Clinical trial results:
To evaluate the safety and effectiveness of human ex vivo expanded autologous limbal stem cells for the treatment of unilateral total limbal stem cell deficiency.

Summary

EudraCT number	2011-000608-16
Trial protocol	GB
Global end of trial date	09 February 2018

Results information

Result version number	v1 (current)
This version publication date	02 June 2024
First version publication date	02 June 2024

Trial information

Trial identification

Sponsor protocol code	5466

Additional study identifiers

ISRCTN number	ISRCTN51772481
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Prof Francisco Figueiredo, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 0191 282 5582, f.c.figueiredo@ncl.ac.uk
Scientific contact	Prof Francisco Figueiredo, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 0191 282 5582, f.c.figueiredo@ncl.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	17 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2018
Global end of trial reached?	Yes
Global end of trial date	09 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy (or capacity to produce a desired effect) of ex vivo expanded autologous Limbal Stem Cells transplantation (transplant derived from the same patient, animal free and grown ex vivo or outside the body) for the treatment of unilateral total Limbal Stem Cell Deficiency (a severe corneal disease resulting in painful blindness). The product is manufactured according to GMP guidelines and under a Quality Management System.

Protection of trial subjects:

All non-serious adverse events/reaction will be recorded at all visits up to visit 7 at 12 months and all non-serious
adverse reactions from visit 7 at 12 months to visit 10 at 36 months.

Any serious adverse events will be recorded throughout the duration of the study until 36 months.

Background therapy:

Ex vivo expansion of autologous limbal stem cells transplantation on amniotic membrane has been used in a few centres around
the world, including the UK for the treatment of unilateral total limbal stem cell deficiency, even though this is an unlicensed
indication. For purposes of this study, Ex vivo expansion of autologous limbal stem cells transplantation on amniotic
membrane is both an Advanced Therapeutic Medicinal Product (ATMP) and an Investigational Medicinal Product and thus it meets the combined definition of an Advanced Therapeutic Investigational Medicinal Product (ATIMP) Regulation (EU) No 1394/2007.

Evidence for comparator:

Corneal vascularisation and opacity cause blindness in ~8 million people worldwide pa, but the importance of limbal stem cells (LSC), and the symptoms of their dysfunction as a major cause of corneal blindness, have been appreciated only recently. In LSC deficiency (LSCD), reduced vision is due to corneal pathology as the eye is otherwise healthy; effective treatment of LSCD and associated corneal scarring would restore vision.

This group has developed a system to culture human limbal epithelium without the use of animal cells/products, and has successfully transplanted nine patients with unilateral severe LSCD. Autologous human serum drops, from patients' blood, and the culture medium, are used post-operatively to treat any ocular surface problems. Significantly declined symptom severity, significant improvement in visual impairment scores, and in Snellen visual acuity, were observed. Corneal impression cytology at six months post-procedure confirmed the reversal of conjunctivalisation.

Treatment of severe symptomatic total LSCD is mainly surgical – a limbal tissue autograft from the patient's healthy other eye. In bilateral LSCD, allografts from living related/cadaveric donors are used, with potent immunosuppression. However, much healthy tissue is required, potentially causing LSCD in the donor.

Recently, small amounts of healthy human limbal epithelium have been expanded ex vivo in culture to form epithelial sheets, and transplanted, with reduced risk of donor LSCD.

This formal clinical trial aims to establish transplantation of cultured limbal epithelium as a clinical treatment option for LSCD. Most current techniques also use animal products, precluding their clinical use to treat UK patients legally. There is also an increasing need to substitute animal-based products during the ex vivo expansion of the cells, due to the risk of transmission of retroviruses, other

pathogens or other infectious agents to patients and the wider population.

Actual start date of recruitment	30 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	0
Adults (18-64 years)	25
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period ran from 15 May 2012 to 05 January 2015 from one NHS hospital site in the United Kingdom. This was the Royal Victoria Infirmary in Newcastle upon Tyne (The Newcastle upon Tyne Hospitals NHS Foundation Trust).

Pre-assignment

Screening details:

Potential participants were identified by the CI via routine clinic outpatient appointments. The CI/Co-I/Authorised Delegate explained the study to eligible patients. Eligibility screening forms were completed, to document patients' fulfilment of the eligibility criteria, whether included or not.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	LSC Transplant

Arm description: -

Arm type	surgical intervention
Investigational medicinal product name	Autologous LSC transplant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ophthalmic insert
Routes of administration	Route of administration not applicable

Dosage and administration details:

Autologous Limbal Stem Cell (LSC) transplantation

Number of subjects in period 1	LSC Transplant
Started	27
Biopsy	26
Completed	23
Not completed	4
No cell growth	2
failed biopsy	1
Consent withdrawn by subject	1

Period 2	
Period 2 title	6 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:
Not applicable

Arms

Arm title	LSC Transplant

Arm description: -

Arm type	surgical intervention
Investigational medicinal product name	Autologous LSC transplant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ophthalmic insert
Routes of administration	Route of administration not applicable

Dosage and administration details:
Autologous Limbal Stem Cell (LSC) transplantation

Number of subjects in period 2	LSC Transplant
Started	23
Completed	23

Period 3	
Period 3 title	12 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:
Not applicable

Arms

Arm title	LSC Transplant

Arm description: -

Arm type	surgical intervention
Investigational medicinal product name	Autologous LSC transplant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ophthalmic insert
Routes of administration	Route of administration not applicable

Dosage and administration details:
Autologous Limbal Stem Cell (LSC) transplantation

Number of subjects in period 3	LSC Transplant
Started	23
Completed	23

Period 4	
Period 4 title	36 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:
Not applicable

Arms

Arm title	LSC Transplant

Arm description: -

Arm type	surgical intervention
Investigational medicinal product name	Autologous LSC transplant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ophthalmic insert
Routes of administration	Route of administration not applicable

Dosage and administration details:
Autologous Limbal Stem Cell (LSC) transplantation

Number of subjects in period 4	LSC Transplant
Started	23
Completed	22
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	27	27	
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			
median	44.5		
inter-quartile range (Q1-Q3)	29.9 to 51.5	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	22	22	
Race Units: Subjects			
White/Caucasian	27	27	
Currently employed Units: Subjects			
Yes	11	11	
No	9	9	
Stopped due to LSCD	7	7	
Occupation Units: Subjects			
Professional	1	1	
Technical	4	4	
Administrative	2	2	
Labourer	7	7	
Sales	1	1	
Housewife/ husband	2	2	
Retired	5	5	
Other	4	4	
Unknown	1	1	
Ophtmalmic history at screening- Eye affected			

Units: Subjects			
Right	14	14	
Left	13	13	
Cause of LSCD Units: Subjects			
Chemical burn	21	21	
Thermal burn	4	4	
Iatrogenic	1	1	
Infection	1	1	

End points

End points reporting groups

Reporting group title	LSC Transplant
Reporting group description: -	
Reporting group title	LSC Transplant
Reporting group description: -	
Reporting group title	LSC Transplant
Reporting group description: -	
Reporting group title	LSC Transplant
Reporting group description: -	

Primary: The percent of subjects with treatment emergent ocular AEs

End point title	The percent of subjects with treatment emergent ocular AEs[1]
End point description:	
The percent of subjects with treatment emergent ocular AEs.	
End point type	Primary
End point timeframe:	
12 months.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive summary is only available.

End point values	LSC Transplant			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Percentage points	10			

Statistical analyses

No statistical analyses for this end point

Primary: Ocular surface pain/discomfort

End point title	Ocular surface pain/discomfort
End point description:	
The first end-point of the phase II clinical trial will assess changes of patients' reported outcomes: ocular surface pain/discomfort (the primary outcome on which the study was powered) and visual impairment scores from baseline to visit 7 at 12 months. This will be measured in both cases using an analogue scale, which has already been validated in the phase I component of the project (Attachment III).	
End point type	Primary
End point timeframe:	
baseline to visit 7 at 12 months	

End point values	LSC Transplant	LSC Transplant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[2]	23		
Units: number				
median (inter-quartile range (Q1-Q3))	62.5 (50 to 75)	75 (62.5 to 100)		

Notes:

[2] - 1 missing result

Statistical analyses

Statistical analysis title	Difference in Pain

Statistical analysis description:

The change in pain between baseline and Visit 7 (12 months post-op) was recorded by 'ocular pain' in the National Eye Institute – Visual Function Questionnaire and a Visual Analogue Score for pain. A high score for the Visual Function Questionnaire indicates better functioning and the percentage recorded is the achieved percentage of a total possible score.

Comparison groups	LSC Transplant v LSC Transplant
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Wilcoxon signed ranks test

Primary: Visual impairment score

End point title	Visual impairment score[3]

End point description:

The first end-point of the phase II clinical trial will assess changes of patients' reported outcomes: ocular surface pain/discomfort (the primary outcome on which the study was powered) and visual impairment scores from baseline to visit 7 at 12 months. This will be measured in both cases using an analogue scale, which has already been validated in the phase I component of the project (Attachment III).

End point type	Primary

End point timeframe:

12 months and 36 months.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive summary is only available.

End point values	LSC Transplant			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: number				
median (inter-quartile range (Q1-Q3))	-1 (-3 to 0)			

Statistical analyses

No statistical analyses for this end point

Primary: Corneal impression cytology

End point title	Corneal impression cytology[4]

End point description:

The second end point will be the reversal of LSCD by corneal impression cytology at 6 months post-operatively.

End point type	Primary

End point timeframe:

Six months, post-operative.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive summary is only available.

End point values	LSC Transplant			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: number				
number (confidence interval 95%)	70.3 (49.8 to 86.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Corneal re-epithelialisation

End point title	Corneal re-epithelialisation[5]

End point description:

The third end point is ocular surface reconstruction (i.e. corneal re-epithelialisation).

End point type	Primary

End point timeframe:

12 months and 36 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive summary is only available.

End point values	LSC Transplant	LSC Transplant	LSC Transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[6]	22[7]	21[8]	
Units: number				
number (confidence interval 95%)	81.4 (61.9 to 93.7)	85.1 (66.3 to 95.8)	77.8 (57.7 to 91.4)	

Notes:

[6] - 22 patients in ITT group

[7] - 22 patients in ITT group

[8] - 21 patients analysed in ITT group

Statistical analyses

No statistical analyses for this end point

Secondary: Best corrected visual acuity

End point title	Best corrected visual acuity

End point description:

Changes over the same period in best corrected visual acuity, reversal in central corneal vascularisation, reduction in corneal opacity, improvement in patient's reported outcomes, assessment of corneal opacity by anterior segment OCT, assessment of corneal/limbal epithelia by confocal microscopy and potential side effects as described in the case for support.

End point type	Secondary

End point timeframe:

12 months and 36 months.

End point values	LSC Transplant	LSC Transplant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	13		
Units: number				
median (inter-quartile range (Q1-Q3))	-0.04 (-0.82 to 0.14)	-0.3 (-0.8 to -0.06)		

Statistical analyses

Statistical analysis title	Change in LogMAR score

Statistical analysis description:

Wilcoxon signed ranks test

Comparison groups	LSC Transplant v LSC Transplant
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Wilcoxon signed ranks test

Secondary: Reversal in central corneal vascularisation

End point title	Reversal in central corneal vascularisation

End point description:

Changes over the same period in best corrected visual acuity, reversal in central corneal vascularisation, reduction in corneal opacity, improvement in patient's reported outcomes, assessment of corneal opacity by anterior segment OCT, assessment of corneal/limbal epithelia by confocal microscopy and potential side effects as described in the case for support.

