Clinical trial results:
Pilot Clinical Assessment of Ex Vivo Expanded Corneal Limbal Stem Cell Transplantation in Patients with Severe Ocular Surface Disease (OSD) Arising from Limbal Stem Cell Deficiency

Summary

EudraCT number	2010-024409-11
Trial protocol	GB
Global end of trial date	14 March 2016

Results information

Result version number	v1 (current)
This version publication date	30 March 2017
First version publication date	30 March 2017

Trial information

Trial identification

Sponsor protocol code	LSC-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	SNBTS
Sponsor organisation address	21 Ellens Glen road,, Edinburgh, United Kingdom, EH17 7QT
Public contact	Regulatory Compliance Officer, Scottish National Blood Transfusion Service, 0044 131 314 5591, emily.hargreaves@nhs.net
Scientific contact	Associate Director Research Development and Innovation, Scottish National Blood Transfusion Service, 0044 1313145677, johncampbell3@nhs.net
Sponsor organisation name	NHS Lothian
Sponsor organisation address	47 Little France Cres, , Edinburgh, United Kingdom, EH16 4TJ
Public contact	Douglas Young, NHS Lothian, 0044 1312423337, douglas.young@luht.scot.nhs.uk
Scientific contact	Douglas Young, NHS Lothian, 0044 1312423337, douglas.young@luht.scot.nhs.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	02 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2016
Global end of trial reached?	Yes
Global end of trial date	14 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Pilot study examining the efficacy and safety of transplanting ex vivo expanded corneal epithelial limbal stem cells on Amniotic Membrane (AM) as a procedure to restore sight and relieve pain for patients with severe Ocular Surface Disease (OSD) arising from Limbal Stem Cell Deficiency (LSCD). Aim was to:
•Generate the data required for reliable sample size calculations for subsequent studies
•Evaluate all the practicalities and logistics of the study including the recruitment process, follow-up procedures, data collection and analysis
•Obtain information on actual recruitment rate
•The study also aimed to obtain preliminary answers to the following questions:-
•Is transplantation of ex vivo expanded corneal limbal stem cells feasible, efficient and safe?
•Does this procedure lead to improvements in vision and quality of the ocular surface?
•How does immunosuppression and limbal stem cell transplantation compare with using immunosuppression and amniotic membrane alone?

Protection of trial subjects:

Bandage contact lens was placed atop the graft for comfort and protection, also Botox injections were applied to the affected eye lid this induced temporary ptosis which aimed to facilitate the survival of the graft and to protect the epithelium, also a short course of topical antibiotic and steroid eye drops were prescribed to be applied to the affected eye, post surgery.

Background therapy:

Immunosuppressive therapy was tailored according to the patient's individual clinical response.
- Prednisolone: Initial dose of 60 mg daily tapering at 5mg weekly until 10 mg maintenance dosage

plus
- Cyclosporine: Initial dose of 100 mg twice a day then tapered to 50mg twice a day

or
- Mycophenolate mofetil. Dose between 750mg to 1g twice a day

Further, prior to surgery, each patient made a single autologous donation of blood. This allowed preparation of autologous serum eye drops for the patient's own use post-surgery.

Evidence for comparator:

The control product amniotic membrane (AM) is a used extensively to treat ocular surface disorders. It is hypothesised that immunosuppressive therapy and AM alone may allow ocular surface reconstruction by eliminating the inflammatory environment that is detrimental to the function of stem cells. Therefore, one group of patients received donor derived ex vivo expanded corneal limbal stem cells on AM and immunosuppressive therapy, and the second group received AM graft and immunosuppressive therapy.

Actual start date of recruitment	01 July 2011
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: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	15
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 1st July 2011 and ceased early due to slow recruitment at 17 patients, amendment to cease recruitment approved by the MHRA 09/12/2014. A total of 30 patients were screened for the trial of whom 13 were either not suitable (6) or declined (7). 17 were enrolled of whom 16 were treated (one patient withdrew prior to treatment)

Pre-assignment

Screening details:

Subjects diagnosed with LSCD were screened for inclusion in trial in compliance with inclusion/exculsion criteria defined in study protocol LSC001. Informed consent for participation in trial gained prior to any study related procedures taking place.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The randomisation schedule was generated using Random Permuted Blocks (Pocock S. 1993). Neither the patient, nor the study staff performing the post-operative evaluations, knew to which treatment group they had been allocated.
The randomisation was only broken by the Pharmacovigilance Manager at the end of the study, or would have been in the event of an unexpected Serious Adverse Reaction (SAR)

Arms

Are arms mutually exclusive?	Yes
Arm title	IMP Test Arm

Arm description:

Subjects had either bilateral or unilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder
All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Arm type	Experimental
Investigational medicinal product name	Allogeneic Ex-vivo Expanded Corneal Epithelial Stem Cells on Amniotic Membrane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Ocular use, Ophthalmic use

Dosage and administration details:

Each product was considered to be a single ‘dose’ based with ≥200mm2 macroscopic outgrowth and a diameter ≥15mm in all directions. Administration was via the removal of abnormal tissue over the cornea and the conjunctiva resected and recessed. The graft was placed atop the defect and the edge sewn to the peripheral cornea with 10-0 nylon. The posterior peripheral edge of the AM was sewn to the resected and recessed conjunctiva. A second AM was sewn on top of the product and a bandage contact lens placed to help protect the cells. One of the explants was sewn in the 12 o’clock position. The AMs dissolved gradually and the stem cells establish to the grafted surface

Arm title	Control Arm

Arm description:

Subjects had bilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder

All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Arm type	Active comparator
Investigational medicinal product name	Amniotic Membrane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Ocular use

Dosage and administration details:

Control AM for transplantation alone was prepared using an identical technique as for the IMP Allogeneic Ex-vivo Expanded Corneal Epithelial Stem Cells on AM, the AM was administered in the same way as the IMP arm.
Each cultured AM was considered to be a single 'dose'. Administration was via the removal of abnormal tissue over the cornea and the conjunctiva resected and recessed. The graft was placed atop the defect and the edge sewn to the peripheral cornea with 10-0 nylon. The posterior peripheral edge of the AM was sewn to the resected and recessed conjunctiva. A second amniotic membrane was sewn on top of the product and a bandage contact lens placed to help protect the graft.

Number of subjects in period 1	IMP Test Arm	Control Arm
Started	9	8
Completed	8	5
Not completed	1	3
Adverse event, serious fatal	-	1
Physician decision	-	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups

Reporting group title	IMP Test Arm

Reporting group description:

Subjects had either bilateral or unilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder
All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Reporting group title	Control Arm

Reporting group description:

Subjects had bilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder
All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Reporting group values	IMP Test Arm	Control Arm	Total
Number of subjects	9	8	17
Age categorical			
Inclusion Criteria Adult patients, of either sex, with corneal blindness due to limbal stem cell deficiency			
Units: Subjects			
Adults (18-64 years)	9	6	15
From 65-84 years	0	2	2
Age continuous			
Units: years			
arithmetic mean	46	53	
standard deviation	± 12	± 12	-
Gender categorical			
Units: Subjects			
Female	5	3	8
Male	4	5	9

Subject analysis sets

Subject analysis set title	aniridia
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Aniridia is a congenital, bilateral, panocular disorder which can develop to affect the iris, cornea, anterior chamber angle, lens, retina and optic nerve with frequent association with multiple ocular abnormalities including limbal stem cell deficiency

Subject analysis set title	chemical injury
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Burns involving the eye can lead to destruction of part or all of the limbus on a unilateral or bilateral basis causing LSCD.

Subject analysis set title	Autoimmune disorder
Subject analysis set type	Sub-group analysis

Subject analysis set description:

autoimmune including pemphigoid, may lead to LSCD.

Reporting group values	aniridia	chemical injury	Autoimmune disorder
Number of subjects	7	8	2
Age categorical			
Inclusion Criteria Adult patients, of either sex, with corneal blindness due to limbal stem cell deficiency			
Units: Subjects			
Adults (18-64 years)	6	7	2
From 65-84 years	1	1	0
Age continuous			
Units: years			
arithmetic mean	53	48	43
standard deviation	± 9	± 16	± 20
Gender categorical			
Units: Subjects			
Female	3	4	1
Male	3	4	1

End points

End points reporting groups

Reporting group title	IMP Test Arm

Reporting group description:

Subjects had either bilateral or unilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder
All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Reporting group title	Control Arm

Reporting group description:

Subjects had bilateral LSCD resulting from one of the following underlying condition:
- Aniridia
-Chemical injury
-Autoimmune disorder
All subjects treated met inclusion/exclusion criteria defined in the study protocol LSC001 .

Subject analysis set title	aniridia
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Aniridia is a congenital, bilateral, panocular disorder which can develop to affect the iris, cornea, anterior chamber angle, lens, retina and optic nerve with frequent association with multiple ocular abnormalities including limbal stem cell deficiency

Subject analysis set title	chemical injury
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Burns involving the eye can lead to destruction of part or all of the limbus on a unilateral or bilateral basis causing LSCD.

Subject analysis set title	Autoimmune disorder
Subject analysis set type	Sub-group analysis

Subject analysis set description:

autoimmune including pemphigoid, may lead to LSCD.

Primary: visual acuity

End point title	visual acuity

End point description:

Best corrected visual acuity

End point type	Primary

End point timeframe:

The end point of the trial was 18 months post treatment, subjects were reviewed at pre treatment, then post treatment at day 1, 2/3, 7, 14 and month 1, 3, 6, 9,12, 15 and 18 months

End point values	IMP Test Arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	5		
Units: average reduction in logmar score				
arithmetic mean (standard deviation)	-0.82 (± 0.97)	-0.89 (± 0.51)		

Statistical analyses

Statistical analysis title	visual acuity

Statistical analysis description:

analysis of reduction in Logmar score by unpaired t-test

Comparison groups	IMP Test Arm v Control Arm
Number of subjects included in analysis	13
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.228 [1]
Method	t-test, 1-sided

Notes:

[1] - no significant difference shown between IMP and control arm for visual acuity

Secondary: Ocular Surface Score

End point title	Ocular Surface Score

End point description:

A composite score for the ocular surface disease status of the patients was obtained throughout the study according to the following 5 criteria:
corneal epithelium
conjunctivalisation
corneal neovascularisation
corneal opacification
conjunctival hyperaemia
Each criteria was scored from 0-3 (normal-severe damage) by the trial physicians, and an aggregate score out of 15 obtained.

End point type	Secondary

End point timeframe:

18 months , measurements at pre treatment, post treatment at day 1, 2/3, 7, 14 and month 1, 3, 6, 9,12, 15 and 18 months

End point values	IMP Test Arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	5		
Units: ocular surface score				
number (not applicable)	2.07	1.42		

Attachments (see zip file)	results summary charts/Appendix XVII Summary of Preliminary

Statistical analyses

Statistical analysis title	ocular surface score

Statistical analysis description:

8 patients in the IMP test arm and 5 patients in the control arm had ocular surface scores which were evaluated throughout, and at conclusion of the trial. All patients showed lower (improved) ocular surface scores at the conclusion of the trial. However, only patients in the test arm who received the IMP Allogeneic Ex-vivo Expanded Corneal Epithelial Stem Cells on Amniotic Membrane product showed a statistically significant higher mean improvement in combined ocular surface score.

Comparison groups	IMP Test Arm v Control Arm
Number of subjects included in analysis	13
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.004 [2]
Method	t-test, 1-sided

Notes:

[2] - Statistically significant improvement in combined ocular surface scores when treated with IMP (p=0.0040, unpaired t-test) compared with Control arm, based on the mean change from pre treatment to 18 months post treatment ocular surface score +/- SD.

