 6 prior to cross-over was carried forward to Month 12. To justify the use of the LOCF approach for imputing missing data, the Applicant claimed that keratoconus and corneal ectasia were either stable or progressive in nature, and therefore K_{max} was expected to either increase (worsen) or remain the same over time if the disease was not treated; data imputed using the LOCF approach would be expected to underestimate the progression of disease in the control group, making it more difficult to demonstrate a statistically significant difference between treatment groups.

The studies had the opportunity to generate data to show the progression of disease in the setting of the studies and provide support to the Applicant's argument for LOCF approach. Although the majority of the study eyes in the control group crossed over to receive CXL treatment, more than half of the fellow eyes remained untreated. If data had been collected for these untreated fellow eyes, these data could potentially demonstrate the progression of the disease in untreated condition. Unfortunately, the Applicant reported that data was only collected for a few subjects.

When K_{max} at Month 3 or Month 6 prior to cross-over was carried forward to Month 12, the Applicant's primary efficacy analysis at Month 12 was essentially a comparison of CXL at Month 12 with the control at Month 3 and Month 6. If K_{max} at Month 3 and Month 6 is not representative of K_{max} at Month 12, the estimated treatment effect is not reliable. To further evaluate the study results based on LOCF approach, a multiple imputation was carried out to handle missing data for the K_{max} parameter at each post-baseline visit. The multiple imputation used a regression model including K_{max} observed at previous visits. Instead of using a single observation as in the LOCF approach, the multiple imputation procedure utilized all available data for a subject. Due to the lack of data at Month 12, the multiple imputation was not implemented at Month 12. Table 10 makes a comparison between the LOCF approach and the multiple imputation approach with respect to the change of K_{max} from baseline to Month 6. Month 6 is a time-point at which the observed treatment effect could be indicative of the treatment effect at Month 12. The treatment effect estimated using LOCF was not consistent with the treatment effect estimated using multiple imputation in UVX-003. In the other two studies, LOCF and multiple imputation yielded similar estimates of the treatment effects. In this analysis, potentially erroneous K_{max} values were set to missing for Subject (b) (6) at Month 1, Subject (b) (6) at Month 1, and Subject (b) (6) at Month 3.

Table 10: Change in K_{max} from baseline at Month 6: Comparing LOCF and Multiple Imputation

				Change from Baseline			
Approach	Statistic	CXL Group	Control Group	CXL Group	Control Group	Difference[1]	p-value [2]
			UVX-001 Keratoconus Subjects				
LOCF	Mean (SD)	59.7 (8.1)	62.3 (9.5)	-0.9 (2.6)	0.5 (3.0)		
	Median	57.7	60.8	-1.1	0		
	Min, Max	48.0, 82.6	47.5, 84.1	-5.2, 7.1	-6.8, 7.6	-1.4 (-2.9,0.1)	0.0674
Multiple Imputation	LS Mean			-1.0	0.5	-1.5 (-3.2,0.1)	0.0728
			UVX-002 Keratoconus Subjects				
LOCF	Mean (SD)	59.9 (8.3)	60.4 (9.8)	-1.1 (5.1)	0.6 (2.8)		
	Median	57.9	58.0	-0.5	-0.2		
	Min, Max	47.3, 87.5	49.4, 91.1	-36.2, 11.6	-8.5, 13.8	-1.6 (-3.0,-0.3)	0.0156
Multiple Imputation	LS Mean			-1.1	0.7	-1.8 (-3.7,0.1)	0.0569
			UVX-001 Corneal Ectasia Subjects				
LOCF	Mean (SD)	55.7 (6.6)	56.0 (6.2)	-0.6 (1.6)	1.0 (1.7)		
	Median	53.2	56.6	-0.8	0.6		
	Min, Max	47.7, 70.4	47.6, 70.0	-4.5, 3.3	-1.0, 6.9	-1.7 (-2.6,-0.7)	0.0010
Multiple Imputation	LS Mean			-0.7	1.3	-1.9 (-3.2,-0.7)	0.0022
			UVX-003 Corneal Ectasia Subjects				
Month 6	Mean (SD)	54.6 (6.6)	55.2 (7.0)	-0.5 (2.0)	0.5 (2.3)		
	Median	53.3	53.8	-0.2	0.5		
	Min, Max	45.0, 71.4	43.3, 77.6	-8.4, 2.6	-8.6, 11.9	-1.0 (-1.8,-0.3)	0.0084
Multiple Imputation	LS Mean			-0.5	-0.1	-0.4 (-2.6,1.8)	0.7026

[1] Difference = CXL – Control.
[2] P-value on difference between CXL and Control by t-test.

Potentially erroneous K_{max} was set to missing for: subject (b) (6) at Month 1, subject (b) (6) at Month 1, and subject (b) (6) at Month 3.

Source: Reviewer's analysis.

An alternative analysis according to the intent-to-treat principle was also conducted by the reviewer. For subjects in the control group, their efficacy data after cross-over from control to CXL treatment was included in the analysis. This analysis compares the efficacy in subjects who had been treated with CXL for 12 months to the efficacy in subjects whose CXL treatment was delayed by three months or six months depending on the visit at which the subject crossed over from control to CXL. A statistically significant and clinically meaningful improvement in K_{max}

was demonstrated in UVX-002 for keratoconus subjects and in UVX-001 for corneal ectasin subjects (Table 11).

Table 11: K_{max} and Change in K_{max} from Baseline to Month 12 in the Randomized Study Eye (Keratoconus Subjects, ITT Population; LOCF)

UVX-001

		CXL Group (N=29)	Control Group (N=29)	Change from Baseline			
	Statistic			CXL (N=29)	Control (N=29)	Difference[1]	p-value [2]
Baseline	Mean (SD)	60.6 (7.3)	61.9 (8.3)				
Applicant's Analysis	Mean (SD)	59.2 (7.8)	62.3 (9.5)	-1.4 (2.8)	0.5 (3.0)	----	0.0170 *
	Median	58.4	60.8	-1.0	0	-1.9 (-3.4,-0.3)	0.0175 **
	Min, Max	48.6, 82.6	47.5, 84.1	-7.8, 7.1	-6.8, 7.6	-1.8 (-3.4,-0.3)	0.0217 ***
	95% CI			(-2.5,-0.3)	(-0.7,1.6)		
True ITT Analysis	Mean (SD)	59.2 (7.8)	61.5 (9.7)	-1.4 (2.8)	-0.3 (4.1)	----	0.0914 *
	Median	58.4	62.5	-1.0	0.1	-1.1 (-2.9,0.8)	0.2534 **
	Min, Max	48.6, 82.6	47.7, 89.3	-7.8, 7.1	-12.1, 8.0	-1.0 (-2.9,0.8)	0.2734 ***
	95% CI			(-2.5,-0.3)	(-1.9,1.2)		

UVX-002

		CXL Group (N=73)	Control Group (N=74)	Change from Baseline			
	Statistic			CXL (N=73)	Control (N=74)	Difference[1]	p-value [2]
Baseline	Mean (SD)	61.0 (9.8)	59.8 (9.2)				
Applicant's Analysis	Mean (SD)	59.3 (8.5)	60.4 (9.8)	-1.7 (4.7)	0.6 (2.8)	----	<0.0001*
	Median	58.0	58.0	-1.0	-0.1	-2.3 (-3.5,-1.0)	0.0004 **
	Min, Max	46.6, 90.9	49.4, 91.1	-31.6, 7.3	-8.5, 13.8	-2.1 (-3.4,-0.9)	0.0015 ***
	95% CI			(-2.8,-0.6)	(-0.0,1.2)		
True ITT Analysis	Mean (SD)	59.3 (8.5)	59.7 (9.6)	-1.7 (4.7)	-0.1 (2.7)	----	0.0060*
	Median	58.0	57.5	-1.0	-0.2	-1.5 (-2.8,-0.3)	0.0159 **
	Min, Max	46.6, 90.9	48.6, 90.6	-31.6, 7.3	-10.4, 7.8	-1.4 (-2.6,-0.2)	0.0225 ***
				(-2.8,-0.6)	(-0.8,0.5)		

[1] Difference = CXL – Control.
[2] Three p-values are presented here, including
* P-value on difference in distribution between CXL and Control by Wilcoxon test.
** P-value on difference between CXL and Control by t-test.
*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

Potentially erroneous K_{max} was set to: 62 for subject (b) (6) at Month 1, 58.4 for subject (b) (6) at Month 1, and 63.6 for subject (b) (6) at Month 3.

Source: Reviewer's analysis.

Table 12: K_{max} and Change in K_{max} from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, ITT Population; LOCF)

UVX-001

	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline CXL (N=24)	Change from Baseline Control (N=25)	Difference 95% CI [1]	p-value [2]
Baseline	Mean (SD)	56.3 (6.3)	55.0 (5.5)				
Applicant's Analysis	Mean (SD)	55.3 (6.6)	56.0 (6.2)	-1.0 (1.7)	1.0 (1.7)	----	<0.0001 *
	Median	53.3	56.6	-0.9	0.6	-2.0 (-3.0,-1.1)	0.0001 **
	Min, Max	47.0, 71.4	47.6, 70.0	-4.6, 3.3	-1.0, 6.9	-2.1 (-3.1,-1.2)	<.0001 ***
	95% CI			(-1.7,-0.3)	(0.3,1.7)		
True ITT Analysis	Mean (SD)	55.3 (6.6)	55.8 (6.9)	-1.0 (1.7)	0.8 (3.4)	----	0.0078 *
	Median	53.3	54.4	-0.9	0.4	-1.8 (-3.4,-0.2)	0.0243 **
	Min, Max	47.0, 71.4	47.4, 78.8	-4.6, 3.3	-2.9, 15.7	-1.9 (-3.5,-0.3)	0.0207 ***
	95% CI			(-1.7,-0.3)	(-0.6,2.2)		

UVX-003

	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline CXL (N=67)	Change from Baseline Control (N=63)	Difference[1]	p-value [2]
Baseline [3]	Mean (SD)	55.1 (7.1)	54.7 (6.8)				
Applicant's	Mean (SD)	54.5 (6.8)	55.2 (7.0)	-0.5 (2.2)	0.5 (2.3)	----	0.0017 *
	Median	53.5	54.1	-0.3	0.5	-1.1 (-1.9,-0.3)	0.0080 **
	Min, Max	44.9, 74.3	43.3, 77.6	-10.2, 3.8	-8.6, 11.9	-1.1 (-1.8,-0.3)	0.0087 ***
	95% CI			(-1.1,0.0)	(-0.0,1.1)		
True ITT Analysis	Mean (SD)	54.5 (6.8)	54.5 (6.4)	-0.5 (2.2)	-0.2 (2.7)	----	0.4235 *
	Median	53.5	53.6	-0.3	-0.1	-0.4 (-1.3,0.5)	0.3791 **
	Min, Max	44.9, 74.3	43.3, 72.1	-10.2, 3.8	-8.6, 12.9	-0.3 (-1.2,0.5)	0.4199 ***
	95% CI			(-1.1,0.0)	(-0.8,0.5)		

[1] Difference = CXL – Control.

[2] Three p-values are presented here, including

* P-value on difference in distribution between CXL and Control by Wilcoxon test.

** P-value on difference between CXL and Control by t-test.

*** P-value on difference between CXL and Control by ANCOVA with baseline as covariate.

[3] Baseline K_{max} missing for 4 subjects.

Source: Reviewer's analysis.

The reviewer conducted an additional analysis for the proportion of subjects who had at least 1.0 diopter improvement in K_{max} at Month 3 from baseline (Table 13). Statistical significance was only observed for UVX-003.

Table 13: Proportion (%) of Subjects Who Had at Least 1.0 Diopter Decrease in K_{max} from Baseline (LOCF, ITT Population)

Study/ Indication	Visit	Response	CXL Group n (%)	Control Group n (%)	p-value
UVX-001 Keratoconus	Month 3		**N=29**	**N=29**	0.1757
		Yes	13 (44.8%)	8 (27.6%)	
		No	16 (55.2%)	21 (72.4%)	
UVX-002 Keratoconus	Month 3		**N=73**	**N=74**	0.1696
		Yes	22 (30.1%)	15 (20.3%)	
		No	51 (69.9%)	59 (79.7%)	
UVX-001 Ectasia	Month 3		**N=24**	**N=25**	0.2823
		Yes	3 (12.5%)	1 (4.0%)	
		No	21 (87.5%)	24 (96.0%)	
UVX-003 Ectasia	Month 3		**N=63** [1]	**N=63**	0.0115
		Yes	17 (27.0%)	6 (9.5%)	
		No	46 (73.0%)	57 (90.5%)	

[1] Four subjects in CXL group did not have a K_{max} measurement at baseline.

Source: Reviewer's analysis.

3.2.4.2 Change from Baseline in Visual Acuity

BSCVA and its changes from baseline are presented in the following tables (Table 11 and Table 12 for keratoconus subjects; Table 13 and Table 14 for corneal ectasia subjects).

A transient reduction in BSCVA is an expected and well documented effect of corneal debridement. A loss in BSCVA from baseline at Month 1 was observed in all three studies for CXL-treated subjects. At Month 3, BSCVA improved from baseline for these subjects.

For keratoconus subjects, the mean BSCVA was comparable between treatment groups at baseline. At Month 3, a difference of 2.8 letters and 1.2 letters in the mean change in BSCVA from baseline between the CXL group and the control group was observed in UVX-001 and UVX-002, respectively; this difference between treatments was not statistically significant.

For corneal ectasia subjects, the mean BSCVA differed by approximately 3 letters between treatment groups at baseline. At Month 3, a difference of 5.6 letters and 1.6 letters in the mean change in BSCVA from baseline between the CXL group and the control group was observed in UVX-001 and UVX-003, respectively; this difference between treatments in UVX-001 was statistically significant.

Table 14: Best Spectacle-Corrected Visual Acuity and its Change from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=29)	Control Group (N=29)	Change from Baseline CXL (N=29)	Change from Baseline Control (N=29)	Difference[1]	p-value [2]
Baseline	Mean (SD)	32.4 (11.6)	31.7 (13.0)				
	Median	35.0	33.0				
	Min, Max	5.0, 48.0	2.0, 50.0				
Month 1	Mean (SD)	31.4 (12.4)	35.7 (12.2)	-1.0 (9.9)	3.9 (10.4)	-4.9 (-10.3,0.4)	0.0688
	Median	34.0	40.0	1.0	3.0		
	Min, Max	10.0, 50.0	5.0, 52.0	-30.0, 20.0	-15.0, 24.0		
Month 3	**Mean (SD)**	**39.0 (10.0)**	**35.5 (14.3)**	**6.5 (10.6)**	**3.8 (9.4)**	**2.8 (-2.5,8.0)**	**0.2985**
	Median	**42.0**	**40.0**	**5.0**	**3.0**		
	Min, Max	**14.0, 52.0**	**1.0, 54.0**	**-27.0, 26.0**	**-14.0, 22.0**		
Month 6	Mean (SD)	38.1 (10.1)	35.2 (12.6)	5.7 (10.8)	3.4 (10.0)	2.2 (-3.2,7.7)	0.4157
	Median	39.0	38.0	7.0	2.0		
	Min, Max	17.0, 53.0	2.0, 54.0	-14.0, 34.0	-14.0, 23.0		
Month 12	Mean (SD)	39.6 (11.0)	35.2 (12.6)	7.2 (10.4)	3.4 (10.0)	3.7 (-1.6,9.1)	0.1685
	Median	43.0	38.0	7.0	2.0		
	Min, Max	22.0, 55.0	2.0, 54.0	-14.0, 28.0	-14.0, 23.0		

[1] Difference = CXL – Control.
[2] P-value on difference between CXL and Control by t-test.

Source: UVX-001 CSR Table 14.3.8.1 and Reviewer's analysis for the difference estimate.

Table 15: Best Spectacle-Corrected Visual Acuity and its Change from Baseline in the Randomized Study Eye (Keratoconus Subjects, UVX-002, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=73)	Control Group (N=74)	Change from Baseline CXL (N=73)	Change from Baseline Control (N=74)	Difference[1]	p-value [2]
Baseline	Mean (SD)	33.6 (14.1)	33.2 (13.9)				
	Median	37.0	38.0				
	Min, Max	0, 52.0	0, 55.0				
Month 1	Mean (SD)	33.3 (13.1)	35.2 (13.6)	-0.3 (9.5)	1.9 (6.9)	-2.2 (-4.9,0.5)	0.1156
	Median	35.0	37.5	0.0	2.0		
	Min, Max	3.0, 52.0	0, 57.0	-31.0, 21.0	-15.0, 21.0		
Month 3	**Mean (SD)**	**36.5 (12.8)**	**35.2 (13.9)**	**3.0 (10.2)**	**1.7 (7.8)**	**1.2 (-1.7,4.2)**	**0.4089**
	Median	**38.0**	**36.5**	**3.0**	**2.0**		
	Min, Max	**3.0, 59.0**	**0, 59.0**	**-31.0, 25.0**	**-30.0, 20.0**		
Month 6	Mean (SD)	38.1 (12.9)	35.0 (14.3)	4.5 (11.7)	1.5 (8.1)	3.0 (-0.3,6.3)	0.0725
	Median	43.0	37.0	3.0	2.0		
	Min, Max	5.0, 59.0	0, 59.0	-31.0, 45.0	-33.0, 20.0		
Month 12	Mean (SD)	38.6 (12.1)	35.0 (14.3)	5.1 (11.1)	1.6 (8.1)	3.5 (0.3,6.7)	0.0307
	Median	40.0	37.0	3.0	2.0		
	Min, Max	4.0, 59.0	0, 59.0	-17.0, 45.0	-33.0, 20.0		

[1] Difference = CXL – Control.
[2] P-value on difference between CXL and Control by t-test.

Source: UVX-002 CSR Table 14.2.5.1 and Reviewer's analysis for the difference estimate.

Table 16: Best Spectacle-Corrected Visual Acuity and its Change from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-001, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=24)	Control Group (N=25)	Change from Baseline: CXL (N=24)	Change from Baseline: Control (N=25)	Difference[1]	p-value [2]
Baseline	Mean (SD)	37.7 (11.3)	34.5 (13.3)				
	Median	39.5	37.0				
	Min, Max	0, 52.0	2.0, 50.0				
Month 1	Mean (SD)	37.2 (10.9)	34.6 (14.1)	-0.5 (9.4)	0.1 (6.7)	-0.6 (-5.3,4.1)	0.7913
	Median	38.0	40.0	0.0	-1.0		
	Min, Max	6.0, 52.0	5.0, 53.0	-18.0, 19.0	-10.0, 20.0		
Month 3	**Mean (SD)**	**43.6 (10.1)**	**34.7 (12.9)**	**5.9 (9.0)**	**0.2 (7.0)**	**5.7 (1.1,10.3)**	**0.0165**
	Median	**44.5**	**37.0**	**7.5**	**1.0**		
	Min, Max	**18.0, 54.0**	**4.0, 52.0**	**-17.0, 19.0**	**-16.0, 20.0**		
Month 6	Mean (SD)	43.6 (12.2)	33.6 (12.5)	5.9 (10.5)	-0.9 (6.4)	6.8 (1.8,11.7)	0.0086
	Median	46.5	37.0	3.5	0.0		
	Min, Max	2.0, 56.0	3.0, 52.0	-11.0, 24.0	-14.0, 16.0		
Month 12	Mean (SD)	42.8 (11.0)	33.6 (12.5)	5.0 (10.2)	-0.9 (6.4)	5.9 (1.0,10.8)	0.0184
	Median	45.0	37.0	4.0	0.0		
	Min, Max	2.0, 55.0	3.0, 52.0	-17.0, 24.0	-14.0, 16.0		

[1] Difference = CXL – Control.
[2] P-value on difference between CXL and Control by t-test.

Source: UVX-001 CSR Table 14.3.8.1 and Reviewer's analysis for the difference estimate.

Table 17: Best Spectacle-Corrected Visual Acuity and its Change from Baseline in the Randomized Study Eye (Corneal Ectasia Subjects, UVX-003, ITT Population; LOCF)

Visit	Statistic	CXL Group (N=67)	Control Group (N=63)	Change from Baseline: CXL (N=67)	Change from Baseline: Control (N=63)	Difference[1]	p-value [2]
Baseline	Mean (SD)	36.7 (13.7)	39.5 (11.9)				
	Median	41.0	42.0				
	Min, Max	0, 60.0	0, 59.0				
Month 1	Mean (SD)	34.8 (14.5)	40.2 (11.4)	-1.9 (9.9)	0.7 (9.5)	-2.6 (-6.0,0.8)	0.1307
	Median	39.0	43.0	-1.0	0.0		
	Min, Max	5.0, 55.0	3.0, 58.0	-28.0, 19.0	-35.0, 30.0		
Month 3	**Mean (SD)**	**38.8 (13.2)**	**40.0 (12.2)**	**2.1 (8.9)**	**0.5 (9.6)**	**1.6 (-1.6,4.8)**	**0.3328**
	Median	**40.0**	**42.0**	**2.0**	**1.0**		
	Min, Max	**1.0, 60.0**	**4.0, 58.0**	**-21.0, 39.0**	**-22.0, 30.0**		
Month 6	Mean (SD)	40.1 (14.2)	39.3 (12.2)	3.4 (9.0)	-0.2 (9.6)	3.6 (0.4,6.8)	0.0300
	Median	44.0	42.0	3.0	0.0		
	Min, Max	0, 65.0	4.0, 58.0	-15.0, 31.0	-22.0, 30.0		
Month 12	Mean (SD)	41.8 (13.6)	39.4 (12.3)	5.0 (8.4)	-0.1 (9.6)	5.2 (2.0,8.3)	0.0014
	Median	44.0	42.0	4.0	0.0		
	Min, Max	0, 64.0	4.0, 58.0	-16.0, 30.0	-22.0, 30.0		

[1] Difference = CXL – Control.
[2] P-value on difference between CXL and Control by t-test.

Source: UVX-003 CSR Table 14.3.8.1 and Reviewer's analysis for the difference estimate.

3.3 Evaluation of Safety

The most common adverse events associated with CXL treatment observed in these three studies were corneal opacity (haze), punctate keratitis, corneal epithelium defect, eye pain, and blurred vision. According to the Applicant, these are expected sequelae following debridement of the cornea. Most of the adverse events were mild or moderate in intensity and resolved over time. Other potential complications of the CXL procedure, including infectious keratitis; corneal edema, melting, perforation, and scarring; and sterile corneal infiltrates, rarely occurred in the studies. There was no indication that CXL therapy resulted in endothelial cell damage, nor was it associated with long-lasting corneal thinning or significant elevations in IOP.

A comprehensive safety evaluation can be found in the clinical review by Dr. William Boyd.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Because of the relatively small number of subjects in UVX-001 in each subgroup of keratoconus subjects and corneal ectasia subjects, this study was combined with the other two studies in the subgroup analysis.

The primary efficacy endpoint was evaluated for the following subgroups: gender (male or female), and race (white or non-white). Overall, subgroup analyses show that the efficacy of CXL is generally maintained regardless of gender and race (Tables A5 – A8 in Appendices).

The studies did not enroll subjects 65 years of age or older. Therefore, the riboflavin ophthalmic solution/KXL® System was not adequately tested in elderly subjects ≥65 years of age. As a result, the Applicant will not seek approval of CXL therapy for these subjects. The Applicant conducted a subgroup analysis by age according to the median age in the studies (< median or ≥ median). Because the median age differed between studies, the composition of the subgroups varied by studies; and the subgroup analysis by age group was not consistent across studies. The results of this subgroup analysis are not included in the review.

4.2 Other Special/Subgroup Populations

For keratoconus subjects, the primary efficacy endpoint was also evaluated by disease severity (mild or moderate/severe). Slightly less than one-third of subjects had moderate or severe keratoconus at baseline. A greater difference (3.0 D) was observed in these subjects between CXL treatment group and the control group in the mean change from baseline in K_{max} at Month 3.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were two major statistical issues in this submission.

- The time-point for the primary efficacy analysis was changed to Month 12 from Month 3 after the studies had been completed. The practice of changing the time-point of the primary efficacy analysis after the study completion compromised the credibility of the study conduct and the study results.
- The Applicant concluded that a clinically meaningful and statistically significant difference in the mean change in K_{max} from baseline to Month 12 was observed between the CXL group and the control group in all three studies. In their analyses, the comparison between the CXL group and the control group after Month 3 was based on the imputed data using LOCF approach. Because the study design allowed the subjects in the control group to cross over to receive the CXL treatment in the study eyes after Month 3, no subjects or only few subjects in the control groups remained in the assigned treatment and had efficacy data at Month 12. Therefore, the studies did not have adequate data to allow a direct treatment comparison at Month 12.

5.2 Collective Evidence

Based on the efficacy evaluation at Month 3 as originally planned in the protocols, the difference in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was 0.5 D and 1.3 D in UVX-001 and UVX-002, respectively, for keratoconus subjects. The difference observed in UVX-001 was neither statistically significant nor clinically meaningful (less than 1.0 D). The observed mean difference of 1.3 D in UVX-002 was likely caused by one large decrease in K_{max} (-32.7 D) experienced by one subject in CXL group and one large increase in K_{max} (43.6 D) experienced by one subject in control group. These two groups were not differentiable in terms of the median (0 vs -0.1 D). Both the t-test and Wilcoxon test concluded that the difference was not statistically significant.

For corneal ectasia subjects, a statistically significant difference in the mean change in K_{max} from baseline to Month 3 between the CXL group and the control group was observed in UVX-001 and UVX-003, respectively. The difference of 0.9 D and 0.8 D in these two studies is close to 1.0 D, a threshold considered for the clinical success.

The Applicant's analysis indicated that CXL treatment resulted in statistically significant and clinically meaningful improvements in K_{max} for both indications in all three studies. Their analysis included a significant amount of imputed data using LOCF approach at Month 12 for the control group. To further evaluate the study results based on the LOCF approach, a multiple imputation was performed to impute missing data for the K_{max} parameter at post-baseline visits up to Month 6. The multiple imputation procedure used a regression model including K_{max} observed at previous visits. At Month 6, the treatment effect estimated using LOCF was not consistent with the treatment effect estimated using multiple imputation in UVX-003. In the other two studies, LOCF and multiple imputation yielded similar estimates of the treatment

effects. The observed treatment effect at Month 6 could be indicative of the treatment effect at Month 12.

An alternative analysis adhering to the intent-to-treat principle yielded different results. This analysis included the efficacy data after cross-over from control to CXL treatment. Statistically significant and clinically meaningful improvements in K_{max} were demonstrated in UVX-002 for keratoconus subjects and in UVX-001 for corneal ectasia subjects.

Various analyses had led to different conclusions. However, the CXL groups in these studies demonstrated the utility of CXL in treating keratoconus and corneal ectasia. The subjects in this treatment group remained in their assigned treatment and the majority of them had K_{max} measurement through Month 12. The improvement in K_{max} continued or was maintained over time.

5.3 Conclusions and Recommendations

The efficacy of CXL treatment observed in corneal ectasia subjects was shown to be statistically significant and clinically meaningful according to the protocol-defined analysis. The data provided in this submission seems adequate to support the intended indication in treating corneal ectasia subjects. Although CXL does appear to have activity in keratoconus subjects, the study design makes a conclusive recommendation based on the statistical evaluation difficult.

5.4 Labeling Recommendations

We recommend that the 'Clinical Studies' section in the label includes the treatment comparison with respect to efficacy endpoints at Month 3, instead of Month 12 as they are currently presented in the label. In addition, we recommend that the label includes a graph to show improvement in K_{max} over time for CXL groups.

APPENDICES

APPEARS THIS WAY ON ORIGINAL

Table A.1: Demographics (ITT Population): UVX-001 (Keratoconus Subjects), UVX-002, and Pooled Studies

	UVX-001		UVX-002		Pooled Studies	
Parameter/Statistic	**CXL (N=29)**	**Sham (N=29)**	**CXL (N=73)**	**Sham (N=74)**	**CXL (N=102)**	**Sham (N=103)**
Age (yrs)						
Mean (SD)	33.3 (7.59)	36.9 (12.53)	30.2 (10.08)	34.2 (11.52)	31.1 (9.51)	35.0 (11.82)
Min, max	19.9, 50.1	15.8, 60.0	14.0, 57.4	14.8, 62.6	14.0, 57.4	14.8, 62.6
Gender, n (%)						
Female	8 (27.6%)	11 (37.9%)	19 (26.0%)	24 (32.4%)	27 (26.5%)	35 (34.0%)
Male	21 (72.4%)	18 (62.1%)	54 (74.0%)	50 (67.6%)	75 (73.5%)	68 (66.0%)
Ethnicity, n (%)						
Hispanic/Latino	3 (10.3%)	3 (10.3%)	7 (9.6%)	3 (4.1%)	10 (9.8%)	6 (5.8%)
Not Hispanic/Latino	26 (89.7%)	26 (89.7%)	31 (42.5%)	36 (48.6%)	57 (55.9%)	62 (60.2%)
Not Reported	0	0	35 (47.9%)	35 (47.3%)	35 (34.3%)	35 (34.0%)
Race, n (%)						
White	19 (65.5%)	19 (65.5%)	54 (74.0%)	61 (82.4%)	73 (71.6%)	80 (77.7%)
Black/African American	4 (13.8%)	4 (13.8%)	7 (9.6%)	7 (9.5%)	11 (10.8%)	11 (10.7%)
Asian	1 (3.4%)	2 (6.9%)	0	1 (1.4%)	1 (1.0%)	3 (2.9%)
Others	5 (17.2%)	4 (13.8%)	10 (13.7%)	5 (6.8%)	15 (14.7%)	9 (8.7%)
Not Reported	0	0	2 (2.7%)	0	2 (2.0%)	0

Source: UVX-001 CSR Table 21 and UVX-002 CSR Table 13.

Table A.2: Ocular Risk Factors and Contact Lens Wear (ITT Population): UVX-001 (Keratoconus Subjects), UVX-002, and Pooled Studies

		UVX-001		UVX-002		Pooled Studies	
Category	**Parameter, n (%)**	**CXL (N=29)**	**Sham (N=29)**	**CXL (N=73)**	**Sham (N=74)**	**CXL (N=102)**	**Sham (N=103)**
Risk Factors	Eye Rubbing						
	Yes	22 (75.9%)	21 (72.4%)	53 (72.6%)	43 (58.1%)	75 (73.5%)	64 (62.1%)
	No	7 (24.1%)	8 (27.6%)	20 (27.4%)	31 (41.9%)	27 (26.5%)	39 (37.9%)
	NA	0	0	0	0	0	0
	Family History						
	Yes	1 (3.4%)	5 (17.2%)	17 (23.3%)	13 (17.6%)	18 (17.6%)	18 (17.5%)
	No	28 (96.6%)	24 (82.8%)	55 (75.3%)	61 (82.4%)	83 (81.4%)	85 (82.5%)
	NA	0	0	1 (1.4%)	0	1 (1.0%)	0
	Ocular History						
	Yes	20 (69.0%)	17 (58.6%)	29 (39.7%)	26 (35.1%)	49 (48.0%)	43 (41.7%)
	No	9 (31.0%)	12 (41.4%)	44 (60.3%)	48 (64.9%)	53 (52.0%)	60 (58.3%)
	NA	0	0	0	0	0	0
	Other Risk History						
	Yes	4 (13.8%)	5 (17.2%)	1 (1.4%)	0	5 (4.9%)	5 (4.9%)
	No	24 (82.8%)	23 (79.3%)	69 (94.5%)	74 (100%)	93 (91.2%)	97 (94.2%)
	NA	1 (3.4%)	1 (3.4%)	3 (4.1%)	0	4 (3.9%)	1 (1.0%)
Contact Lens	Soft Lens						
	Yes	8 (27.6%)	10 (34.5%)	20 (27.4%)	23 (31.1%)	28 (27.5%)	33 (32.0%)
	No	19 (65.5%)	18 (62.1%)	52 (71.2%)	48 (64.9%)	71 (69.6%)	66 (64.1%)
	NA	2 (6.9%)	1 (3.4%)	1 (1.4%)	3 (4.0%)	3 (2.9%)	4 (3.9%)
	Soft Toric Lens						
	Yes	7 (24.1%)	6 (20.7%)	7 (9.6%)	10 (13.5%)	14 (13.7%)	16 (15.5%)
	No	21 (72.4%)	22 (75.9%)	63 (86.3%)	58 (78.4%)	84 (82.4%)	80 (77.7%)
	NA	1 (3.4%)	1 (3.4%)	3 (4.1%)	6 (8.1%)	4 (3.9%)	7 (6.8%)
	Soft Extended Wear						
	Yes	3 (10.3%)	2 (6.9%)	1 (1.4%)	1 (1.4%)	4 (3.9%)	3 (2.9%)
	No	24 (82.7%)	24 (82.8%)	70 (95.9%)	65 (87.8%)	94 (92.2%)	89 (86.4%)

Category	Parameter, n (%)	UVX-001		UVX-002		Pooled Studies	
		CXL (N=29)	Sham (N=29)	CXL (N=73)	Sham (N=74)	CXL (N=102)	Sham (N=103)
	NA	2 (6.9%)	3 (10.3%)	2 (2.7%)	8 (10.8%)	4 (3.9%)	11 (10.7%)
	Rigid Gas Permeable						
	Yes	17 (58.6%)	21 (72.4%)	34 (46.6%)	41 (55.4%)	51 (50.0%)	62 (60.2%)
	No	12 (41.4%)	8 (27.6%)	39 (53.4%)	32 (43.2%)	51 (50.0%)	40 (38.8%)
	NA	0	0	0	1 (1.4%)	0	1 (1.0%)

Source: UVX-001 CSR Table 22 and UVX-002 CSR Table 14. NA = Not Available.

Table A.3: Demographics (ITT Population): UVX-001 (Corneal Ectasia Subjects), UVX-003, and Pooled Studies

	UVX-001		UVX-003		Pooled Studies	
Parameter/Statistic	**CXL (N=24)**	**Sham (N=25)**	**CXL (N=67)**	**Sham (N=63)**	**CXL (N=91)**	**Sham (N=88)**
Age (yrs)						
Mean (SD)	45.0 (8.95)	40.0 (7.7)	43.0 (8.72)	42.5 (9.08)	43.5 (8.78)	41.8 (8.73)
Min, max	27.5, 62.7	24.4, 57.2	22.1, 59.7	24.2, 61.8	22.1, 62.7	24.2, 61.8
Gender, n (%)						
Female	10 (41.7%)	8 (32.0%)	23 (34.3%)	16 (25.4%)	33 (36.3%)	24 (27.3%)
Male	14 (58.3%)	17 (68.0%)	44 (65.7%)	47 (74.6%)	58 (63.7%)	64 (72.7%)
Ethnicity, n (%)						
Hispanic/Latino	2 (8.3%)	1 (4.0%)	9 (13.4%)	9 (14.3%)	11 (12.1%)	10 (11.4%)
Not Hispanic/Latino	22 (91.7%)	23 (92.0%)	18 (26.9%)	18 (28.6%)	40 (44.0%)	41 (46.6%)
Not Reported	0	1 (4.0%)	40 (59.7%)	36 (57.1%)	40 (44.0%)	37 (42.0%)
Race, n (%)						
White	18 (75.0%)	21 (84.0%)	50 (74.6%)	45 (71.4%)	68 (74.7%)	66 (75.0%)
Black/African American	3 (12.5%)	2 (8.0%)	7 (10.5%)	5 (7.9%)	10 (11.0%)	7 (8.0%)
Asian	0	0	3 (4.5%)	4 (6.3%)	3 (3.3%)	4 (4.5%)
Others	3 (12.5%)	2 (8.0%)	3 (4.5%)	3 (4.8%)	6 (6.6%)	5 (5.7%)
Not Reported	0	0	4 (6.0%)	6 (9.5%)	4 (4.4%)	6 (6.8%)

Source: UVX-001 CSR Table 23 and UVX-003 CSR Table 13.

Table A.4: Ocular Risk Factors and Contact Lens Wear (ITT Population): UVX-001 (Corneal Ectasia Subjects), UVX-003, and Pooled Studies

		UVX-001		UVX-003		Pooled Studies	
Category	**Parameter, n (%)**	**CXL (N=24)**	**Sham (N=25)**	**CXL (N=67)**	**Sham (N=63)**	**CXL (N=91)**	**Sham (N=88)**
Risk Factors	Eye Rubbing						
	Yes	8 (33.3%)	7 (28.0%)	22 (32.8%)	15 (23.8%)	30 (33.0%)	22 (25.0%)
	No	16 (66.7%)	17 (68.0%)	45 (67.2%)	47 (74.6%)	61 (67.0%)	64 (72.7%)
	NA	0	1 (4.0%)	0	1 (1.6%)	0	2 (2.3%)
	Family History						
	Yes	0	2 (8.0%)	2 (3.0%)	3 (4.8%)	2 (2.2%)	5 (5.7%)
	No	24 (100%)	22 (88.0%)	65 (97.0%)	59 (93.6%)	89 (97.8%)	81 (92.0%)
	NA	0	1 (4.0%)	0	1 (1.6%)	0	2 (2.3%)
	Ocular History						
	Yes	22 (91.7%)	25 (100%)	62 (92.5%)	59 (93.7%)	84 (92.3%)	84 (95.5%)
	No	2 (8.3%)	0	5 (7.5%)	4 (6.3%)	7 (7.7%)	4 (4.5%)
	NA	0	0	0	0	0	0
	Other Risk History						
	Yes	4 (16.7%)	8 (32.0%)	2 (3.0%)	1 (1.6%)	6 (6.6%)	9 (10.2%)
	No	19 (79.2%)	17 (68.0%)	64 (95.5%)	60 (95.2%)	83 (91.2%)	77 (87.5%)
	NA	1 (4.2%)	0	1 (1.5%)	2 (3.2%)	2 (2.2%)	2 (2.3%)
Contact Lens	Soft Lens						
	Yes	9 (37.5%)	10 (40.0%)	26 (38.8%)	22 (34.9%)	35 (38.5%)	32 (36.4%)
	No	14 (58.3%)	15 (60.0%)	40 (59.7%)	38 (60.3%)	54 (59.3%)	53 (60.2%)
	NA	1 (4.2%)	0	1 (1.5%)	3 (4.8%)	2 (2.2%)	3 (3.4%)
	Soft Toric Lens						
	Yes	5 (20.8%)	6 (24.0%)	9 (13.4%)	11 (17.5%)	14 (15.4%)	17 (19.3%)
	No	17 (70.8%)	18 (72.0%)	57 (85.1%)	45 (71.4%)	74 (81.3%)	63 (71.6%)
	NA	2 (8.3%)	1 (4.0%)	1 (1.5%)	7 (11.1%)	3 (3.3%)	8 (9.1%)
	Soft Extended Wear						
	Yes	5 (20.8%)	7 (28.0%)	1 (1.5%)	3 (4.8%)	6 (6.6%)	10 (11.4%)
	No	19 (79.2%)	16 (64.0%)	64 (95.5%)	54 (85.7%)	83 (91.2%)	70 (79.5%)
	NA	0	2 (8.0%)	2 (3.0%)	6 (9.5%)	2 (2.2%)	8 (9.1%)
	Rigid Gas Permeable						
	Yes	12 (50.0%)	12 (48.0%)	24 (35.8%)	27 (42.9%)	36 (39.6%)	39 (44.3%)
	No	11 (45.8%)	13 (52.0%)	43 (64.2%)	35 (55.6%)	54 (59.3%)	48 (54.6%)
	NA	1 (4.2%)	0	0	1 (1.6%)	1 (1.1%)	1 (1.1%)

Category	Parameter, n (%)	UVX-001		UVX-003		Pooled Studies	
		CXL (N=24)	Sham (N=25)	CXL (N=67)	Sham (N=63)	CXL (N=91)	Sham (N=88)

Source: UVX-001 CSR Table 24 and UVX-003 CSR Table 14. NA = Not Available.

Table A.5: Change in K_{max} from Baseline in the Randomized Study Eye by Gender (Keratoconus Subjects, UVX-001 and -002, ITT Population; LOCF)

Category/ Statistic [1]	Female		Male	
	CXL (N=27)	Control (N=35)	CXL (N=75)	Control (N=68)
Baseline				
Mean (SD)	59.6 (11.2)	58.8 (9.0)	61.4 (8.3)	61.2 (8.9)
Change from baseline at Month 1				
Mean (SD)	0.6 (2.5)	-1.7 (10.1)	1.5 (3.4)	-0.9 (7.9)
Difference in LS means (vs. Control)	2.2		2.4	
95% CI for the difference	(-1.7, 6.2)		(0.5, 4.4)	
p-value (vs. Control)	0.2630		0.0161	
Change from baseline at Month 3				
Mean (SD)	-0.7 (1.9)	1.5 (7.7)	-0.5 (4.5)	0.1 (2.5)
Difference in LS means (vs. Control)	-2.2		-0.5	
95% CI for the difference	(-5.2, 0.8)		(-1.8, 0.7)	
p-value (vs. Control)	0.1548		0.3902	
Change from baseline at Month 6				
Mean (SD)	-1.4 (1.9)	1.6 (7.7)	-0.9 (5.1)	0.6 (3.0)
Difference in LS means (vs. Control)	-3.1		-1.5	
95% CI for the difference	(-6.1, -0.0)		(-2.9, -0.1)	
p-value (vs. Control)	0.0483		0.0352	
Change from baseline at Month 12				
Mean (SD)	-2.0 (3.7)	1.7 (7.7)	-1.5 (4.4)	0.6 (3.0)
Difference in LS means (vs. Control)	-3.7		-2.1	
95% CI for the difference	(-6.9, -0.5)		(-3.4, -0.8)	
p-value (vs. Control)	0.0241		0.0014	

[1] Difference = CXL – Control; P-value on difference between CXL and Control by t-test.
Source: 2.7.3 Summary of Clinical Efficacy (Keratoconus) Tables 14.2.3.2.1 and 14.2.3.2.2 and Reviewer's analysis of the difference.

Table A.6: Change in K_{max} from Baseline in the Randomized Study Eye by Gender (Corneal Ectasia Subjects, UVX-001 and -003, ITT Population; LOCF)

	Female		Male	
Category/ Statistic [1]	**CXL (N=33)**	**Control (N=24)**	**CXL (N=58)**	**Control (N=64)**
Baseline				
Mean (SD)	56.9 (6.8)	53.6 (5.7)	54.7 (6.8)	55.2 (6.6)
Change from baseline at Month 1				
Mean (SD)	0.9 (1.9)	-0.0 (1.1)	1.1 (1.9)	0.4 (1.4)
Difference in LS means (vs. Control)	0.9		0.7	
95% CI for the difference	(0.1, 1.8)		(0.1, 1.3)	
p-value (vs. Control)	0.0349		0.0209	
Change from baseline at Month 3				
Mean (SD)	-0.5 (2.5)	0.8 (2.6)	0.1 (1.9)	0.7 (1.5)
Difference in LS means (vs. Control)	-1.3		-0.6	
95% CI for the difference	(-2.7, 0.1)		(-1.2, -0.0)	
p-value (vs. Control)	0.0721		0.0490	
Change from baseline at Month 6				
Mean (SD)	-0.7 (2.1)	1.1 (2.7)	-0.4 (1.7)	0.5 (1.9)
Difference in LS means (vs. Control)	-1.8		-0.9	
95% CI for the difference	(-3.1, -0.5)		(-1.6, -0.3)	
p-value (vs. Control)	0.0088		0.0048	
Change from baseline at Month 12				
Mean (SD)	-1.3 (2.2)	1.1 (2.7)	-0.3 (1.9)	0.5 (1.8)
Difference in LS means (vs. Control)	-2.4		-0.9	
95% CI for the difference	(-3.7, -1.0)		(-1.5, -0.2)	
p-value (vs. Control)	0.0010		0.0014	

[1] Difference = CXL – Control; P-value on difference between CXL and Control by t-test.
Source: 2.7.3 Summary of Clinical Efficacy (Corneal Ectasia) Tables 14.2.3.2.1 and 14.2.3.2.2, and Reviewer's analysis of the difference.

Table A.7: Change in K_{max} from Baseline in the Randomized Study Eye by Race (Keratoconus Subjects, UVX-001 and -002, ITT Population; LOCF)

Category/ Statistic [1]	White		Non-White	
	CXL (N=73)	Control (N=80)	CXL (N=27)	Control (N=23)
Baseline				
Mean (SD)	61.1 (9.1)	59.9 (8.8)	60.7 (9.6)	62.2 (9.5)
Change from baseline at Month 1				
Mean (SD)	1.6 (2.8)	-1.6 (9.7)	0.3 (3.9)	0.3 (3.0)
Difference in LS means (vs. Control)	3.2		-0.0	
95% CI for the difference	(0.9, 5.6)		(-2.0, 2.0)	
p-value (vs. Control)	0.0070		0.9883	
Change from baseline at Month 3				
Mean (SD)	0.1 (2.5)	0.6 (5.3)	-2.1 (6.5)	0.4 (3.1)
Difference in LS means (vs. Control)	-0.5		-2.5	
95% CI for the difference	(-1.9, 0.8)		(-5.5, 0.4)	
p-value (vs. Control)	0.4380		0.0925	
Change from baseline at Month 6				
Mean (SD)	-0.6 (2.8)	1.0 (5.6)	-2.3 (7.4)	0.8 (2.9)
Difference in LS means (vs. Control)	-1.6		-3.1	
95% CI for the difference	(-3.0, -0.2)		(-6.4, 0.2)	
p-value (vs. Control)	0.0299		0.0623	
Change from baseline at Month 12				
Mean (SD)	-1.2 (3.2)	1.0 (5.6)	-2.7 (6.3)	0.8 (2.9)
Difference in LS means (vs. Control)	-2.3		-3.5	
95% CI for the difference	(-3.7, -0.8)		(-6.4, -0.6)	
p-value (vs. Control)	0.0026		0.0195	

[1] Difference = CXL – Control; P-value on difference between CXL and Control by t-test.
Source: 2.7.3 Summary of Clinical Efficacy (Keratoconus) Tables 14.2.3.2.1 and 14.2.3.2.2 and Reviewer's analysis of the difference.

Table A.8: Change in K_{max} from Baseline in the Randomized Study Eye by Gender (Corneal Ectasia Subjects, UVX-001 and -003, ITT Population; LOCF)

	White		Non-White	
Category/ Statistic [1]	**CXL (N=68)**	**Control (N=66)**	**CXL (N=19)**	**Control (N=16)**
Baseline				
Mean (SD)	55.2 (6.5)	54.3 (6.3)	56.1 (8.3)	55.8 (5.0)
Change from baseline at Month 1				
Mean (SD)	1.1 (1.8)	0.2 (1.1)	0.5 (2.1)	0.6 (2.1)
Difference in LS means (vs. Control)	0.9		-0.1	
95% CI for the difference	(0.4, 1.4)		(-1.5, 1.4)	
p-value (vs. Control)	0.0010		0.8974	
Change from baseline at Month 3				
Mean (SD)	-0.0 (2.1)	0.7 (2.0)	-0.4 (2.4)	0.6 (1.2)
Difference in LS means (vs. Control)	-0.7		-1.0	
95% CI for the difference	(-1.4, -0.0)		(-2.4, 0.4)	
p-value (vs. Control)	0.0468		0.1421	
Change from baseline at Month 6				
Mean (SD)	-0.4 (1.9)	0.6 (2.4)	-0.9 (1.6)	0.6 (1.2)
Difference in LS means (vs. Control)	-1.0		-1.5	
95% CI for the difference	(-1.8, -0.3)		(-2.5, -0.5)	
p-value (vs. Control)	0.0070		0.0049	
Change from baseline at Month 12				
Mean (SD)	-0.6 (2.3)	0.6 (2.4)	-0.8 (1.5)	0.6 (1.2)
Difference in LS means (vs. Control)	-1.2		-1.3	
95% CI for the difference	(-2.0, -0.4)		(-2.3, -0.4)	
p-value (vs. Control)	0.0027		0.0065	

[1] Difference = CXL – Control; P-value on difference between CXL and Control by t-test.
Source: 2.7.3 Summary of Clinical Efficacy (Corneal Ectasia) Tables 14.2.3.2.1 and 14.2.3.2.2, and Reviewer's analysis of the difference.

Table A.9: Change in K_{max} from Baseline in the Randomized Study Eye by Keratoconus Severity (Keratoconus Subjects, UVX-001 and -002, ITT Population; LOCF)

	Mild		Moderate/Severe	
Category/ Statistic [1]	**CXL (N=62)**	**Control (N=65)**	**CXL (N=28)**	**Control (N=28)**
Baseline				
Mean (SD)	57.5 (6.3)	56.8 (6.1)	68.0 (9.8)	70.1 (8.4)
Change from baseline at Month 1				
Mean (SD)	1.4 (2.0)	-2.0 (10.6)	0.9 (5.0)	0.3 (3.7)
Difference in LS means (vs. Control)	3.4		0.5	
95% CI for the difference	(0.7, 6.1)		(-1.8, 2.9)	
p-value (vs. Control)	0.0132		0.6478	
Change from baseline at Month 3				
Mean (SD)	-0.3 (1.9)	0.1 (1.9)	-1.2 (7.0)	1.9 (8.9)
Difference in LS means (vs. Control)	-0.4		-3.1	
95% CI for the difference	(-1.1, 0.3)		(-7.4, 1.2)	
p-value (vs. Control)	0.2823		0.1566	
Change from baseline at Month 6				
Mean (SD)	-0.7 (2.7)	0.3 (2.5)	-2.0 (7.5)	2.6 (8.7)
Difference in LS means (vs. Control)	-1.0		-4.7	
95% CI for the difference	(-1.9, -0.1)		(-9.0, -0.3)	
p-value (vs. Control)	0.0277		0.0365	
Change from baseline at Month 12				
Mean (SD)	-0.9 (2.1)	0.3 (2.5)	-3.7 (7.0)	2.7 (8.7)
Difference in LS means (vs. Control)	-1.2		-6.4	
95% CI for the difference	(-2.0, -0.4)		(-10.6, -2.2)	
p-value (vs. Control)	0.0041		0.0037	

[1] Difference = CXL – Control; P-value on difference between CXL and Control by t-test.
Source: 2.7.3 Summary of Clinical Efficacy (Keratoconus) Tables 14.2.3.2.1 and 14.2.3.2.2 and Reviewer's analysis of the difference.

Table A.10: Timing of CXL Crossover and Tabulation of Subjects Remaining on Study, Remaining on Randomized Treatment, and Subjects with K_{max} Measurements

UVX-001 Keratoconus

Visit	CXL Group (N=29)			Control Group (N=29)			
	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects with K_{max}	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects Crossed Over	# of Subjects with K_{max}
Month 1	29	29	29	29	29	0	28
Month 3	29	29	29	29	29	0	29
Month 6	28	28	28	27	18	9	27
Month 12	20	20	20	14	0	14	14

UVX-001 Corneal Ectasia

Visit	CXL Group (N=24)			Control Group (N=25)			
	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects with K_{max}	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects Crossed Over	# of Subjects with K_{max}
Month 1	24	24	24	25	25	0	25
Month 3	24	24	23	25	25	0	24
Month 6	22	22	22	23	13	10	23
Month 12	20	20	20	12	0	12	12

UVX-002

Visit	CXL Group (N=73)			Control Group (N=74)			
	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects with K_{max}	# of Subjects Remaining in the Study	# of Subjects Stayed with Randomized Treatment	# of Subjects Crossed Over	# of Subjects with K_{max}
Month 1	73	73	70	74	74	0	73
Month 3	72	72	67	72	72	0	67
Month 6	72	72	67	69	21	48	66
Month 12	70	70	69	62	1	61	61

		CXL Group (N=67)			Control Group (N=63)			
UVX-003	**Visit**	**# of Subjects Remaining in the Study**	**# of Subjects Stayed with Randomized Treatment**	**# of Subjects with K_{max}**	**# of Subjects Remaining in the Study**	**# of Subjects Stayed with Randomized Treatment**	**# of Subjects Crossed Over**	**# of Subjects with K_{max}**
	Month 1	67	67	64	63	63	0	61
	Month 3	67	67	65	62	62	0	61
	Month 6	66	66	62	57	19	38	55
	Month 12	56	56	56	48	2	46	48
Source: Table 15 and Table 16 in UVX-001 CSR, Table 10 in UVX-002 and UVX-003 CSR.								

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/s/

DONGLIANG ZHUANG
02/28/2014

YAN WANG
02/28/2014
I concur.

DIONNE L PRICE
02/28/2014
Concur with overall conclusions