EFFECT OF CORNEAL CROSS-LINKING vs STANDARD CARE ON KERATOCONUS PROGRESSION IN YOUNG PATIENTS: THE KERALINK RANDOMIZED CONTROLLED TRIAL

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Running head: Cross-linking vs standard care in young patients with keratoconus

Key words: cornea, keratoconus, cornea cross-linking

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Abstract

Objective
To examine the efficacy and safety of corneal cross linking (CXL) for stabilisation of progressive keratoconus.

Design
Observer-masked, randomized, controlled, parallel group superiority trial.

Participants
60 participants aged 10-16 years with progressive keratoconus. One eye of each patient was deemed the study eye.

Intervention
According to randomization the study eye received either CXL plus standard care or standard care alone, with spectacle or contact lens correction as necessary for vision.

Main outcome measures
The primary outcome was K2 in the study eye as a measure of the steepness of the cornea at 18 months. Secondary outcomes included keratoconus progression defined as 1.5 dioptres (D) increase in K2, visual acuity, keratoconus apex corneal thickness and quality of life.

Results
Of 60 participants, 30 were randomized to CXL and standard care groups. Of these, 30 patients in the CXL group and 28 patients in the standard care group were analyzed. The mean (SD) K2 in the study eye 18 months post-randomization was 49.7D (3.8) in CXL and 53.4D (5.8) in standard care groups. The adjusted mean difference in K2 in the study eye was -3.0D (95% CI -4.9 to -1.1; p=0.002), favouring CXL. Uncorrected and corrected differences in logMAR vision at 18 months was better in eyes receiving CXL, -0.31 (95% CI -0.50 to -0.11, p=0.002) and -0.30 (95% CI -0.48 to -0.11, p=0.002). Keratoconus progression in the study eye occurred in 2 patients (7%) randomized to CXL compared to 12 (43%) randomized to standard care. The unadjusted odds ratio (OR) suggests that on average
patients in the CXL arm had 90% (OR 0.1, 95% CI 0.02 to 0.48, \( p = 0.004 \)) lower odds of experiencing
progression compared to those on standard care. Quality of life outcomes were similar in both
groups.

**Conclusions**

CXL arrests progression of keratoconus in the great majority of young patients. These data suggest
that CXL should be considered as first line treatment in progressive disease. If the arrest of
keratoconus progression induced by CXL is sustained in longer follow up, there may be particular
benefit in avoiding a later requirement for contact lens wear or corneal transplantation.
Keratoconus, characterized by distortion and thinning of the cornea, is usually bilateral but can be asymmetric. In its early stages keratoconus causes worsening of vision due to increasing myopia and irregular astigmatism: spectacle correction can only provide good visual acuity in early disease, until increasingly irregular astigmatism requires correction with rigid contact lenses for best vision. If lenses are not tolerated these individuals can be functionally blind in affected eyes. Patients with more advanced keratoconus lose contact lens-corrected visual acuity as a result of corneal opacification and require corneal replacement by transplantation. Reported keratoconus prevalence is 1:375 (265 per 100 000) in the Netherlands, 1:84 in Australian 20 year olds and as high as 1:45 in some ethnic groups. Onset is rare before the age of 10 years and the age at diagnosis is usually between 15 and 30 years, with progression in affected eyes until spontaneous stabilization in the mid-30s. Diagnosis and monitoring of progression is by corneal tomography, which quantifies irregularity of corneal curvature and corneal thickness. While standard care involves treatment of the refractive consequences of keratoconus or replacement of the diseased cornea by a transplant, the concept of arresting progression of keratoconus at an early stage when there is still good unaided or spectacle-corrected vision is relatively recent. Corneal cross linking (CXL) has been reported to be effective in arresting keratoconus progression in the majority of treated adult eyes based on evidence from three randomized controlled trials, but the findings are limited by uncertainty (wide confidence intervals) and likely risk of bias. CXL increases the biomechanical rigidity of the cornea but direct ultrastructural evidence of the mechanism of action has not been found.

Keratoconus is often more advanced if first diagnosed in children than in adults, and some suggest faster subsequent disease progression. A number of retrospective observational studies of CXL in younger patients, with varying age ranges and duration of follow-up, have reported a beneficial effect of CXL. Treatment of young patients by conventional (‘Dresden’) and accelerated CXL protocols have been reported to be similarly effective. However more robust randomized evidence is required to inform practice, particularly in children and adolescents for whom there are few published studies.
As subclinical or early keratoconus can be detected by tomography in young patients, and if CXL can halt disease progression, there is an opportunity to stabilize disease at an early stage, prior to the requirement for contact lenses or corneal transplantation. The Keralink randomised controlled trial assesses the efficacy and safety of CXL in 10 to 16 year olds with progressive keratoconus to determine whether CXL plus standard care stabilizes progressive keratoconus, is associated with better vision and quality of life and is safe compared with standard care alone.

Methods

Study design and participants

The Keralink trial is an observer-masked, individually randomized, controlled, parallel group superiority trial. The trial protocol is published and available online as follows.

https://www.journalslibrary.nihr.ac.uk/programmes/eme/142318/#/

Keralink was approved by the UK Health Research Authority, the Medicines and Healthcare Products Regulatory Agency and ethics approval was granted by the Brent Ethics Committee (reference 16/LO/0913). The trial adhered to the tenets of the Declaration of Helsinki. Consecutive newly referred patients at four UK hospitals aged 10-16 years with suspected keratoconus were identified.

Keratoconus was confirmed in one or both eyes by corneal tomography (Pentacam HR, Oculus GmbH, Wetzlar, Germany) and patients were monitored 3-monthly for progression. To differentiate true keratoconus progression from measurement artefact, an increase over an interval of at least three months in the mean corneal power in the steepest meridian (K2) or in the steepest corneal power (Kmax) of at least 1.5 D in one or both eyes was used as the threshold for eligibility. For each patient, the eye with the more advanced keratoconus at baseline was categorized as the study eye, unless that eye had undergone prior surgery such as corneal transplantation. Patients with corneal apex thickness <400 μ were excluded (therefore all study eyes had keratoconus classified as Amsler-Krumreich stage I and II). Additional exclusion criteria were corneal opacification, corneal apex thickness <400μ, K2 >62 D, Down syndrome or inability to abstain from contact lens wear for 7 days.
prior to follow-up tomography examinations. Written informed consent was obtained from parents of all recruited participants. This trial is registered in the European Union clinical trials register (EudraCT 2016-001460-11).

**Baseline assessment**

At baseline all patients were assessed as set out in Table 1.

**Randomization and masking**

Randomization used a minimization algorithm incorporating a random element with minimization factors of treatment centre and whether progression was confirmed in one or both eyes at randomization. After verification of eligibility a web-based randomization service ([https://www.sealedenvelope.com](https://www.sealedenvelope.com)) issued a randomization assignment. Participants were randomized in a 1:1 ratio to either CXL or standard care in the study eye. Due to the invasive nature of the CXL intervention, neither the trial participants nor the treating clinicians were masked to the treatment allocation. However, optometrists performing all outcome examinations and questionnaire evaluations were masked as to the randomized allocation. The treating clinicians were masked to primary outcome data (K2) measured by optometrists during the follow-up assessments.

**CXL procedure**

CXL was performed under local or general anaesthesia in one or both eyes (according to whether progression was confirmed in one eye or both). Following removal of the corneal epithelium with a spatula and administration of riboflavin drops (Vibex Rapid, Avedro, Waltham, USA) every 2 minutes for 10 minutes, ultraviolet light was applied using standardized parameters of 10 mW/cm² for a 5.4 J/cm² total energy dose administered over 9 min in a continuous manner (Avedro KXL). At completion of the procedure a protective contact lens was applied to the eye until corneal epithelialisation was complete. Subsequent management with topical steroid and topical antibacterial prophylaxis is described elsewhere. Participants randomized to CXL received spectacle or contact lens correction as necessary for the study eye, as in the Standard care comparator trial arm.

**Standard care**
The trial control arm was standard management alone, including refraction testing with provision of glasses and/or contact lens fitting for one or both eyes as required for best-corrected visual acuity. Participants randomized to standard care with confirmed progression (see below) were offered crossover to the CXL arm; this was undertaken no earlier than 9 months post-randomization.19

Outcomes.

The most important parameters used in the assessment of progression of keratoconus are the curvature of the cornea (measured as dioptre power K), corneal thickness in μm, refraction, and best-corrected visual acuity. The primary outcome measure was mean corneal power in the steepest meridian (K2) in the study eye, measured using corneal tomography at 18 months post-randomization. The mean of triplicate K2 measurements at baseline and at each follow-up assessment was used in analyses. Secondary outcomes were keratoconus progression, defined as K2 increase >1.5D, unaided and best-corrected visual acuity, corneal thickness at the keratoconus apex and vision-related quality of life (QoL) assessed by CVAQC22 and CHU9D23 questionnaires. Safety was documented in all participants.

Statistical analysis

All study analyses were done according to a predefined statistical analysis plan, reported elsewhere.24 On the basis of a previous study of CXL in adults6 we estimated that a sample size of 60 patients would be required to detect a difference between the two groups of 1.5D in the change in K2 at 18 months after randomization. These calculations were based on a common SD of 1.5D, 90% power and a type 1 error rate of 5%. Additionally we allowed for a loss-to-follow-up rate of 24%. All efficacy analyses were conducted following the intention to treat (ITT) principle where all randomized patients were analysed in their allocated group whether or not they received their randomized treatment. If a tomography scan was categorized as being of unreliable quality by a red flag indicator on the Pentacam software then the K2 measurement from that scan was not used. For the primary analysis, the mean K2 at each visit was calculated using measurements from reliable scans only. Two patients were considered to have missing K2 data at the 18 month visit as all three scans had an
associated red flag indicator (Fig 1). We did not perform multiple imputation as there were minimal missing data.

A multilevel repeated measures linear regression model was used to estimate the difference between the treatment groups in K2 values at 18 months. The model included fixed effects for K2 at randomization, treatment group, time, treatment by time interaction, and the minimisation factors centre and number of eyes progressed at randomization. A random patient effect was included to take account of clustering within patients. The model coefficients were estimated using the robust standard errors technique, to allow for unequal variances in the two randomised groups. Model assumptions were assessed using residual plots. We carried out pre-specified subgroup analysis by whether a history of atopy was reported and by ethnicity. All statistical tests used a two-sided p value of 0.05, unless otherwise specified. There were no formal adjustments of p values as per our SAP. Two-sided 95% confidence intervals were presented for all estimates. Findings for the secondary outcomes are not corrected for multiple comparisons.\(^\text{25}\) The confidence intervals and statistical tests are considered to provide supportive evidence in relation to the primary objective and additional clinical characterisation of treatment effects. STATA/MP 15.0 was used for all analyses.

### Results

Between 28 October 2016 and 26 September 2018, 240 patients were screened for eligibility, 60 of whom were randomly assigned to either CXL or standard care in the study eye. The number of participants recruited and included in the analysis is set out in Fig 1. Two patients on standard care withdrew from the trial before their three month follow-up visit. A further two patients were lost-to-follow-up or discontinued the study after the three month visit, but their data were included in the ITT analysis. One patient in the CXL group did not undergo the randomized procedure having withdrawn consent, but continued follow-up assessments as per protocol. Baseline demographic and ocular characteristics are shown in Table 2. Patients randomized to CXL had a higher proportion of male participants (83% vs 63%) and a higher proportion from the white
ethnic group (40% vs 17%) compared to those in standard care. Mean (SD) age of the participants was similar in both treatment arms: 15 (1.1) years in the CXL arm and 15 (1.6) in standard care. Overall, 45% were of south Asian or Asian British ethnicity. Seven patients (12%) had progression in both eyes meeting the eligibility criteria for randomization. For these patients, the eye with the most advanced disease was deemed to be the study eye and received randomized treatment. 68% of patients were using a refractive corrective aid at baseline - the majority (85%) using glasses, five patients used both glasses and contact lenses and one patient reported using only contact lenses. Of those using contact lenses, three patients reported using rigid contact lenses at baseline. Mean (SD) K2 in the study eye was 49 D (3.5) in patients randomized to CXL and 50 D (3.4) in standard care. The baseline measurements including uncorrected visual acuity, best-corrected visual acuity, apical corneal thickness and maximum keratometry (Kmax) for the study eye are summarized in Table 2. The table also includes baseline QoL scores of patients measured using the CVAQC and CHU9D questionnaires.

Findings for the primary outcome, K2 in the study eye, are set out in Fig 2 and Table 3. At 18 months, CXL patients had a mean (SD) K2 of 49.7D (3.8) compared to 53.4D (5.8) in standard care patients. The adjusted difference of -3.0D (95% CI: -4.93 to -1.08) suggests that on average, patients who received CXL in the study eye had a K2 3D lower than those in standard care arm at 18 months post randomization. This difference is statistically significant (p=0.002). The 95% confidence interval contains the clinically important difference of 1.5D, which corresponds to keratoconus progression.

Five patients crossed-over from standard care to CXL between 12 and 18 months (as per protocol provision) and one patient in the CXL arm did not undergo their allocated procedure. A further patient randomized to CXL was subsequently found to be ineligible for the trial. As the patient had already had CXL when this error was discovered, follow-up continued. Per-protocol analysis excluding this patient at baseline and patients at the time of cross-over did not change the observed ITT results.

Data from patients were excluded at some visits from the mean K2 calculation due to tomography measurements categorised as unreliable by Pentacam software (designated by a red flag). It is
recognized that repeatability of tomography scans is reduced in eyes with advanced keratoconus.\textsuperscript{20,26} In order to evaluate the impact of inclusion of these patients with advanced disease on the observed treatment difference we carried out exploratory sensitivity analysis on the primary outcome by including K2 measures from red-flagged scans of patients with advanced disease (see Supplementary material and Supplementary Fig 1). The difference in means between the treatment arms increased at 18 months in Supplementary Fig 1 compared to that in Fig 2.

Findings for the secondary outcomes are set out in Table 4. There was increasing difference in mean uncorrected and best-corrected visual acuity between the groups at follow-up visits (Fig 3A and B). Adjusted analysis shows that, on average, patients in CXL group had significantly lower logMAR values for uncorrected and best-corrected visual acuity compared to those on standard care ($p=0.002$ and 0.002, respectively) (Table 4), indicating that patients randomized to CXL had significantly better visual acuity at 18 months. We found no significant differences at 18 months between the CXL and standard care groups in apical corneal thickness (Fig 3C) and refraction measured as spherical equivalent. Mean Kmax in the study eye at 18 months post-randomization was 57D (6.2) in the CXL arm and 60D (7.7) in standard care. The adjusted difference (95% CI) in Kmax of -2.11 (-4.81, 0.60) at 18 months was not statistically significant ($p=0.13$). There were no significant differences in patients’ quality of life at 18 months as measured using CVAQC and CHU9D questionnaires. By 18 months, two patients (7%) in the CXL arm had experienced keratoconus progression, compared to 12 (43%) on standard care. The unadjusted odds ratio (OR) suggests that on average patients in the CXL arm have 90\% (OR 0.1, 95\% CI 0.02 to 0.48, $p=0.004$) lower odds of experiencing progression compared to those on standard care. Cox proportional hazards regression of time to progression suggests an 87\% lower hazard for the CXL arm. Figure 4 shows the Kaplan-Meier plot of time-to-progression in the two arms. There were no serious adverse events (SAEs) reported during the trial.

There was no significant interaction between treatment allocation and a history of atopy ($p=0.59$) or ethnicity ($p=0.95$). We also did post hoc comparison of those patients in whom progression occurred and those in whom it did not by age and ethnicity. We were unable to demonstrate a difference in
average age between the groups \((p=0.31)\) and no significant association between progression and ethnicity \((p=0.21)\). As these were not pre-specified analyses and in particular as the age of recruited patients was skewed towards the upper end of the range, this test might not be sufficiently sensitive to detect such an effect.

**Discussion**

In this observer masked randomized controlled trial involving young patients aged 10-16 years we found that at 18 months participants randomized to CXL plus standard care were less likely to have clinically significant progressive keratoconus and visual loss in the study eye than those treated with standard care alone. The primary trial outcome finding was the demonstration that, on average at 18 months post-randomization, patients receiving CXL in the study eye had corneal power in the steepest meridian \((K2)\) 3D lower than those receiving standard care, a statistically significant difference \((p=0.002)\). In addition, the 95% confidence interval for the difference includes the clinically important difference of 1.5D, which was the trial protocol definition of keratoconus progression. We found no adverse events associated with CXL, suggesting also that this is a relatively safe intervention.

The secondary outcomes demonstrating that efficacy of CXL in halting keratoconus progression was clinically important were (i) a significant difference in uncorrected and best-corrected visual acuity \((p=0.002\) and 0.002, respectively) between the trial arms, and (ii) the finding that only 2 patients (7%) randomized to CXL experienced keratoconus progression in the study eye compared to 12 (43%) in the standard care group at 18 months. Taken together these findings provide clear evidence of the efficacy of CXL in stabilizing keratoconus progression in 10 to 16 year olds.

These findings are generally in keeping with data from RCTs reported in a Cochrane review comparing CXL with standard care for keratoconus in adult patients and reduce current uncertainty. In the three trials eligible for inclusion in that review the data suggest that eyes treated by CXL were less likely to have an increase in \(K_{\text{max}}\) of 1.5D or more at 12 months compared to eyes treated with standard care. On average they reported that treated eyes had a less steep cornea (approximately 2D less steep) and...
better uncorrected visual acuity (approximately 2 lines or 10 letters better) (MD -0.20, 95% CI: -0.31
to -0.09; participants = 94; studies = 1, low quality evidence). The quality of the evidence was
deemed low as it was largely derived from one trial at high risk of bias, the data on corneal thickness
were inconsistent and adverse effects were frequent but mostly transient. No randomized trial of CXL
in young patients has been reported. Uncontrolled observational studies of CXL in keratoconus
patients <19 years have been published, each with limitations but each reporting effectiveness.
Caporossi et al. reported an uncontrolled study of 152 keratoconus patients ranging in age from 10 to
18 years, on whom follow up post-CXL was available on only 61% of patients. In addition to short-
term follow-up, the inclusion criteria included several parameters which are well recognised to be
characterised by high inter-test variability. In this treated patient group, there was reduction of K2 by
-0.4 D at 36 months suggesting stabilization. Vinciguerra et al reported 40 CXL-treated eyes in
patients with progressive keratoconus aged 9-18 (mean 14.2) years in a non-randomized prospective
study. Findings included reduced myopic spherical equivalent on refraction testing and reduction in
mean K2 from 51.48 pre-CXL to 50.21 at 24 months. Our finding in the CXL-treated trial group of
continued apical corneal thinning from baseline, although to a lesser extent than in the standard care
group, is in keeping with other reports following CXL.
We were unable to demonstrate a significant improvement in quality of life between trial arms.
Impact on quality of life (QoL) in keratoconus is significantly influenced by whether one or both eyes
are affected, for which reason a major determinant of QoL in the trial is very likely to have been
the vision in the non-study eye. Moreover, the problems with reduced contact lens tolerance as
keratoconus progresses and the eventual need to have corneal transplantation have major impacts
on QoL, and would not be expected in these trial participants with early keratoconus. Follow up of
Keralink participants, including serial assessment of general and vision-related quality of life
outcomes, will be continuing to four years post-randomization.
Because there is a high risk of progression of keratoconus to severe disease in children and young
people it is important to confirm the safety and efficacy of CXL in this population.\textsuperscript{10} A strength of this trial was that the upper eligible age limit was 16 years, compared to previous uncontrolled studies in young patients that included patients up to the age of 19 years. Demonstration of efficacy in the younger patients is of additional importance because corneal tomography is becoming more widely available in community settings, which will in turn lead to younger age at diagnosis and referral to secondary care clinics. A further strength of our study is the use of a measurement protocol that addresses the key problem of measurement variability in corneal tomography, the standard imaging technique for assessing progression of keratoconus. Repeatability of most tomographic parameters is good in mild keratoconus but worsens as disease progresses, in particular the single steepest power measurement Kmax.\textsuperscript{20,26} To obtain data reliably identifying change we used K2, the mean corneal power in the steepest corneal meridian, rather than Kmax as the primary outcome measure. As K2 is a measure of the mean curvature in the central 3mm zone of the cornea, change in K2 would be expected to correlate with change in vision; Kmax is the maximum curvature/power, at whatever point that might be, and may not be close to the visual axis - thus and as found in this trial it can correlate poorly with vision effects of the ectasia. As K2 represents a mean value it would inherently allow more reliable discrimination between change of functional significance between study groups. Use of the mean of triplicate readings for all assessments - at trial eligibility screening, baseline and outcome examinations - is a further methodological strength which gives validity to the finding of differences in outcomes between the two trial groups. Finally, the definition of progression post-randomization, a K2 increase >1.5 dioptres, corresponds to change in corneal power of visual significance.

As there is known ethnic variation in prevalence of severe keratoconus, a limitation of our study may be the applicability of our findings to other populations. South Asian ethnicity is strongly associated with keratoconus in the UK\textsuperscript{29,30} and accounted for 45% of patients recruited to this trial, a very significant over-representation compared to UK census statistics. However, this study is too small to
demonstrate an interaction between treatment effect and ethnicity. An unanticipated measurement problem which emerged during our trial is that measurements of K2 in those eyes with most significant progression were in some cases marked with a red flag by Pentacam device software. In two patients in the standard care group at month 18 measurements from all three scans were excluded for this reason, although not specified in the trial protocol. However, sensitivity analyses of our primary outcome of K2 including all red flag measurements (Supplementary Fig. 1) and also a per protocol analysis did not change our conclusions.

Despite documented progression of 1.5D prior to randomization, it is of interest that only 43% of subjects receiving standard care subsequently progressed clinically during the 18-month follow up period. This suggests that the proportion of keratoconus patients that have spontaneous stabilisation may be higher than expected, at least in 10 to 16 year olds. Earlier reports from uncontrolled studies of effectiveness of CXL in halting keratoconus progression in young patients should now be re-evaluated in the light of this observation. Even though CXL is a relatively safe procedure, it is important that children with non-progressive keratoconus are not managed by CXL.

Keralink provides high quality randomized evidence of efficacy of CXL in arresting progression of keratoconus in the great majority of young patients. Our data support a change in practice such that CXL should be considered for disease stabilisation in young patients with evidence of keratoconus progression. In such patients with early onset keratoconus in whom there is potential for further progression to the end of the third decade, there may be particular benefit in avoiding the later requirement for contact lens wear or corneal transplantation. There is emerging evidence that CXL can reduce the risk of transplantation.\textsuperscript{31,32}

Key questions to investigate are whether the arrest of keratoconus progression induced by CXL is permanent and whether an increasing proportion of those receiving standard care significantly progress. Longer follow-up of our trial population is already under way, and will allow us to address...
these questions. A health economic evaluation modelling the impact of CXL in young patients, beyond
the scope of our trial and taking into consideration Keralink longer term follow-up data, is warranted.
The first cost-effectiveness analyses based on adult CXL studies reported a high likelihood of cost
effectiveness.\textsuperscript{33,34} CXL is an efficacious and safe intervention which stabilises keratoconus progression
in young patients; in the event that stabilisation is sustained our findings may be the first line of
evidence justifying the screening of young patients with astigmatism for keratoconus, and
consideration of early CXL before there has been significant visual loss.

**Contributors**
DFPL, JMB, CB and CJD designed the trial. DFPL is the chief investigator, acquired funding with input
from JMB, CB and CJD, and ethics approval with input from EC. DFPL, MR, ME and SJT recruited and
followed up patients. DFPL, JMB, CB, EC and CJD were responsible for study oversight. KC, CB and CJD
planned the statistical analysis; KC did the statistical analysis with input from CB and CJD. DFPL and KC
wrote the first draft of the Article, which all authors critically revised. All authors approved the final
submission.

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**Declarations of interests**
DFPL has received consultancy fees from Recordati Rare Diseases and honoraria from Spectrum Thea;
there are no conflicts of interest. DFPL, CB and SJT have received financial support through the
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authors declare no competing interests.

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Figure legends

Figure 1: Trial profile (Consort diagram)
All 58 patients who had baseline K2 measurement and at least one follow-up were included in the mixed model for the primary outcome analysis.
*Two participants who withdrew before the 3 month follow-up examination could not contribute data to the primary outcome, but were included in the baseline characteristics table.
**One further patient randomized to CXL was subsequently found to have pre-randomization K2 increase of 1.2 D and therefore did not meet the 1.5D K2 increase criterion for trial eligibility. As the patient had already had CXL in the study eye when this error was discovered we continued to follow-up the patient; a protocol deviation was recorded.

Figure 2: K2 in the study eye in patients in Corneal cross-linking (CXL) and Standard care groups in primary outcome population at study visit intervals
K2 is the mean corneal power in the steepest meridian of the cornea, measured in dioptres (D). Data are means. Error bars represent 95% confidence intervals of the mean.

Figure 3: Uncorrected visual acuity (A), best-corrected visual acuity (B), and corneal thickness at the corneal apex (C) in the study eye, in Corneal cross-linking (CXL) and Standard care groups at study visit intervals
Data are means. Error bars represent 95% confidence intervals of the mean.

Figure 4: Kaplan-Meier plot of time to keratoconus progression in Corneal cross-linking (CXL) and Standard care groups
Progression was defined as K2 increase >1.5 dioptres with respect to value at randomization.
Table 1

<table>
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<th>Measurement of corneal power in steepest meridian (K2) and maximum power (Kmax), triplicate&lt;sup&gt;1&lt;/sup&gt;</th>
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<tr>
<td>Visual acuity</td>
<td>Unaided or with preferred correction (logMAR)</td>
</tr>
<tr>
<td>Refraction</td>
<td>Subjective, both eyes</td>
</tr>
<tr>
<td>Apical corneal thickness measurement</td>
<td>Ultrasonic pachymetry&lt;sup&gt;2&lt;/sup&gt; and Pentacam imaging</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Vision-related (CVAQC)&lt;sup&gt;3&lt;/sup&gt;, generic paediatric health outcome (CHU9D)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Baseline assessments of the study eye and quality of life

<sup>1</sup> Mean of triplicate measurements were used in assessment of progression for eligibility, baseline and all follow-up assessments.

<sup>2</sup> Pachymate DGH55 (DGH Technology Inc., Exton, PA, USA)

<sup>3</sup>CVAQC: Cardiff Visual Ability Questionnaire for Children.<sup>17</sup>

<sup>4</sup> CHU9D: Child Health Utility 9D.<sup>18</sup>
<table>
<thead>
<tr>
<th></th>
<th>CXL ((n = 30))</th>
<th>Standard care ((n = 30))</th>
<th>Total ((n = 60))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MINIMIZATION FACTORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment centre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moorfields</td>
<td>25 (84%)</td>
<td>25 (84%)</td>
<td>50 (83%)</td>
</tr>
<tr>
<td>Sheffield</td>
<td>2 (7%)</td>
<td>4 (13%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Liverpool</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Royal Gwent</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Manchester</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Number of eyes with progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One eye</td>
<td>27 (90%)</td>
<td>26 (87%)</td>
<td>53 (88%)</td>
</tr>
<tr>
<td>Two eyes</td>
<td>3 (10%)</td>
<td>4 (13%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td><strong>PATIENT CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>15.2 (1.1)</td>
<td>15.2 (1.6)</td>
<td>15.2 (1.4)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25 (83%)</td>
<td>19 (63%)</td>
<td>44 (73%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (17%)</td>
<td>11 (37%)</td>
<td>16 (27%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12 (40%)</td>
<td>5 (17%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (13%)</td>
<td>2 (7%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Asian or Asian British</td>
<td>10 (34%)</td>
<td>17 (56%)</td>
<td>27 (45%)</td>
</tr>
<tr>
<td>Black or Black British</td>
<td>3 (10%)</td>
<td>4 (13%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Other ethnic groups</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Use of refractive correction aid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9 (30%)</td>
<td>10 (33%)</td>
<td>19 (32%)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (70%)</td>
<td>20 (67%)</td>
<td>41 (68%)</td>
</tr>
<tr>
<td>Refractive correction aid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasses</td>
<td>18 (60%)</td>
<td>17 (57%)</td>
<td>35 (58%)</td>
</tr>
<tr>
<td>Contact Lenses</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (10%)</td>
<td>2 (7%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Type of lenses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft lenses</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>RGP</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Family history of keratoconus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (80%)</td>
<td>28 (93%)</td>
<td>52 (87%)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (20%)</td>
<td>2 (7%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>History of atopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (67%)</td>
<td>14 (47%)</td>
<td>34 (57%)</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (33%)</td>
<td>16 (53%)</td>
<td>26 (43%)</td>
</tr>
<tr>
<td><strong>STUDY EYE CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Baseline demographic and ocular characteristics of the intention-to-treat population

Summary measures are mean (SD), n (%).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (56)</th>
<th>Group 2 (57)</th>
<th>Group 3 (56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K2 (D)</td>
<td>49.1 (3.5)</td>
<td>50.2 (3.4)</td>
<td>49.7 (3.5)</td>
</tr>
<tr>
<td>Kmax (D)</td>
<td>56.0 (4.8)</td>
<td>57.2 (5.7)</td>
<td>56.6 (5.3)</td>
</tr>
<tr>
<td>Uncorrected visual acuity (logMar)</td>
<td>0.6 (0.4)</td>
<td>0.7 (0.4)</td>
<td>0.7 (0.4)</td>
</tr>
<tr>
<td>Best-corrected visual acuity (logMar)</td>
<td>0.5 (0.4)</td>
<td>0.5 (0.4)</td>
<td>0.5 (0.4)</td>
</tr>
<tr>
<td>Apical corneal thickness (µm)</td>
<td>512 (47.9)</td>
<td>507 (41.2)</td>
<td>509 (44.5)</td>
</tr>
<tr>
<td>Refraction (spherical equivalent) (D)</td>
<td>-0.6 (2.3)</td>
<td>-1.0 (1.6)</td>
<td>-0.8 (2.0)</td>
</tr>
<tr>
<td>CVAQC score</td>
<td>-1.1 (1.0)</td>
<td>-1.2 (1.1)</td>
<td>-1.2 (1.0)</td>
</tr>
<tr>
<td>CHU9D utility score</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
</tr>
</tbody>
</table>
Table 3

<table>
<thead>
<tr>
<th>CORNEAL CROSS-LINKING</th>
<th>STANDARD CARE</th>
<th>Adjusted difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 (D) - ITT population</td>
<td>30</td>
<td>49.7 (3.8)</td>
<td>23</td>
</tr>
<tr>
<td>Sensitivity analysis of primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K2 (D) - PP population</td>
<td>28</td>
<td>49.4 (3.4)</td>
<td>19</td>
</tr>
<tr>
<td>K2 (D) (including all scans with red flags)</td>
<td>30</td>
<td>49.7 (3.8)</td>
<td>25</td>
</tr>
</tbody>
</table>

K2 in study eye at 18 months post-randomization, by treatment group

1Adjusted difference is based on 58 patients in the Intention-To-Treat (ITT) mixed model, 55 in the Per Protocol (PP) model and 58 in the model including tomography scans with red flags who had a baseline K2 measurement and at least one follow-up examination.

2Adjusted for K2 and minimization factors site and number of eyes with progression at baseline.
### Table 4

<table>
<thead>
<tr>
<th></th>
<th>CORNEAL CROSS-LINKING</th>
<th>STANDARD CARE</th>
<th>Adjusted difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong> Mean (SD)</td>
<td><strong>n</strong> Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apical corneal thickness (µm)</strong></td>
<td>28 501.8 (38.0)</td>
<td>22 479.9 (46.3)</td>
<td>16.37 (-2.87 to 35.61)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Uncorrected visual acuity (logMAR)²</strong></td>
<td>29 0.5 (0.3)</td>
<td>25 0.8 (0.6)</td>
<td>-0.31 (-0.50 to -0.11)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Best-corrected visual acuity (logMAR)²</strong></td>
<td>29 0.4 (0.4)</td>
<td>25 0.6 (0.6)</td>
<td>-0.51 (-1.37, 0.35)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Refraction (spherical equivalent) (D)</strong></td>
<td>30 -0.6 (2.0)</td>
<td>25 -0.3 (2.3)</td>
<td>-0.75 (-1.69 to 0.18)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Kmax (D)</strong></td>
<td>30 57.0 (6.2)</td>
<td>22 60.3 (7.7)</td>
<td>-2.11 (-4.81, 0.60)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>CVAQC score³</strong></td>
<td>29 -1.2 (0.8)</td>
<td>25 -1.1 (0.9)</td>
<td>-0.26 (-0.69 to 0.14)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>CHU9D utility score⁴</strong></td>
<td>28 1.0 (0.1)</td>
<td>25 0.9 (0.1)</td>
<td>0.02 (-0.017 to 0.05)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>n (%)</strong></th>
<th><strong>n (%)</strong></th>
<th>Unadjusted odds ratio (95% CI)⁵</th>
<th><strong>n (%)</strong></th>
<th><strong>n (%)</strong></th>
<th>Unadjusted hazard ratio (95% CI)⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed keratoconus progression</strong></td>
<td>30 2 (7%)</td>
<td>28 12 (43%)</td>
<td></td>
<td></td>
<td>0.10 (0.02 to 0.48)</td>
</tr>
</tbody>
</table>

| **Time to confirmed keratoconus progression** | 30 See Figure 4 | 30 See Fig 4                     | 0.13 (0.03 to 0.59) | 0.008 |

**Secondary outcomes at 18 months, by treatment group**

1 Adjusted for baseline and minimization factors site and number of eyes with progression at baseline.

2 Lower logMAR scores correspond to better visual acuity.

3 Lower questionnaire scores indicate better outcome.

4 Higher questionnaire scores indicate better outcome.

5 Analysis unadjusted due to the small proportion of participants having progression event.
HR 0.13 (95% CI 0.03 to 0.59); p=0.008

Progression-free survival

Number at risk

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Standard care</th>
<th>CXL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Standard care</th>
<th>30</th>
<th>28</th>
<th>19</th>
<th>16</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXL</td>
<td>30</td>
<td>30</td>
<td>28</td>
<td>28</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 1: Trial profile

240 screened for eligibility
60 enrolled
80 randomised

30 assigned to OXL
29 received OXL
1 randomised and treated incorrectly
80 included in intention-to-treat analysis

180 ineligible
94 did not progress
60 did not meet inclusion criteria
22 had previous eye surgery
17 declined consent
11 not keratoconus
4 had Down syndrome
2 were unsuitable for trial

30 assigned to Standard Care
28 included in intention-to-treat analysis
23 completed 18-month follow-up
18 missed 18-month assessment
2 KF 18-month data were excluded due to unreliable scan results

1 did not undergo treatment
2 withdrew after randomisation
2 did not undergo treatment
1 lost to follow-up
1 withdrew consent
26 received Standard Care
5 crossed-over as per protocol
Figure 2
Figure 3A

A

Uncorrected visual acuity (logMAR)

0.00 0.20 0.40 0.60 0.80 1.00 1.20

Baseline 3 Month 6 Month 9 Month 12 Month 15 Month 18 Month

OUL Standard care
Figure 3B
Figure 3C

![Graph showing changes in axial corneal thickness (μm) over time (Baseline, 3 Month, 6 Month, 9 Month, 12 Month, 15 Month, 18 Month). Two lines represent DKU and Standard care groups.](image-url)
Larkin et al.
Effect of corneal cross-linking vs standard care on keratoconus progression in young patients: the Keralink randomized controlled trial

PRECIS

In 10-16 year old patients with confirmed progressive keratoconus, cross-linking had a significant advantage at 18 months compared to those treated by standard care with glasses or contact lenses.
Keralink Trial Study Group

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