Secondary: Quality of Life

End point title	Quality of Life

End point description:

Quality of life (QoL) assessments using the SF-36 scoring system were analysed as a whole data set, and as delta in each patient relative to each individual's starting score in each category. There were no statistically significant changes in QoL scoring throughout the trial. The one exception was a significant decrease at 6 months (p= 0.0024) in the Social Function component of the SF36 score which returned to non-significance over baseline thereafter. This likely contributed to a trend towards initial reduction in overall SF-36 score at 6 months which recovered subsequently. Although there was fluctuation over time, SF-36 scores closely tracked to the pre-trial baseline levels by the end of the study

End point type	Secondary

End point timeframe:

18 months

End point values	IMP Test Arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[3]	5[4]		
Units: number				
number (not applicable)	0	0		

Notes:

[3] - Outcome of anaysis is given in the appended document

[4] - Outcome of anaysis is given in the appended document

Attachments (see zip file)	Quality of Life analysis/quality of life data.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: WBC and Cytokine levels

End point title	WBC and Cytokine levels

End point description:

12/13 patients showed normal WBC levels throughout the study. 1 patient with chemical injury had an elevated WBC – this patient had ongoing ocular inflammation and had to be withdrawn from the study

for corneal transplant.
Patients could be stratified into normal or high serum cytokines at the start of the study – the normal group consisted of chemical burns patients and the one patient with autoimmune disease, while the high group consisted of all aniridia patients, 2 chemical burns, and the other patient with an autoimmune disease (pemphigus).
In the high cytokine group, IL-8 was highly elevated in all patients, but IFN-gamma and TNF-alpha levels were not increased. The high group also showed variably increased levels of IL-2, 4, 10 and 12, but there was no consistent pattern. There was no correlation between IL-8 levels and WBC.
the results of this post hoc analysis are appended.

End point type	Post-hoc

End point timeframe:

up to 18 months

End point values	IMP Test Arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[5]	5[6]		
Units: number				
number (not applicable)	0	0		

Notes:

[5] - Outcome of anaysis is given in the appended document

[6] - Outcome of anaysis is given in the appended document

Attachments (see zip file)	wbc cytokine analysis/WBC cytokine analysis.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
18 months post treatment	
Adverse event reporting additional description:	
Patients were monitored for any adverse events during the study period. Any serious adverse event which arose following use of the limbal stem cell graft or the AM was immediately notified to the SNBTS .	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	IMP Corneal epithelial stem cells on amniotic membrane
Reporting group description:	
AEs from patients receiving the IMP	
Reporting group title	control arm amniotic membrane
Reporting group description:	
Control group receiving amniotic membrane	

Serious adverse events	IMP Corneal epithelial stem cells on amniotic membrane	control arm amniotic membrane	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	2 / 7 (28.57%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Death	Additional description: The patient's death due to a perforated bowel and sepsis was not considered to be related to the product.		
alternative dictionary used: MedDRA 15			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laser therapy			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colostomy			

alternative dictionary used: MedDRA 15			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal epithelium defect	Additional description: patient withdrawn		
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Spinal compression fracture			
alternative dictionary used: MedDRA 15			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IMP Corneal epithelial stem cells on amniotic membrane	control arm amniotic membrane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	7 / 7 (100.00%)	

Investigations			
Intraocular pressure increased			
alternative dictionary used: MedDRA 15			
subjects affected / exposed	1 / 9 (11.11%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Blood pressure ambulatory increased			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Presyncope			
alternative dictionary used: MedDRA 15			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye swelling			
alternative dictionary used: MedDRA 15			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Corneal abrasion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eye inflammation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Conjunctival scar			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Corneal deposits			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			

alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
alternative dictionary used: MedDRA 15			
subjects affected / exposed	1 / 9 (11.11%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Testicular mass			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus			
alternative dictionary used: MedDRA 17.0			

subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary tract infection			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Urinary retention postoperative			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 9 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Lithotripsy			
alternative dictionary used: MedDRA 17.0			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Pituitary cyst			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 9 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2012	Following a Serious Adverse Event, that was unrelated to the study product but resulted in the death of the patient, Information for Patients was updated to include additional information on the possible risks of concomitant trial medication, including immunosuppressive therapy. in addition, new investigator site at St Pauls Eye unit Liverpool added as an additional investigator site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminted early due to slow recruitment, therefore only 17 patients were recruited instead of the planned 20 (10 in each arm), 13 patients completed the study.

Notes: