



## Clinical trial results:

### Corneal cross-linking versus standard care in children with keratoconus, a randomised, multicentre, observer-masked trial of efficacy and safety

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2016-001460-11   |
| Trial protocol           | GB               |
| Global end of trial date | 20 December 2023 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 03 May 2024  |
| First version publication date | 03 May 2024  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 15/0599 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN17303768 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |                                                                                 |
|------------------------------|---------------------------------------------------------------------------------|
| Sponsor organisation name    | UCL                                                                             |
| Sponsor organisation address | 90 High Holborn, London, United Kingdom,                                        |
| Public contact               | Clinical Project Manager, UCL CCTU, +44 020 3108 3942 ,<br>v.mccudden@ucl.ac.uk |
| Scientific contact           | Clinical Project Manager, UCL CCTU, +44 020 3108 3942 ,<br>v.mccudden@ucl.ac.uk |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 26 January 2023  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 26 January 2023  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 20 December 2023 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the clinical trial is to establish whether cross-linking is efficacious in stabilising the progression of keratoconus, and whether it is safe in patients under 17 years. The main outcome measure will be the change in Kmax overall in the 2 groups in the time from randomisation and completion of 18 months follow-up. Kmax is an indicator derived from corneal topography and changes in this measure indicate whether keratoconus is progressing or not. Safety of CXL will also be monitored carefully at all follow up time points.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act 2018, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Averse Events were collected throughout the trial and treated accordingly. As participation was voluntary, participants were free to discontinue at any given time without giving reason and without it affecting their normal standard of care.

Background therapy: -

Evidence for comparator: -

|                                                           |                                       |
|-----------------------------------------------------------|---------------------------------------|
| Actual start date of recruitment                          | 01 July 2016                          |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Safety, Efficacy, Scientific research |
| Long term follow-up duration                              | 30 Months                             |
| Independent data monitoring committee (IDMC) involvement? | Yes                                   |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 60 |
| Worldwide total number of subjects   | 60                 |
| EEA total number of subjects         | 0                  |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|                                          |    |
|------------------------------------------|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 60 |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 60 |
| Number of subjects completed | 60 |

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Baseline                |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Assessor <sup>[1]</sup> |

Blinding implementation details:

Assessors were masked to treatment allocation.

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Cross-linking (CXL) |

Arm description:

Corneal collagen cross-linking (CXL) in one or both eyes (according to whether progression is confirmed in one eye or both), under general or local anaesthesia as applicable, followed by standard management.

|                                        |                               |
|----------------------------------------|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | Riboflavin eye drops          |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Ear/eye/nasal drops, solution |
| Routes of administration               | Ocular use                    |

Dosage and administration details:

Following removal of corneal epithelium and administration of riboflavin drops, ultraviolet light will be administered according to standardised parameters of 10mW/cm<sup>2</sup> for a 5.4J/cm<sup>2</sup> total energy dose.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Standard care |
|------------------|---------------|

Arm description:

Standard management alone, including refraction testing with provision of glasses and/or specialist contact lens fitting. Glasses or contact lenses to be provided for one or both eyes as required for best corrected visual acuity. Those patients who develop advanced disease and poor spectacle- and lens corrected visual acuity during the course of the trial will be offered corneal transplantation.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | No IMP            |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Not assigned      |
| Routes of administration               | Other use         |

Dosage and administration details:

No IMP.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: We reported the trial as an observer-masked trial. We did not call it a single-blind trial as neither the main investigators nor the patients were masked. However, the only way to add clarification of masking of assessor is by clicking the single-blind option on the form.

| Number of subjects in period 1 | Cross-linking (CXL) | Standard care |
|--------------------------------|---------------------|---------------|
| Started                        | 30                  | 30            |
| Completed                      | 30                  | 30            |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | ITT                     |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Assessor <sup>[2]</sup> |

## Arms

|                                        |                               |
|----------------------------------------|-------------------------------|
| Are arms mutually exclusive?           | Yes                           |
| <b>Arm title</b>                       | Cross-linking (CXL)           |
| Arm description: -                     |                               |
| Arm type                               | Experimental                  |
| Investigational medicinal product name | Riboflavin eye drops          |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Ear/eye/nasal drops, solution |
| Routes of administration               | Ocular use                    |

Dosage and administration details:

Following removal of corneal epithelium and administration of riboflavin drops, ultraviolet light will be administered according to standardised parameters of 10mW/cm<sup>2</sup> for a 5.4J/cm<sup>2</sup> total energy dose.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Standard care |
|------------------|---------------|

Arm description:

Standard management alone to include provision of glasses and/or contact lenses as required for best corrected visual acuity.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | No IMP            |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Not assigned      |
| Routes of administration               | Other use         |

Dosage and administration details:

No IMP

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: We reported the trial as an observer-masked trial. We did not call it a single-blind trial as

neither the main investigators nor the patients were masked. However, the only way to add clarification of masking of assessor is by clicking the single-blind option on the form.

| <b>Number of subjects in period 2</b> | Cross-linking (CXL) | Standard care |
|---------------------------------------|---------------------|---------------|
| Started                               | 30                  | 30            |
| Completed                             | 30                  | 28            |
| Not completed                         | 0                   | 2             |
| Consent withdrawn by subject          | -                   | 2             |

### Period 3

|                              |                |
|------------------------------|----------------|
| Period 3 title               | LTFU           |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Cross-linking (CXL) |

Arm description: -

|                                        |                               |
|----------------------------------------|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | Riboflavin eye drops          |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Ear/eye/nasal drops, solution |
| Routes of administration               | Ocular use                    |

Dosage and administration details:

Following removal of corneal epithelium and administration of riboflavin drops, ultraviolet light will be administered according to standardised parameters of 10mW/cm<sup>2</sup> for a 5.4J/cm<sup>2</sup> total energy dose.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Standard care |
|------------------|---------------|

Arm description: -

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | No IMP            |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Not assigned      |
| Routes of administration               | Other use         |

Dosage and administration details:

Not an IMP - standard management alone to include provision of glasses and/or contact lenses as required for best corrected visual acuity.

| <b>Number of subjects in period 3</b> | Cross-linking (CXL) | Standard care |
|---------------------------------------|---------------------|---------------|
| Started                               | 30                  | 28            |
| Completed                             | 22                  | 16            |
| Not completed                         | 8                   | 12            |
| Consent withdrawn by subject          | 8                   | 12            |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                |                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Cross-linking (CXL) |
| Reporting group description:<br>Corneal collagen cross-linking (CXL) in one or both eyes (according to whether progression is confirmed in one eye or both), under general or local anaesthesia as applicable, followed by standard management.                                                                                                                                                                                                |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Standard care       |
| Reporting group description:<br>Standard management alone, including refraction testing with provision of glasses and/or specialist contact lens fitting. Glasses or contact lenses to be provided for one or both eyes as required for best corrected visual acuity. Those patients who develop advanced disease and poor spectacle- and lens corrected visual acuity during the course of the trial will be offered corneal transplantation. |                     |

| Reporting group values                              | Cross-linking (CXL) | Standard care | Total |
|-----------------------------------------------------|---------------------|---------------|-------|
| Number of subjects                                  | 30                  | 30            | 60    |
| Age categorical<br>Units: Subjects                  |                     |               |       |
| In utero                                            |                     |               | 0     |
| Preterm newborn infants (gestational age < 37 wks)  |                     |               | 0     |
| Newborns (0-27 days)                                |                     |               | 0     |
| Infants and toddlers (28 days-23 months)            |                     |               | 0     |
| Children (2-11 years)                               |                     |               | 0     |
| Adolescents (12-17 years)                           |                     |               | 0     |
| Adults (18-64 years)                                |                     |               | 0     |
| From 65-84 years                                    |                     |               | 0     |
| 85 years and over                                   |                     |               | 0     |
| Age continuous<br>Units: years                      |                     |               |       |
| arithmetic mean                                     | 15.2                | 15.2          |       |
| standard deviation                                  | ± 1.1               | ± 1.6         | -     |
| Gender categorical<br>Units: Subjects               |                     |               |       |
| Female                                              | 5                   | 11            | 16    |
| Male                                                | 25                  | 19            | 44    |
| Number of eyes eligible<br>Units: Subjects          |                     |               |       |
| One                                                 | 27                  | 26            | 53    |
| Two                                                 | 3                   | 4             | 7     |
| Ethnicity<br>Units: Subjects                        |                     |               |       |
| White                                               | 12                  | 5             | 17    |
| Mixed                                               | 4                   | 2             | 6     |
| Asian or Asian British                              | 10                  | 17            | 27    |
| Black or Black British                              | 3                   | 4             | 7     |
| Other                                               | 1                   | 2             | 3     |
| Use of refractive correction aid<br>Units: Subjects |                     |               |       |

|                                                                                                     |               |               |    |
|-----------------------------------------------------------------------------------------------------|---------------|---------------|----|
| Yes                                                                                                 | 21            | 20            | 41 |
| No                                                                                                  | 9             | 10            | 19 |
| Family history of Keratoconus<br>Units: Subjects                                                    |               |               |    |
| Yes                                                                                                 | 10            | 16            | 26 |
| No                                                                                                  | 20            | 14            | 34 |
| K2 in Study eye<br>Units: Dioptre<br>arithmetic mean<br>standard deviation                          | 49.1<br>± 3.5 | 50.2<br>± 3.4 | -  |
| Apical thickness<br>Units: µm<br>arithmetic mean<br>standard deviation                              | 512<br>± 47.9 | 507<br>± 41.2 | -  |
| Uncorrected visual acuity in study eye<br>Units: logMar<br>arithmetic mean<br>standard deviation    | 0.6<br>± 0.4  | 0.7<br>± 0.4  | -  |
| Best corrected visual acuity in study eye<br>Units: logMar<br>arithmetic mean<br>standard deviation | 0.5<br>± 0.4  | 0.5<br>± 0.4  | -  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                |                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Cross-linking (CXL) |
| Reporting group description:<br>Corneal collagen cross-linking (CXL) in one or both eyes (according to whether progression is confirmed in one eye or both), under general or local anaesthesia as applicable, followed by standard management.                                                                                                                                                                                                |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Standard care       |
| Reporting group description:<br>Standard management alone, including refraction testing with provision of glasses and/or specialist contact lens fitting. Glasses or contact lenses to be provided for one or both eyes as required for best corrected visual acuity. Those patients who develop advanced disease and poor spectacle- and lens corrected visual acuity during the course of the trial will be offered corneal transplantation. |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Cross-linking (CXL) |
| Reporting group description: -                                                                                                                                                                                                                                                                                                                                                                                                                 |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Standard care       |
| Reporting group description:<br>Standard management alone to include provision of glasses and/or contact lenses as required for best corrected visual acuity.                                                                                                                                                                                                                                                                                  |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Cross-linking (CXL) |
| Reporting group description: -                                                                                                                                                                                                                                                                                                                                                                                                                 |                     |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                          | Standard care       |
| Reporting group description: -                                                                                                                                                                                                                                                                                                                                                                                                                 |                     |

### Primary: Difference in K2

|                                                         |                  |
|---------------------------------------------------------|------------------|
| End point title                                         | Difference in K2 |
| End point description:                                  |                  |
| End point type                                          | Primary          |
| End point timeframe:<br>At 18months post randomisation. |                  |

| End point values                     | Cross-linking (CXL) | Standard care   |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 30                  | 23              |  |  |
| Units: D                             |                     |                 |  |  |
| arithmetic mean (standard deviation) | 49.7 (± 3.8)        | 53.4 (± 5.8)    |  |  |

### Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | Primary analysis                    |
| Comparison groups          | Standard care v Cross-linking (CXL) |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| Number of subjects included in analysis | 53                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.002                          |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | -3                               |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -4.93                            |
| upper limit                             | -1.08                            |

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | Per protocol analysis               |
| Comparison groups                       | Standard care v Cross-linking (CXL) |
| Number of subjects included in analysis | 53                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.001                             |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | -3.23                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -5.21                               |
| upper limit                             | -1.26                               |

## Secondary: Difference in apical thickness

|                                 |                                |
|---------------------------------|--------------------------------|
| End point title                 | Difference in apical thickness |
| End point description:          |                                |
| End point type                  | Secondary                      |
| End point timeframe:            |                                |
| At 18 months from randomisation |                                |

| End point values                     | Cross-linking (CXL) | Standard care   |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 28                  | 22              |  |  |
| Units: µm                            |                     |                 |  |  |
| arithmetic mean (standard deviation) | 501.8 (± 38.0)      | 479.9 (± 46.3)  |  |  |

## Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | Secondary outcome analysis          |
| Comparison groups                       | Standard care v Cross-linking (CXL) |
| Number of subjects included in analysis | 50                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.1                               |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | 16.37                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -2.87                               |
| upper limit                             | 35.61                               |

## Secondary: Difference in uncorrected visual acuity

|                                |                                         |
|--------------------------------|-----------------------------------------|
| End point title                | Difference in uncorrected visual acuity |
| End point description:         |                                         |
| End point type                 | Secondary                               |
| End point timeframe:           |                                         |
| At 18months from randomisation |                                         |

|                                      |                     |                 |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>              | Cross-linking (CXL) | Standard care   |  |  |
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 29                  | 25              |  |  |
| Units: logMar                        |                     |                 |  |  |
| arithmetic mean (standard deviation) | 0.5 (± 0.3)         | 0.8 (± 0.6)     |  |  |

## Statistical analyses

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | Secondary outcome analysis          |
| Comparison groups                 | Standard care v Cross-linking (CXL) |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 54                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.002                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.13                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.5                           |
| upper limit                             | -0.11                          |

## Secondary: Difference in best corrected visual acuity

|                                  |                                            |
|----------------------------------|--------------------------------------------|
| End point title                  | Difference in best corrected visual acuity |
| End point description:           |                                            |
|                                  |                                            |
| End point type                   | Secondary                                  |
| End point timeframe:             |                                            |
| At 18 months from randomisation. |                                            |

| End point values                     | Cross-linking (CXL) | Standard care   |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 29                  | 25              |  |  |
| Units: logMar                        |                     |                 |  |  |
| arithmetic mean (standard deviation) | 0.4 (± 0.4)         | 0.6 (± 0.6)     |  |  |

## Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | Secondary outcome analysis          |
| Comparison groups                       | Standard care v Cross-linking (CXL) |
| Number of subjects included in analysis | 54                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.002                             |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | -0.3                                |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.48                               |
| upper limit                             | -0.11                               |

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**Secondary: Progression free survival**

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|                 |                           |
|-----------------|---------------------------|
| End point title | Progression free survival |
|-----------------|---------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomisation to 18 months.

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| End point values              | Cross-linking (CXL) | Standard care   |  |  |
|-------------------------------|---------------------|-----------------|--|--|
| Subject group type            | Reporting group     | Reporting group |  |  |
| Number of subjects analysed   | 30                  | 28              |  |  |
| Units: Number of progressions |                     |                 |  |  |
| Progressed                    | 2                   | 12              |  |  |
| Did not progress              | 28                  | 16              |  |  |

**Statistical analyses**

|                            |                            |
|----------------------------|----------------------------|
| Statistical analysis title | Secondary outcome analysis |
|----------------------------|----------------------------|

|                   |                                     |
|-------------------|-------------------------------------|
| Comparison groups | Cross-linking (CXL) v Standard care |
|-------------------|-------------------------------------|

|                                         |    |
|-----------------------------------------|----|
| Number of subjects included in analysis | 58 |
|-----------------------------------------|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |         |
|---------|---------|
| P-value | = 0.008 |
|---------|---------|

|        |                 |
|--------|-----------------|
| Method | Regression, Cox |
|--------|-----------------|

|                    |                         |
|--------------------|-------------------------|
| Parameter estimate | Cox proportional hazard |
|--------------------|-------------------------|

|                |      |
|----------------|------|
| Point estimate | 0.13 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.03 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 0.59 |
|-------------|------|

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**Other pre-specified: Difference in K2**

---

|                 |                  |
|-----------------|------------------|
| End point title | Difference in K2 |
|-----------------|------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At 48 months from randomisation.

---

| <b>End point values</b>              | Cross-linking (CXL) | Standard care   |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 20                  | 11              |  |  |
| Units: D                             |                     |                 |  |  |
| arithmetic mean (standard deviation) | 48.8 (± 3.4)        | 54.0 (± 5.7)    |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | LTFU outcome analysis               |
|-----------------------------------------|-------------------------------------|
| Comparison groups                       | Standard care v Cross-linking (CXL) |
| Number of subjects included in analysis | 31                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.02                              |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | -3.23                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -5.99                               |
| upper limit                             | -0.46                               |

### Other pre-specified: Difference in apical thickness

|                                 |                                |
|---------------------------------|--------------------------------|
| End point title                 | Difference in apical thickness |
| End point description:          |                                |
| End point type                  | Other pre-specified            |
| End point timeframe:            |                                |
| At 48 months from randomisation |                                |

| <b>End point values</b>              | Cross-linking (CXL) | Standard care   |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 21                  | 15              |  |  |
| Units: µm                            |                     |                 |  |  |
| arithmetic mean (standard deviation) | 475.7 (± 31.3)      | 446.2 (± 42.2)  |  |  |

## Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | LTFU outcome analysis               |
| Comparison groups                       | Standard care v Cross-linking (CXL) |
| Number of subjects included in analysis | 36                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.02                              |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | 25.86                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 3.54                                |
| upper limit                             | 48.18                               |

## Other pre-specified: Difference in uncorrected visual acuity

|                                  |                                         |
|----------------------------------|-----------------------------------------|
| End point title                  | Difference in uncorrected visual acuity |
| End point description:           |                                         |
| End point type                   | Other pre-specified                     |
| End point timeframe:             |                                         |
| At 48 months from randomisation. |                                         |

|                                      |                     |                 |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>              | Cross-linking (CXL) | Standard care   |  |  |
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 21                  | 15              |  |  |
| Units: logMar                        |                     |                 |  |  |
| arithmetic mean (standard deviation) | 0.5 (± 0.4)         | 0.9 (± 0.5)     |  |  |

## Statistical analyses

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | LTFU outcome analysis               |
| Comparison groups                 | Standard care v Cross-linking (CXL) |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 36                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.005                        |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.36                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.62                          |
| upper limit                             | -0.11                          |

### Other pre-specified: Difference in best corrected visual acuity

|                                 |                                            |
|---------------------------------|--------------------------------------------|
| End point title                 | Difference in best corrected visual acuity |
| End point description:          |                                            |
| End point type                  | Other pre-specified                        |
| End point timeframe:            |                                            |
| At 48 weeks post randomisation. |                                            |

| End point values            | Cross-linking (CXL) | Standard care   |  |  |
|-----------------------------|---------------------|-----------------|--|--|
| Subject group type          | Reporting group     | Reporting group |  |  |
| Number of subjects analysed | 21                  | 16              |  |  |
| Units: logMar               |                     |                 |  |  |
| median (standard deviation) | 0.4 (± 0.4)         | 0.7 (± 0.5)     |  |  |

### Statistical analyses

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| <b>Statistical analysis title</b>       | LTFU outcome analysis               |
| Comparison groups                       | Cross-linking (CXL) v Standard care |
| Number of subjects included in analysis | 37                                  |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | superiority                         |
| P-value                                 | = 0.004                             |
| Method                                  | Mixed models analysis               |
| Parameter estimate                      | Mean difference (final values)      |
| Point estimate                          | -0.32                               |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | -0.55                               |
| upper limit                             | -0.11                               |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomisation to 18 months.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |   |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Cross-linking (CXL) |
|-----------------------|---------------------|

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | Standard care |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events                            | Cross-linking (CXL) | Standard care  |  |
|---------------------------------------------------|---------------------|----------------|--|
| Total subjects affected by serious adverse events |                     |                |  |
| subjects affected / exposed                       | 0 / 30 (0.00%)      | 0 / 30 (0.00%) |  |
| number of deaths (all causes)                     | 0                   | 0              |  |
| number of deaths resulting from adverse events    | 0                   | 0              |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                                          | Cross-linking (CXL) | Standard care  |  |
|---------------------------------------------------------------------|---------------------|----------------|--|
| Total subjects affected by non-serious adverse events               |                     |                |  |
| subjects affected / exposed                                         | 4 / 30 (13.33%)     | 2 / 30 (6.67%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                |  |
| Cyst on Right eyebrow                                               |                     |                |  |
| subjects affected / exposed                                         | 1 / 30 (3.33%)      | 0 / 30 (0.00%) |  |
| occurrences (all)                                                   | 1                   | 0              |  |
| Congenital, familial and genetic disorders                          |                     |                |  |
| ADHD                                                                |                     |                |  |
| subjects affected / exposed                                         | 0 / 30 (0.00%)      | 1 / 30 (3.33%) |  |
| occurrences (all)                                                   | 0                   | 1              |  |
| Autism spectrum disorder                                            |                     |                |  |
| subjects affected / exposed                                         | 0 / 30 (0.00%)      | 1 / 30 (3.33%) |  |
| occurrences (all)                                                   | 0                   | 1              |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| General disorders and administration site conditions |                |                |  |
| Flu like symptoms                                    |                |                |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences (all)                                    | 1              | 0              |  |
| Hayfever                                             |                |                |  |
| subjects affected / exposed                          | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)                                    | 0              | 1              |  |
| Tonsillitis                                          |                |                |  |
| subjects affected / exposed                          | 2 / 30 (6.67%) | 0 / 30 (0.00%) |  |
| occurrences (all)                                    | 2              | 0              |  |
| Hypermobility syndrome                               |                |                |  |
| subjects affected / exposed                          | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)                                    | 0              | 1              |  |
| Loose suture to graft (non-eye)                      |                |                |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences (all)                                    | 1              | 0              |  |
| Eye disorders                                        |                |                |  |
| Eye pain                                             |                |                |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences (all)                                    | 1              | 0              |  |
| Lump on cornea                                       |                |                |  |
| subjects affected / exposed                          | 1 / 30 (3.33%) | 0 / 30 (0.00%) |  |
| occurrences (all)                                    | 1              | 0              |  |
| Psychiatric disorders                                |                |                |  |
| Anxiety                                              |                |                |  |
| subjects affected / exposed                          | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)                                    | 0              | 1              |  |
| Musculoskeletal and connective tissue disorders      |                |                |  |
| Clavicle pain post fracture                          |                |                |  |
| subjects affected / exposed                          | 0 / 30 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)                                    | 0              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 June 2016     | <ul style="list-style-type: none"><li>• Measurement of corneal thickness was changed from central to apical</li><li>• To clarify in the protocol that the ophthalmologist will be blinded to the Kmax value which will be measured by optometrist.</li><li>• To clarify the secondary outcome measure from 'Time to Keratoconus Progression' to 'Time to Keratoconus progression (defined as &gt;1.5 dioptres increase in Kmax)'</li><li>• Administrative changes throughout the protocol.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 23 January 2017  | <ol style="list-style-type: none"><li>1. Clarification of inclusion criterion 1 - Progression for eligibility is defined as an increase of at least 1.5 dioptres in Kmax on Pentacam corneal topography (or equivalent on other topography devices) between two examinations done using the same scanning technique at least 3 months apart.</li><li>2. Clarification of exclusion criterion 3 – Addition of another parameter under exclusion criteria and changing the upper limit of Kmax. Steepest corneal meridian (K2) &gt;62 dioptres and maximum corneal curvature (Kmax) &gt;70 dioptres</li><li>3. Clarification of primary outcome - Primary outcome measure is the value of the steepest corneal meridian (K2) in the study eye at 18 months post randomisation using standard Pentacam corneal topography</li><li>4. Changing the outcome measure from Kmax to K2 – Across the entire protocol</li><li>5. Administrative changes throughout the protocol</li></ol> |
| 08 November 2017 | <ol style="list-style-type: none"><li>1. Amended the Primary Registry to EudraCT as this was where the study was first registered</li><li>2. Updated the number of sites participating in Keralink</li><li>3. Re-defined the 'end of trial' taking into account the added longer term follow up sub-study</li><li>4. Clarified the change in data collection from UCL CCTU receiving copies of paper CRFs and updating the MACRO database to sites team members remotely entering the data in the MACRO database</li><li>5. Confirmed that the study data will be published in two stages: following the end of the main study and following completion of the longer term follow up sub-study</li><li>6. Confirmed the addition of one optional sub-study (longer term follow up)</li><li>7. Appendix 1 – the addition of the longer term follow up sub-study</li><li>8. Administrative changes throughout the protocol</li></ol>                                              |
| 12 February 2020 | Appendix 1 / Section 11.1.5 – the addition of remote consent for participants of the main KERALINK study who have previously declined consent to participate in the long term follow up sub-study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31515418>

<http://www.ncbi.nlm.nih.gov/pubmed/32532321>

<http://www.ncbi.nlm.nih.gov/pubmed/33892046>