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 , v.mccudden@ucl.ac.uk
Scientific contact	Clinical Project Manager, UCL CCTU, +44 020 3108 3942 , 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[1]

Blinding implementation details:

Assessors were masked to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	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/cm2 for a 5.4J/cm2 total energy dose.

Arm title	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[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	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/cm2 for a 5.4J/cm2 total energy dose.

Arm title	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.

Number of subjects in period 2	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
Arm title	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/cm2 for a 5.4J/cm2 total energy dose.

Arm title	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.

Number of subjects in period 3	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:	
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:	
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 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 Units: years			
arithmetic mean	15.2	15.2	
standard deviation	± 1.1	± 1.6	-
Gender categorical Units: Subjects			
Female	5	11	16
Male	25	19	44
Number of eyes eligible Units: Subjects			
One	27	26	53
Two	3	4	7
Ethnicity 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 Units: Subjects			

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

End points

End points reporting groups

Reporting group title	Cross-linking (CXL)
Reporting group 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.	
Reporting group title	Standard care
Reporting group 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.	
Reporting group title	Cross-linking (CXL)
Reporting group description: -	
Reporting group title	Standard care
Reporting group description:	
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:	
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

Statistical analysis title	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

Statistical analysis title	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	

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)	0.5 (± 0.3)	0.8 (± 0.6)		

Statistical analyses

Statistical analysis title	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

Statistical analysis title	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

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 18 months.

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

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.

End point values	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

Statistical analysis title	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

End point values	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

Statistical analysis title	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.	

End point values	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

Statistical analysis title	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

Statistical analysis title	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	
Tonsilitis			
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 sutureto 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	• Measurement of corneal thickness was changed from central to apical • To clarify in the protocol that the ophthalmologist will be blinded to the Kmax value which will be measured by optometrist. • To clarify the secondary outcome measure from 'Time to Keratoconus Progression' to 'Time to Keratoconus progression (defined as >1.5 dioptres increase in Kmax)' • Administrative changes throughout the protocol.
23 January 2017	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. 2. Clarification of exclusion criterion 3 – Addition of another parameter under exclusion criteria and changing the upper limit of Kmax. Steepest corneal meridian (K2) >62 dioptres and maximum corneal curvature (Kmax) >70 dioptres 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 4. Changing the outcome measure from Kmax to K2 – Across the entire protocol 5. Administrative changes throughout the protocol
08 November 2017	1. Amended the Primary Registry to EudraCT as this was where the study was first registered 2. Udated the number of sites participating in Keralink 3. Re-defined the 'end of trial' taking into account the added longer term follow up sub-study 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 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 6. Confirmed the addition of one optional sub-study (longer term follow up) 7. Appendix 1 – the addition of the longer term follow up sub-study 8. Administrative changes throughout the protocol
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

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