Central corneal neovascularisation (new vessel formation, crossing the limbus onto the clear cornea by ≥ 2mm) (Akpek EK et al.
2004) will be categorised:

0 Absent No evidence of new vessel formation

1 Mild Presence of neovascularisation in 1 quadrant of cornea
2 Moderate Presence of neovascularisation in 2 quadrants of cornea
3 Severe Presence of neovascularisation in ≥ 3 quadrants of cornea

End point type	Secondary

End point timeframe:

12 months and 36 months.

End point values	LSC Transplant	LSC Transplant	LSC Transplant	LSC Transplant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[9]	23	23	22
Units: number				
Absent	1	13	11	10
Mild	1	6	6	8
Moderate	4	2	3	2
Severe	20	2	3	1

Notes:

[9] - missing result from 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in corneal opacity

End point title	Reduction in corneal opacity

End point description:

Changes over the same period in best corrected visual acuity, reversal in central corneal vascularisation, reduction in corneal opacity, improvement in patient's reported outcomes, assessment of corneal opacity by anterior segment OCT, assessment of corneal/limbal epithelia by confocal microscopy and potential side effects as described in the case for support.

Corneal opacity will be categorised as:
0 Clear cornea
+1 Mild scarring
+2 Moderate scarring, iris details still visible
+3 Moderate scarring, iris details obscured
+4 Marked corneal scarring, iris not visible

End point type	Secondary

End point timeframe:

12 months and 36 months.

End point values	LSC Transplant	LSC Transplant	LSC Transplant	LSC Transplant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27[10]	23	23[11]	22
Units: number				
Clear Cornea	0	0	1	10
Mild Scarring	1	4	3	9
Moderate scarring, iris details still visible	6	10	8	2
Moderate scarring, iris details obscured	16	6	7	1
Marked corneal scarring, iris not visible	3	3	3	0

Notes:

[10] - missing result from 1 patient

[11] - missing result from 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in patient-reported outcomes

End point title	Improvement in patient-reported outcomes

End point description:

Ocular surface disease impact questionnaire

End point type	Secondary

End point timeframe:

12 months and 36 months.

End point values	LSC Transplant	LSC Transplant	LSC Transplant	LSC Transplant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[12]	22[13]	23	21[14]
Units: number				
median (inter-quartile range (Q1-Q3))	36.1 (20 to 52.1)	30.7 (21.7 to 38.9)	29.2 (13.9 to 46.7)	23.5 (17.1 to 44.6)

Notes:

[12] - 4 patient results missing

[13] - 1 missing result

[14] - missing result for 2 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of corneal opacity by anterior segment OCT

End point title	Assessment of corneal opacity by anterior segment OCT

End point description:

Assessment of corneal opacity by anterior segment OCT:

Scale 0-4
0= clear cornea
1= mild scarring
2= moderate scarring, iris details still visible,
3=moderate scarring, iris details obscured
4= marked corneal scarring, iris not visible

End point type	Secondary

End point timeframe:

12 months and 36 months.

End point values	LSC Transplant	LSC Transplant	LSC Transplant	LSC Transplant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[15]	23	22[16]	22
Units: number				
Clear cornea	0	0	1	10
mild scarring	1	4	3	9
moderate scarring, iris details still visible	6	10	8	2
moderate scarring, iris details obscured	16	6	7	1
marked corneal scarring, iris not visible	3	3	3	0

Notes:

[15] - missing result from 1 patient

[16] - missing result from 1 patient

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in patient-reported outcomes: National Eye Institute Visual Function Questionnaire

End point title	Improvement in patient-reported outcomes: National Eye Institute Visual Function Questionnaire

End point description:

National Eye Institute Visual Function Questionnaire

End point type	Secondary

End point timeframe:

Baseline, 6 months, 12 months and 36 months

End point values	LSC Transplant	LSC Transplant	LSC Transplant	LSC Transplant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[17]	23	23	21[18]
Units: number				
median (inter-quartile range (Q1-Q3))	73.4 (56.7 to 83.8)	78.8 (58.7 to 84.3)	79.2 (56 to 87.6)	79.6 (64.9 to 89.4)

Notes:

[17] - results missing from 4 patients

[18] - 2 results missing

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Assessment of adverse events will be performed at follow-up visits.	
Adverse event reporting additional description:	
AEs will be assessed at each trial follow-up visit, in person.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Verbatim
Dictionary version	1.0

Reporting groups	
Reporting group title	LSC Transplant

Reporting group description:

In summary:
- there were 42 reported AE in 18 (78% of 23) unique patients
- there were 10 AE related (possibly, probably or definitely) to intervention reported in 7 (30% of 23) unique patients.

Serious adverse events	LSC Transplant		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 27 (37.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
left eye blunt injury with rupture of corneal graft wound			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cellulitis right elbow			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Right corneal graft rejection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

left corneal ulcer, severe ocular surface inflammation? cornea graft rejection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left cornea ulcer with hypopyon				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left corneal graft rejection				
subjects affected / exposed	2 / 27 (7.41%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Left cornea ulcer				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right corneal graft rejection/neurotrophic keratopathy				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perforation of corneal ulcer in the R eye.				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Patient attempted suicide by drug overdose				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LSC Transplant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 27 (66.67%)		
Surgical and medical procedures			
Patient had R hand surgery due to osteoarthitis as a day case on 06/02/14			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Epithelial defect + Associated anterior uveitis.			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Binocular diplopia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Epithelial Defect + associated anterior uveitis + hypopyon			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Epithelial Defect+ localized delayed staining.			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Epithelial Defect + Associated anterior uveitis + Hypopyon.			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
corneal epithelium filaments			

subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
slightly elevated IOP				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
elevated IOP				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
suspected elevated IOP on digital examination to bandage contact lens- caused by steroid medication				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Raised IOP				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Raised IOP to 32mmHg. This is due to steroid treatment. Pressure controlled with topicalantiglaucoma				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Partial Conjuctivalization				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences (all)	3			
metastatic lashes causing epitheliopathy				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	4			
leakage of aquous fluid from central corneal bullae				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
Sharp pain. One off. To be expected after this surgery				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			
scleral perforation at time of corneal transplantation				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences (all)	1			

difficult to identify the explant on the recipient eye. Initially due to local haemorrhage Additional description: difficult to identify the explant on the recipient eye. Initially due to local haemorrhage, now that the blood has resolved, the explant is not definitely visible, although it may be incorporate near a blood vessel.			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Corneal Ulcer			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Filamentary Keratites			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Slow siedel positive corneal leak at site of previous lamellar graft wound.			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Poked self in the eye and dislodge the contact lenses			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
bleeding/oozing from the eye 2 days post- transplant			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Elevated Intra Ocular Pressure			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Bandage Contact Lenses fall out			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Dellen formation inside PKP			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Irritation/Foreign body sensation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Raised IOP digitally			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Bandage contact lens fell out. Patient			

replaced it himself. subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Perforation of cornea. subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Bandage contact lens fell out. Large epithelial defect. subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Bandage contact lens fell out subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Right pos operative cystoid macula edema subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2012	In response to the conditions of favourable opinion specified by REC, the Patient Information Sheet has been amended to include further information on alternative options, if cells do not grow well, and correct REC name. Substantial changes to the study, in response to the MHRA CTA, regarding its duration (to 36 months), and the prohibition of concurrent enrolment of participants in another study.
11 September 2013	The proposed changes to the protocol were the removal of previous amniotic membrane grafting to the donor eye, as an exclusion criterion; and the amendment to specify that only those patients who have been previously transplanted with ex vivo expanded autologous limbal stem cells being excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported